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MERCURY-ASSISTED SOLVOLYSES OF ALKYL HALIDES

SIMPLE PROCEDURES FOR THE PREPARATION OF NITRATE ESTERS, ACETATE ESTERS, ALCOHOLS AND ETHERS

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Abstract—The reactions of a wide variety of alkyl halides with mercury(I) and/or (II) nitrate in 1,2-dimethoxyethane, mercury(II) acetate in acetic acid, aqueous mercury(II) perchlorate, and mercury(II) perchlorate in alcohol solvents have been investigated; as a result, simple high yield procedures for the conversion of alkyl halides into the corresponding nitrate esters, acetate esters, alcohols and ethers have been developed.

INTRODUCTION

The electrophilicity shown by many metal salts towards halogen and organic halides is a well known and relatively well understood phenomenon which has been widely utilised in synthesis—for example in electrophilic aromatic substitution reactions and in metal-assisted solvolyses of alkyl halides.[1,2] Certain mercury(II) salts have been found to act as "catalysts" or "promoters" in the latter type of reaction (Eq 1),[3] but little definitive information is

$$\mathrm{Nu} + \mathrm{R{-}X} \cdots\cdots \mathrm{Hg}^{2+} \rightarrow \mathrm{Nu{-}R} + \mathrm{X} \;\; + \mathrm{Hg}^{2+} \qquad (1)$$

$$\mathrm{X} = \mathrm{Cl, Br, I}$$

currently available on the scope and limitations of these reactions with respect to either the alkyl halide, the mercury(II) salt or, most importantly, perhaps, the nature of the incoming nucleophile Nu. Thus, most synthetic applications of mercury(II)-assisted S_N reactions of alkyl halides have been concerned with ether syntheses, and mercury(II) salts have been used in preparations of propargyl ethers from allenic bromides,[4,5] in several modifications[6-9] of the Koenigs-Knorr[10] synthesis of glycosides, in formation of di- and polysaccharides,[11] and in improved procedures for the preparation of N-glycosyl heterocycles.[12-14]

We have studied the mercury(II)-assisted solvolyses of alkyl halides with a number of oxygen nucleophiles and wish to report that treatment of alkyl bromides with mercury(I) or (II) nitrate in 1,2-dimethoxyethane, mercury(II) acetate in acetic acid, aqueous mercury(II) perchlorate, and mercury(II) perchlorate in aqueous alcoholic solvents results in rapid formation, in high yield, of the corresponding nitrate esters, acetate esters, alcohols, and ethers respectively (Eqs 2–5). The scope and limitations of each process have been determined.

$$\mathrm{RBr} + \mathrm{Hg(NO_3)_n} \rightarrow \mathrm{R{-}ONO_2} \qquad (2)$$

$$n = 1 \text{ or } 2$$

$$\mathrm{RBr} + \mathrm{Hg(OOCCH_3)_2} + \mathrm{CH_3COOH} \rightarrow \mathrm{R{-}OOCCH_3} \qquad (3)$$

$$\mathrm{RBr} + \mathrm{Hg(ClO_4)_2} + \mathrm{H_2O} \rightarrow \mathrm{R{-}OH} \qquad (4)$$

$$\mathrm{RBr} + \mathrm{Hg(ClO_4)_2} + \mathrm{R'OH} \rightarrow \mathrm{R{-}OR'} \qquad (5)$$

DISCUSSION

Preparation of nitrate esters (Eq 2). Nitrate esters are useful synthetic intermediates for which there are only two general methods of preparation, namely direct esterification of the appropriate alcohol and metathetical reaction of the corresponding alkyl halide with silver nitrate. The former method employs nitric acid either alone,[15] or in admixture with sulphuric acid,[16-20] in acetic anhydride or acetic anhydride-acetic acid as solvent;[21,22] yields of nitrate esters are generally good to excellent, but considerable care and control must be exercised in carrying out these esterifications in order to avoid undesirable side reactions, particularly oxidation of the substrate.[23] The latter procedure for the synthesis of nitrate esters is experimentally simpler,[15,23] and consists of treatment of an alkyl halide with silver nitrate in a solvent such as benzene,[24] ether,[25] nitromethane[26] or nitrobenzene[26] (heterogeneous conditions) or, more commonly, acetonitrile[27,28] (homogeneous conditions). Many nitrate esters have been prepared in this manner in yields which range from moderate to good;[28] from a practical viewpoint the only significant disadvantage of the procedure is that it necessitates the use of an expensive, photosensitive reagent.

