

Mercury(II) Oxide/Tetrafluoroboric Acid¹; Enhanced Alkylating Ability of Alkyl Bromides: A General Synthesis of Alcohols and Ethers

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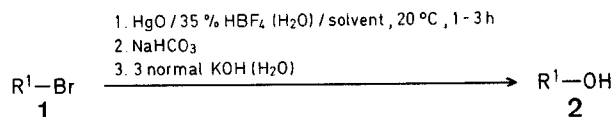
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In recent years, many new and powerful alkylating agents have been developed², several of them presenting handling problems because of toxicity or carcinogenic properties³ and also due to the fact that they may be decomposed by atmospheric moisture. On the other hand, alkyl halides have been widely used in alkylation reactions, in particular in glycoside⁴, polysaccharide⁵, and *N*-glycosylheterocycle⁶ synthesis, but their reactivity towards uncharged nucleophiles⁷ is low. For this reason, nucleophiles bearing a negative charge at the hetero atom site are usually employed, for instance, in the classical Williamson ether synthesis⁸; however, varying amounts of olefin are obtained as side or even major product, depending on the structure of the alkyl halide, by the competing elimination reaction.

The presence of heavy metal salts enhances the reactivity of alkyl halides. This fact is best exemplified by the silver(I)-catalyzed Koenigs-Knorr synthesis of *O*-glycosides⁴ and also by the mercury(II) perchlorate-assisted solvolysis of non-activated alkyl halides⁷. More covalent mercury(II) salts are only effective in the solvolyses of activated alkyl halides, and salts with anions of higher nucleophilicity than perchlorate give esters in a competitive process⁷. On the other hand, mercury(II) perchlorate is a dangerous reagent because of its tendency to undergo explosive decomposition so that it is advisable to use this reagent only in small-scale preparations. The investigation of other highly electrophilic mercury(II) salts having anions of low nucleophilicity is therefore of practical interest.

We have recently described a reagent which possesses these desired properties: the mercury(II) oxide/tetrafluoroboric acid (HgO/TFBA) system¹.

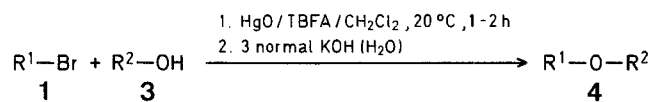
As a first test of the HgO/TFBA-promoted alkylating ability of alkyl bromides, we chose the reaction with an organic solvent/water mixture. We found that this reaction provides a simple and general method for the conversion of alkyl bromides (**1**) with various substitution patterns (including olefinic compounds **1**) into the corresponding alcohols (**2**).



The reactions are carried out at room temperature using dioxan, tetrahydrofuran, or dichloromethane as solvent. The use of dioxan or tetrahydrofuran is recommended for the hydrolysis of higher alkyl bromides whereas from the lower alkyl bromides the best yields of isolated alcohol are obtained using dichloromethane as solvent. The low alcohols may even be obtained in the absence of an organic solvent; with increasing molecular weight the solubility of the halide **1** in water decreases so that the presence of an organic solvent is required.

Mercury(II) oxide is quantitatively recovered after alkaline work-up of the reaction mixture and can be recycled after treatment with 35% aqueous tetrafluoroboric acid.

The reaction of alkyl bromides (**1**) with stoichiometric amounts of alcohols (**3**) in the presence of HgO/TFBA results in the formation of ethers (**4**) in good yields.

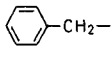


For use in this reaction, the mercury(II) salt is prepared separately and dried under vacuum to avoid competition between the water and the alcohol as nucleophiles. Under these conditions, the formation of the alcohol $\text{R}^1\text{-OH}$ (**2**) was not detected. The reaction is in all cases carried out in dichloromethane as solvent whereby a sufficiently homogeneous medium is maintained.

The structures of the product alcohols (**2**) and ethers (**4**) were ascertained by microanalyses or (for known products) comparison of the boiling points observed with the literature data and by the ¹H-N.M.R. and ¹³C-N.M.R. spectra. In all cases, the ¹³C-N.M.R. spectra of the crude reaction products showed a single signal of C-1 (linked to O) and thus proved the absence of any detectable rearrangement products, except for the solvolysis of the β-branched 1-bromo-2-methylpropane.

