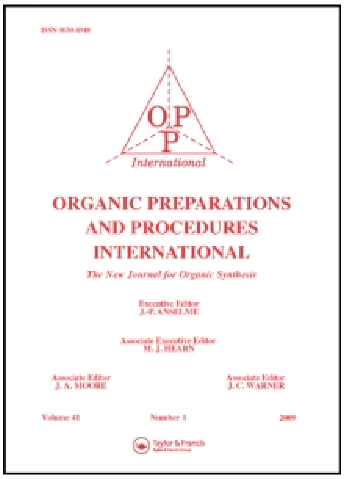

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REACTIONS OF SODIUM BOROHYDRIDE IN ACIDIC MEDIA.

XIV. REDUCTIVE CLEAVAGE OF CYCLIC ACETALS AND KETALS TO HYDROXYALKYL ETHERS

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The classical methods for reducing acetals and ketals to ethers involve relatively harsh chemical ($LiAlH_4$, $AlCl_3$[1]; DIBAL[2]; $LiAlH_4$, $TiCl_4$[3]) or catalytic (H_2, Ni[4]; H_2, Rh, Al_2O_3, HCl[5]; H_2, CO, $Co_2(CO)_8$[6]) conditions. More recently, several other chemical methods have been reported to effect this transformation (Et_3SiH, CF_3CO_2H[7]; $NaBH_3CN$, HCl, MeOH[8]; Me_3SiH, Me_3SiOTf[9]; BH_2Cl[10]).

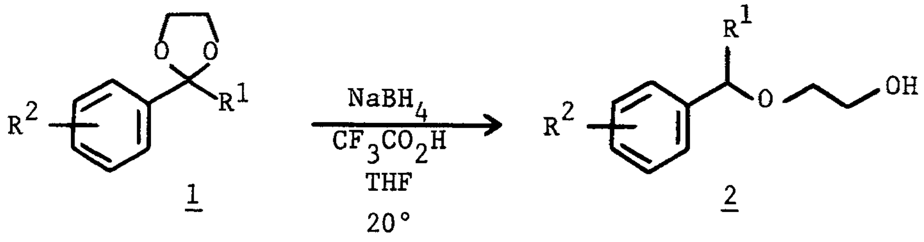
In continuation of our survey[11] of the chemistry of $NaBH_4$ in acidic media, we now report that acetals and ketals 1 of aromatic aldehydes and ketones are smoothly converted to the corresponding hydroxyethyl ethers 2 on treatment with $NaBH_4$ and trifluoroacetic acid (TFA) in tetrahydrofuran (THF) at 20°C. Similarly, the dioxane acetal 3 gives hydroxypropyl ether 4 under these conditions. Our results are summarized in the Table.

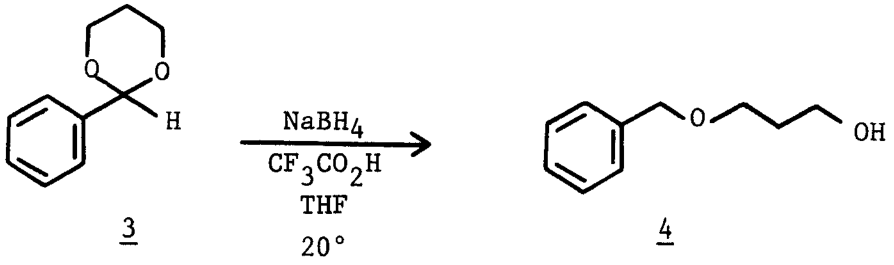
The mechanism of this transformation presumably involves the TFA-promoted cleavage of the dioxolane or dioxane ring to give a resonance-stabilized carbocation which is intercepted by a borohydride species. Consistent with this pathway is the

Table. Reductive Cleavage of Cyclic Acetals and Ketals with $NaBH_4$/TFA at 20°C in THF

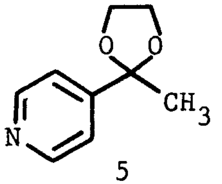
Substrate[a]	R^1	R^2	Product	Yield[b] (%)	IR[c] (cm^{-1})	^1H NMR[d] (ppm)	^{13}C NMR[d] (ppm)
1a	H	H	2a	83	3440	3.05 (m, 1H), 3.5 (m, 4H), 4.4 (s, 2H), 7.25 (s, 5H)	61.7, 71.3, 73.1, 127.5, 128.2, 137.8
1b	H	4-OCH_3	2b	75	3440	3.05 (m, 4H), 3.7 (s, 3H), 4.4 (s, 2H), 7.0 (m, 4H), 7.2 (s, 1H)	55.1, 61.7, 71.0, 72.7, 113.7, 129.2, 129.9, 159.1
1c	CH_3	H	2c	76	3440	1.45 (d, 3H), 2.8 (m, 1H), 3.5 (m, 4H), 4.35 (q, 1H), 7.3 (s, 5H)	23.7, 61.7, 69.6, 78.2, 125.9, 127.3, 128.2, 143.3
1d	CH_3	4-CH_3	2d	83	3440	1.4 (d, 3H), 2.25 (s, 3H), 3.1 (m, 1H), 3.45 (m, 4H), 4.35 (q, 1H), 7.1 (s, 4H)	21.0, 23.7, 61.9, 69.5, 78.1, 126.0, 129.0, 137.1, 140.3
1e	CH_3	4-Cl	2e	66	3430	1.4 (d, 3H), 2.65 (m, 1H), 3.55 (m, 4H), 4.4 (q, 1H), 7.75 (s, 4H)	23.7, 61.9, 69.7, 77.7, 127.3, 128.5, 133.1, 141.9
1f	H	2-NO_2	2f	36[e]	3420	3.2 (m, 1H), 3.7 (m, 4H), 4.9 (s, 2H), 7.7 (m, 4H)	61.7, 69.6, 72.3, 124.5, 128.1, 128.7, 133.3, 134.4
1g	H	3-NO_2	2g	11[e]	3430	3.1 (m, 1H), 3.7 (m, 4H), 4.65 (s, 2H), 7.55 (m, 2H), 8.1 (m, 2H)	61.8, 71.9, 122.1, 122.5, 129.3, 133.1, 140.2
3			4	78	3410	1.8 (m, 2H), 3.45 (m, 5H), 4.4 (s, 2H), 7.3 (s, 5H)	32.1, 61.4, 69.0, 73.1, 127.4, 128.2, 138.0
7			8	33[e]	3420	3.25 (m, 3H), 3.55 (m, 6H), 7.2 (s, 5H)	36.2, 61.7, 71.8, 71.9, 126.1, 128.3, 128.7, 138.7
9			10	40[e]	3450	2.75 (m, 5H), 3.3 (s, 4H), 3.65 (m, 1H), 7.15 (s, 10H)	41.1, 61.7, 71.1, 82.7, 126.2, 128.2, 129.2, 138.7

