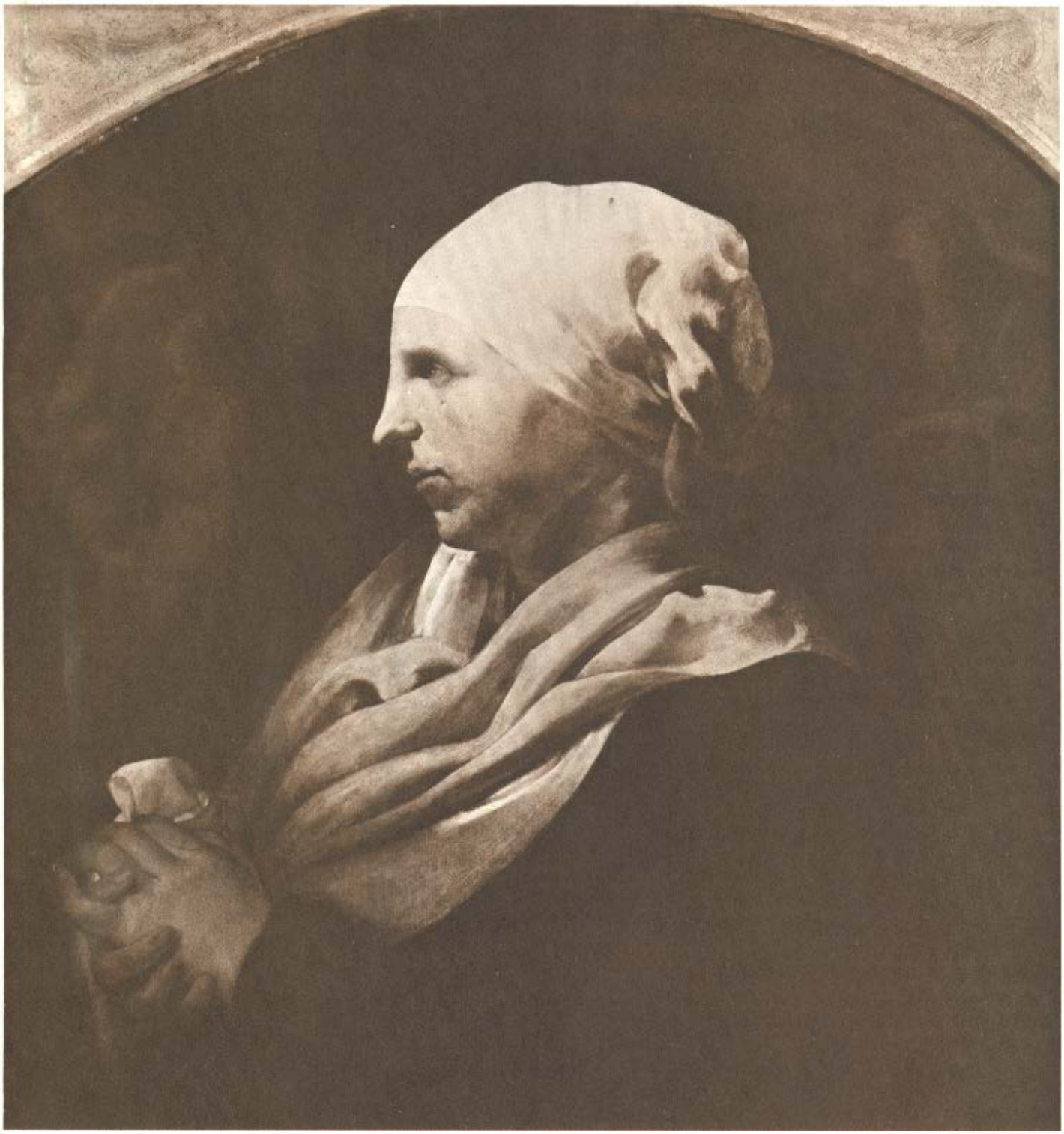
Aldrichimica Acta

Volume 8, Number 1, 1975



Sodium cyanoborohydride. A highly selective reducing agent.

A publication of Aldrich Chemical Company, Inc.

Aldrichimica Acta

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A publication of ALDRICH CHEMICAL COMPANY, INC.

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About the Cover

It is a great moment in the life of a collector when he finds himself confronted by a hitherto unknown masterpiece by a great artist — be it in a junk store, an auction or — as happened to our chemist-collector — in a farmhouse near Delft where he first saw this moving work by the greatest of Utrecht painters, Hendrick Terbrugghen. If only, he explains, it happened more often!

Our chemist believes that this painting may depict a very rare subject, *Mary Praying for the Condemned in Purgatory*. However, the iconography seems almost irrelevant. What we see here is the timeless tragedy of a woman bemoaning man's inhumanity to man — be this at Golgotha, at Auschwitz or at My Lai.

That an artist can depict anguish so that it almost hurts us physically to look at this study in grey, persuades us that art, like music, is one of God's means of communication with man.

Overexposed detail photographs of the background of our cover painting.

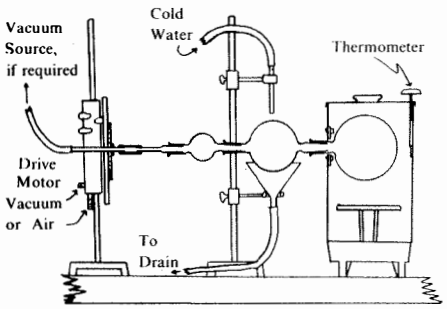
Are you interested in our Acta covers? *Selections from the Bader Collection,* with 30 duotone reproductions, many of previous Acta covers, and an introduction by the late Professor Wolfgang Stechow is now available to all chemist art-lovers.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Lab Notes

How often have you encountered the problem where separation by crystallization is unsuccessful and distillation is impractical because of possible product solidification in the distillation apparatus?

In many instances, a Kugelrohr short-path distillation of the crude reaction product provides a simple method of purification, virtually eliminating any problem of plugging-up of the apparatus, while ensuring a reasonably clean separation.



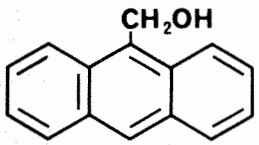
Note - 2nd bulb required only for very volatile materials.

No rotating seal is present and high vacuum may be achieved, thus making the Kugelrohr especially useful for sensitive high boiling compounds. Fractionation can be easily accomplished by changing distillation tubes or receivers.

The Kugelrohr apparatus can be built according to plans published in *J. Chem. Educ.*, **41,** 279 (1964), or the complete unit may be purchased from Aldrich as stock number Z10,046-3 at

Any interesting shortcut or laboratory hint you'd like to share with ACTA readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome red and white ceramic Aldrich coffee mug. All entries become the property of Aldrich Chemical Company, Inc., and cannot be returned.

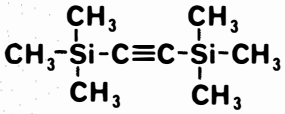
9-Anthracenemethanol



9-Anthracenemethanol is used as a protecting group for carboxylic acids. The ester is stable to hydrolysis under acidic and basic conditions but is readily cleaved under mild, selective conditions by treatment with the sodium salt of methyl mercaptan in DMF or HMPA.

N. Kornblum and A. Scott, *J. Amer. Chem. Soc.*, **96,** 590 (1974).

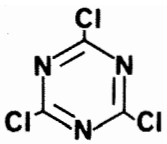
Bis(trimethylsilyl)acetylene (BTMSA)



Bis(trimethylsilyl)acetylene is a useful reagent for the synthesis of acetylenic compounds, *e.g.*, terminal alkynyl ketones[1] and aryl ethynyl sulfones.[2]

1) D.R.M. Walton and F. Waugh, *J. Organometal. Chem.*, **37,** 45 (1972).
2) S.N. Bhattacharya, B.M. Josiah, and D.R.M. Walton, *Organometal. Chem. Syn.*, **1,** 145 (1970/1971).

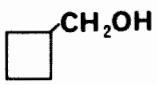
Cyanuric Chloride



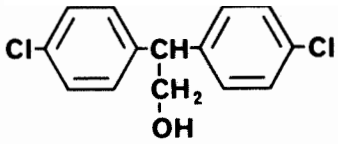
Cyanuric chloride reacts with anhydrous alcohols, without the use of free acid, to give alkyl chlorides.[1] Iodides are similarly produced with this reagent in the presence of NaI.[2] Oximes are rapidly converted to nitriles by reaction with cyanuric chloride in pyridine under mild, convenient conditions.[3]

1) S.R. Sandler, *J. Org. Chem.*, **35,** 3967 (1970).
2) S.R. Sandler, *Chem. Ind.*, 1416(1971).
3) J.K. Chakrabarti and T.M. Hotten, *Chem. Commun.*, 1226 (1972).

New Cyclobutane Derivative



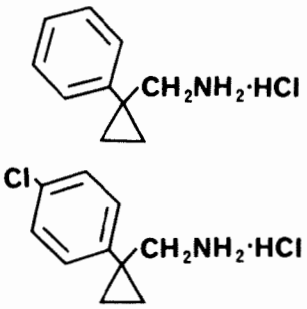
2,2-Bis(*p*-chlorophenyl)ethanol



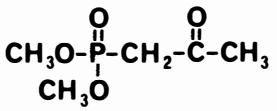
2,2-Bis(*p*-chlorophenyl)ethanol is a metabolite of DDT and a substrate for liver alcohol dehydrogenase in mammals.

J.E. Suggs, R.E. Hawk, A. Curley, and E.L. Boozer, *Science,* **168,** 582 (1970).

Interesting New Phenethylamines



Dimethyl (2-oxopropyl)phosphonate



Dimethyl (2-oxopropyl)phosphonate undergoes specific alkylation at the γ-carbon *via* the dianion. It is a precursor in the general high yield synthesis of β-ketophosphonates, *e.g.*, dimethyl 2-oxoheptylphosphonate which provides a new route to a key prostaglandin reagent.

P.A. Grieco and C.S. Pogonowski, *J. Amer. Chem. Soc.*, **95,** 3071 (1973).

Sodium Cyanoborohydride: A Highly Selective Reducing Agent

Clinton F. Lane
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The synthetic organic chemist, faced with the need to prepare compounds of ever-increasing complexity, has had the problems confronting him greatly simplified by the development of numerous selective reducing agents.[1,2] Reagents that are capable of reducing a given functional group in the presence of various other sensitive functional groups have been prepared by modifying the reducing power of complex metal hydrides. For example, substituted borohydrides are a particularly successful modification. The steric and electronic effects of the substituents greatly influence the reactivity of the borohydride ion.[3] Thus, sodium cyanoborohydride with its strongly electron-withdrawing cyano group is a milder and more selective reducing agent than sodium borohydride.

The initial exploratory work on the utility of an alkali metal cyanoborohydride as a reducing agent resulted in almost totally negative results. Of all the functional groups studied, only aldehydes were reported to have been reduced.[4] Fortunately, the reagent was not forgotten and recent investigations have shown that, under the proper conditions, sodium cyanoborohydride is an extremely useful reagent for the selective reduction of organic functional groups.

PHYSICAL PROPERTIES

Sodium cyanoborohydride is highly soluble in a variety of solvents including water, alcohols, amines, and tetrahydrofuran (THF) but is insoluble in hydrocarbons. Complete solubility data are summarized in Table I.

The $NaBH_3CN$ available from the Aldrich Chemical Company is of sufficient purity for most applications. However, if ultra-pure material is required, one of the following purification procedures should be used. The $NaBH_3CN$ is dissolved in THF (20%w/v), filtered and reprecipitated by a four-fold volume of methylene chloride.[5] The $NaBH_3CN$ is then collected and dried *in vacuo*. Alternatively, the $NaBH_3CN$ is dissolved in dry nitromethane and filtered, and the filtrate is poured into a ten-fold volume of carbon tetrachloride with vigorous stirring.[6] The white precipitate of $NaBH_3CN$ is filtered, washed several times with carbon tetrachloride and dried *in vacuo*. A third method for the purification of $NaBH_3CN$ involving precipitation and recrystallization of the dioxane complex has been reported in detail by Borch and coworkers.[7]

Solvent-free $NaBH_3CN$ is a white amorphous powder, m.p. 240-242° (dec.). Contact with air should be kept to a minimum because $NaBH_3CN$ is very hygroscopic.

CHEMICAL PROPERTIES

1. Hydrolysis

The utility of $NaBH_3CN$ as a reducing agent is greatly enhanced by its stability in acid to pH 3.[8] The hydrolysis of $NaBH_3CN$ is acid-catalyzed. However, its rate of hydrolysis is 10^{-8} times that of $NaBH_4$.[9] The

$$BH_3CN^- + 3H_2O \xrightarrow{12N\ HCl} B(OH)_3 + CN^- + 3H_2 \qquad (1)$$

decomposition of $NaBH_3CN$ in water at pH 7 as measured by hydrogen evolution at concentrations from 10^{-3} to $0.3M$ is less than 0.5 mole % after 24 hr.[6] In $12N$ hydrochloric acid, relatively rapid hydrolysis occurs (eq 1).[6]

Table I. Solubility of $NaBH_3CN$[a]

Solvent	Temp., °C	Solubility, g/100g solvent
THF	28	37.2
	46	41.0
	62	42.2
Water	29	212
	52	181
	88	121
Methanol	25	Very soluble
Ethanol	25	Slightly soluble
Diglyme	25	17.6
Isopropylamine	25	Slightly soluble
Diethyl ether	25	Insoluble
Benzene	25	Insoluble
Hexane	25	Insoluble

[a]Data taken from Ref. 5.

The acid stability of $NaBH_3CN$ has resulted in numerous applications of this reagent that would not be possible with $NaBH_4$ (*vide infra*). For example, $NaBH_4$ can be used to trap carbonium ions formed in the ionization of readily ionizable organic halides in an aqueous diglyme solution.[10] The rate of solvolysis would, of course, be enhanced by the presence of acid, but this would also rapidly destroy the $NaBH_4$. This serious limitation is not present with $NaBH_3CN$, which has been used to trap carbonium ions generated with hydrogen chloride in aqueous THF.[11]

The addition of one equivalent of hydrogen chloride to a solution of $NaBH_3CN$ in THF results in incomplete hydrolysis with the formation of cyanoborane, which was postulated to exist in THF as the $BH_2CN \cdot THF$ complex (eq 2).[12] The addition of amines to this solution has been used for the preparation of various amine-cyanoborane adducts.[13,14] This procedure appears generally useful for the synthesis of donor-cyanoborane complexes. If diethyl ether is used as the solvent instead of THF, then various polymeric forms of cyanoborane are formed.[15]

$$NaBH_3CN + HCl \xrightarrow{THF} BH_2CN \cdot THF + NaCl + H_2 \quad (2)$$

Measurement of the volume of hydrogen evolved upon complete hydrolysis in aqueous acid can be used for the quantitative analysis of sodium borohydride.[16] However, this procedure cannot be used conveniently to analyze $NaBH_3CN$ due to its slow rate of hydrolysis even in aqueous acid. Iodometric titration has been used to determine the purity of $NaBH_4$[17] and $NaBH_3CN$.[7,9] The half-reaction for this redox reaction is as shown (eq 3).[6]

$$BH_3CN^- + 3H_2O \longrightarrow B(OH)_3 + CN^- + 6H^+ + 6e^- \quad (3)$$

2. Exchange

At pH 3, the hydrogens of BH_3CN^- can be readily exchanged for either deuterium or tritium,[8] thus permitting the direct synthesis of $NaBD_3CN$ and $NaBH_3CN$-*t*.[7] When D_2O is used, the rate of exchange is about 15 times as fast as the rate of hydrolysis.[9] In the case of $NaBH_4$, hydrolysis competes with exchange so that exchange is barely detectable.

Recent experimental results have shown that as the solvent becomes more basic, the ratio of the exchange rate to the hydrolysis rate becomes greater.[18] For example, the ratio k_{ex}/k_{hy} is equal to 34 in pure water while in 4:1 DMSO-water, the ratio is equal to 374.

3. Industrial Applications

The reducing properties of alkali metal cyanoborohydrides have led to a number of interesting industrial applications. Lithium cyanoborohydride has been used to cure a liquid nitrile polymer[19] and a polymer made from an aliphatic mercaptan and a conjugated diene.[20] Cyanoborohydrides have been used for the reductive bleaching of groundwood pulp, sulfate pulp and chemigroundwood pulp without corrosion of the equipment.[21] Finally, chemical metal plating baths have been described where a cyanoborohydride is used as the reducing agent[22] or as an additive to improve the stability and efficiency of the chemical plating solution.[23]

4. Transition Metal Complexes

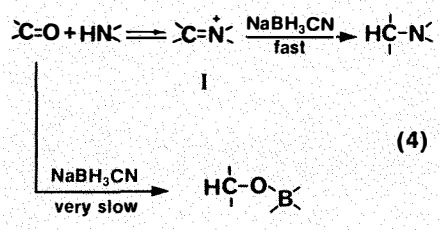
The cyanoborohydride ion can act as a ligand for transition metal complexes, and the preparation, structure, physical properties and spectra of a number of these complexes have been described. Complexes have been reported where the transition metal is copper,[24-30] silver,[24,26] nickel,[24,27,30] cobalt,[27,30] ruthenium,[31] rhodium,[27,32,33] or iridium.[27,32]

The synthesis of these complexes is quite simple. For example, a copper complex is readily prepared by adding an ethanol solution of $NaBH_3CN$ to a chloroform solution of $(Ph_3P)_3CuCl$.[24] On standing, this solution develops colorless crystals of $(Ph_3P)_3Cu(NCBH_3)$.

A systematic investigation of the chemical properties of these transition metal cyanoborohydride complexes has not been undertaken. These complexes may show interesting and useful characteristics for the reduction of organic functional groups. For example, aromatic nitro groups are normally inert to $NaBH_4$ but are readily reduced to amines in the presence of $(Ph_3P)_3NiCl_2$.[34] This process may be more complicated but it could involve an intermediate nickel borohydride complex.[35]

SELECTIVE REDUCING PROPERTIES

Sodium cyanoborohydride is a versatile reagent that will reduce a variety of organic functional groups with remarkable selectivity. For example, many selective reductions have resulted from the observation that an imminium ion (I) is reduced much faster than a carbonyl group (eq 4).[7,8]



(4)

Also, the stability of $NaBH_3CN$ in protic solvents at low pH has allowed reductions under conditions that would rapidly hydrolyze $NaBH_4$. Finally, the solubility of $NaBH_3CN$ in polar aprotic solvents has further enhanced its utility as a reducing agent.

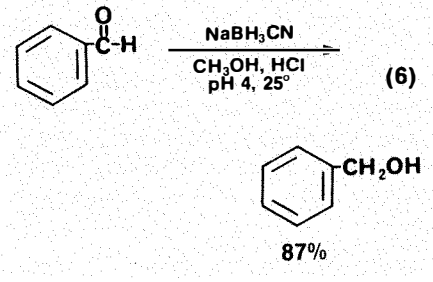
Sodium cyanoborohydride is a very selective reducing agent because, even under the diverse reaction conditions employed, many sensitive functional groups are not reduced. For example, amides, esters, lactones, nitriles, nitro compounds and epoxides are inert toward this reagent.

The various selective reductions will now be discussed in detail.

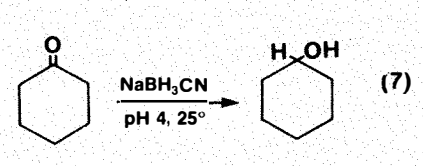
1. Reduction of Aldehydes and Ketones

Under neutral conditions in water or methanol, there is negligible reduction of aldehydes and ketones. However, at pH 3-4, the rate of reduction is sufficiently rapid to be synthetically useful.[7,36] Since the reduction consumes hydrogen ions (eq 5), a buffered system is required or acid must be added to maintain the necessary low pH.[7] Some specific examples are illustrated below (eq 6,7).[7]

$$3HCOH + BH_3CN^- + 3ROH + H^+ \longrightarrow 3HCOH + B(OR)_3 + HCN \quad (5)$$



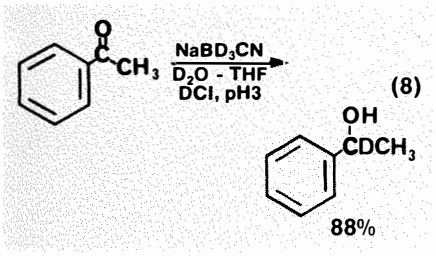
(6)



(7)

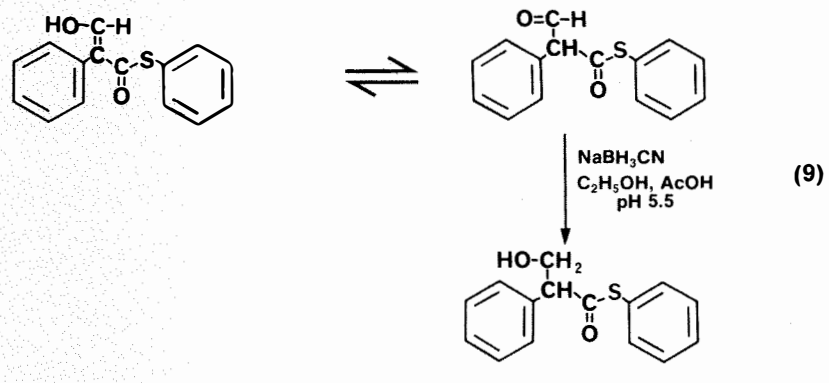
The reduction of cyclopentenone with $NaBH_3CN$ gives mainly cyclopentanol.[7] However, this may not be a general result for α,β-unsaturated systems. Recently, it was shown that, in the reduction of a series of conjugated ketones of the cholestenone type with $NaBH_3CN$ in THF, the major product was usually the corresponding allylic alcohol.[16]

For $NaBD_3CN$ reductions, the recommended solvent is THF-D_2O and the pH is maintained by adding a solution of DCl-AcOD in THF-D_2O.[7] High yields of deuterated alcohols are possible as shown in equation 8.