Table 2. Conversion of aliphatic bromides into nitrate esters $RBr \rightarrow RONO_2$

R	Temp, °C	Time, h	Yield, %[a,b]
n-C_9H_{19}	85	3·0	99
$HOOC(CH_2)_{10}$	85	3·0	90
$(CH_2)_5$[c]	85	2·0	99
$(CH_2)_{10}$[c]	85	2·0	98
$C_6H_5(CH_2)_2$	85	3·0	95
$C_6H_5CH_2CHCH_3$	85	2·5	94
$C_6H_5(CH_2)_3$	85	3·0	99
$NC(CH_2)_4$	85	3·0	98
$Cl(CH_2)_4$	85	3·0	98
n-$C_6H_{13}CHCH_3$	85	3·0	99
n-$C_7H_{15}CHCH_3$	85	1·0	74
cyclo-C_6H_{11}	85	0·25	60[d]
cyclo-C_7H_{13}	85	0·25	88
exo-1-norbornanyl	20	0·33	83
$C_6H_5CHCOOH$	85	0·25	98
$C_6H_5COCHC_6H_5$	85	0·5	92
$CH_2CH{=}CHCH_2$[c]	85	1·0	99
$C_6H_5CH{=}CHCH_2$	85	0·5	83
$C_6H_5CH_2$	85	0·25	98
$C_6H_5CHCH_3$	20	0·5	95
4-$NO_2C_6H_4CH_2$	85	1·25	87
4-$ClC_6H_4CH_2$	85	0·25	93
2,6-$Cl_2C_6H_3CH_2$	85	1·0	94
3-$CH_3OC_6H_4CH_2$	85	0·5	98
3-$CNC_6H_4CH_2$	85	1·0	88
4-$CNC_6H_4CH_2$	85	1·0	89
4-$CH_3C_6H_4CH_2$	85	0·16	95
1-$C_{10}H_7CH_2$	85	0·25	80

[a] Isolated material.

[b] Owing to the known thermal instability of liquid nitrate esters,[15,21] it was necessary to estimate the purity of liquid products by IR and NMR spectroscopy.

[c] Refers to formation of the diester.

[d] Low yield due to product volatility.

The synthetic utility of mercury-assisted halogen-nitrate metathesis has not previously been investigated. The kinetics of the reactions of alkyl halides with mercury(II) nitrate in aqueous dioxane have been investigated by both Oae[29,30] and Hammett,[31] in the latter study it was found that benzyl alcohol and benzyl nitrate (*ca* 15:85) were the major products formed when benzyl chloride was treated with mercury(II) nitrate in 60% aqueous dioxane, and that inclusion of either nitric acid or alkali nitrates in the reaction mixture had little effect on the product distribution. Reinvestigation of these reactions has now shown that alcohol formation can be suppressed simply by employing mercury(I) nitrate as reagent and 1,2-dimethoxyethane as solvent. Thus, a series of preliminary experiments was carried out with n-nonyl chloride, bromide and iodide as substrates, mercury(I) and mercury(II) nitrates as reagents, and 1,2-dimethoxyethane as solvent, and the results are summarised in Table 1. These not only confirmed the expected order of reactivity of the alkyl halides, but indicated that treatment of alkyl bromides—which are both more stable and more readily accessible than the corresponding iodides—with mercury(I) nitrate in 1,2-dimethoxyethane could constitute a general synthesis of alkyl nitrates. This was found to be the case, and experimental data for the preparation of a wide variety of alkyl nitrate esters are summarised in Table 2.

From the data in Table 2 it is evident that the mercury(I) nitrate procedure is of considerable synthetic utility in the conversion of primary aliphatic, allylic and benzylic bromides into the corresponding nitrate esters, and in almost all the cases listed represents the method of choice. Results obtained with secondary bromides were generally satisfactory, and only in the case of cyclohexyl bromide was a poor yield (< 50%) of the nitrate ester obtained; formation of cyclohexene was the major reaction pathway. The only simple tertiary bromide which was examined in detail was 1-bromoadamantane: reaction in this case was slow and led to an approximately 1:1 mixture of alcohol and nitrate ester.