[a]Prepared in the usual manner: aldehyde or ketone, diol, p-toluenesulfonic acid, benzene, Dean-Stark trap, reflux. [b]Yields refer to flash chromatographed (silica gel) product identified by spectral data, in several cases by comparison with literature data. [c]Neat film. [d]$CDCl_3$ solution; chemical shifts reported downfield from internal tetramethylsilane. [e]Reaction run at reflux (bath temp = 75°C) for 24 h.





fact that the nitro-substituted acetals 1f and 1g give product in lower yields and only at reflux temperatures. Moreover, pyridine ketal 5 and dithiane 6 fail to react even after refluxing the reaction mixture for 24 h.



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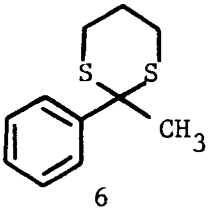

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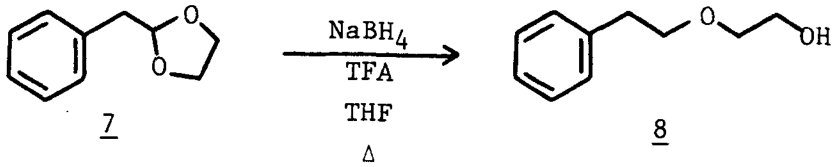
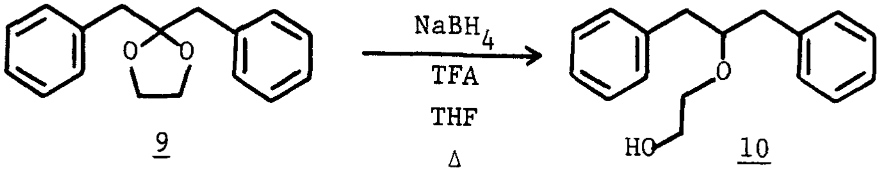
The $NaBH_4$/TFA reductive cleavage of aliphatic acetals and ketals is less successful. Thus, dioxolanes 7 and 9 give hydroxyethyl ethers 8 and 10, respectively, in relatively low yield after 24 h at reflux (Table).

In conclusion, the reductive cleavage of the acetals and ketals of aromatic aldehydes and ketones using $NaBH_4$/TFA is a very mild alternative to the existing methods,[1-10] and, unlike



7 → 8



9 → 10

these procedures, offers the possibility of chemoselective reduction since aliphatic acetals and ketals are much less reactive under these conditions.

EXPERIMENTAL SECTION

General Procedure. 2-Benzyloxyethanol (2a).- To a magnetically stirred suspension of NaBH$_4$ (1.0 g, 0.026 mol) and 2-phenyldioxolane (1a) (0.75 g, 0.005 mol) in dry THF (50 mL) at 5°C under N$_2$ was added dropwise over 1.5 h a solution of TFA (20 mL, 0.26 mol) in THF (25 mL). The solution was allowed to warm to 20°C while stirring for 3.5 hrs. The reaction mixture was poured into 10% aqueous KOH (150 mL) and extracted with ether (3 x 100 mL). The ethereal layer was dried (Na$_2$SO$_4$) and concentrated *in vacuo* to afford a yellow oil. Flash chromatography on silica gel gave 0.63 g (83%) of 2-benzyloxyethanol (2a) as a colorless oil, whose spectral data agreed with those reported.[12]

The following hydroxyethyl ethers have apparently not been previously characterized:

<u>2-(1-(4-methylphenyl)ethoxy)ethanol</u> (<u>2d</u>): bp 100°C/0.4 torr (bath temp); calcd. for $C_{11}H_{16}O_2$ (180.2): C, 73.30; H, 8.95; found: C, 73.36; H, 8.97.

<u>2-(1-(4-chlorophenyl)ethoxy)ethanol</u> (<u>2e</u>): bp 100°C/ 0.3 torr (bath temp); calcd. for $C_{10}H_{13}ClO_2$ (200.7): C, 59.86; H, 6.53; Cl, 17.67; found: C, 59.72; H, 6.56; Cl, 17.67.

<u>2-(2-nitrophenylmethoxy)ethanol</u> (<u>2f</u>): bp 165°C/0.25 torr (bath temp); calcd. for $C_9H_{11}NO_4$ (197.2): C, 54.84; H, 5.62; N, 7.10; found: C, 54.90; H, 5.62; N, 7.09.

<u>2-(dibenzylmethoxy)ethanol</u> (<u>10</u>): bp 145°C/0.25 torr (bath temp); calcd. for $C_{17}H_{20}O_2$: m/e 256.1463; found m/e 256.1469.

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