(8)

The mild conditions employed for these reductions with $NaBH_3CN$ should result in many applications for the selective reduction of aldehydes and ketones. Recently, a specific example was reported which showed that an aldehyde group can be selectively reduced with $NaBH_3CN$ in the presence of a thiol ester group (eq 9).[38]



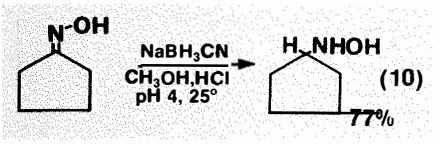
(9)

By changing the cation and solvent, it is possible to carry out an even more selective reduction. Thus, tetrabutylammonium cyanoborohydride in acidified hexamethylphosphoramide (HMPA) selectively reduces aldehydes in the presence of almost all other functional groups including cyano, ester, amido, nitro, and even the keto group.[39]

A recent patent disclosed that a new class of reducing agents can be prepared by the reaction of sodium cyanide with dialkylboranes in THF.[40] The resulting Na-[R_2BHCN] reagent was claimed to be useful for carbonyl reductions.

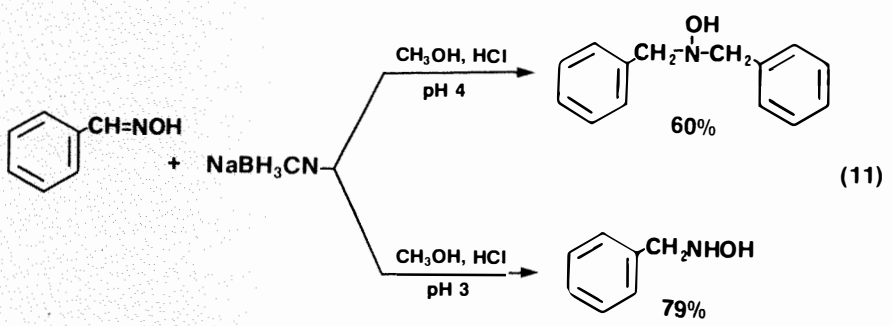
2. Reduction of Oximes

Under acid conditions, the reduction of a ketoxime proceeds smoothly to the corresponding *N*-alkylhydroxylamine with no trace of the amine which would result from overreduction (eq 10).[7]



(10)

The reduction of aldoximes is extremely pH-dependent. When the reduction is carried out at pH 4, the major product is the dialkylhydroxylamine, while at pH 3, the major product is the monoalkylhydroxylamine (eq 11).[7]



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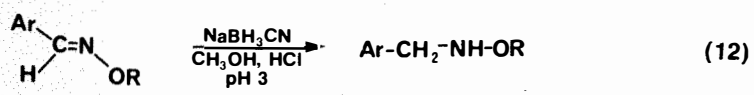

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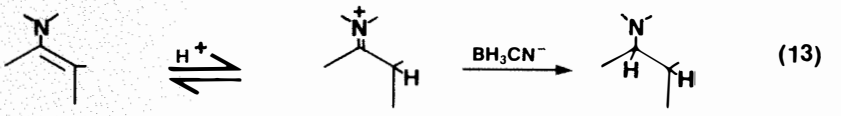

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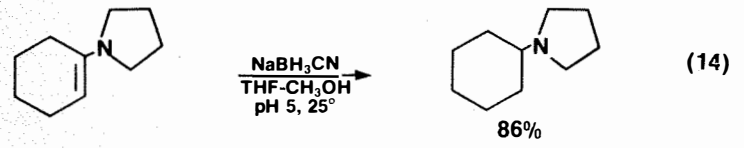


(14)

Reduction with $NaBH_3CN$ provides what is apparently the only known method for the conversion of *O*-alkylbenzaldoximes to the corresponding *N,O*-dialkylhydroxylamines (eq 12).[41]

The reduction of oximes with borane-THF provides an alternative method for the preparation of *N*-alkylhydroxylamines.[42] However, this procedure cannot be used to prepare *N,O*-dialkylhydroxylamines because reduction of oxime ethers[43] and oxime esters[43,44] with borane-THF proceeds readily to give the corresponding amines in excellent yields. Also, catalytic hydrogenation of arylketoximes gives amines,[45] while aldoximes afford *N,N*-disubstituted hydroxylamines[45] and *O*-alkylbenzaldoximes give benzyl and dibenzylamines.[46]

3. Reduction of Enamines

Although the enamine group should be resistant to reduction by $NaBH_3CN$, rapid and reversible protonation of the β-carbon generates a readily reducible imminium salt (eq 13).

Simple enamines are rapidly reduced by $NaBH_3CN$ at an initial pH of 5 in a 15:1 THF-methanol solvent mixture (eq 14).[7]

If the enamine is conjugated with a carbonyl group, the reduction becomes more difficult and acid must be added to maintain a pH of 4 (eq 15).[7]

4. Reductive Amination of Aldehydes and Ketones

Since the imminium ion is reduced much faster than a carbonyl group, it is possible to reductively aminate an aldehyde or ketone by simply reacting the carbonyl compound with an amine at pH 6-8 in the presence of $NaBH_3CN$ (eq 16).[7]

The reaction is general for ammonia, primary and secondary amines, all aldehydes, and unhindered ketones. Hindered and diaryl ketones fail to react and aromatic amines react somewhat sluggishly. Some interesting examples of reductive amination are given below along with isolated yields (eq 17-20).

The reductive amination process is not limited to the simple amines. The reaction of a ketone with hydroxylamine has been used to prepare the *N*-alkylhydroxylamines **II** and **III**.[7]

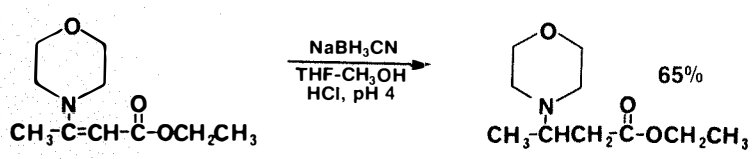
The reaction of a dicarbonyl compound with an amine in the presence of $NaBH_3CN$ provides an interesting new synthesis of nitrogen heterocycles, as illustrated in the preparation of compounds **IV**,[7] **V**,[7] **VI**,[48] and **VII**.[49]

The mild conditions employed for these reductive aminations obviously indicate that numerous highly selective reductions should be possible. Recently, it has been shown that reductive amination with $NaBH_3CN$ can be used to prepare each of the following functionally substituted amines: aminoester (**VIII**),[7] aminoepoxide (**IX**),[50] and aminonitroxide free radical (**X**).[51] An unhindered ketone can be selectively aminated in the presence of a relatively hindered ketone to give the aminoketone (**XI**).[52] Finally, a selective amination of a formyllactone gave the aminolactone (**XII**).[53] This was then used as the key step in a convenient and high yield synthesis of the plant antifungal agent, tulipalin A (**XIII**).[54]

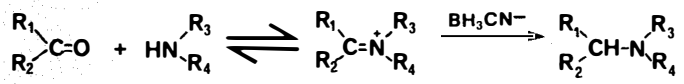
The reductive amination of substituted pyruvic acids provides a useful new synthesis of *dl*-α-amino acids (eq 21,22).[7] This procedure is apparently the most efficient and economical route for preparing ^{15}N-labelled amino acids (eq 23).[7]

5. Reductive Alkylation of Amines and Hydrazines

A mild and efficient method for the synthesis of tertiary methylated amines has been developed that involves simply the reductive amination of formaldehyde.[55] The reaction of an aliphatic or aromatic amine with aqueous formaldehyde and $NaBH_3CN$ in acetonitrile results in excellent isolated yields of methylated amines (eq 24-27).



(15)



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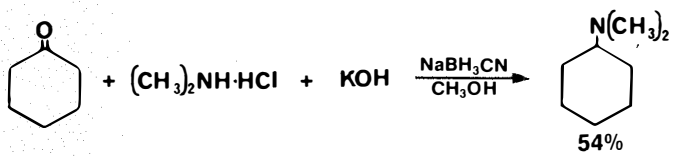

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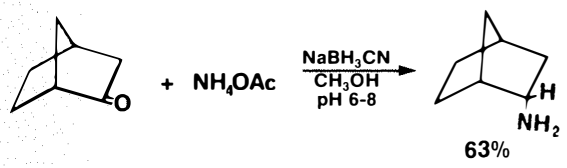

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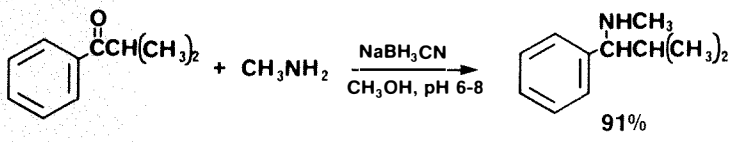

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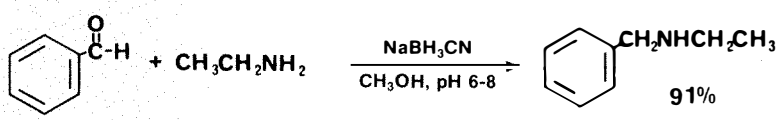

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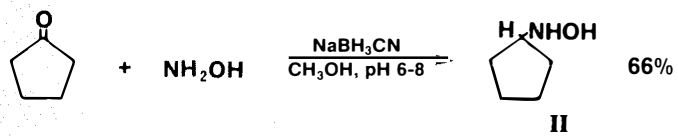

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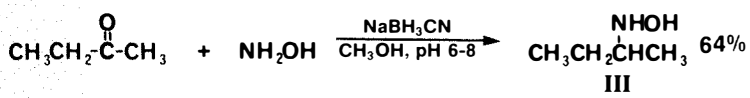

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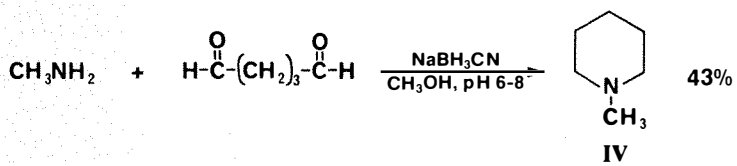

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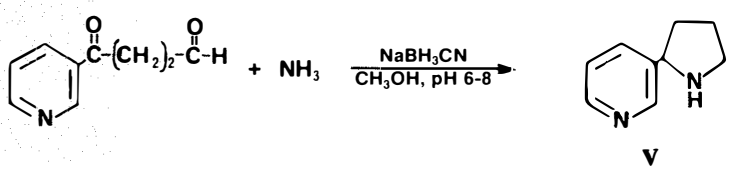
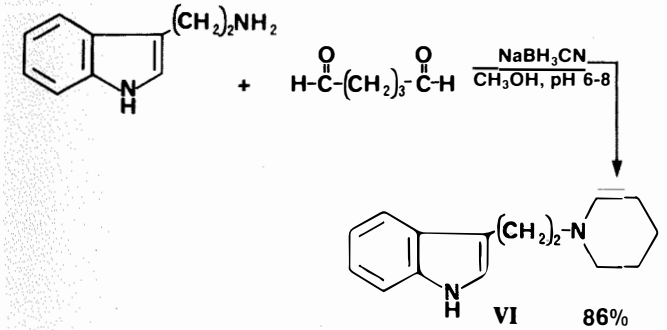
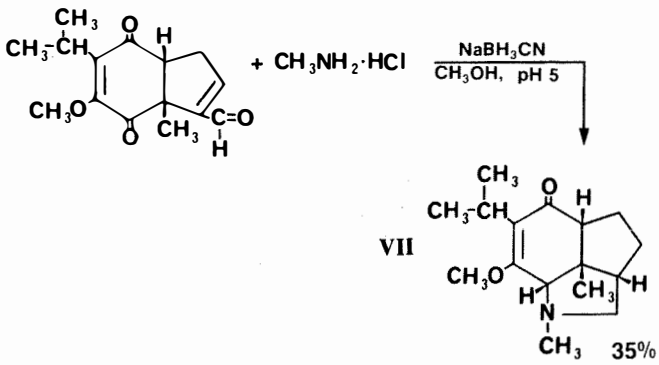
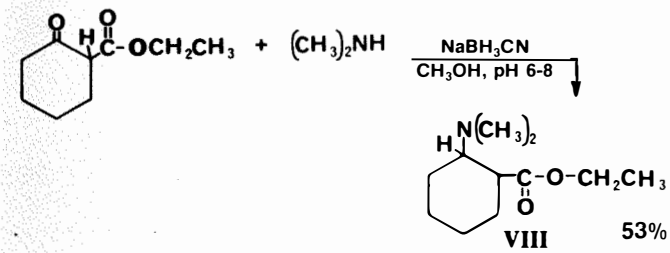
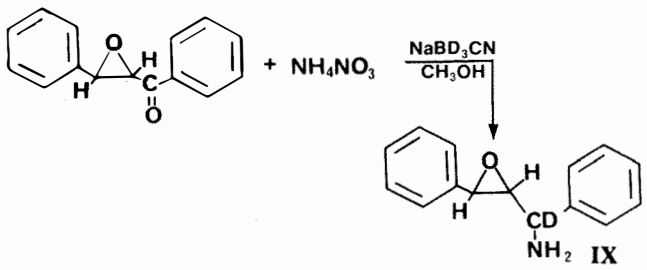


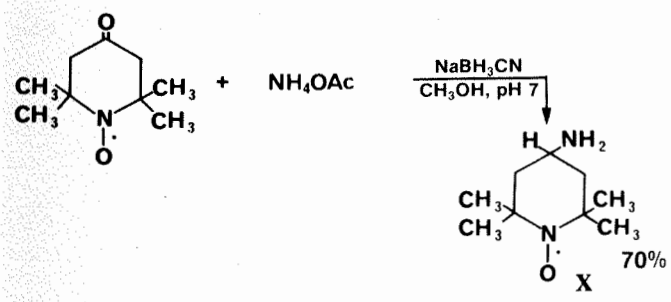
V

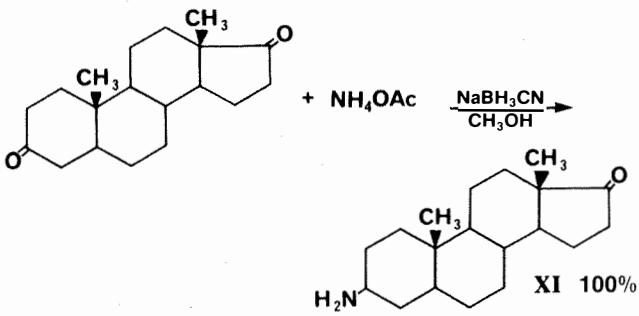

NaBH3CN
CH3OH, pH 6-8
VI 86%

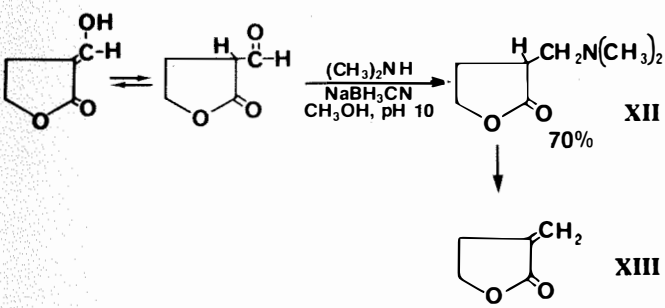

+ CH3NH2·HCl
NaBH3CN
CH3OH, pH 5
VII 35%

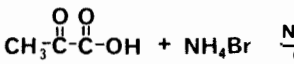

+ (CH3)2NH
NaBH3CN
CH3OH, pH 6-8
VIII 53%

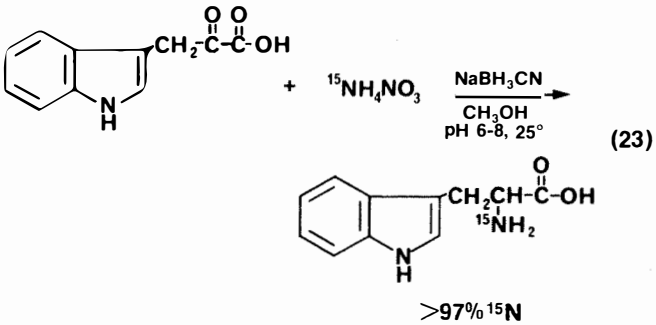

+ NH4NO3
NaBD3CN
CH3OH
IX

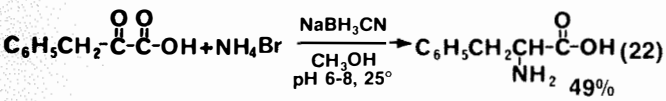

+ NH4OAc
NaBH3CN
CH3OH, pH 7
70%
X

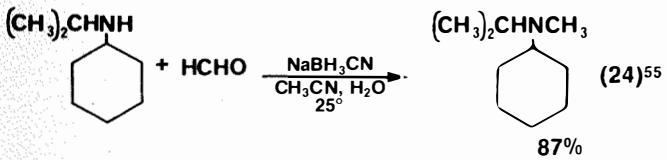

+ NH4OAc
NaBH3CN
CH3OH
XI 100%

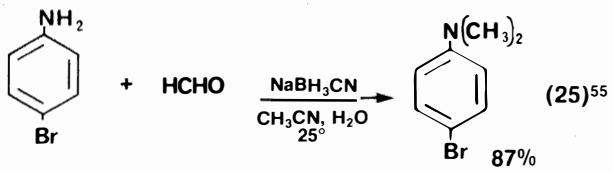

(CH3)2NH
NaBH3CN
CH3OH, pH 10
70%
XII
XIII

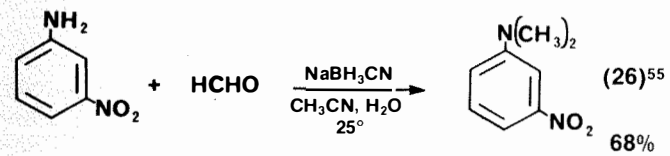

NaBH3CN
CH3OH
pH 6-8, 25°
(21)
50%

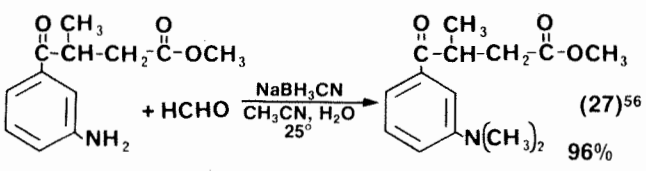

+ 15NH4NO3
NaBH3CN
CH3OH
pH 6-8, 25°
(23)
>97% 15N


NaBH3CN
CH3OH
pH 6-8, 25°
(22)
49%


+ HCHO
NaBH3CN
CH3CN, H2O
25°
(24)55
87%


+ HCHO
NaBH3CN
CH3CN, H2O
25°
(25)55
87%


+ HCHO
NaBH3CN
CH3CN, H2O
25°
(26)55
68%


+ HCHO
NaBH3CN
CH3CN, H2O
25°
(27)56
96%

The mild conditions, ease of experimental manipulation and the high yield of pure product appear to make this the method of choice for the reductive methylation of amines.

Hydrazines can also be reductively alkylated using $NaBH_3CN$ to provide a simple synthesis of some interesting tetraalkylhydrazines (eq 28-30).[57]

6. Reductive Displacement of Halides and Tosylates

Sodium cyanoborohydride in HMPA provides a rapid, convenient, and exceedingly selective system for the reductive removal of iodo, bromo and tosyloxy groups.[58,59] The following examples give an indication of the scope of this reductive displacement procedure (eq 31-33).

Primary alcohols may be converted by a simple two-step-in-one process to the corresponding hydrocarbons. The process involves conversion of the alcohol to the iodide with methyltriphenoxyphosphonium iodide in HMPA at room temperature followed by addition of $NaBH_3CN$ and stirring at 70°. Equations 34 and 35 illustrate this procedure.