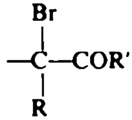
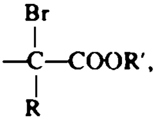
In addition to cyclohexyl bromide and 1-bromoadamantane the only significant limitation with respect to bromide substrate was found with

Table 1. Reactions of n-nonyl halides with mercury(I)/(II) nitrate

	$Hg_2(NO_3)_2$[a,b]	$Hg(NO_3)_2$[a,b]
n-$C_9H_{19}Cl$	99% recovery of unchanged starting material after 3 h/85°	*ca* 90% nitrate ester, with *ca* 5% n-$C_9H_{19}OH$ and n-$C_8H_{17}CHO$ after 21 h/85°
n-$C_9H_{19}Br$	99% n-$C_9H_{19}ONO_2$ after 3 h/85°, or 6 h/20°	99% n-$C_9H_{19}ONO_2$ after 2 h/20° if excess water removed from reagent before addition to reaction mixture; otherwise 5–15% n-$C_9H_{19}OH$ formed
n-$C_9H_{19}I$	90% n-$C_9H_{19}ONO_2$ after 2 h/20°	*ca* 90% n-$C_9H_{19}ONO_2$, with *ca* 10% n-$C_9H_{19}OH$, after 1 h/20°

[a] Composition of mixtures estimated by NMR and IR analysis of the crude material, owing to the thermal instability of liquid nitrate esters.[11,21]

[b] All percentages calculated on total isolated material.

α-bromo carbonyl compounds of the type $ArCOCH_2Br$ and $BrCH_2COOR$. In agreement with Hammett's kinetic results,[31] the reactions of halides of these types with mercury(I) nitrate were too slow to be of preparative use. Only traces of nitrate esters were detectable after reaction for several hours at 85°, while use of mercury(II) nitrate led to production of complex mixtures of products which were not examined in detail. On the other hand, compounds of the types  $-\overset{\overset{\displaystyle Br}{|}}{\underset{\underset{\displaystyle R}{|}}{C}}-COR'$ and  $-\overset{\overset{\displaystyle Br}{|}}{\underset{\underset{\displaystyle R}{|}}{C}}-COOR'$, in which the incipient positive charge on the carbon atom α to the carbonyl group is stabilised by an alkyl or aryl group R, reacted smoothly under the standard reaction condition to give the corresponding nitrate esters in high yield.

Preparation of acetate esters (Eq 3). A variety of experimental procedures is available for the preparation of esters from carboxylic acids and alkyl halides. Most of the common methods involve S_N2-type substitution of halogen by a carboxylate anion; consequently, these processes give good yields of esters only when relatively reactive alkyl halides are employed, e.g. allylic and benzylic bromides or primary iodides. Otherwise, competitive elimination of hydrogen halide can often be a troublesome side-reaction.

Very little research appears to have been carried out into the use of metal-assisted solvolysis for the synthesis of carboxylate esters. Treatment of *vic*-dihalides or bromohydrin acetates with silver acetate in acetic acid has been reported to give the corresponding diol mono- and/or di-acetates in good yield,[32] while reaction of *gem*-dihalocyclopropanes under the same conditions leads to 2-halo-3-acetoxy-1-propenes.[33,34] Both racemisation and acetolysis of *exo*-norbornyl chloride in acetic acid have been shown to take place much more rapidly in the presence of mercury(II) acetate than in the presence of mercury(II) chloride,[3] and the former salt has been used under similar conditions to facilitate the acetolysis of glycosyl halides.[35,36]

In the present study we have found that the rate of acetolysis of alkyl halides is markedly enhanced by mercury(II) acetate. The expected order of reactivity of alkyl halides with respect to halogen was confirmed in preliminary experiments. Treatment of n-nonyl chloride with mercury(II) acetate in acetic acid at 118° gave 16% of the corresponding acetate ester after reaction for 3 h. Under similar conditions n-nonyl bromide was converted into the acetate (97%) in one hour, while n-nonyl iodide reacted smoothly at 20° to give 96% of n-nonyl acetate in 2 h. The reactions of a variety of alkyl bromides with mercury(II) acetate in acetic acid at 118° were then examined, and details of the conversions are summarised in Table 3. Certain limitations were observed during this study, namely: (i) complex mixtures of difficultly separable products were obtained from tertiary bromides and cyclohexyl bromide; (ii) mixtures of products were also obtained from substrates incorporating a cyano group due to simultaneous hydrolysis of the CN function, e.g. 4-bromobutyronitrile gave only 32% of 4-acetoxybutyronitrile; and (iii) acetolysis is considerably slower than oxymercuration and certain mercuration reactions, and hence substrates containing either olefinic bonds or highly activated aromatic rings gave only the corresponding organomercurials under the standard reaction conditions.