The results obtained show that alkyl bromides are converted into powerful alkylating agents by the action of HgO/TBFA. The two reaction types described here provide a useful preparative method for the conversion of alkyl bromides (**1**) into alcohols (**2**) or ethers (**4**) which compares favorably with other methods for the same conversion in terms of generality, convenience of performance, and mildness of reaction conditions. As regards a comparison with the mercury(II) perchlorate and the silver salt methods, our method has the advantage that explosion hazard is avoided and that less expensive reagents are used. On the other hand, the alkylation of water and alcohols

Table 1. Preparation of Alcohols 2 and Ethers 4

Product No.	R ¹	R ²	Solvent	Reaction time [h]	Yield [%]	b.p. [°C] or b.p. [°C]/torr	Lit. data ^a or Molecular formula
2a	<i>n</i> -C ₆ H ₉		CH ₂ Cl ₂	2	67	116–118°	117.25°
2b			dioxan	2	65	158–159°	158–160°
2c			THF	3	79	204–206°	205.35°
2d	<i>n</i> -C ₇ H ₁₅		THF	3	93	174–177°	176°
2e	<i>n</i> -C ₈ H ₁₇		dioxan	3	95	193–194°	194.45°
2f			THF	3	72	159–160°	161.1°
2g	<i>n</i> -C ₅ H ₁₁ -CH- CH ₃		THF	1	77	159–161°	160–162°
2h	<i>t</i> -C ₄ H ₉		THF	2	81	80–82°	82.2°
2i	C ₂ H ₅ -CH- CH ₃		THF	1	69	100–101°	102°
4a	C ₂ H ₅		CH ₂ Cl ₂	1	77	146–148°	149.5°
4b	C ₂ H ₅		CH ₂ Cl ₂	2	76	182–184°	185°
4c	Br-CH ₂ -CH ₂ -		CH ₂ Cl ₂	1	70	44–49°/0.01	C ₉ H ₁₁ BrO ^b (215.1)
4d	<i>n</i> -C ₃ H ₇		CH ₂ Cl ₂	2	63	205–208°	203.5°/752
4e	<i>n</i> -C ₄ H ₉		CH ₂ Cl ₂	2	69	95–97°/15	223°
4f		<i>i</i> -C ₃ H ₇	CH ₂ Cl ₂	1	60	78–81°/15	83°/16
4g		H ₂ C=CH-CH ₂ -	CH ₂ Cl ₂	1	80	200–203°	204–205°
4h		<i>t</i> -C ₄ H ₉	CH ₂ Cl ₂	1	60	204–207°	206–209°
4f	<i>i</i> -C ₃ H ₇		CH ₂ Cl ₂	1	80	78–81°/15	83°/16
4i	C ₂ H ₅ -CH- CH ₃	<i>n</i> -C ₈ H ₁₇	CH ₂ Cl ₂	1	55	215–217°	C ₁₂ H ₂₆ O ^c (186.3)
4j			CH ₂ Cl ₂	1	63	142–145°/15	146°/17
4h	<i>t</i> -C ₄ H ₉		CH ₂ Cl ₂	1	68	204–208°	206–209°

^a From *Handbook of Chemistry and Physics*, 57th edition. CRC Press, Inc., Cleveland, Ohio; or from *Beilsteins Handbuch der Organischen Chemie*.

^b calc. C 50.25 H 5.15
found 49.98 5.23
^c calc. C 77.35 H 14.06
found 77.09 14.18