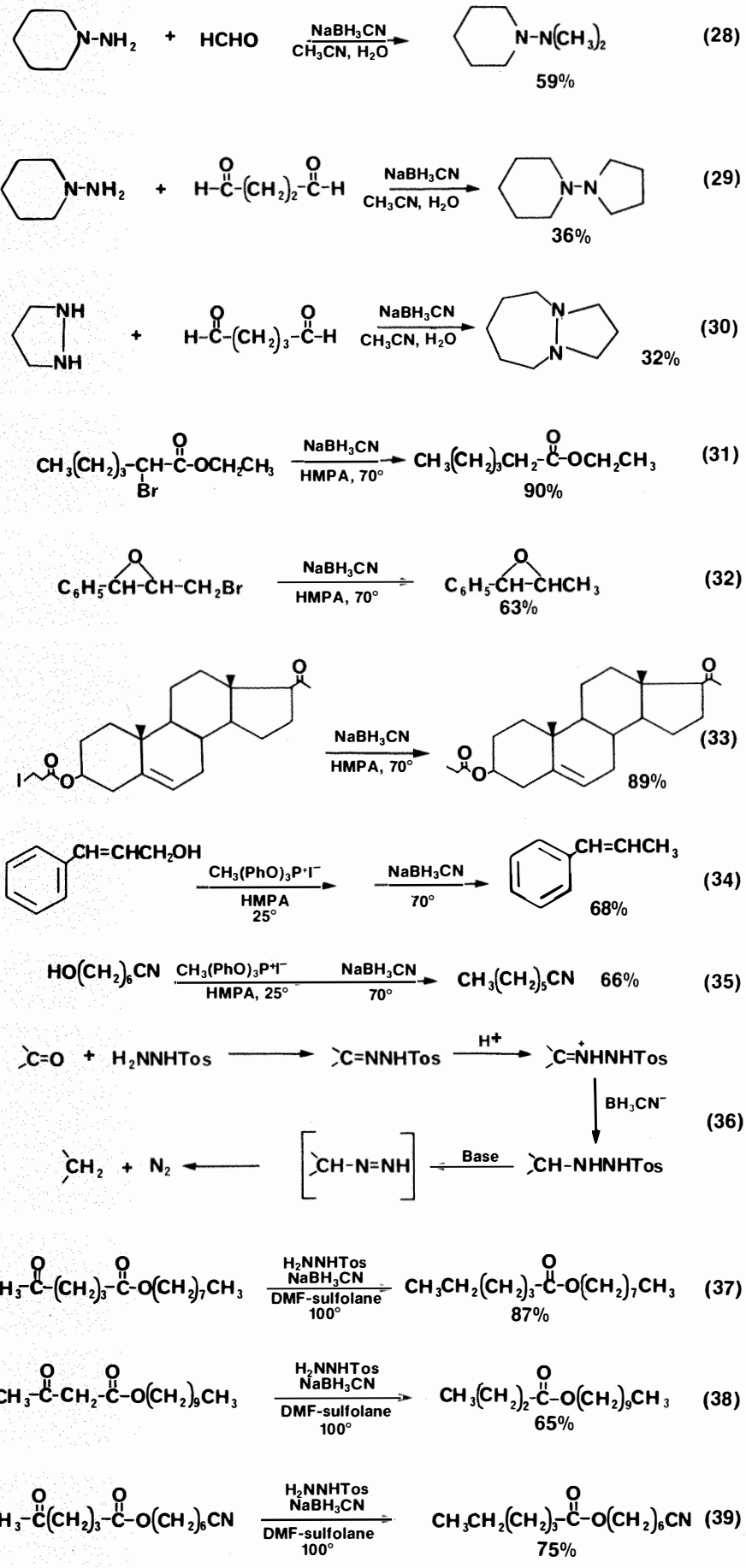
The superior selective feature of this reductive displacement reaction is demonstrated by its inertness toward almost all other functional groups including ester, amide, nitro, chloro, cyano, alkene and even such sensitive groups as epoxide, ketone, and aldehyde.[58] This selectivity becomes even more pronounced when tetrabutylammonium cyanoborohydride is used.[39]

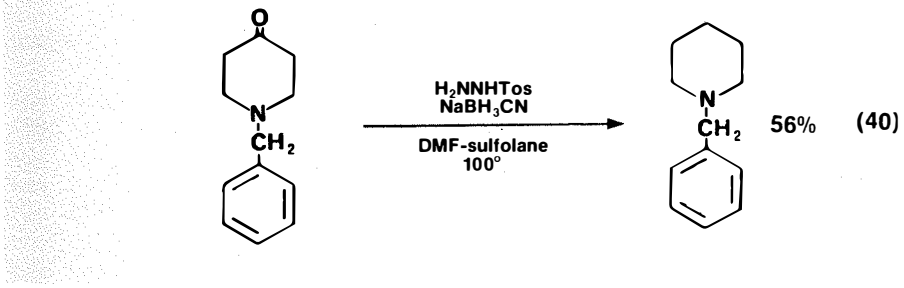
7. Deoxygenation of Aldehydes and Ketones

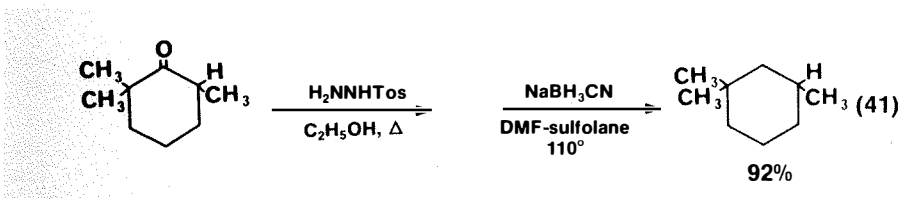
The propensity for $NaBH_3CN$ to reduce imminium ions has resulted in the development of still another useful synthetic reaction. The reduction of aliphatic ketone and aldehyde tosylhydrazones with $NaBH_3CN$ in acidic 1:1 DMF-sulfolane provides a mild, selective, convenient, and high-yield alternative to the Wolff-Kishner and Clemmensen reductions (eq 36).[60-62]

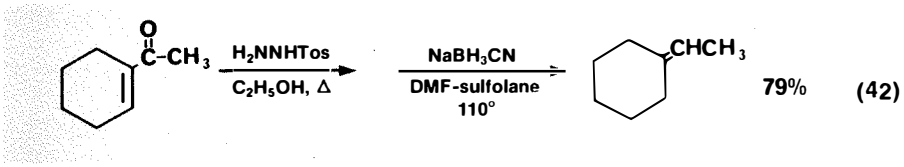
The prior preparation of the tosylhydrazone is unnecessary in many cases since the slow rate of carbonyl reduction permits the *in situ* generation from tosylhydrazine and the carbonyl compound.

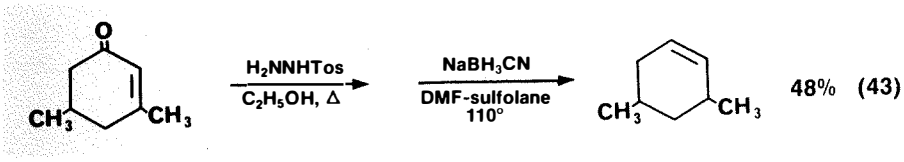
A number of general deoxygenation procedures have been developed depending on the structure of the carbonyl compound. The original investigation, in which over 60 different carbonyl compounds were studied, should be consulted for experimental details,[61] but the following examples should indicate the utility and selectivity of this method for the deoxy-

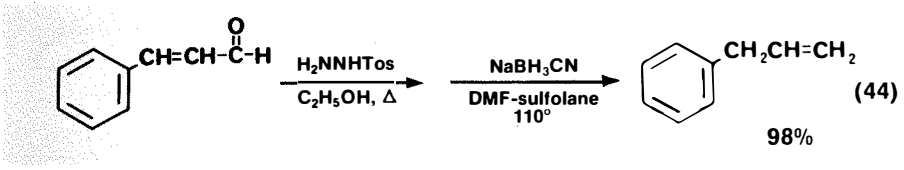


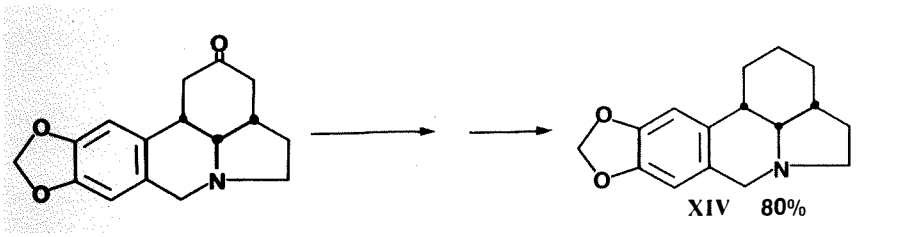


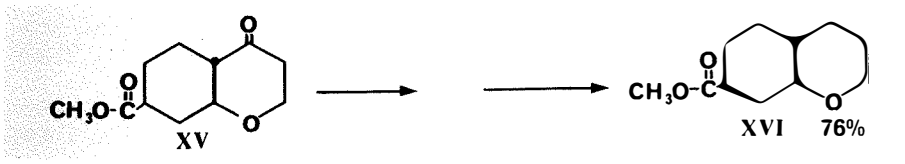


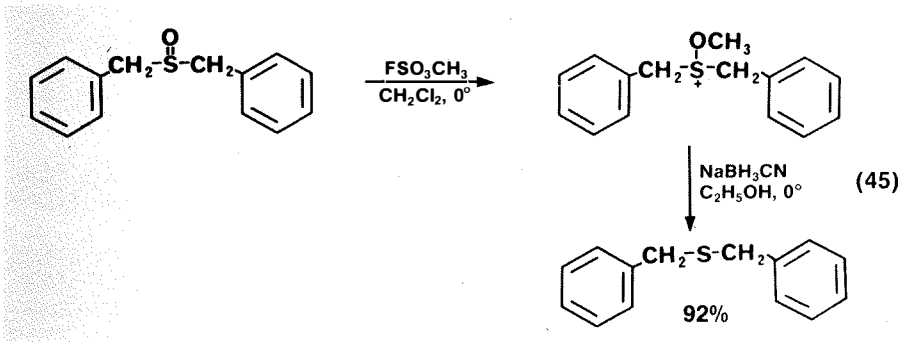












genation of carbonyl compounds (eq 37-44).

Aryl carbonyl compounds proved to be quite resistant to reduction by this method regardless of the procedure used.[61] However, this might prove to be useful because aliphatic ketones and aldehydes could probably be selectively removed in the presence of an aryl carbonyl group.

The mild conditions required for this modified Wolff-Kishner process should result in numerous applications in synthetic organic chemistry. For example, this deoxygenation procedure was recently used as a key step in the stereoselective synthesis of the ring skeleton of the alkaloid lycorine.[63] An 80% isolated yield of γ-lycorane (**XIV**) was obtained. Deoxygenation of **XV** also occurred without bridgehead epimerization giving a 76% conversion to the desired *trans*-1-oxadecalin structure **XVI**.[64]

A procedure has also been developed for the deoxygenation of sulfoxides using $NaBH_3CN$ which involves the prior formation of an alkoxysulfonium salt using methyl fluorosulfonate (eq 45).[65]

In conclusion, the stability and reactivity of the cyanoborohydride ion in aqueous systems at pH 6-8 indicate the potential for carrying out imine reductions and carbonyl aminations on complex biological systems. Recently, such an application has been reported where the imino linkage between 11-*cis*-retinal and the lipoprotein, opsin, has been reduced under mild conditions (aqueous, pH 5, 3°) using $NaBH_3CN$.[66] Also, the observed deactivation by $NaBH_3CN$ in aqueous acid medium was used in a recent characterization of an aldolase enzyme.[67]

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About the Cover

Our chemist-collector has confided to us that, whenever he becomes too discouraged by events in the Middle-East, he thinks of the Book of Ruth. Hence, we were not surprised at this recent acquisition, a beautiful painting of *Boaz and Ruth* (oil on canvas, 28-1/4 x 31-1/2 inches) by one of Rembrandt's students, Gerbrand van den Eeckhout, signed and dated 1656. It shows Ruth, the Moabite, in the fields of Bethlehem meeting her future husband, Boaz.

Though the Moabites were related to the Jews through Lot, the nephew of Abraham, there was bitter enmity between them after the Exodus from Egypt. The Moabites even enlisted Balaam, one of the greatest prophets of his time, to curse the Jews, who retaliated by excluding Moabites from Israel, 'even to their tenth generation.'

Luckily, enmity on that level is often mitigated by the kindness of individuals. It is hard to find a more moving expression of such personal kindness than Ruth's words to her widowed mother-in-law, Naomi: "Thy people shall be my people, and thy God my God. Where thou diest will I die, and there will I be buried; the Lord do so to me, and more also, if aught but death part thee and me."

It is surely significant that King David, and hence the Messiah, are direct descendants of Ruth, the Moabite. Maybe there is hope for us yet.

The miracle of the Book of Ruth is not that the Messiah is a descendant of a Moabite, nor that Jews and Moabites could live together happily. Rather it lies in the true love that two people can have for one another — Naomi's and Ruth's — devoid of sex and materialism, and as beautiful as anything we know.

Are you interested in our Acta covers? *Selections from the Bader Collection,* with 30 duotone reproductions, many of previous Acta covers, and an introduction by the late Professor Wolfgang Stechow is now available to all chemist art-lovers.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Organoboranes in Organic Synthesis

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Organoboranes are playing an increasingly important role in synthetic organic chemistry. A number of factors has contributed to the utility of the organoboranes as synthetic intermediates. Of primary importance are their reactivity and their availability. The purpose of this article is to demonstrate that the reactivity of organoboranes is readily understandable (and predictable) in terms of a few basic organic chemistry concepts.

BACKGROUND

Preparation

The myriad of new synthetic manipulations involving organoboranes would not have evolved had it not been for their ready availability. They may be prepared *via* the hydroboration reaction in essentially quantitative yields (eq 1).[1] Furthermore, the rapidity and selectivity of this

$$3RCH{=}CH_2 + BH_3 \longrightarrow (RCH_2CH_2{-})_3B \qquad (1)$$

reaction permit the incorporation of numerous functional substituents in the organoborane. For the first time, the synthetic chemist has available a reactive intermediate which can contain a variety of functional groups.[2,3]

Reactivity

The availability of the organoboranes would be of little value if they were of limited reactivity. Fortunately, they are quite reactive in synthetic manipulations involving carbon-carbon bond formation. The boron-carbon bond does not exhibit the ionic characteristics of many organometallic reagents, however organoboranes are capable of delivering a carbanionic center under certain conditions. Due to the low polarity of the boron-carbon bonds, organoboranes do not react with electrophilic reagents at ambient temperatures.[4] Except for benzylic, allylic and allenic derivatives, organoboranes are stable to hydrolysis and do not react with carbonyl reagents.

The organoboranes are electron deficient at boron and consequently are good Lewis acids. They react readily with nucleophiles forming stable compounds known as "ate" complexes.[5] The storage of organoboranes as amine "ate" complexes has been used commercially (eq 2).

$$(CH_3)_3B + {:}N(CH_3)_3 \longrightarrow (CH_3)_3\overset{(-)}{B}\text{-}\overset{(+)}{N}(CH_3)_3 \qquad (2)$$

$$\Delta H = -17 \text{ Kcal/mole}$$

The fact that certain organoborane complexes can rearrange provides the key to understanding many of the new synthetic reactions involving organoboranes.

REARRANGEMENT OF ORGANOBORANE COMPLEXES

The electronic configuration, and thus the reactivity, of the boron center is significantly different in the "ate" complex than in the organoborane itself. In the uncomplexed organoborane the boron is electron deficient, whereas the opposite is true in the "ate" complex. The boron center in the "ate" complex becomes a potential carbanion donor. The donation can be intermolecular or intramolecular. The hydrolysis of tetrasubstituted borates by mineral acids is an example of an intermolecular reaction (eq 3).[6]

$$Ph_4B^{(-)} \xrightarrow{H^+} Ph_3B + PhH \qquad (3)$$

The case of intramolecular donation of an anionic center to an electron deficient center has been well documented. Such anionotropic rearrangements provide the mechanistic pathway for much of the new organoborane chemistry.[2] The rearrangements are analogous to the well known organic rearrangements such as the Beckmann, Curtius, pinacol, etc., which involve the migration of an anionic center to an electron deficient center. The electron deficiency may be due to a number of factors such as a sextet of electrons or the attachment of an electronegative substituent. A straightforward example involves the oxidation of organoboranes with amine oxides (eq 4). The reaction meets the necessary requirements for a successful rearrangement: an anion source (boron), a migrating group (alkyl), and an electron deficient center (oxygen).[7]

$$R\text{-}\overset{R}{\underset{R}{B}} + {:}\overset{(-)}{\ddot{O}}\text{-}\overset{(+)}{N}R_3 \longrightarrow R\text{-}\overset{R}{\underset{R}{\overset{(-)}{B}}}\text{-}\ddot{O}\text{-}\overset{(+)}{N}R_3 \longrightarrow R_2B\text{-}\ddot{O}R + {:}NR_3 \qquad (4)$$

The reaction provides an efficient oxidation procedure. Another oxidation procedure (the traditional method) proceeds *via* an analogous mechanism (eq 5).[8]

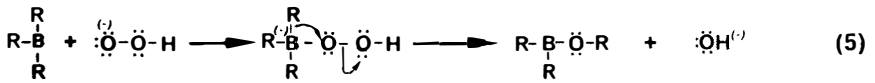
A number of such rearrangements is now known. They provide for the conversion of organoboranes into alcohols and amines.[8,9]

The energetics of such rearrangements are favorable. In nearly every case a boron-carbon bond is replaced by a boron-oxygen bond, resulting in a net increase in bonding energy of greater than 50 Kcal/mole.

REARRANGEMENTS INVOLVING CARBON-CARBON BOND FORMATION

The recognition that "ate" complexes were prone to rearrangement brought expansion of the concept into a much more important area: the formation of carbon-carbon bonds. Fertile minds envisioned numerous types of "ate" complexes which possessed electron deficient carbon centers adjacent to the boron atom. As in the classical organic rearrangements, the electron deficiency could be due to a sextet of electrons or the attachment of electronegative substituents. Furthermore, the deficiency could be present during the formation of the "ate" complex, or the "ate" complex could be modified after formation.

The following discussion attempts to delineate the development of the use of "ate" complexes as intermediates in organic synthesis. In every case, the goal was to create an electron deficiency adjacent to the electron-rich boron atom in the "ate" complex.



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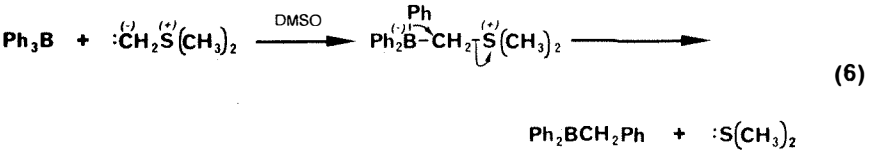

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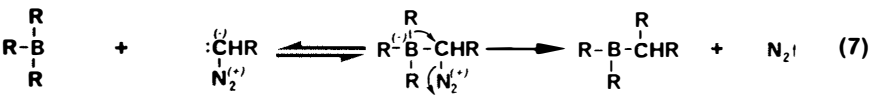

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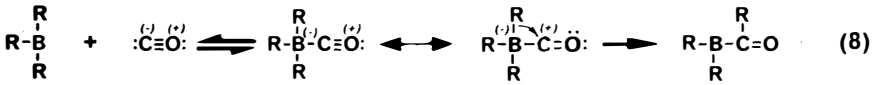

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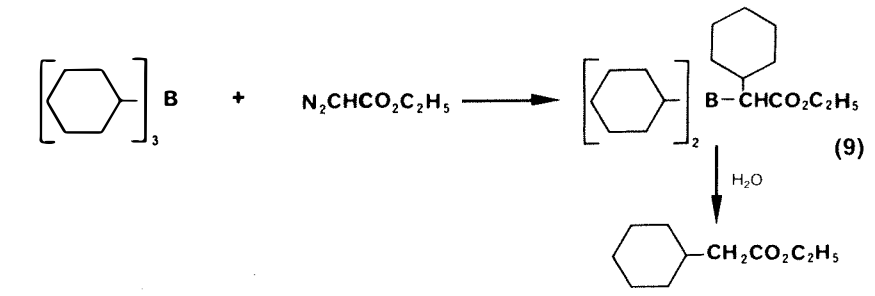

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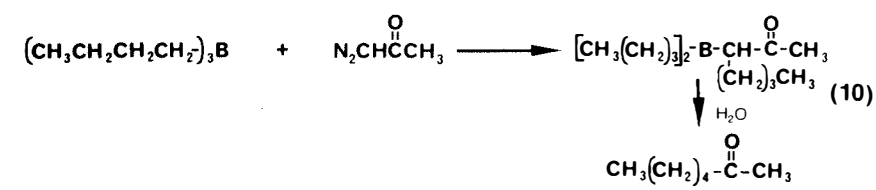

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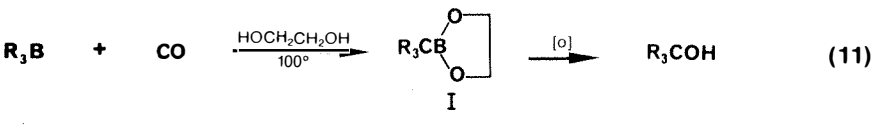

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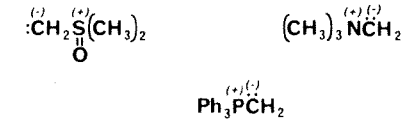
Ylides

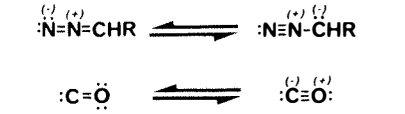
Ylides appear to be ideal for reaction with organoboranes. They are good Lewis bases and yet contain electron deficient centers. The oxidation reaction utilizing amine oxides illustrates the utility of the ylide rearrangement reaction. There are numerous carbon analogs of this reaction. For example, the reaction of dimethylsulfonium methylide with organoboranes has been reported (eq 6).[10] The reaction provides for the one-carbon homologation of organoboranes. A number of other ylides undergo this homologation



reaction.[11] These reactions have not been utilized extensively due to problems in generating a single homologated product; a mixture of products is often obtained.

Pseudo-Ylides

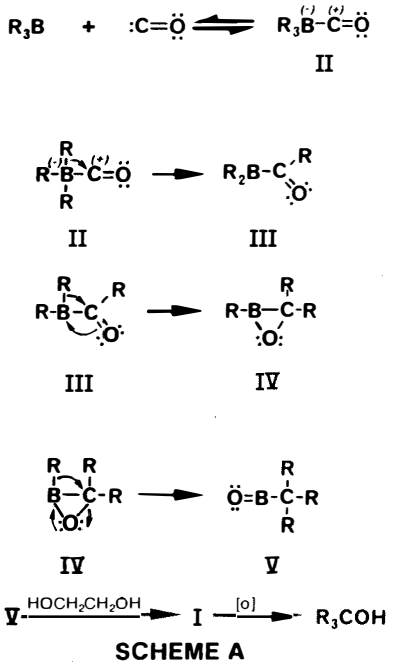
Investigations have also focused on reagents that possess a nucleophilic carbon atom. Two important reagents are diazo compounds and carbon monoxide. In each case one of the contributing resonance



forms that is required to describe the molecule is an ylide and thus these reagents may be loosely termed "pseudo-ylides". The corresponding "ate" complexes would contain electron deficient centers and therefore undergo rearrangements (eq 7,8). These reactions form the basis of many new and useful synthetic transformations. The reactions of diazomethane derivatives are of greater utility than those of diazomethane.[12-14] Hydrolysis of the boron-containing product is facilitated by the carbonyl group (eq 9,10).

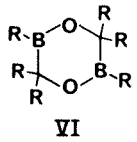
The reaction of organoboranes with carbon monoxide is of even greater utility[15] because it involves more extensive rearrangements. For example, reaction with carbon monoxide in the presence of ethylene glycol yields the cyclic boronic ester, **I**, which is readily oxidized to the tertiary alcohol (eq 11).[16] The reaction may be visualized as occurring through the following sequence (Scheme A).

