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A NEW SYNTHESIS OF ETHERS BY THE REDUCTION OF ALDEHYDES WITH PYRIDINE-BORANE IN TRIFLUOROACETIC ACID[1)]

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Pyridine-borane in trifluoroacetic acid reduced aldehydes to symmetric ethers, and to unsymmetric ethers with the combination of alcohols.

It is generally accepted that aldehydes are easily reduced to the corresponding alcohols with borane and borohydride reagents. In the course of investigation on the reduction of various functional groups with pyridine-borane,[2)] which was easily prepared from sodium borohydride and pyridine hydrochloride,[3)] reduction of aldehydes was carried out in trifluoroacetic acid and unexpectedly the products were not the alcohols but symmetric ethers.

$$2\ \mathrm{RCHO}\ \xrightarrow[\text{2) Hydrolysis } (\mathrm{H^+} \text{ or } \mathrm{OH^-})]{\text{1) } \mathrm{Py\cdot BH_3} \text{ in TFA, 5 min}}\ \mathrm{RCH_2OCH_2R}$$

The general procedure is as follows: To a mixture of trifluoroacetic acid (3 ml) and an aldehyde (2.5 mmol) was added pyridine-borane (0.3-0.4 ml) with cooling. After a 5-min stirring, trifluoroacetic acid was evaporated in vacuo and 10% HCl or 10% NaOH (15 ml) was added to the residue. The aqueous solution was refluxed for 0.5-1 h to decompose the boron complex and extracted with benzene (50-60 ml). The benzene solution was dried over anhyd. Na_2SO_4. After evaporation of benzene, the residue was purified by column chromatography (SiO_2, benzene for elution) to give an ether which was distilled and identified by IR and mass spectral analysis. The results are presented in the table. Although the presence of a substantial amount of ethers can be detected before hydrolysis, a small amount of boron complex remains in acid hydrolysate and is stable to more concentrated acid hydrolysis.

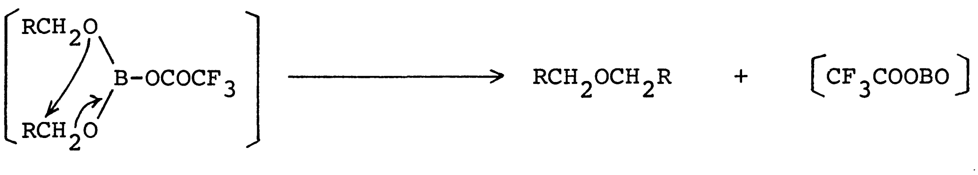
Table Synthesis of Ethers from Aldehydes

Aldehyde	Yield of ether[a] (%) 10% HCl hydrolysis	 10% NaOH hydrolysis	MS (m/e, M^+)	Bp, °C/Torr or mp, °C	Reference bp, °C/Torr or mp, °C
m-$CH_3OC_6H_4CHO$	63[b]	55[b]	258	174/5	-------
C_6H_5CHO	67	87	c	128-130/3	295-298/760[4]
p-ClC_6H_4CHO	63(9)	67(trace)	266	54-56(69-70)[d]	54-55[5] (75)[d,6]
m-$NO_2C_6H_4CHO$	--(56)	---	---	e	-------
$C_6H_5CH_2CH_2CHO$	72	81	254	168-170/4	220-222/19[7]
$C_7H_{15}CHO$	59	70	c	131-134/6	288/778[8]

a) Figures in parentheses indicate yield (%) of the corresponding alcohols.

b) Ten min of reflux for hydrolysis. c) The corresponding ether was identified by comparison of IR spectrum and retention time in gas chromatography with those of the authentic sample because the parent ion could not be observed in mass spectrum analysis. d) Melting point of p-chlorobenzyl alcohol. e) m-Nitrobenzyl alcohol was identified by comparison of its spectral data with those of the authentic sample.

On the other hand, no boron complex remains after alkaline hydrolysis. The accurate structures of the reaction intermediate and the boron complex resisting acid hydrolysis are still obscure, but, IR spectrum of the reaction mixture before hydrolysis shows a strong absorption band at 1780 cm^{-1} due to the trifluoroacetyl group bonded to the boron atom. It is clear that the bonding of boron atom and trifluoroacetyl group will be formed at the first stage of the reaction. The substitution of electron-attracting trifluoroacetyl group on boron atom may stabilize the boron-alkoxyl bond,[9] which causes further reaction to give ethers, as evidenced by absence of the corresponding alcohols.



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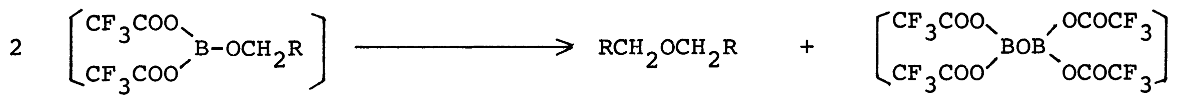

$$2\left[(CF_3COO)_2B\text{-}OCH_2R\right] \longrightarrow RCH_2OCH_2R + \left[(CF_3COO)_2BOB(OCOCF_3)_2\right]$$

Trifluoroacetic acid is essential for this reduction because normal product alcohols were obtained when acetic acid was used in place of trifluoroacetic acid.

Reduction of m-nitrobenzaldehyde, which has a strong electron-withdrawing group on the benzene ring, is an exceptional case and the corresponding alcohol was obtained. The reaction mechanism of ether formation should be almost the same as described for the formation of α-chloroethers from boron trichloride and aldehydes.10)

For the synthesis of unsymmetric ethers, the combination of an aldehyde with an alcohol can be successfully employed. From phenylpropionaldehyde (1 mmol), benzyl alcohol (3 mmol), and pyridine-borane (0.35 ml) in trifluoroacetic acid (3 ml), benzyl phenylpropyl ether (bp 146-148 °C/6 Torr; m/e 226 (M^+)) was obtained in 63% yield.11) Benzyl p-chlorobenzyl ether (bp 136-137 °C/2.5 Torr; m/e 232 (M^+), yield 68%) was also obtained from the reduction of p-chlorobenzaldehyde and benzyl alcohol. For the control experiment, benzyl alcohol alone was submitted to the same reduction conditions (alkaline hydrolysis) and it was recovered in 78% yield without isolation of benzyl ether. Although a useful method for synthesis of ethers from aldehydes with trialkylsilanes in trifluoroacetic acid has been reported,12) this method is inconvenient for the separation of ethers from silane products when ethers have boiling points close to those of silane products (silanols, trifluoroacetates, and disiloxanes),12b) and formation of by-products was often observed. According to the report on the reduction with silanes published by a Russian group,13) introduction of electron-donating substituents into the aromatic ring permits hydrogenation of the aldehydes to the methyl group and, in the case of the reduction of aliphatic aldehydes, the ether formation competed with alcohol formation in nearly equal ratios.

The pyridine-borane reduction of aldehydes will be an attractive alternative method for the preparation of ethers. Studies on the scope and limitation of this reaction on other aldehydes are in progress.

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References and Notes

1) This report constitutes Part VII of a series entitled "Chemistry of Amine-Boranes." Part VI: Y. Kikugawa and M. Kawase, Synth. Commun., 9, 49 (1979).

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