Table 2. N.M.R.-Spectral Data of Compounds 2 and 4^a

Compound	¹ H-N.M.R. (TMS _{int})		¹³ C-N.M.R. (TMS _{int})	
	(Conditions)	δ [ppm]	(Conditions)	δ [ppm]
2a ^{b,c}				
2b ^b			(CDCl ₃)	14.80; 23.60; 35.60; 63.80; 131.10; 136.60
2c ^b			(CDCl ₃)	65.33; 128.09; 128.33; 129.42; 142.26
2d-h ^{b,c}				
2i ^b			(CDCl ₃)	7.31; 27.29; 35.09; 69.67
4a	(CCl ₄ /capillary D ₂ O)	1.15 (t, 3H); 1.05-2.25 (m, 10H); 3.45 (m, 3H)	(neat/capillary D ₂ O)	16.86; 25.18; 27.34; 63.96; 77.97
4b	(CDCl ₃)	1.20 (t, 2H); 3.50 (q, 2H); 4.40 (s, 2H); 6.9-7.5 (m, 5H)	(CDCl ₃)	14.21; 64.61; 71.58; 126.40; 126.54; 127.29; 137.90
4c	(CCl ₄ /capillary D ₂ O)	3.25 (m, 2H); 3.5 (m, 2H); 4.15 (s, 2H); 7.05-7.35 (m, 5H)	(neat/capillary D ₂ O)	30.61; 70.34; 73.48; 127.68; 127.95; 128.87; 138.30
4d	(CCl ₄ /capillary D ₂ O)	0.90 (t, 3H); 1.55 (m, 2H); 3.35 (t, 2H); 4.35 (s, 2H); 7.0-7.7 (m, 5H)	(neat/capillary D ₂ O)	11.73; 24.07; 72.30; 73.75; 128.39; 128.53; 129.26; 139.91
4e	(CCl ₄ /capillary D ₂ O)	0.90 (t, 3H); 1.45 (m, 4H); 3.35 (t, 2H); 4.35 (s, 2H); 6.9-7.3 (m, 5H)	(neat/capillary D ₂ O)	14.82; 20.42; 38.89; 70.21; 73.59; 127.81; 128.37; 129.17; 139.93
4f	(CCl ₄ /capillary D ₂ O)	1.10 (d, 6H); 3.55 (m, 1H); 4.30 (s, 2H); 6.9-7.2 (m, 5H)	(neat/capillary D ₂ O)	23.71; 71.02; 72.01; 128.51; 128.67; 129.41; 129.64
4g	(CCl ₄ /capillary D ₂ O)	3.85 (m, 2H); 4.40 (s, 2H); 5.1 (m, 3H); 7.0-7.4 (m, 5H)	(neat/capillary D ₂ O)	71.51; 71.62; 116.09; 127.09; 127.20; 127.96; 134.82; 138.33
4h	(CCl ₄ /capillary D ₂ O)	1.25 (s, 9H); 4.40 (s, 2H); 7.05-7.35 (m, 5H)	(neat/capillary D ₂ O)	27.13; 63.64; 73.07; 127.68; 128.15; 128.87; 138.30
4i	(CDCl ₃)	0.90 (br. t, 6H); 1.05 (d, 3H); 1.0-1.7 (m, 14H); 3.1-3.6 (m, 3H)	(CCl ₄ /capillary D ₂ O)	9.59; 13.95; 19.09; 22.56; 26.61; 29.26; 29.46; 29.60; 30.21; 31.32; 68.02; 76.06
4j	(CCl ₄ /capillary D ₂ O)	0.7-1.85 (m, 10H); 4.1 (m, 1H); 4.35 (s, 2H); 6.95-7.25 (m, 5H)	(neat/capillary D ₂ O)	25.47; 26.76; 36.33; 65.33; 71.02; 128.12; 128.25; 129.39; 138.48

^a The spectra were recorded on a Varian FT-80A instrument.

^b Reported in *The Aldrich Library of NMR Spectra*, Aldrich Chem. Co., Inc., Milwaukee, Wisconsin, 1974.

^c Reported in *Atlas of Carbon-13 NMR Data*, E. Breitmaier, G. Haas, W. Voelter, Eds., Ifi/Plenum, New York, 1976.

using mercury(II) perchlorate fails with cyclic and unsaturated alkyl halides and its applicability to the synthesis of ethers seems to be limited to compounds derived from water-soluble alcohols.

The HgO/TBFA mixture which is not sensitive to light represents a convenient alternative reagent for solvolysis reactions usually carried out under silver(I) salt catalysis. The dangers associated with the handling of the often toxic and carcinogenic potent alkylating agents and of toxic mercury derivatives are minimized by the fact that our reagent is produced *in situ* and subsequently destroyed by water or alcohol in the alkylation reaction so that the mercury is manipulated only as the safe, non-volatile mercury(II) oxide.

Mercury(II) oxide/tetrafluoroboric acid was prepared as reported⁹. The alkyl bromides and alcohols were all obtained commercially and used without further purification.

trans-2-Hexenol (2b); Typical Procedure:

To a stirred solution of mercury(II) oxide (1.1 g, 5 mmol) and 35% aqueous tetrafluoroboric acid (2.5 g, 10 mmol) in dioxan (20 ml), *trans*-1-bromo-2-hexene (1.6 g, 10 mmol) is added. The mixture is stirred at room temperature for 2 h and then treated successively with sodium hydrogen carbonate and aqueous 3 normal potassium hydroxide until basic. The precipitated mercury(II) oxide is filtered off (1.0 g, 90%) and the filtrate is extracted with dichloromethane (3 × 20 ml). The extract is dried with anhydrous sodium sulfate, the dichloromethane removed under reduced pressure, and the residual alcohol 2b purified by distillation; yield: 0.65 g (65%); b.p. 116-118 °C.

Ethoxycyclohexane (4a); Typical Procedure:

To a stirred solution of cyclohexanol (1.0 g, 10 mmol) and ethyl bromide (1.6 g, 15 mmol) in dichloromethane (20 ml), dry mercury(II) ox-

ide/tetrafluoroboric acid⁹ (1.9 g, 5 mmol) is added. The mixture is allowed to react for 1 h at room temperature and then treated with aqueous 3 normal potassium hydroxide until basic. The precipitated mercury(II) oxide (1.1 g, 95%) is filtered off and the filtrate is extracted with dichloromethane (3 × 20 ml). The extract is dried with anhydrous sodium sulfate, the dichloromethane removed under reduced pressure, and the residual ether 4a purified by distillation; yield: 1.0 g (77%); b.p. 146-148 °C.

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