The carbonylation reaction has been demonstrated to be an efficient route to numerous trialkylcarbinols. A wide variety of tertiary alcohols has been prepared in almost quantitative yield (eq 12,13). The reaction can also be modified so that only two groups migrate, thereby providing an



SCHEME A

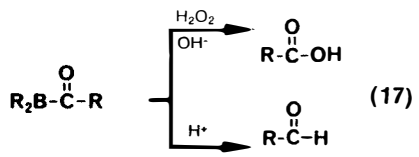
efficient ketone synthesis (eq 14). The modification requires only the presence of water. The water apparently interferes with formation of **V** (or its trimer) presumably by hydrolyzing the boraepoxide **IV** or its dimer, the 2,5-diboradioxane **VI**. The



VI

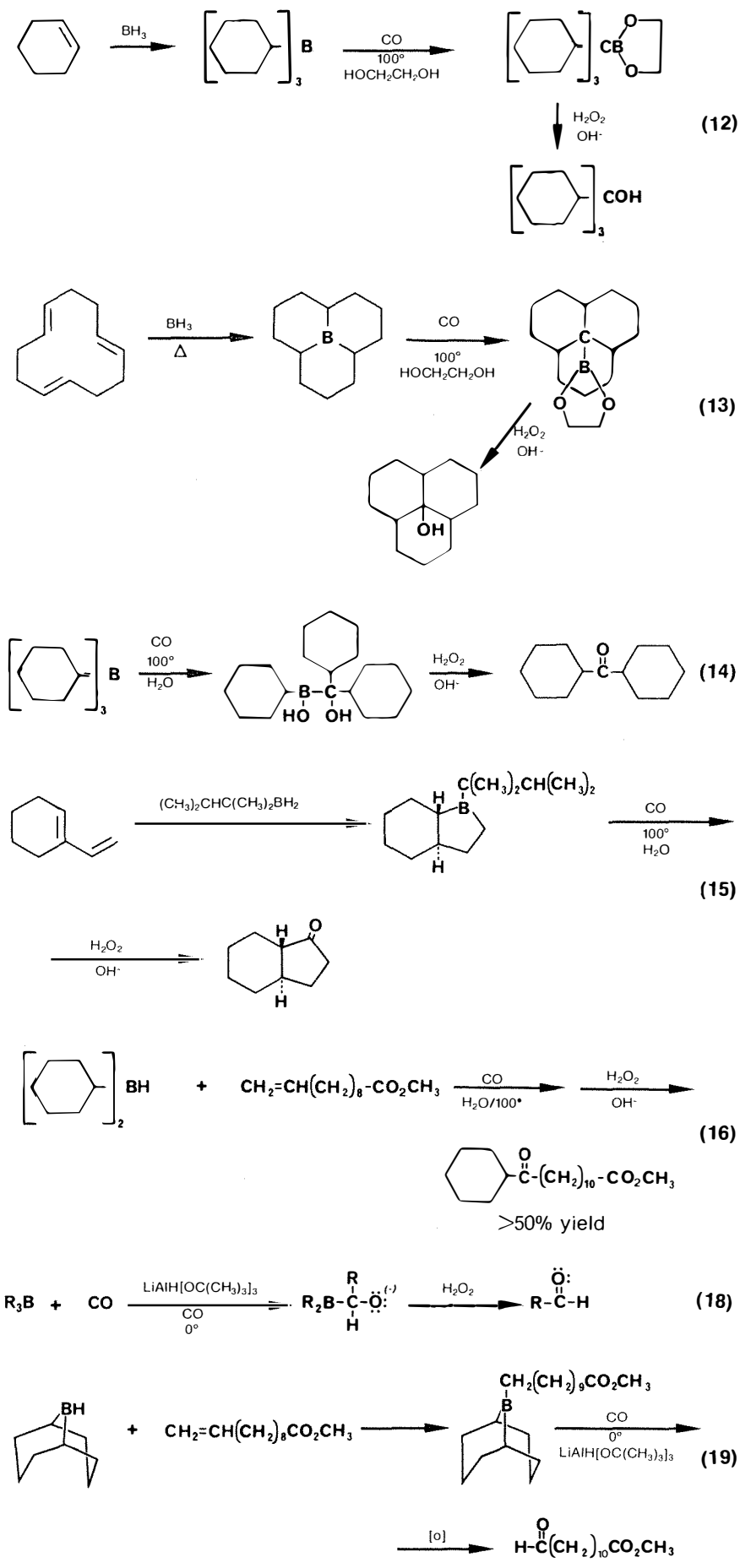
overall reaction is very efficient. Studies indicate that primary alkyl groups migrate faster than secondary, and secondary faster than tertiary, which have permitted a number of exciting syntheses (eq 15).[17] As is true in most of organoborane chemistry, functionality can be incorporated into the organoborane and, consequently, into the final product (eq 16).[18]

It would be ideal if the reaction could be stopped after the migration of one alkyl group, **III**. One would then generate either carboxylic acids or aldehydes (eq 17). The



(17)

synthesis of aldehydes has been achieved. It was discovered that the addition of hydride catalyzes the reaction and effectively stops the reaction after the migration of one alkyl group (eq 18).[19] This allows the synthesis of aldehydes to be carried out at or below 0°. The use of mixed organoboranes has been especially useful in the syntheses of aldehydes *via* the carbonylation reaction (eq **19**).[19]



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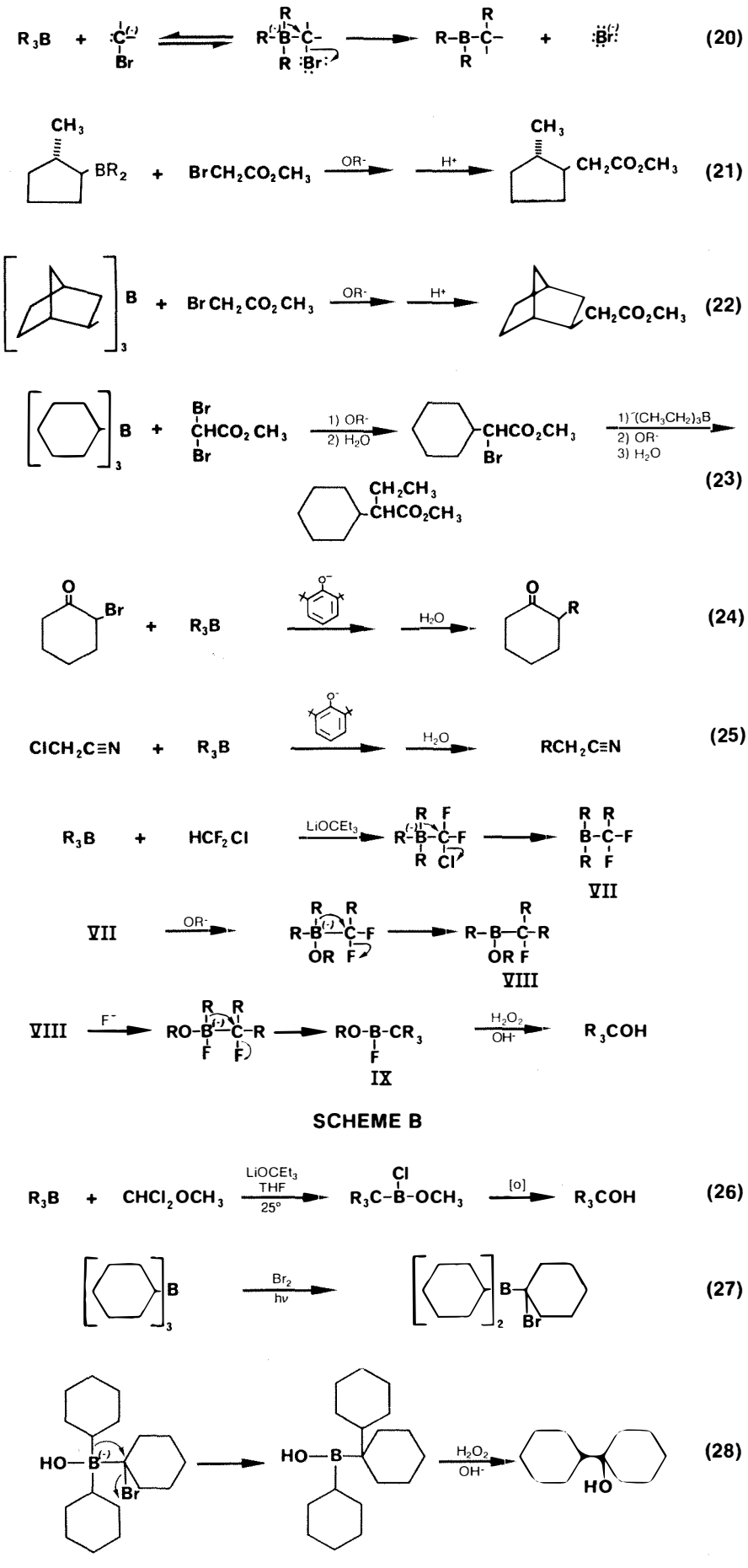
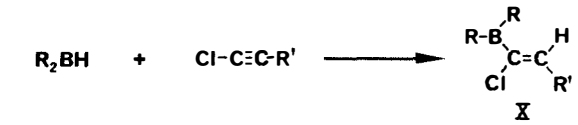
α-Halocarbanions

In addition to ylides and kindred species, there is a large number of nucleophiles available which contain electron deficient centers, α-halocarbanions being an especially abundant type. The following rearrangement can be visualized (eq 20). This reaction has been shown to be general especially in situations in which the carbanion is extensively stabilized by resonance.[20] Thus α-haloesters react readily with a variety of organoboranes (eq 21,22). Hydrolysis of the intermediate can be achieved using water or even alcohols. The reactions can be carried out sequentially when dihaloesters are employed (eq 23).[21] The use of a highly hindered base, 2,6-di-*t*-butylphenoxide, minimizes side reactions. The alkylation is now a general one providing for reactions with α-haloketones and α-halonitriles (eq 24,25).[22] The reaction is not limited to resonance stabilized carbanions. A number of carbenoid precursors has been utilized effectively. In fact, the reaction of chlorodifluoromethane in the presence of a hindered base produces high yields of tertiary alcohol (Scheme B).[23] The reaction presumably proceeds *via* sequential rearrangements induced by the base or by F^-.

α,α-Dichloromethyl methyl ether also produces tertiary carbinols when reacted with trialkylboranes in the presence of a base (eq 26).[23] This reagent also reacts with borinic esters. The tertiary α-chloroboronic esters thus produced are readily converted to ketones[24] and alkenes.[25]

It is important that these rearrangements can be effected by treating an α-haloorganoborane (such as **VII** or **VIII**) with a nucleophile. In recent years it has become apparent that organoboranes can be halogenated under suitable conditions to generate the α-halogenated derivatives (eq 27).[26] These α-bromo derivatives rearrange in the presence of nucleophiles such as hydroxide or water (eq 28). The reaction is not limited to trialkyl derivatives. α-Halovinylboranes are readily available *via* the hydroboration of halogenated alkynes (eq 29).[27] These α-halocompounds also rearrange in the presence of base and the resulting product, **XI**, may be protonated to the alkene or oxidized to the ketone (eq 30). The reaction appears to be limited only by the availability of the appropriate halogenated "ate" complex. Two further examples that illustrate the potential of this reaction are the reaction of vinylogs of the α-haloesters (eq 31)[28] and the reaction of γ-halogenated boranes (eq 32).[29] The latter process has also been utilized in a cyclobutane synthesis.





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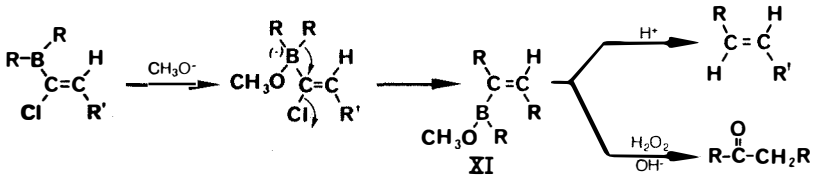

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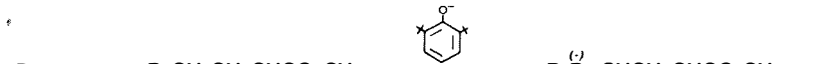

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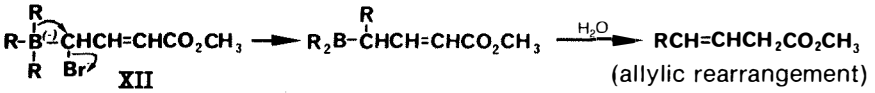

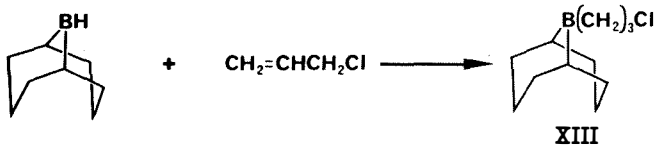

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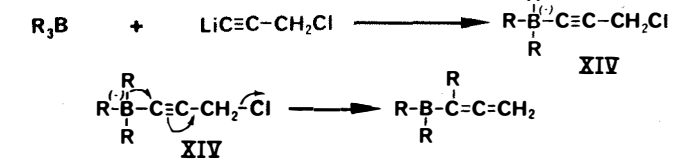

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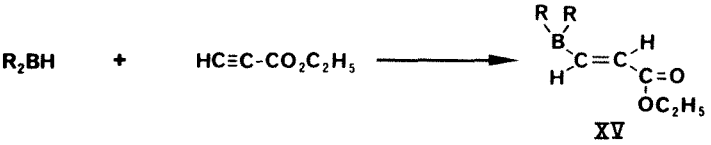

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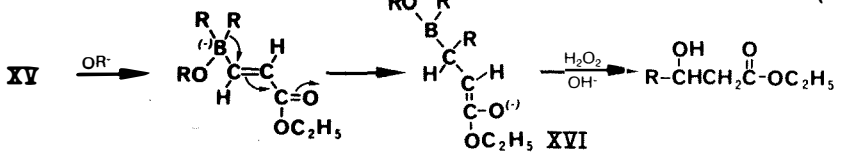

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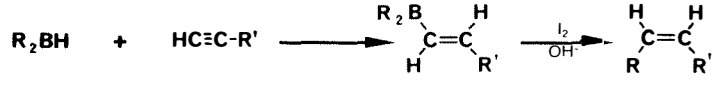

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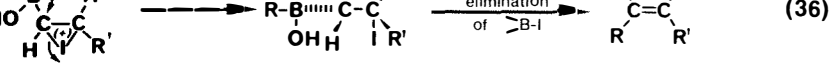


(37)

A recent report indicates that an analogous reaction may be utilized to prepare allenic boranes (eq 33)[30] which can be converted into the corresponding allenes by protonolysis. Alternatively, they may be utilized in organoborane alkylation reactions.

Related Systems

A potential rearrangement system involves an electron deficient carbon in which the electron deficiency is due to interactions between a carbonyl group and the β-carbon in an α,β-unsaturated carbonyl compound. Although this situation has not been extensively exploited, it has been reported that such systems do rearrange to give the expected product (eq 34).[31]

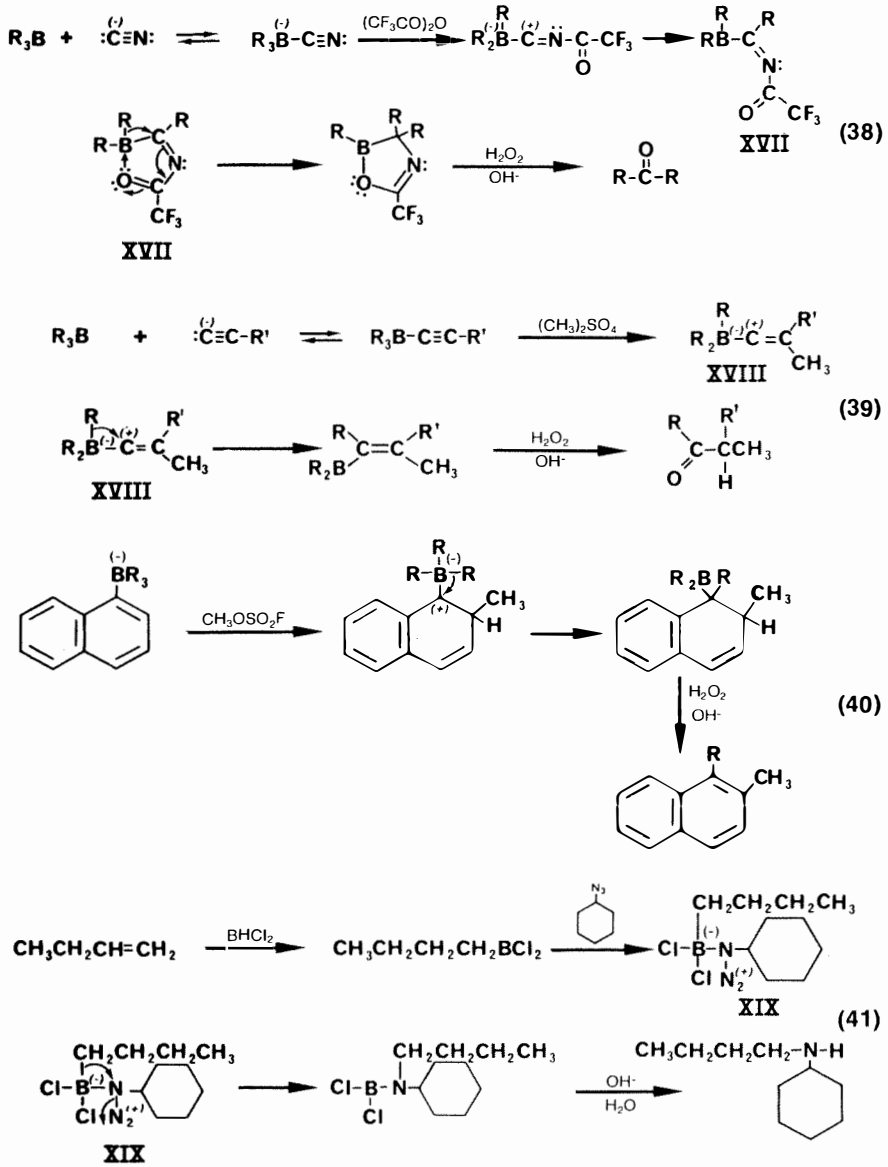
Modifications of "Ate" Complexes

The rearrangement of "ate" complexes has proven to be an exceedingly fertile area for research. Once the reaction was understood, numerous modifications were made. The surface has just been scratched and many new synthetic techniques will surely be reported. The next phase of research in this area, namely modification of "ate" complexes, illustrates the potential in this field. To this point, the "ate" complexes contained an electron deficient center at the time they were formed. It is possible to modify certain "ate" complexes after the fact *via* the addition of electrophiles. The first example of this technique involved the preparation of *cis* alkenes *via* the hydroboration of alkynes (35).[32] The reaction presumably proceeds *via* the iodine-initiated migration of an alkyl group from the boron to an electron deficient carbon. This is then followed by a *trans*-elimination of boron and iodine (eq 36). The rearrangement of various vinylborane derivatives has produced efficient syntheses of alkenes, allenes, dienes, and enynes.[33]

Similar reactions involving alkynyl "ate" complexes were recently reported (eq 37).[34,35] Electrophiles other than the halogens have also been utilized to induce rearrangements in "ate" complexes. For example, acid anhydrides have been employed to prepare ketones and alcohols from cyanide complexes (eq 38).[36] Analogous rearrangements have been reported utilizing acetylide complexes rather than cyanides (eq 39).[37-40] A similar rearrangement utilizing arylborane derivatives has been reported (eq 40).[41]

SUMMARY

The use of organoboranes as alkylation reagents is a new development in synthetic organic chemistry. Recognition that "ate" complexes are prone to anionotropic re-



arrangements has led to the development of a number of new synthetic techniques. These techniques have the advantage that a number of organoboranes are readily available and that they may contain a variety of functional groups. There is little doubt that additional techniques will be developed in the future. Especially exciting will be the development of new organoborane reagents derived from catecholborane,[42] chloroborane,[43] and dichloroborane,[44] which appear to promise even greater stereospecificity and more complete utilization of the alkyl moieties than do the trialkylboranes. As an example, alkyldichloroboranes (available *via* hydroborations with dichloroborane) react readily with organic azides providing a convenient synthesis of secondary amines (eq 41).[45] The reaction provides a nearly quantitative utilization of the starting alkene.

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Organic Synthesis via Organoboranes. IV.[1]

Reduction of Organic Functional Groups with Borane-Methyl Sulfide

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Borane•methyl sulfide (BMS) is a concentrated, reactive, and stable source of BH_3, and we have reported its utility in the hydroboration of alkenes[2] and in the reduction of aromatic carboxylic acids.[3]

Borane•tetrahydrofuran (BH_3•THF) is the most commonly used hydroboration reagent and its use was recently reviewed by Professor Herbert C. Brown.[4] However, this reagent possesses certain characteristics which limit its preparation, storage, and use as a commercial source of borane, namely: (1) BH_3•THF can only be sold as a dilute solution (1*M*) in THF (1.5 wt % BH_3), (2) THF is slowly cleaved by BH_3 at room temperature, (3) sodium borohydride (5 mole %) must be added to BH_3•THF to inhibit the cleavage of THF, and (4) THF is relatively expensive and at times has been in short supply.

BMS has been found to overcome all of these disadvantages. BMS has a molar concentration of BH_3 *ten times* that of the BH_3•THF reagent. It can be stored for months at room temperature without loss of hydride activity and is apparently stable indefinitely when refrigerated. Also, BMS is soluble in and unreactive toward a wide variety of aprotic solvents.

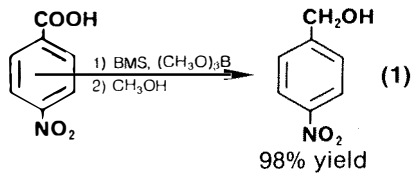
The BMS available from the Aldrich Chemical Company is a clear, colorless liquid with a BH_3 concentration of one mole per 100ml (*ca.* 10*M*). The reagent contains only BMS and *ca.* 5% excess methyl sulfide.

BMS is very soluble in ethyl ether, tetrahydrofuran, hexane, heptane, toluene, xylene, methylene chloride, monoglyme, diglyme, and numerous other aprotic solvents. BMS dissolves readily in alcohols with the quantitative evolution of hydrogen. However, BMS is insoluble in water and only very slow hydrolysis occurs. The addition of water to ether solutions of BMS results in rapid hydrolysis.

We recently reported that quantitative hydroborations with BMS are possible under mild conditions in a variety of aprotic solvents such as ethyl ether, THF, hexane, toluene, and methylene chloride.[2] The vastly improved air stability and ease of handling of this reagent have resulted in its use as a hydroboration reagent in an undergraduate laboratory.[5] The successful hydroboration of olefins with BMS in a variety of solvents prompted a similar study with BMS as a reducing agent.

The reduction of organic functional groups with BMS has been under active investigation for the past two years in the laboratories of Aldrich-Boranes, Inc. The results of this study seem to indicate that the reactivity of BMS parallels that of BH_3•THF.[6] However, BMS reductions usually require somewhat higher temperatures, *i.e.*, with BH_3•THF many reactions occur readily at 0-5° while the analogous reactions with BMS occur readily only at 20-25°. Consequently, it is strongly recommended that the addition of BMS to a reactive molecule be carried out at 20-25° or higher. Addition of BMS at 0° or lower may result in a very slow reaction; upon subsequent warming a vigorous exothermic reaction may then occur.

The reduction of carboxylic acids with BH_3•THF was found to yield the corresponding alcohols rapidly and quantitatively under remarkably mild conditions. A detailed study of the scope of this reduction has been reported.[7] We have investigated the use of BMS for the reduction of carboxylic acids.[3] *n*-Hexanoic acid and benzoic acid were initially studied as representative carboxylic acids. The reduction of *n*-hexanoic acid was found to occur rapidly and quantitatively in THF while the reduction of benzoic acid was appreciably slower, giving a low yield of benzyl alcohol. Fortunately, this difficulty was easily overcome by carrying out the reduction in the presence of trimethyl borate. This improved procedure was then used to reduce a number of functionally substituted benzoic acids on a preparative scale. Equation 1 gives a specific example.



(1)

98% yield

Although THF was used as the solvent in this study, reductions with BMS can be carried out in various aprotic solvents as shown in Table 1.

A wide range of functional groups can be reduced with BMS and, to illustrate this, representative procedures have been developed for the reduction of carboxylic acids, esters, oximes, nitriles, and amides. The selectivity of the reagent is also illustrated by the complete absence of reduction of halides and nitro groups.

An important feature of the following experimental procedures is the ease of product isolation. In the reduction of carboxylic acids and esters, it is only necessary to add an excess of methanol and then remove all volatiles *in vacuo* to give an alcohol residue that is boron-free and of satisfactory purity for most applications. In the reduction of oximes, nitriles, and

Table 1. Reduction of *n*-Hexanoic Acid with BMS Solvent Study[a]

Solvent	Time, hr	1-Hexanol, % yield[b]
Ethyl ether	1	100
THF	4(0.5)[c]	100
Hexane	0.5	100
Toluene	2	99
Triglyme	4	91
Trimethyl borate	0.5	100

[a] *n*-Hexanoic acid (30mmol) added dropwise to BMS (33mmol) in 30ml of solvent at 20-25°. [b] Yield by gc analysis after hydrolysis using an internal standard. [c] BMS added to *n*-Hexanoic acid in 30ml of THF.

amides, it is necessary to add anhydrous hydrogen chloride to hydrolyze the boron-nitrogen intermediates to trimethyl borate and the amine hydrochloride salt. Again, simple removal of all volatiles *in vacuo* on a rotary evaporator or similar apparatus gives the amine hydrochloride which is boron-free and of satisfactory purity for most applications.

The key step in the isolation procedures is the removal of solvent and trimethyl borate *in vacuo*. Although the residue obtained may be reasonably pure, it is usually necessary to carry out a distillation, recrystallization, or a related purification process to obtain a product of high purity. The procedure below for the preparation of 11-bromo-1-undecanol describes the use of the Aldrich Kugelrohr distillation apparatus while that of 2-chloro-4-nitrobenzyl alcohol illustrates another approach to the purification of an alcohol product.

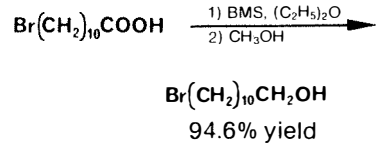
The procedures describing the reduction of an oxime, nitrile, and amide illustrate three different methods that we have found particularly useful for the purification of amine products. The preparation of *N*-cyclohexylhydroxylamine hydrochloride has as its purification step a straightforward recrystallization of the amine hydrochloride salt. The preparation of 2-(2,6-dichlorophenyl)ethylamine illustrates the conversion of the amine hydrochloride salt to the free amine followed by distillation. Finally, the preparation of 4-nitrobenzylamine hydrochloride describes a special technique where only the stoichiometric amount of methanol is added followed by treatment with hydrogen chloride gas which results in the precipitation of the amine hydrochloride salt. Simple removal of the supernate then eliminates the majority of the impurities.

The isolation procedures given are not limited to these specific examples or these specific functional groups. For a given reduction it is usually necessary to proceed with a trial-and-error approach to the best isolation procedure. The following procedures are given for illustrative purposes only and may, in fact, not be the best procedure for the isolation and purification of specific products.

It is hoped that the following examples will make it apparent that BMS is a very useful reagent for the reduction of organic functional groups. The stability, commercial availability in pure form, solubility in a wide variety of solvents, and ease of experimental work-up should make BMS the reagent of choice for many borane reductions.

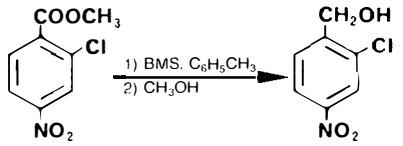
Preparation of 11-bromo-1-undecanol

A one-liter, three-necked, round-bottomed flask equipped with a magnetic stirring bar, pressure-equalizing addition funnel, thermometer well, and reflux condenser is flushed thoroughly with dry, high-purity nitrogen and maintained under a slight positive nitrogen pressure by use of a mercury or mineral oil bubbler attached to the condenser. The flask is opened and quickly charged with 100g (377 mmol) of 11-bromoundecanoic acid. After reflushing the apparatus with nitrogen, anhydrous ethyl ether (500 ml) is added using the double-tipped needle transfer technique (note 1). The resulting clear solution is stirred at room temperature with no external heating or cooling as the BMS (42



ml, 420 mmol, note 2) is added dropwise. Vigorous gas evolution occurs during the addition of the first 12-13 ml of BMS (time of addition 0.5-1hr) and the reaction does not appear to be exothermic. When the gas evolution is complete, the BMS addition is stopped and the reaction is heated to a gentle reflux using a warm water bath. The BMS addition is then continued at a rate sufficient to maintain a gentle reflux . The reaction mixture remains clear throughout the BMS addition which takes a total of 1-1.5hr. Following the BMS addition, the reaction mixture is maintained at reflux for an additional hour (note 3), then cooled to 20° in a cold water bath and poured into 1 liter of ice-cold methanol with gentle swirling (note 4). The resulting clear solution is loosely covered with aluminum foil, allowed to stand overnight in a hood, and concentrated to an oil (note 5) on a rotary evaporator (note 6). Short-path distillation of this oily solid on the Aldrich Kugelrohr[8] gives 89.6g (94.6% yield) of a colorless, crystalline solid, b.p. 140-145° (air bath temp.) at 0.08mm, m.p. 45-47° (uncorrected) (Lit.[9] m.p. 46-49°), with ir and nmr spectra in accordance with assigned structure. The solid product is conveniently removed from the Kugelrohr receiver by melting with a hot-air gun and pouring into an open dish for crystallization.

Preparation of 2-chloro-4-nitrobenzyl alcohol



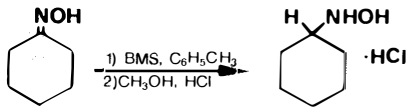
95.3% yield

The reaction apparatus is assembled as described in the foregoing experiment and charged with 87.9g (408 mmol) of methyl 2-chloro-4-nitrobenzoate and 400ml of toluene (note 7). The addition funnel is charged with 43ml (430 mmol) of BMS (note 2). The reaction mixture is then stirred in a 20-25° water bath as the BMS is added dropwise over a 0.5 hr period. The reaction is not exothermic and only a minor amount of gas evolution occurs. Following the BMS addition, the resulting clear solution is stirred for an additional 0.5hr at 20-25°, heated slowly to a gentle reflux and maintained at reflux for 4 hr (note 3), cooled to 20°, and then slowly poured into 400ml of ice-cold methanol with gentle swirling (note 4). The resulting clear solution is loosely covered with aluminum foil, allowed to stand overnight in a hood, and then concentrated to 76.5g of a boron-free (note 6), orange, crystalline solid on a rotary evaporator. This solid shows no carbonyl absorption in its ir spectrum but does contain a small amount of ether-insoluble material. The solid is slurried in ethyl ether (1.5l) and THF (0.5l), heated to reflux, cooled to 20°, filtered, extracted with 25% aqueous potassium carbonate (2 x 250ml) and saturated aqueous sodium chloride (1 x 250ml), dried over anhydrous potassium carbonate, filtered, and concentrated to dryness on a rotary evaporator. The resulting yellow, crystalline solid is further dried *in vacuo* giving 73.0g (95.3% yield) of 2-chloro-4-nitrobenzyl alcohol, m.p. 78-80°, with nmr spectrum identical to that reported for the authentic material.[10] Recrystallization from toluene gives light-yellow needles, m.p. 79-80° (uncorrected).

Preparation of *N*-cyclohexylhydroxylamine hydrochloride

A two-liter, three-necked, round-bottomed flask is equipped and assembled as previously described and charged with

134g (1.18mol) of cyclohexanone oxime and 1 liter of toluene (note 7). The addition funnel is charged with 130ml (1.3mol) of BMS (note 2). After heating the clear reaction mixture to a gentle reflux, the BMS is added dropwise with the heat turned off and at a rate sufficient to maintain a gentle reflux. Vigorous gas evolution and moderate foaming occur during the addition of the first 50ml of BMS (addition time: 0.5-1hr). The remaining 80ml of BMS is then added at an increased rate due to decreased gas evolution. Total time for BMS addition is 1-1.5hr. Following the BMS addition, the clear reaction mixture is heated at reflux with stirring for an additional 3hr period (note 3). After cooling to 20° in a cold water bath, methanol (300ml) is added dropwise (note 4) over a 1hr period. During the methanol addition, a white solid forms in the reaction mixture. This slurry is stirred for an additional hour

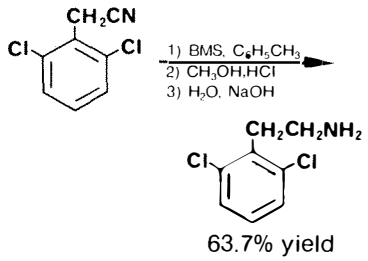


64.8% yield

at 20-25°, and then in an ice-water bath as anhydrous hydrogen chloride is bubbled (note 4) into the reaction mixture until a pH of <2 is reached. During the HCl addition, the reaction temperature is maintained <15° and the solid dissolves giving a clear solution at pH 7. The mixture becomes cloudy as more HCl is added. When stirring is stopped, the cloudy reaction mixture separates into two clear, colorless, liquid layers. This two-phase reaction mixture is stirred overnight at 20-25° and then concentrated to a solid on a rotary evaporator (note 6). The solid (note 8) is dried to constant weight at 20-25°/0.01mm giving 167g (93.4% yield) of a white, crystalline solid, m.p. 125-130°. A trace of boron was indicated by flame test. Recrystallization from methanol-ethyl ether gave 115.9g (64.8% yield) of *N*-cyclohexylhydroxylamine hydrochloride as colorless needles, m.p. 139-141°, with ir and nmr spectra in accordance with assigned structure. Percent Cl calculated for $C_6H_{14}ClNO$: 23.38; found: 24.12. Purity by perchloric acid titration: 99.4%.

Preparation of 2-(2,6-dichlorophenyl)-ethylamine

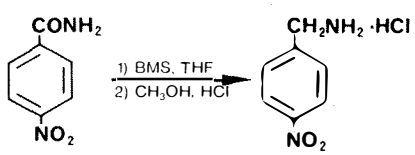
The reaction apparatus is assembled as previously described and charged with 82.0g (441 mmol) of 2,6-dichlorophenylacetonitrile and 0.5l of toluene (note 7). The addition funnel is charged with 48.5ml (485 mmol) of BMS (note 2). The clear reaction mixture is heated to a gentle reflux as the BMS is added dropwise over a 1hr period. The heat is shut off whenever the refluxing becomes too vigorous. Following the BMS addition, the reaction mixture is maintained at a gentle reflux for 24hr (note 3). After cooling to 20° in a water bath, methanol (0.5l) is added dropwise. Gas evolution occurs during the addition of the initial 50ml of methanol which is added



63.7% yield

slowly over 0.5-1hr. The remaining 450ml of methanol is then added rapidly over 0.5hr. After cooling to <10° with stirring in an ice-water bath, anhydrous hydrogen chloride is bubbled into the clear solution until a pH of <2 is reached. The resulting clear, light-yellow solution is heated to reflux, maintained at reflux for 1hr, cooled to 20°, and concentrated to a yellow solid on a rotary evaporator. This solid is redissolved in 0.5l of methanol and again concentrated to a solid on a rotary evaporator. Further drying *in vacuo* at 20-25°/0.01mm gives 102g (100% yield) of a light-yellow crystalline solid. A flame test showed that a trace of boron was present. Percent total chlorine calculated for $C_8H_{10}Cl_3N$: 46.95; found: 43.68. Purity by perchloric acid titration: 92.5%. This solid is dissolved in 250ml of water with gentle heating and the solution is then cooled in an ice-water bath as solid sodium hydroxide pellets are added slowly with swirling until a pH of >10 is reached. The aqueous layer is saturated with solid sodium chloride, extracted with ethyl ether (400ml), and discarded. The ether extract is dried over anhydrous potassium carbonate, filtered, and concentrated to an oil on a rotary evaporator. Short-path distillation of this oil from a few pellets of potassium hydroxide on the Aldrich Kugelrohr[8] gives 53.4g (63.7% yield) of 2-(2,6-dichlorophenyl)ethylamine as a clear, colorless oil, b.p. 68-72° (air bath temp.) at 0.07mm, n_D^{20} 1.5705, with ir and nmr spectra in accordance with assigned structure. Purity by gc analysis: 96%. Sample contains 4% of a single lower boiling impurity.

Preparation of 4-nitrobenzylamine hydrochloride



72.3% yield

The reaction apparatus is assembled as previously described and charged with 50.0g (301 mmol) of *p*-nitrobenzamide and 0.6l of THF. The addition funnel is charged with 73.7ml (737 mmol, note 9) of BMS (note 2). The BMS is then added dropwise with stirring to the amide-THF slurry at 20-25° over a 1hr period. Gas evolution occurs during the BMS addition and the amide dissolves giving a clear solution. This solution is stirred for an additional 0.5hr at 20-25° and is then heated to reflux and maintained at reflux for 5hr (note 3). After cooling to 20-25°, methanol (100ml, 2.43 mol) is added dropwise over a 1hr period at a rate such that the reaction temperature does not exceed 30° (note 4). The resulting clear solution is allowed to stand overnight at room temperature. After cooling to <10° in an ice-water bath, anhydrous hydrogen chloride is bubbled slowly into the solution with stirring while maintaining a temperature <15° (note 4). A white precipitate immediately forms and the HCl addition is stopped when the solution reaches a pH of <2. The resulting white slurry is heated to reflux, maintained at reflux for 1hr and then cooled in an ice-water bath. The solid settles giving a white, crystalline precipitate and a clear, yellow supernate. This supernate is removed *via* a double-tipped needle using nitrogen pressure (note 8) and the solid is dissolved in 1 liter of methanol with gentle heating. Concentration of this solution on a rotary evaporator followed by drying to constant weight *in vacuo* gives 41.0g (72.3% yield) of 4-nitrobenzylamine hydrochloride, m.p. >260° (dec.), with ir and nmr spectra in accordance with assigned structure. Percent Cl calculated for $C_7H_9ClN_2O_2$: 18.79; found: 19.63. Purity by perchloric acid titration: 99.2%.

Notes

1) For a description of syringe and double-tipped needle transfers, please consult the bulletin "Handling Air-Sensitive Solutions," which is available upon request from the Aldrich Chemical Company, Inc.
2) For best results, BMS should be handled using syringe and double-tipped needle techniques (note 1). A few chemists, who have never handled BMS, have expressed concern about a possible odor problem in working with BMS. Naturally, BMS should be handled in a hood, but whether an odor is offensive or otherwise is a highly individual judgment. To the author, working with BMS has never caused any odor problems. In fact, in dilute concentrations he finds the odor reminiscent of tomatoes, and a laboratory aide has expressed the same observation.

3) Depending upon the compound being reduced and the presence of other substituents, it may be necessary to increase or decrease the time and temperature required for complete reduction.
4) Caution: vigorous gas evolution along with foaming may occur.
5) A solid if temperature of water bath on the rotary evaporator is below *ca.* 45°.
6) The presence of boron in the product is indicated by a green flame. Dissolving the product in methanol followed by concentration to dryness removes the boron as the volatile trimethyl borate. This procedure may be repeated until a negative flame test is observed.
7) Commercial, bulk-solvent grade toluene is dried over a small amount of calcium hydride prior to use.
8) Exposure of the hydrochloride salt to air must be kept at a minimum until purified and dried because the crude salt is usually very hygroscopic.
9) For complete reduction, one equivalent of primary amide requires $^{7}/_{3}$ equivalents of BMS, one equivalent of secondary amide requires $^{6}/_{3}$ equivalents of BMS, and one equivalent of tertiary amide requires $^{5}/_{3}$ equivalents of BMS.

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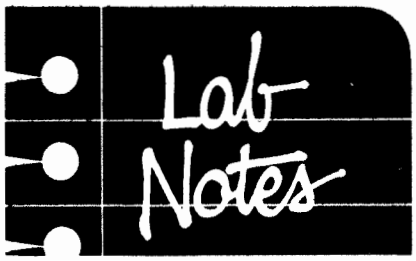


DRYING ACETONITRILE FOR ELECTROCHEMISTRY

The trace amounts of water drawn into acetonitrile from ambient humidity are rarely detectable by gas chromatography. These trace amounts of water prohibit the use of acetonitrile as a solvent for polarography, cyclic voltammetry or other electrochemistry where a broad voltage sweep is desired. The useful range of dry acetonitrile on the anodic side can extend to -2.6 or more volts, whereas micromolar quantities of water lower this to -1.0 to -1.2 volts, essentially prohibiting many electrochemical oxidations, such as the conversion of the carboxylate anion to the free radical.

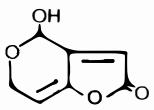
The drying methods for acetonitrile in the literature include distillation from P_2O_5. Unfortunately, this technique causes a gummy residue to form at the bottom of the still, making heat transfer difficult. In addition, the quantity of P_2O_5 used is large. P_2O_5 is also costly and inefficient.

A successful technique using a less expensive dehydrating agent was developed by me at the University of Delaware laboratories of Dr. W.A. Mosher. A three-necked round-bottomed flask, set up with two inlets — one for CH_3CN stored over CaH_2 and the other for concd H_2SO_4 — and a distillation head for removing the dried CH_3CN was placed in a magnetically stirred oil bath. About 1000ml of the CH_3CN was run into the flask until half full, and heated with stirring until reflux started. The heat was then turned off and the concd H_2SO_4 was added dropwise. (CAUTION - The reaction is exothermic!) A grey slurry is formed, but viscosity is low enough to allow continued stirring. After about 100ml H_2SO_4 was added, the inlet was closed, and the mixture heated for 30 minutes. The 500ml distillate was transferred to a bottle in a "glove bag" containing P_2O_5 in open petri dishes. This solvent was usable for up to five days.

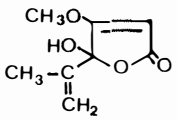
R.D. Athey, Jr.
The General Tire and Rubber Co.
Akron, Ohio 44329

Any interesting short cut or laboratory hint you'd like to share with ACTA readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome red and white ceramic Aldrich coffee mug. All entries become the property of Aldrich Chemical Company, Inc., and cannot be returned.

Patulin and Penicillic Acid Antibiotic Mycotoxins



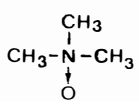
Patulin



Penicillic acid

Patulin and penicillic acid are structurally related carcinogenic lactones which inhibit DNA synthesis. *Jap. J. Exp. Med.*, **42**, 527 (1972); *Chem. Abstr.*, **78**, 56166m (1973).

A Most Interesting, Simple *N*-oxide



Organoboranes. . . *cont'd from page 19*

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Aldrichimica Acta

Volume 8, Number 3, 1975

Chemical Reactions of Polymers. See page 27.

A publication of Aldrich Chemical Company, Inc.

Aldrichimica Acta

Volume 8, Number 3, 1975
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About the Cover

When our chemist-collector first saw this noble portrait (oil on canvas $28^3/_4$ x $23^1/_4$ inches), it was called a portrait of a man, and attributed to Carel Fabritius, one of Rembrandt's ablest students. Our chemist is inclined to think that it is not by Fabritius, but by another Rembrandt student, Willem Drost, and he wonders whether it is not really a study of a woman, perhaps of Hannah praying in the Temple: surely prayer or contemplation could not be depicted more beautifully than by these clasped hands and serene face.

Rembrandt and some of his students occasionally used Italian medals as models for their paintings; and Professor Ulrich Middeldorf has pointed out that Drost used a medal of Don Inigo d'Avalos, Grand Chamberlain of Alfonso of Naples, by Pisanello as a model.

This introspective portrait invariably reminds us of Keats:
"Heard melodies are sweet, but those unheard are sweeter;----"
"She cannot fade---"
"Forever wilt thou love, and she be fair!"

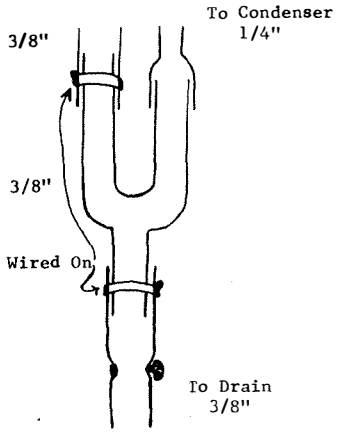
Are you interested in our Acta covers? *Selections from the Bader Collection,* with 30 duotone reproductions, many of previous Acta covers, and an introduction by the late Professor Wolfgang Stechow is now available to all chemist art-lovers.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Lab Notes

PRESSURE RELIEF VALVE

During overnight or weekend refluxing, a combination of erratic water pressure and deteriorated rubber tubing results in loss of solvents and charring of reaction mixtures, or floods.



A simple solution is provided by the use of a pressure relief valve consisting of a 3/8 inch U-shaped connecting tube, two lengths of 3/8 inch soft rubber tubing and one screw clamp. The condenser outflow tube is taped or wired (or equipped with an inexpensive flow meter) so that the exiting water can be seen. The water valve is adjusted to assure a continuous flow and the screw clamp is tightened until an adequate flow of water from the condenser is obtained.

The ultimate value of this little device more than compensates for the extra water used.

Stan Davis
Davis Metals & Chemicals Co.
KB Laboratories Division
2240 Wood Street
Oakland, California 94607

PREVENT VACUUM BREAKER LEAKS

In many locations, vacuum breakers are required to prevent water supply contamination. Vacuum breakers, however, create problems in the laboratory as the slow water flow desired for condensers is insufficient for their operation, resulting in leaks and floods. One solution is to restrict the flow after the vacuum breaker. Since

cont'd on page 34

Chemical Reactions of Polymers

Many polymer technicians, as well as most lay people, generally consider polymerization products as finished materials. In reality, many polymers are modified by chemical reaction after polymerization and several polymers of commercial significance, such as poly(vinyl alcohol), can be synthesized only by the chemical reaction of already formed polymers. From another standpoint, polymers are often formed with terminally reactive segments and of low degrees of polymerization (pre-polymers) with the object of chemically linking similar or dissimilar segments. These modes of reaction provide the chemist with a powerful tool in the tailor-making of plastics with optimized properties for specific end uses.

Chemical modification of polymers began early in the history of polymer chemistry. The nitration of cellulose, a natural polymer, led to the first synthetic plastic, celluloid, in 1870. The chlorination of rubber was accomplished as early as 1859. Since these early times, the various types of chemical reactions utilized to modify polymers have covered nearly every aspect of organic chemistry. A brief outline of the types of reactions which have been applied to polymers is presented below, followed by specific examples of detailed synthetic interest.

TYPES OF POLYMER REACTIONS[1]

Functional Group Polymer Reactions
- Monofunctional reaction
- Polyfunctional reaction

Unsaturated Polymer Reactions
- Isomerization
  - Cyclization
  - Double bond shifts
  - *Cis-trans* isomerization
- Cyclization reactions
- Addition of thiols
- Halogenation
- Epoxidation
- Hydrogenation
- Multiple bond additions

Saturated Polymer Reactions
- Polyolefin substitution
  - Ionic process
  - Free radical process
  - Halogenation
  - Chlorosulfonation
  - Chlorocarbonylation
  - Phosphorylation
  - Oxidation
- Side chain substitution
  - Oxidation
  - Halogenation
- Nuclear substitution of polyvinyl aromatics
  - Chloromethylation
  - Alkylation
  - Acylation
  - Sulfonation
  - Nitration
  - Metallation
  - Halogenation

Terminally Reactive Polymer Formation
- Free radical mechanisms using functional initiators
- Anionic polymers
  - Polymers with "living" terminals
  - Conversion of "living" terminals to functional end groups
    - Hydroxyl end groups
    - Carboxyl end groups
    - Terminal double bonds
    - Amine end groups
- Condensation polymers
  - Ester/hydroxyl end groups
  - Ester/carboxyl end groups
  - Ester/ester end groups

Cleavage Reactions
- Hydrolysis
- Thermal degradation
- Radiation
- Ozonization

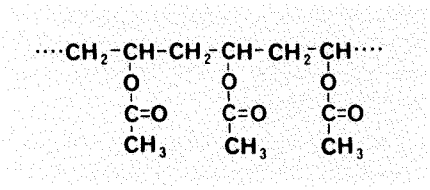
Intermolecular Reactions
- Crosslinking by radiation
- Crosslinking by monomers
- Crosslinking by chemical agents

Branching Reactions
- Branching during polymerization
- Graft polymerization

Coupling Reactions
- Polysulfides
- Epoxides
- Polyurethane/isocyanate polymers

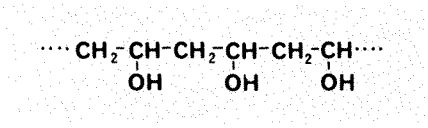
Surface Reactions
- Surface grafting by irradiation
- Chemical surface grafting
- Chemical treatment of surfaces

An excellent example of functional group polymer reactions in an important commercial application is the use of poly(vinyl acetate) as a base polymer in the formation of several derived polymers. The poly(vinyl acetate) is first formed from vinyl acetate monomer in a conventional polymerization reaction and has the following structure:

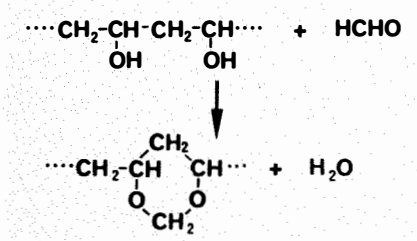


Partial hydrolysis of poly(vinyl acetate) gives copolymers of vinyl acetate and vinyl alcohol[2] commonly listed as poly(vinyl alcohol), % hydrolyzed. A range of materials with varying degrees of hydrolysis and molecular weight is possible by controlling the polymerization reaction and the hydrolysis reaction. These products find many practical applications as emulsion stabilizers and sizing agents.

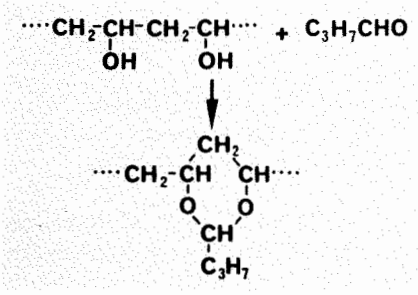
Complete hydrolysis of poly(vinyl acetate) yields a homopolymer of poly(vinyl alcohol):



When treated with an aqueous solution of sodium sulfate containing sulfuric acid and formaldehyde, this normally water soluble polymer is insolubilized by the formation of formal groups. This is an example of a bifunctional polymer reaction:



Poly(vinyl alcohol) is commercially important as a starting material for poly(vinyl acetals), one of which is poly(vinyl formal), shown above.[2] The most important of these polymers is poly(vinyl butyral), formed by condensing poly(vinyl alcohol) with butyraldehyde in the presence of an acid catalyst:



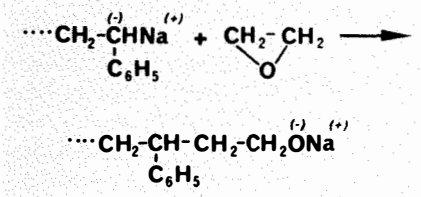
Statistically the condensation cannot be carried to completion since single hydroxyl groups will be isolated by random reactions. The reaction is carried out in dilute solution to minimize intermolecular acetal formation. Since hydroxyl groups improve adhesion to glass, poly(vinyl butyral) produced for safety-glass use is synthesized so that one-quarter of the hydroxyl functionality is retained.

One area of great interest in recent years is the ability of forming terminally reactive polymers by means of anionic polymerization.[3] The formation of "living" polymers as demonstrated by Szwarc and coworkers[3] allows a close control of molecular weight and produces a polymer having a very reactive anion on one or both ends. This anion can be converted to a wide range of reactive end groups by the following reaction schemes.

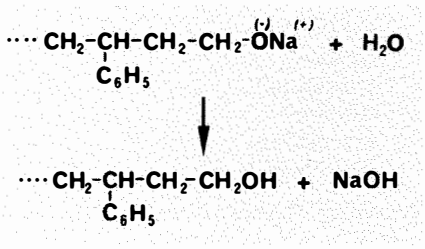
CONVERSION OF "LIVING" TERMINALS INTO FUNCTIONAL END GROUPS

Hydroxyl End Groups

The "living" chain is first reacted with ethylene oxide.

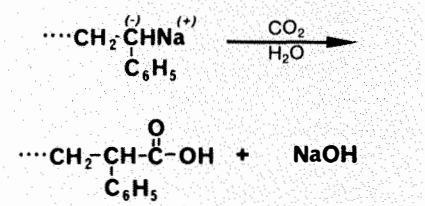


On exposure to moisture the alkoxide is hydrolyzed to hydroxyl.



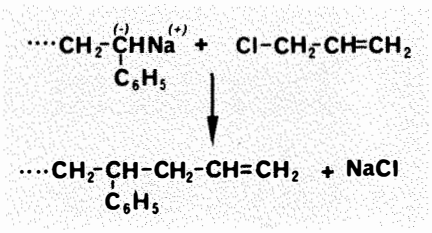
Carboxyl End Groups

Reaction with carbon dioxide followed by a proton donor as in the second step above gives the carboxyl group.



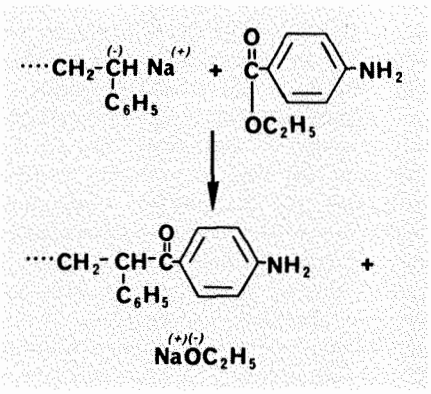
Terminal Double Bonds

Reaction with allyl chloride produces a terminal double bond.



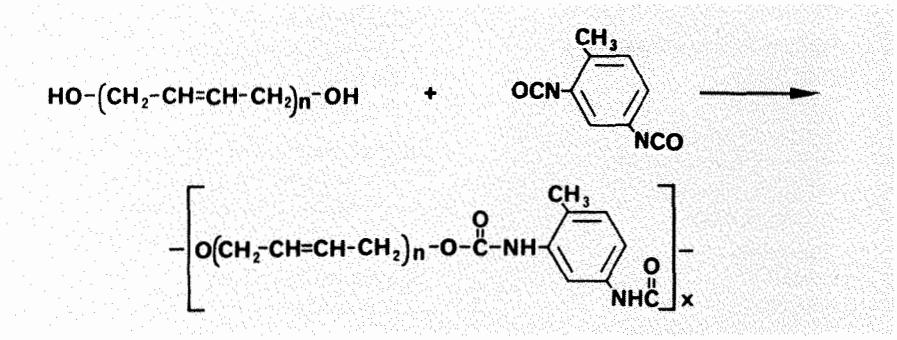
Amine End Group

To overcome the tendency of proton extraction from the amine group itself, the polymeric anion can be reacted with ethyl *p*-aminobenzoate where the ester group preferentially reacts.

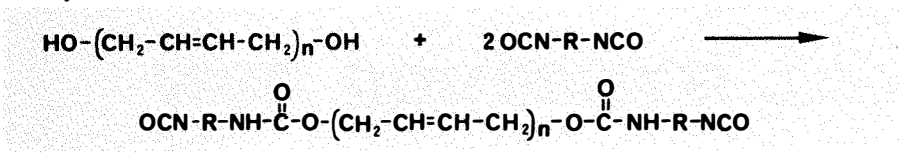


In a similar manner many other types of end groups may be introduced, *e.g.*, halogens, aldehydes, mercapto, etc. This technique provides enormous control in the architecture of macromolecules.

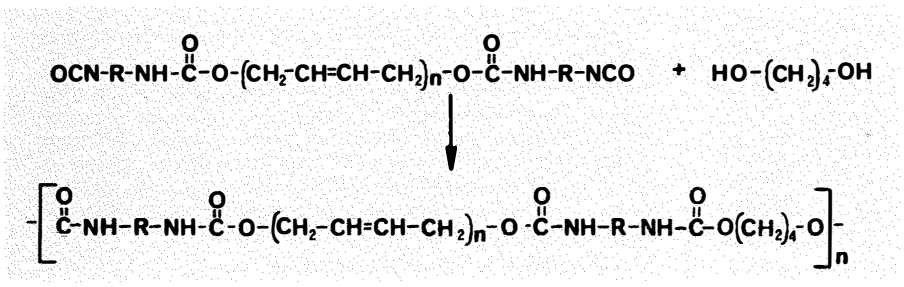
One example of the application of this technique is in hydroxyl-terminated butadienes. Because of their elastomeric properties, diene polymers, such as polybutadiene, offer a very attractive modifying segment when provided with reactive end groups. Hydroxyl terminated homopolymers and copolymers of polybutadiene are readily produced by means of anionic polymerization methods. When produced in low molecular weights (MW 2000-5000), they afford liquid resins which readily react with aromatic diisocyanates to form polyurethane elastomers in one step.



In certain cases, it is desirable to utilize a two-step reaction sequence involving the formation of an isocyanate terminated prepolymer by the reaction of hydroxyl terminated polybutadienes with an excess of diisocyanate.



The product can then be reacted with other polyols or diamines to provide further modification of the urethane polymer formed.



By utilizing various diols, triols, short chain polyols, long chain polyether diols, etc., virtually unlimited combinations of materials are possible to give products with a wide range of physical properties. An example is the combination of polybutadiene diols with polycaprolactone based urethanes.

Elastomers containing predominantly linear structures are formed when very little trifunctional materials are used, and display thermoelastic properties. The combination of diol and triol reactants generally improves all physical properties, especially elongation and tear strength. The use of long chain triols and diols in equal proportions tends to increase tensile strength while keeping other properties constant. Higher percentages of triols improve elongation and tear strength and increase hardness.

These examples suffice to illustrate the possibility of utilizing polymeric species as reactants. The main purpose is the modification or complete alteration of one or more of the properties characteristic of the parent polymer. Polymeric reactions also allow the introduction of a variety of functional groups which are useful in curing reactions at the point of end use.

Thus, technological demands can be satisfied to a greater degree than is possible by the modification of monomer structures. Applications to practical problems have a greater probability of success when the polymer chemist is at least aware of the different possible routes toward property modification even when he is not skilled in the use of such routes.

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1) Fettes, E.M., "Chemical Reactions of Polymers," Interscience Publishers, New York, N.Y., 1964.
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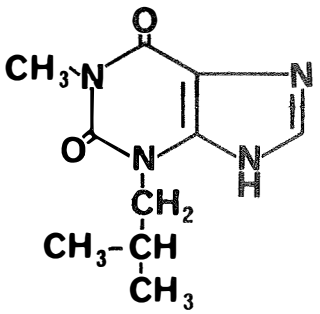
3) Szwarc, M., "Carbanions, Living Polymers and Electron Transfer Processes," Interscience Publishers, New York, N.Y., 1968.

3-Isobutyl-1-methylxanthine a potent phosphodiesterase inhibitor



3-Isobutyl-1-methylxanthine (IBMX) is a potent inhibitor of cyclic AMP phosphodiesterase, about ten times as potent as theophylline.[1,2] The inhibitory action of **IBMX** is of great importance in studying and evaluating the role of the phosphodiesterase system in regulating cyclic AMP levels.[1-4] Thus, **IBMX** inhibits the hydrolysis of cyclic AMP to 5'-AMP, resulting in an accumulation of cyclic AMP. **IBMX** also has great significance in the problem of control of insulin release through inhibition of cyclic AMP phosphodiesterase. **IBMX** reportedly stimulates insulin release by pancreatic islets when initiators of release, such as glucose, are present at an appropriate concentration.[2,5,6] The effect of **IBMX** on insulin release in pregnancy has also been studied.[7] **IBMX** also possesses potent lipolytic activity, believed to result from its inhibition of cyclic AMP.[3]

References:

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5) R. H. Cooper, S. J. H. Ashcroft, and P. J. Randle, *Biochem. J.,* **134,** 599 (1973).
6) W. Montague and S. L. Howell, *ibid.,* **134,** 321 (1973).
7) I. C. Green, S. L. Howell, W. Montague, and K. W. Taylor, *ibid.,* **134,** 481 (1974).

Lab Notes ... *cont'd from page 26*

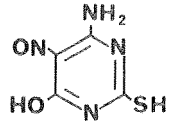
this does not impede operation of the breaker, the breaker can be used under full water pressure.

A very simple device for restricting the flow at the hose fitting is a plastic dropper. Polyethylene tubing may be heated and drawn into droppers. The diameter of the tubing should be selected to fit snugly into the back of the hose fitting adapter. The water flow is determined by the size of the opening at the tip of the plastic dropper. Cutting the dropper so the opening at the tip is the size of a pencil lead or toothpick allows a moderate flow. The plastic dropper is inserted into the hose fitting adapter and the fitting is replaced. The water valve can then be completely opened, yet only a slow flow is obtained through the condenser.

Harvey Hopps
Aldrich-Boranes, Inc.

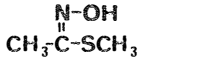
Any interesting shortcut or laboratory hint you'd like to share with ACTA readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome red and white ceramic Aldrich coffee mug. All entries become the property of Aldrich Chemical Company, Inc., and cannot be returned.

Palladium Reagent

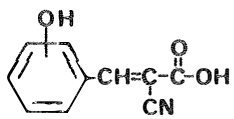


86,055-7
6-Amino-5-nitroso-2-thiouracil
Used for the colorimetric determination of palladium. *Chem. Abstr.,* **66,** 34552j (1967).

Important Heterocyclic Intermediate



Inhibitors of Pyruvate Transport



α-Cyano-3-hydroxycinnamic acid and α-cyano-4-hydroxycinnamic acid are potent specific inhibitors of mitochondrial pyruvate transport. *Biochem. J.,* **138,** 313 (1974); *ibid.,* **148,** 85 (1975).

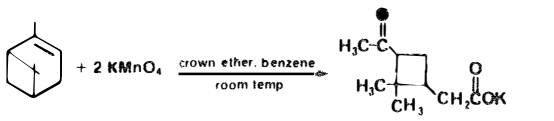
Crown Ethers

- 15-Crown-5: specific for Na^+
- 18-Crown-6: specific for K^+
- Dibenzo-18-crown-6
- Dicyclohexyl-18-crown-6

Since the discovery of their remarkable ability to dissolve alkali metal salts in non-polar solvents, crown ethers,[1a,b] a class of macrocyclic polyethers, have found novel application in synthesis. **18-Crown-6** promises even greater synthetic utility by virtue of its increased complexing ability.[2] For example, in acetonitrile or benzene effective solvation of the potassium ion of potassium fluoride by **18-crown-6** results in a highly reactive fluoride ion ("naked" fluoride).[2] "Naked" fluoride is a potent base and nucleophile,[2] being capable of converting a variety of alkyl, acyl, or activated aryl halides to their respective fluorides in good yields.

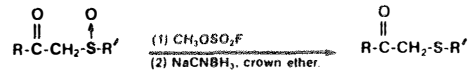
Acetate[3], cyanide[4] and nitrite[4] also display markedly enhanced nucleophilicity in the presence of **18-crown-6**.

In the presence of **dicyclohexyl-18-crown-6,** potassium permanganate readily dissolves in benzene to form a purple solution ("Purple Benzene")[5] which oxidizes alcohols, olefins, aldehydes and aralkyl hydrocarbons in excellent yield under neutral conditions.

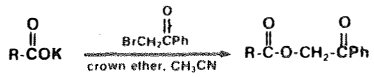


90%, *cis*
(40-60% with no crown ether in an aqueous system)

Alkoxysulfonium salts, formed by alkylation of sulfoxides with Magic Methyl® (methyl fluorosulfonate), are readily reduced with sodium cyanoborohydride in the presence of crown ethers[6] to give sulfides in excellent yield. Similarly, β-ketosulfoxides are reduced to β-ketosulfides,[6] whereas extensive decomposition occurs in the absence of the crown ether.



Phenacyl esters which are difficult to obtain in good yield using classical procedures are formed easily in a refluxing benzene or acetonitrile suspension of acyl salt, crown ether and α-bromoacetophenone.[6]



90% yield

The alkylation of acetoacetic ester enolates gives more *O*-alkylated product in the presence of a crown ether,[7] especially in weakly polar solvents. **Dicyclohexyl-18-crown-6** markedly changes the rates and stereochemical course[8] of alkoxide-catalyzed carbanion-generating reactions; *e.g.*, the reaction of 5-decyl tosylate with potassium alkoxides[9] produces more *trans* olefin in the presence of **dicyclohexyl-18-crown-6.** Crown ethers also find application in the resolution of α-amino acids[10] and show promise for the preparation of organometallics[11] by catalyzing the reaction between metals and C-halogen or acidic C-H compounds. The potassium hydroxide complex of **dicyclohexyl-18-crown-6** reacts with *o*-dichlorobenzene[12] to give *o*-chloroanisole in 40-50% through a non-benzyne mechanism. Finally, crown ethers may be contrasted with our **α- and β-cyclodextrins.** While the cyclodextrins have a lipophilic cavity and hydrophilic shell the reverse is true of the crown ethers.[13]

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13) D.J. Cram and J.M. Cram, *Science,* **183,** 803 (1974).

†Designates molar unit

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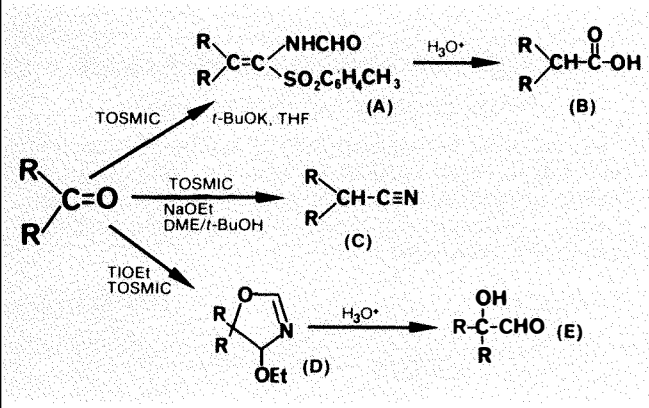
Tosylmethyl isocyanide {TOSMIC}

★ One-carbon elongation of ketones to acids, nitriles, etc.
★ Synthesis of 5-membered heterocycles

Tosylmethyl isocyanide (*TOSMIC*), a stable crystalline solid, enables the facile and convenient conversion of a ketone into the next higher **carboxylic acid**[1] or **nitrile**.[2] Reaction of a ketone with α-metalated *TOSMIC* in THF gives **1-formylamino-1-tosylalkene** (A) which may be hydrolyzed to the corresponding **carboxylic acid** (B). In contrast, if the reaction is performed in dimethoxyethane/*t*-butanol, a high yield of **nitrile** (C) is obtained.



4-Ethoxyoxazolines (D)[3] which serve as excellent intermediates for a new and simple synthesis of **α-hydroxyaldehydes** (E)[4] are formed from the reaction of *TOSMIC* with ketones in the presence of thallous ethoxide.

TOSMIC also permits the synthesis of many difficult-to-prepare heterocycles. For example, the reaction of *TOSMIC* with an aldehyde and potassium carbonate in refluxing methanol affords the **5-substituted oxazole** (F)[5] in excellent yield *via* the intermediate **4-tosyl-Δ²-oxazoline. 4-Tosyl-5-substituted oxazoles** (G) are obtained from acid chlorides or anhydrides.[5] *TOSMIC* and imidoyl chlorides react, in the presence of sodium hydride, to give **4-tosyl-5-substituted imidazoles** (H)[6] while **5-substituted imidazoles** (I) are formed in the analogous reaction with aldimines.[7] Whereas ethyl benzoate does not react readily with the anion of *TOSMIC*,[5] carboxymethyl dithioates give **4-tosyl-5-substituted thiazoles** (J).[8] Diazonium salts react to give **1,2,4-triazoles** (K). Reaction of *TOSMIC* anion with Michael acceptors gives **pyrroles** (L) unsubstituted in the 1 and 2 positions.[9]

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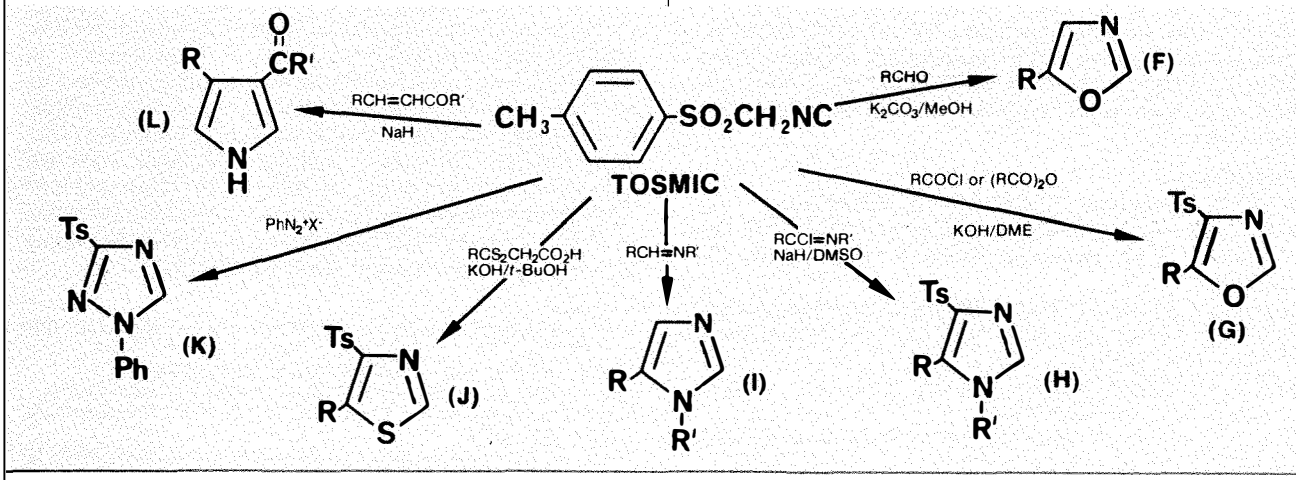

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(Final Issue, 1975)

Highlights. See page 39.

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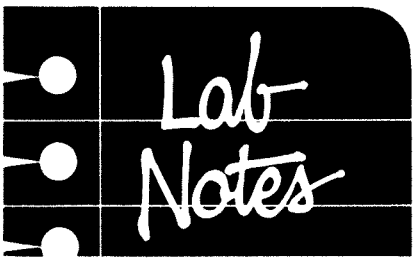
About the Cover

The Bible is the book of dreams, par excellence: dreams of individuals, dreams of a people, dreams of all mankind. It is surely no accident that the very first well known dream in the Bible is not that of a king or of a general but of a man at the lowest point in his life - homeless and hunted, yearning for God's promise that He would return him to his country.

The vision of a ladder with angels going up and down on it is unique in Biblical imagery, and so *Jacob's Dream* has aroused artists' imaginations for centuries. This fine depiction (oil on canvas, 29 1/2 x 60 inches) by a Neapolitan artist of around 1700 was purchased by our chemist collector on one of his most recent visits to Copenhagen. If only, he says, he could find a good many more such dreams of paintings.

Are you interested in our Acta covers? *Selections from the Bader Collection,* with 30 duotone reproductions, many of previous Acta covers, and an introduction by the late Professor Wolfgang Stechow is now available to all chemist art-lovers.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.



Dear Sirs:

A survey of the experimental sections of papers in a leading chemical journal showed clearly that the advantages of dichloromethane as an extraction solvent are generally not fully appreciated.

If an organic product has been extracted from aqueous solution with CH_2Cl_2, it is rarely necessary to wash the CH_2Cl_2 solution with acid, base or water (as in an ether extraction), as the transference of most inorganic compounds (including most acids and bases) from water to CH_2Cl_2 is negligible. Exceptions include ammonium or alkylammonium salts and high-boiling water-miscible organic solvents such as DMSO or DMF; in such cases, the CH_2Cl_2 extracts must be washed several times with water.

Just as useful, and as little appreciated, is the fact that CH_2Cl_2 extracts need not be treated with a drying agent. It is sufficient to run the lower layer from the separatory funnel through a small plug of cotton wool; this will remove any droplets of water, and the last traces will come off as an azeotrope on evaporation of the CH_2Cl_2, whether this is done at atmospheric pressure or on a rotary evaporator *in vacuo*. (The cotton should have been previously washed with a little CH_2Cl_2 to remove fats.)

Errol Lewars
Department of Chemistry
Trent University, Peterborough
Ontario, Canada K9J 7B8

Gentlemen:

How many times have you done suction filtration in a Buchner funnel and flask and badly stained or contaminated your piece of dental dam? Or perhaps you have used a solvent that dissolved gum rubber, so there was no way of removing the last bit of mother liquor from the filter cake?

In such cases I have had good luck substituting thin (.002 - .005 inch) plastic film such as Teflon® FEP or polyethylene for dental dam. Any low modulus, high elongation film insoluble in your solvent should work unless it has pinholes; even

cont'd on page 45

Highlights

David R. Harvey
Vice President, European Operations
Aldrich Chemical Company, Inc.

Every organic or biochemist is faced with the enormous task of trying to cope with an almost exponential growth in scientific knowledge. It is becoming increasingly difficult to keep abreast, even in a specialized field of research, of all the major developments. This increase in chemical knowledge is reflected by the number of organic compounds of known structure having risen over the last hundred years, from about 10,000 to several million. The current *Aldrich Catalog-Handbook of Organic and Biochemicals* — listing 18,000 compounds — in fact lists more compounds than were known a century ago!

Aldrich, as a major world producer and supplier of organic and biochemicals, has always been aware of the real need to introduce important new compounds and their applications to the research community. Articles in the *Aldrichimica Acta,* technical data sheets and technical advertising in the chemical journals have been tailored with this in mind. Such publications have received wide acclaim. Indeed, when meeting chemists and biochemists, we are constantly queried regarding the latest interesting compounds featured by our company.

However, over recent years we have included thousands of new chemicals in our Catalog-Handbook, and inevitably, many research workers will have missed noticing certain of their very interesting applications. Therefore, the author wishes in this article just to "highlight" a few of our compounds* which we believe may be of particular importance in the future.

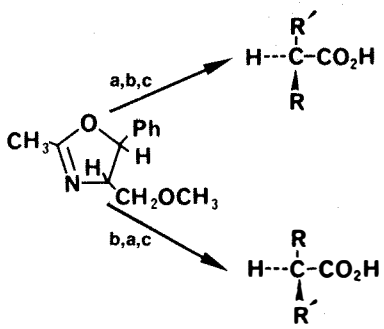
ORGANIC APPLICATIONS

The Aldrich Chemical Company is one of the major world producers of fine organic chemicals, with extensive production facilities in the USA and in West Germany at EGA Chemie, a wholly owned subsidiary. At both locations, compounds are constantly being evaluated with respect to their more general applicability. Our own laboratory experience has especially underlined the tremendous potential of the following compounds.

Asymmetric Syntheses — Oxazolines

Certain oxazolines can be very conveniently used for asymmetric syntheses.

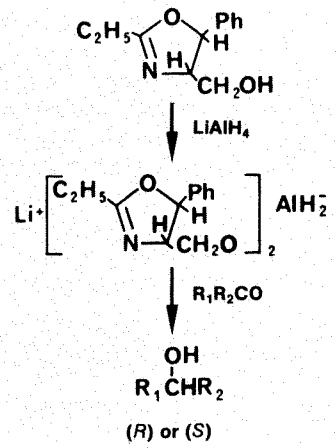
Thus, *R* and *S* dialkylacetic acids can be readily prepared from (4*S*,5*S*)-(-)-4-methoxymethyl-2-methyl-5-phenyl-2-oxazoline *via* asymmetric induction.[1] Lithium diisopropylamide (LDA) at -78° converts the oxazoline to its lithio salt. Alkylation followed by another treatment with LDA and a second alkylating agent gives, upon acid hydrolysis, the chiral acid of high optical purity (50-70%). The order of alkyl introduction controls the stereochemistry of the final product. When an alkyl group of lower priority (Cahn-Ingold-Prelog sequencing) is introduced, followed by a second alkyl group of higher priority, the *S* enantiomer is obtained; reversal of this order gives the *R* enantiomer.



Reagents:
a) lithium diisopropylamide (LDA), R'X
b) LDA, RX (R precedes R', Cahn-Ingold-Prelog sequencing)
c) H_3O^+

This oxazoline also finds application in the preparation of optically active 3-hydroxy- or 3-methoxyalkanoic acids, secondary and tertiary alcohols, and 3-methylalkanoic acids.

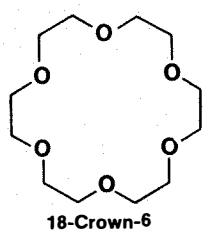
The analog, (4*S*,5*S*)-(-)-2-ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline reacts with $LiAlH_4$ to give a chiral reducing agent which converts ketones to chiral secondary alcohols.[2]



Crown Ether Technology — Macrocyclic Polyethers

Macrocyclic polyethers named "crown" compounds were discovered by Dr. Pedersen of Du Pont.[3,4] He gave them the name "crown" since a molecular model looks like a crown and because metal cations could be crowned and uncrowned without physical damage to either, just as is the case for the heads of royalty.

Aldrich produces 15-crown-5, 18-crown-6, dibenzo-18-crown-6 and dicyclohexyl-18-crown-6.



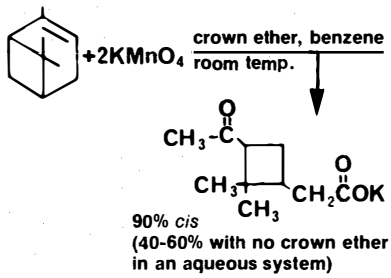
18-Crown-6

These compounds are of particular interest since they form neutral complexes with alkali metal ions in non-polar solvents. Crown ethers thus allow alkali metal salts to be dissolved in non-polar

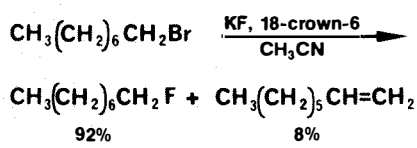
*Literature references will be given sparingly since, for all the compounds detailed, free technical literature is available from Aldrich.

organic solvents and enable certain very novel reactions.

For example, in the presence of dicyclohexyl-18-crown-6, potassium permanganate readily dissolves in benzene to form a purple solution ("Purple Benzene")[5] which oxidizes alcohols, olefins, aldehydes and aralkyl hydrocarbons in excellent yield under neutral conditions.



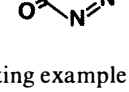
18-Crown-6 promises even greater synthetic utility by virtue of its increased complexing ability.[6] Thus, in acetonitrile or benzene, effective solvation of the potassium ion of potassium fluoride by 18-crown-6 results in a highly reactive fluoride ion ("naked" fluoride). This "naked" fluoride is a potent base and nucleophile, being capable of converting a variety of alkyl, acyl, or activated aryl halides to their respective fluorides in good yields.



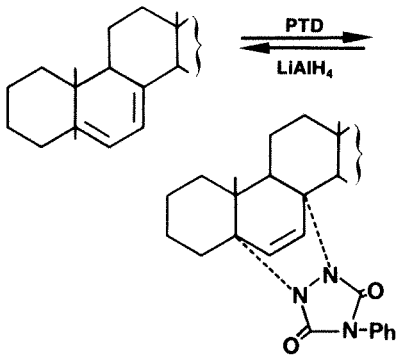
The solubilizing power of crown ethers suggests many other potential applications in enhancement of chemical reactivity, catalysis, separation and recovery of salts, electro- and analytical chemistry, etc.

Diels-Alder Reaction — 4-Phenyl-1,2,4-triazoline-3,5-dione

4-Phenyl-1,2,4-triazoline-3,5-dione (PTD), readily prepared *in situ* by mild oxidation of 4-phenylurazole, is the most reactive dienophile known for Diels-Alder reactions.[7] Thus, it reacts instantly with cisoid dienes, even at -78° to give stable crystalline adducts in high yield. Because of its exceptional reactivity, it has also found application for trapping transient intermediates.



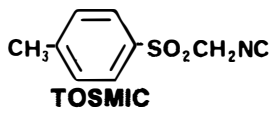
An interesting example is its use for the protection of steroidal dienes.[8] The Diels-Alder adduct forms readily in high yield to give a protected steroid which can then be modified under more vigorous conditions. The retro reaction is achieved virtually in quantitative yield upon treatment of the adduct with $LiAlH_4$.

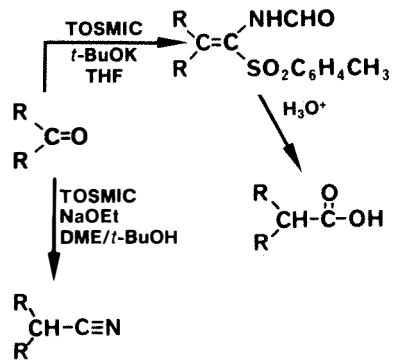


The number of Diels-Alder reactions is of course legion, encompassing the synthesis of many cyclic and heterocyclic systems. Aldrich offers literally hundreds of dienes and dienophiles suitable for this important type of reaction and adds new reagents daily. By furnishing us with the structural requirements of the compound type desired, we will send you a free computer search of our listings which may well show up the type of compound you are seeking.

One-carbon Elongation of Ketones — Tosylmethyl Isocyanide (TOSMIC)

Tosylmethyl isocyanide (TOSMIC), a stable crystalline solid, enables the facile and convenient conversion of a ketone into the next higher carboxylic acid [9,10] or nitrile.[11,12] Reaction occurs with the α-metalated TOSMIC in tetrahydrofuran to give 1-formylamino-1-tosylalkene which may be hydrolyzed to the corresponding carboxylic acid. In contrast, if the reaction is performed in dimethoxyethane/*t*-butanol, a high yield of nitrile is obtained.





TOSMIC also permits the synthesis of many difficult-to-prepare heterocycles.

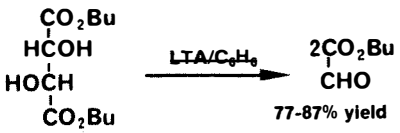
It is thus proving to be a most versatile compound in organic syntheses.

Oxidation — Pyridinium Chlorochromate/Lead Tetraacetate

Pyridinium chlorochromate ($C_5H_5NHCrO_3Cl$), a stable crystalline reagent, readily oxidizes a variety of alcohols to the corresponding aldehydes and ketones in high yield under mild conditions.[13] Yields of aldehydes and ketones obtained with 1.5 molar equivalents of pyridinium chlorochromate are equal or superior to those obtained with Collins reagent (using a five or six-fold excess). These results suggest that pyridinium chlorochromate qualifies as an important addition to the present methodology, particularly for moderate to large scale oxidations.[14]

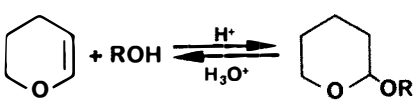
The chemist should, of course, never neglect the well established methods of oxidation. The author particularly refers to lead tetraacetate, first isolated over a century ago, but still one of the most versatile oxidizing agents.[15] We at Aldrich are constantly surprised by its ever increasing applications. The author should however admit a particular affection for lead tetraacetate, having spent a considerable period of his doctoral research work attempting to resolve certain mechanisms of its fascinating reactions.[16]

The classical cleavage of vicinal glycols has been used both for structure elucidation and for preparative purposes. Thus, *n*-butyl glyoxylate is obtained from its reaction with di-*n*-butyl D-tartrate.[17] But this is only one example of lead tetraacetate's supreme oxidizing power.



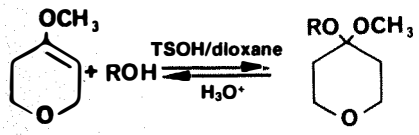
Protecting Groups for Alcohols — Dihydropyrans; *tert*-Butyldimethylsilyl Chloride

The formation of tetrahydropyranyl ethers by the reaction of 2,3-dihydropyran with alcohols under mild acid catalysis[18] is a very useful method for protecting alcohols because such ethers are stable to bases, Grignard reagents, metal hydrides, lithium alkyls, chromic acid oxidation, and epoxidation with alkaline hydrogen peroxide, yet are easily cleaved by dilute acids.

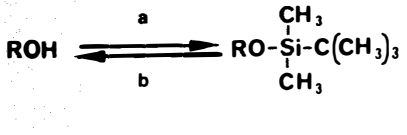


However, for the protection of hydroxyls of chiral alcohols, the use of the simple tetrahydropyranyl group is not very satisfactory since it leads to the introduction of another chiral center, and hence, undesirable mixtures of diastereoisomeric products.

For the protection of such optically active alcohols, the 4-methoxy substituted pyran (5,6-dihydro-4-methoxy-2*H*-pyran) is an excellent reagent[19] because the 4,4-disubstituted tetrahydropyran moiety of the product is symmetrical, and its introduction does not lead to an additional chiral center. The derivatives, which are usually crystalline, are formed in high yields by *p*-toluenesulfonic acid-catalyzed reactions in anhydrous dioxane; they are base-stable, yet are easily hydrolyzed by dilute acids. 5,6-Dihydro-4-methoxy-2*H*-pyran has been employed mainly in the syntheses of nucleotides and oligonucleotides, but has also found application for steroidal alcohol protection.



Similarly, *tert*-butyldimethylsilyl ethers formed from *tert*-butyldimethylsilyl chloride and alcohol are useful protecting groups as they are labile to treatment with tetra-*n*-butylammonium fluoride and acid hydrolysis but are stable to basic and neutral hydrolyses, metal hydride reduction, Grignard reactions, Wittig reactions, Jones oxidations and phosphorylation of nucleosides.[20] The silyl ethers have no additional chiral centers, are frequently crystalline, and are suitable for gas chromatographic and mass spectral analysis.



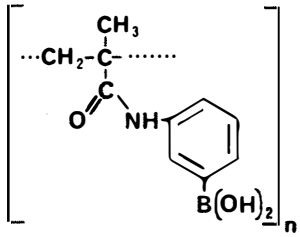
a = ClSi(CH3)2C(CH3)3, imidazole

b = F⁻ or HOAc

Separation Technique — Boric Acid Gels

Aldrich produces a boric acid gel suitable for preparative as well as analytical procedures.

Boric acid gel is a cross-linked polymer insoluble in water and organic solvents. It is prepared by the cross-linking copolymerization of dihydroxyborylanilino-substituted methacrylic acid with 1,4-**butanediol** dimethacrylate.[21] It serves as an exceedingly useful packing material for the column chromatographic separation of mixtures of organic compounds which form complexes of varying stability with boric acid.



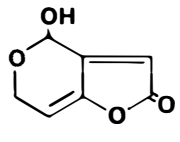
Separation techniques based on boric acid complex formation are of course standard practice in sugar and nucleic acid chemistry. However, preparative separation using borate complexes requires considerable effort as the borate moiety of the complexes can only be removed with difficulty from the separated components. This problem does not arise when using boric acid gel as the boric acid, due to covalent linkage to the polymer, remains in the stationary phase. There are obviously numerous potential applications. The separations of mono- and oligosaccharides, ribonucleosides-deoxyribonucleosides, oligonucleotides and *t*RNA mixtures have already been reported.[22]

BIOCHEMICAL APPLICATIONS

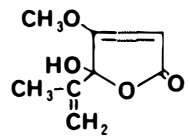
The important developments in the biochemical sector during this century have been greatly aided by the commercial availability of complex organic compounds of high purity. The following highlighted examples illustrate the diverse applications of various important compounds which Aldrich currently offers:

Antibiotic Mycotoxins—Patulin and Penicillic Acid

Patulin and penicillic acid are structurally related carcinogenic lactones which inhibit DNA synthesis.[23,24]



Patulin



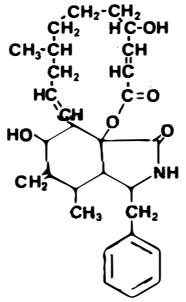
Penicillic Acid

Their interesting molecular configurations suggest many avenues of profitable biochemical research.

Cytological Probes—The Cytochalasins

The Cytochalasins (Greek: *cytos,* cell; *chalasis,* relaxation) are a group of structurally related fungal metabolites discovered in 1964 in the laboratories of the Pharmaceuticals Division of Imperial Chemical Industries Ltd., England.

During the last couple of years, there has been a tremendous upsurge in research with these compounds, since they exhibit unusual, interesting and characteristic effects on the cell. The Cytochalasins are in fact becoming very important research probes in cytology. Aldrich offers Cytochalasins A, B, C, D and E. Cytochalasins A, B, and E are manufactured in England by Imperial Chemical Industries Ltd., and distributed by Aldrich. To date Cytochalasin B, which is a metabolite of *Helminthosporium dematioideum,*[25] has been used in the vast majority of reported experiments.



Cytochalasin B

The major biological effects observed with the Cytochalasins include:

1. Inhibition of cytoplasmic cleavage while division of the nucleus continues.[26,27]
2. Reversible inhibition of cell movement.[26,27]
3. Induction of nuclear extrusion by the cell.[26]

The Cytochalasins also exert inhibitory effects on the following biological processes: phagocytosis, platelet aggregation and clot retraction, glucose transport, thyroid secretion, and release of growth hormone. Research continues to rapidly uncover new effects.

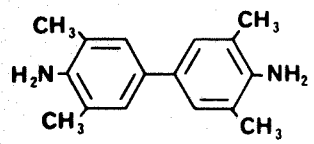
A comprehensive data sheet and a bibliography containing over 300 references are now available free from Aldrich.

Detection of Blood—3,3′,5,5′-Tetramethylbenzidine

Blood exhibits a peroxidase-like activity, yielding, in the presence of hydrogen peroxide, colored products with certain substrates, especially amines. This is a particularly sensitive reaction with benzidine and the latter had consequently been used for many years as a specific reagent for the detection of blood. However, benzidine's extreme carcinogenicity has curtailed its use in recent years and prompted the search for a safe substitute.

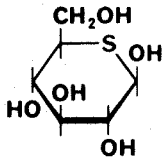
It has been reported that 3,3′,5,5′-tetramethylbenzidine appears to be a sensitive and safe substitute for benzidine.[28]

Thus, subcutaneous injection of 3,3',5,5'-tetramethylbenzidine into rats *"produced no tumors specifically attributable to it, in doses greater than those in which benzidine or o-tolidine cause a high yield of neoplasms."*[28b]



D-Glucose Transport Inhibitor—5-Thio-D-glucose

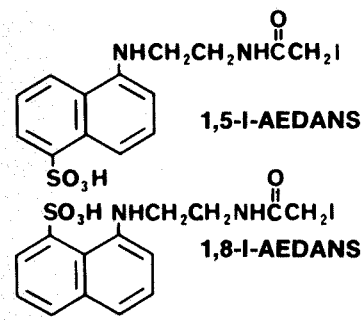
5-Thio-D-glucose is the analog of D-glucose in which the ring oxygen atom is replaced by sulfur.[29] It is a potent inhibitor of D-glucose transport and D-glucose-mediated insulin release. Thus, 5-thio-D-glucose produces a pseudodiabetic condition in rats, an effect rapidly reversed by insulin administration.



The increase in blood D-glucose caused by 5-thio-D-glucose causes a depression in appetite, making the compound potentially useful for weight control.[30] Preliminary experimentation in mice indicates 5-thio-D-glucose also shows promise as a male contraceptive as well as an antitumor agent.[30] Thus, the replacement of the ring oxygen of D-glucose by sulfur has resulted in a compound with extremely interesting properties.

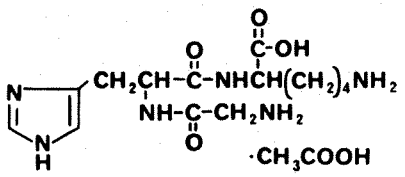
Fluorescent Sulfhydryl Probes—1,5-and 1,8-I-AEDANS

N-Iodoacetyl-*N'*-(5-sulfo-1-naphthyl)-ethylenediamine (1,5-I-AEDANS) and *N*-iodoacetyl-*N'*-(8-sulfo-1-naphthyl)ethylenediamine (1,8-I-AEDANS) are fluorescent thiol reagents[31] which react specifically with sulfhydryl groups in proteins, *e.g.*, globin and papain. These compounds combine the reactivity of iodoacetamide toward sulfhydryl groups with the fluorescence properties of naphthalenesulfonic acids.



They offer certain advantages over conventional fluorescent probes.[31] The reagents are of high purity and are stable indefinitely when stored in the dark. Although the reagents are sensitive to degradation by light, their protein conjugates are photostable. The reagents are water soluble, thus permitting homogeneous reactions which can be easily controlled and reproduced. These reagents show exceptional promise for the elucidation of complex protein structures.[32]

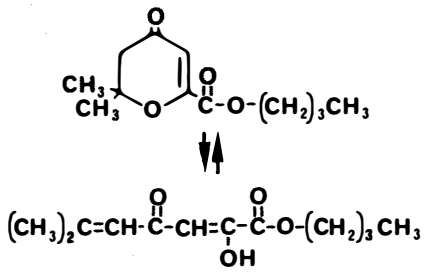
Growth Promoting Tripeptide — Glycyl-L-histidyl-L-lysine acetate



This synthetic tripeptide is analogous to the biological tripeptide[33] isolated from human serum and possesses equal protective and growth-stimulatory activity.[34] Maximal effects on the stimulation of RNA and DNA synthesis were obtained with nanogram quantities of the synthetic, as well as the native, tripeptide. It is believed that the properties of the peptide may reside in an interaction with cellular DNA. The synthetic glycyl-L-histidyl-L-lysine appears more stable to prolonged storage than the native factor.

Insect Repellent — Butopyronoxyl

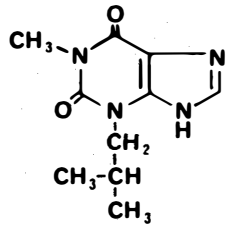
Butopyronoxyl exists mainly as the dihydropyrone in equilibrium with the open chain enol form.[35] The insect repellent activity of butopyronoxyl is well known, including its action against the yellow fever mosquito.[35,36]



The use of butopyronoxyl with *N,N*-dimethyl-*m*-toluamide, greatly enhances the latter's repellent activity against flies, gnats, etc. It has also been used in conjuction with dimethyl phthalate and 2-ethylhexane-1,3-diol.

Phosphodiesterase Inhibitor — 3-Isobutyl-1-methylxanthine

3-Isobutyl-1-methylxanthine is a potent inhibitor of cyclic AMP phosphodiesterase, about ten times as potent as theophylline.[37] It is therefore of great importance in studying the role of the phosphodiesterase system in regulating cyclic AMP levels. It also reportedly



stimulates insulin release by pancreatic islets, in the presence of glucose, and possesses potent lipolytic activity, believed to result from its inhibition of cyclic AMP.[38]

DEUTERATED COMPOUNDS

The use of deuterated compounds has led to the elucidation of many intriguing mechanisms of organic and biochemical reactions. The range of their application is virtually limited only by the ingenuity of the investigator.

Aldrich produces a wide variety of deuterated chemicals with special emphasis on high quality. Our Diaprep Division has, in fact, been manufacturing deuterated solvents and compounds for over ten years, during which time a wealth of experience has been accumulated. We now produce and supply over 100 deuterated compounds, all of which undergo very stringent quality control.

We offer a comprehensive range of high purity deuterated solvents for nmr spectroscopy. The purity specifications of these compounds are expressed as atom % deuterium as determined by nmr dilution experiments. Thus, 99.5% D benzene-d_6 contains less than five protons per thousand deuterons with no other impurities detectable by gas chromatography. Among other solvents available are 99.5% D acetone-d_6, 99.8% D chloroform-d, 99.8% D deuterium oxide, 99.5% D methyl sulfoxide-d_6, 99% D pyridine-d_5, 98% D tetrahydrofuran-d_8, 99% D dimethylformamide-d_7, and 99% D hexamethylphosphoramide-d_{18}.

Our THF-d_8, DMF-d_7, and HMPA-d_{18} deserve special mention. THF, DMF and HMPA are of course excellent solvents for many compounds, yet are completely useless for most nmr spectroscopy studies because of large absorptions in their nmr spectra. This problem is overcome by using deuterated solvents. Chemists will consequently find these deuterated solvents highly useful as nmr solvents, particularly THF-d_8 for nmr studies of Grignard reagents, organometallic compounds and

other chemicals which react with or are insoluble in commonly used deuterated solvents.

As more sophisticated nmr instruments appeared, we foresaw the need for deuterated solvents of even higher isotopic purity and developed the technology to produce materials containing 100.0 atom % deuterium. In fact, many solvents are now available as 100.0 atom % D deuterated, eliminating the problem of partially masked nmr spectra due to solvent absorptions. They are especially useful for Fourier transform nmr and routine scanning of very dilute solutions.

The nmr spectra of the more common deuterated solvents are recorded in the opening pages of volume 1 of our eleven-volume series "The Aldrich Library of NMR Spectra". This publication is a compilation of the nmr spectra of about 6,000 Aldrich chemicals conveniently arranged in order of increasing molecular complexity and functionality.

The Aldrich range of deuterated compounds is being continually extended. For a complete listing of deuterated solvents and compounds useful in nmr studies, please send for our special deuterated solvents booklet.

ORGANOBORANES

A highlight of Aldrich compounds would be very incomplete without mentioning the fascinating chemistry of organoboranes.

During the last couple of years, our company has been carrying out major development work in this sector; the wholly owned subsidiary, Aldrich-Boranes, Inc. is devoted to developing the chemical technology of hydroboration. The fundamental aim is to make readily available the more important organoboranes, examine their potential applicability and to establish safe handling techniques.

Professor H.C. Brown of Purdue University, who discovered this new field of chemistry, is in fact a member of the Board of Directors of Aldrich and naturally devotes considerable time to aiding our developments.

This branch of chemistry has often been featured in the *Aldrichimica Acta*[39] and we know from the vast number of reprints distributed that such articles have had a most welcome reception. However, we well appreciate that because of the large number of compounds and their diverse reactions, it is difficult for the non-specialist to quickly sort the wheat from the chaff.

Consequently, we only intend to highlight here those compounds and their reactions which we believe could achieve very wide laboratory and industrial scale uses.

Overall, we envisage borane-type compounds will be used in synthesis particularly for the following type of reactions:

Selective reductions
Stereospecific reductions and synthesis
Hard-to-make alcohols or amines
Production of aldehydes

An important general factor is that high yields are often achieved in such syntheses.

Borane — Tetrahydrofuran or Methyl Sulfide

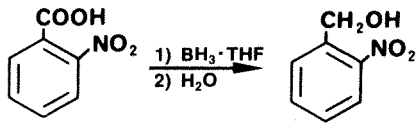
These reducing agents are more selective than lithium aluminum hydride (and much safer to handle), but are generally more powerful than sodium borohydride.

Hydride Reducing Agents

	$NaBH_4$	BH_3 (THF)	$LiAlH_4$
Aldehyde	+	+	+
Ketone	+	+	+
Acid chloride	+	-	+
Lactone	-	+	+
Epoxide	-	+	+
Ester	-	±	+
Carboxylic acid	-	+	+
Carboxylic acid salt	-	-	+
Amide	-	+	+
Nitrile	-	+	+
Nitro	-	-	+
Olefin	-	+	-

+ Reduction
- No reduction

Borane-tetrahydrofuran is at present the most commonly used hydroboration agent. It has found considerable use in selective reductions, *e.g.*, nitro-substituted benzoic acids to nitro-substituted benzyl



99.8% yield

alcohols.[40] However, this reagent possesses certain properties which limit its preparation, storage and use as a commercial source of borane:

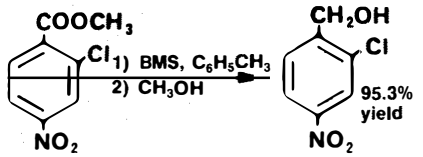
- It can only be sold as a dilute solution (1*M*) in tetrahydrofuran (1.5wt% borane).
- Tetrahydrofuran is slowly cleaved by borane at room temperature; hence sodium borohydride (< 5 mole %) is added to inhibit such cleavage.
- Tetrahydrofuran is a relatively expensive solvent.

Borane-methyl sulfide overcomes the disadvantages listed for borane-tetrahydrofuran:

- Molar concentration of borane is ten times that of borane-tetrahydrofuran.
- It can be stored for months at room temperature without loss of hydride activity and is apparently stable indefinitely when refrigerated.

Furthermore, borane-methyl sulfide is soluble and unreactive toward a wide variety of aprotic solvents: ethyl ether, tetrahydrofuran, hexane, toluene, methylene chloride, etc.

The hydroboration of alkenes and the reduction of organic functional groups with borane-methyl sulfide is currently under active investigation in the laboratories of Aldrich-Boranes, Inc. It has been shown that methyl 2-chloro-4-nitrobenzoate can be readily reduced to 2-chloro-4-nitrobenzyl alcohol in excellent yield.[41]

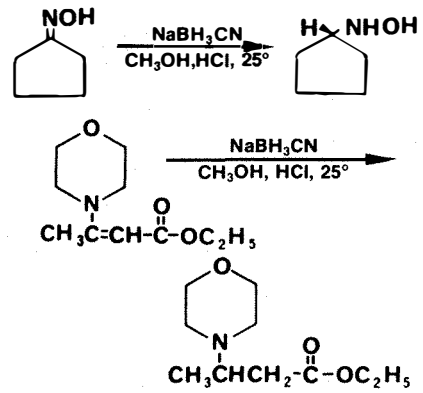


95.3% yield

Preliminary results indicate that its reactivity parallels that of borane-tetrahydrofuran, but the reactions usually require somewhat higher temperatures. This compound provides a very concentrated source of hydride and is ideally suited for large scale reactions in a variety of solvents. It has enormous potential for pharmaceutical applications.

Sodium cyanoborohydride, $NaBH_3CN$

Because of its electron-withdrawing cyano group, sodium cyanoborohydride is a milder and more selective reducing agent than $NaBH_4$. It reduces a variety of organic functional groups with remarkable selectivity.[42] The most useful application appears to be for the selective reduction of the imminium ion ($>C=\overset{+}{N}<$). This is illustrated by the reduction of oximes and enamines:



That the imminium ion (>C=$\overset{+}{N}$<) is reduced much faster than a carbonyl group, provides a convenient and efficient route to the reductive amination of aldehydes and ketones.

The stability in protic solvents at low pH also allows reductions under conditions that would rapidly hydrolyze $NaBH_4$. It is actually hydrolyzed 10^8-fold slower than $NaBH_4$. Another property which has enhanced its utility as a reducing agent is its solubility in aprotic solvents.

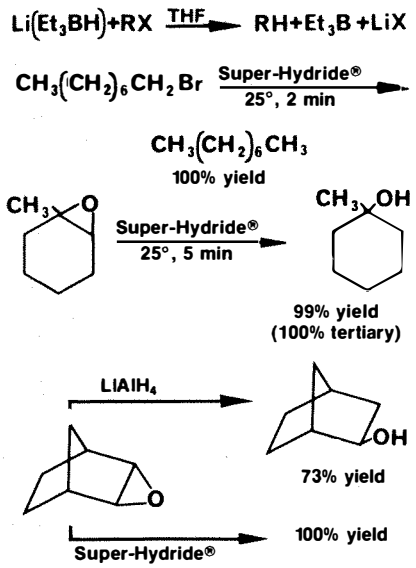
The new Aldrich compound, sodium cyanoborodeuteride, 98% D, obviously allows the synthesis of a wide variety of deuterated compounds, which would otherwise be fairly inaccessible.

At present Aldrich is the only commercial producer of high purity sodium cyanoborohydride and its deuterated analog.

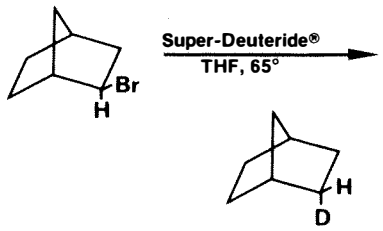
Trialkyl borohydrides — MBR_3H

These compounds are highly active nucleophilic selective reducing agents, which open up a vast new area of synthetic possibilities.[43]

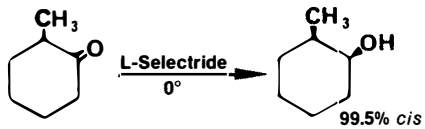
Super-Hydride™ (lithium triethylborohydride) is an extraordinarily powerful reducing agent, far more powerful than lithium aluminum hydride and lithium borohydride. Applications include the dehalogenation of alkyl halides and the regiospecific and stereospecific reduction of epoxides. Lithium triethylborohydride is also considerably more powerful as a nucleophile than thiophenoxide and alkyl mercaptans, hitherto considered to be the most powerful simple nucleophiles available for *SN*2 displacements.



Super-Deuteride® (lithium triethylborodeuteride) can of course be used to readily produce deuterium labelled compounds by the reduction of alkyl halides, epoxides, ketones, imines and other groups. It offers advantages in cost and convenience over sodium borodeuteride and lithium aluminum deuteride.



L-Selectride® and K-Selectride® (lithium and potassium tri-*sec*-butylborohydride) are sterically hindered trialkylborohydrides which show improved stereoselectivity in their reduction reactions.[43] Thus, they exhibit an almost enzyme-like sensitivity in the reduction of cyclic and bicyclic ketones unequalled by any other known reducing agents. Such hindered ketones as 2-methylcyclohexanone are reduced rapidly and quantitatively with over 99% stereoselectivity to the correspondingly less stable *cis* epimers.

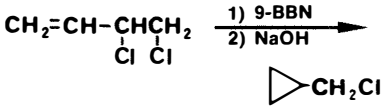


These trialkylborohydrides have already found many important applications, including use in the synthesis of prostaglandins.

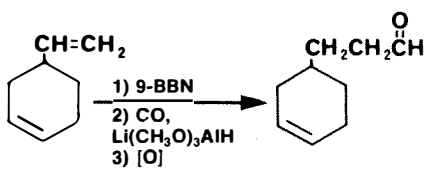
9-Borabicyclo[3.3.1]nonane Dimer (9-BBN)

Our company is very interested in the commercial possibilities of this compound due to its stability (crystalline powder, mp 150-152°C, may be handled in air with reasonable precautions). 9-BBN undergoes two reactions which are of particular interest and importance.

It enables a very simple synthesis of cyclopropanes.[44]

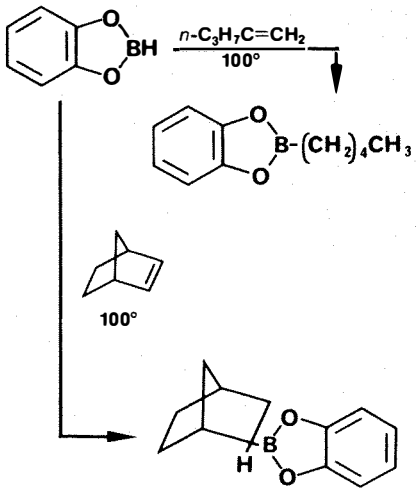


Alkenes can be readily converted to the next C-higher aldehyde.[45] This reaction is of considerable importance to the perfumery and flavoring chemist.



Catecholborane (1,3,2-benzodioxaborole)

This is a stable, useful new hydroboration reagent for the conversion of alkenes to alkaneboronic esters which are easily hydrolyzed to alkaneboronic acids.[46] It



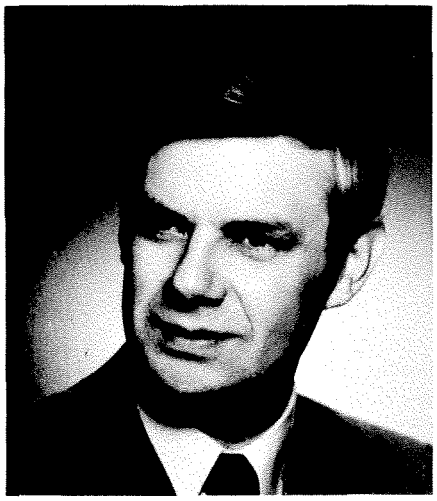
also reacts readily with alkynes to provide a simple convenient, regioselective and stereospecific synthesis of alkeneboronic esters and acids.[47]

This brief review illustrates the remarkable chemistry of the organoboranes. Clearly these developments will have a major future impact on synthetic organic chemistry, especially in the industrial field. Indeed, certain major companies are already making valuable use of our boranes and technology.

However, as Professor H.C. Brown has stated, "it will require another generation of chemists to conquer fully this new continent." Thus, many chemists will inevitably become increasingly involved with this branch of chemistry.

CONCLUSION

It has, of course, only been possible to highlight a few of the many intriguing Aldrich compounds. The examples, however, do strikingly indicate Aldrich's close world wide ties both with the academic and industrial research communities. Such contacts enable us to continually add carefully chosen new compounds to our already wide range of organic and biochemicals. By featuring their properties in *Aldrichimica Acta*, data sheets and technical advertising, we firmly believe a valuable contribution is being made to the dissemination of scientific knowledge. Consequently, we shall continue this policy of highlighting new compounds in the conviction that this will further aid research and discovery.



Dr. David R. Harvey

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Lab Notes.....*cont'd from page 38*

then a dental dam could be used as a back up. You can also cut filter paper-size discs of film or aluminum foil to interpose between the filter cake and the dental dam.

R.H. Sill
E.I. du Pont de Nemours & Co., Inc.
Film Department
Circleville, Ohio

Gentlemen:

In cases where it may be impractical or undesirable to esterify by normal techniques (*e.g.*, H_2O azeotrope in a Dean-Stark trap), one method I have used is simply to reflux a benzene solution of the components, usually with a catalytic amount of *p*-toluenesulfonic acid, in a Soxhlet extractor whose thimble has been filled with 3Å molecular sieves. The sieves, by drying the refluxing benzene-water azeotrope, allow for shorter reaction time, smaller reactant requirements and easier purification.

Walter J. Wawro, Sr.
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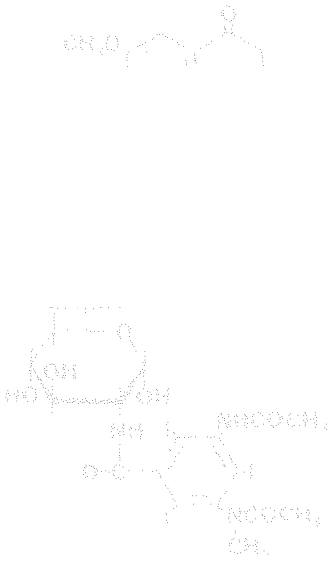
Important Medicinal Intermediate



A new density gradient medium for the centrifugation of biological particles.

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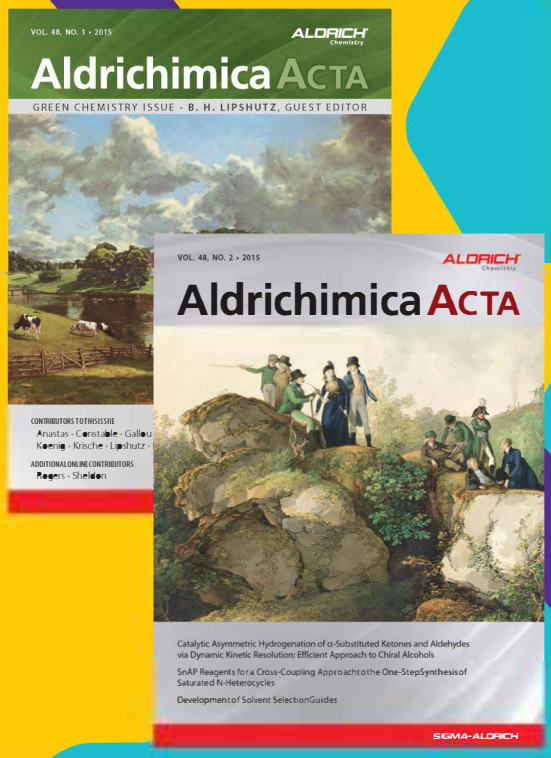

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