In summary, the present procedure for the synthesis of acetate esters is somewhat less general with respect to halide substrate than halide-acetate displacement reactions carried out in dipolar, aprotic solvents. It does, however, represent a useful method for the preparation of many acetate esters; one particularly important feature is that, as the reaction is carried out under acidic conditions, losses due to dehydrohalogenation—a problem frequently encountered in unassisted S_N displacement reactions—are virtually completely eliminated.

Preparation of alcohols (Eq 4). Most of the commonly used methods for the preparation of alkyl halides utilise the corresponding alcohols as starting materials and hence the reverse reaction, viz. conversion of an alkyl halide into an alcohol, has seldom been used synthetically except in special cases such as the Woodward–Prévost reaction[37] or the hydrolytic ring expansion of gem-dihalocyclopropanebicyclo[n.1.0] systems.[33,34] There are now, however, a number of general procedures available for the synthesis of alkyl halides which do not necessitate use of the corresponding alcohols as precursors, and hence a simple technique for the direct conversion of halides into alcohols could be of considerable synthetic utility. This transformation has been accomplished both by simple alkaline and silver-mediated hydrolysis, but is normally only successful with simple primary aliphatic halides and halides in which the positively charged intermediates are stabilised either by resonance effects or by anchimeric assistance.[38–41] Moderate to good yields of alcohols are generally obtained in such cases and, as with the conversion of halides into esters, these methods are inefficient only when there is significant competition between E and S_N pathways.[42,43]

No serious studies have been reported on the mercury(II)-assisted hydrolysis of aliphatic halides. Inclusion of mercury(II) bromide has been found to facilitate the hydrolysis of secondary and tertiary alkyl bromides in aqueous acetone at 50°,[44] while benzyl alcohol has been isolated as a by-product from the reaction of benzyl chloride with mer-

Table 3. Conversion of aliphatic bromides into acetates

$RBr \rightarrow ROCOCH_3$

R	Time, h	Yield, %[a]	b.p., °C	Lit. b.p., °C
n-C_9H_{19}	3·0	97	101–2/10 mm	90/5 mm[b]
$(CH_2)_{10}$[c]	3·0	98	m.p. 24–5	m.p. 25·5[d]
$C_6H_5(CH_2)_2$	3·0	94	220–2/760 mm	224/760 mm[e]
$C_6H_5(CH_2)_3$	3·0	92	80–82/0·7 mm	87/1 mm[f]
cyclo-$C_6H_{11}CH_2$	1·5	96	180–3/760 mm	182–7/760[g]
$HOOC(CH_2)_{10}$	1·5	94	m.p. 30–2	m.p. 34[h]
(n-C_4H_9)(C_2H_5)$CHCH_2$	1·5	92	74–6/10 mm	95/25 mm[i]
n-$C_6H_{13}CH(CH_3)$	2·0	99	76–8/10 mm	78–9/10 mm[j]
$C_6H_5CH_2$	0·25	98	90–92/10 mm	215/760 mm[k]
1-$C_{10}H_7CH_2$	0·33	95	162–4/10 mm	175/18 mm[l]
4-$ClC_6H_4CH_2$	0·33	86	118–20/10 mm	120–3/12·5 mm[m]
4-$NO_2C_6H_4CH_2$	0·5	87	m.p. 76–77	m.p. 78[n]
2,4,6-$Br_3C_6H_2CH_2$	0·5	93	m.p. 56·5–57·5	*o*
$C_6H_5CHCH_3$	0·25	98	210–12/760 mm	213–16/760 mm[p]
$(C_6H_5)_2CH$[q]	0·5	88	m.p. 40	m.p. 39–41[r]

[a] Refers to pure, isolated material.
[b] K. Ziegler and H. G. Gellert, *Liebigs Ann.* **567**, 195 (1050).
[c] Refers to formation of the diacetate ester.
[d] R. Scheuble, *Monatsh.* **24**, 630 (1903).
[e] B. Radziszewski, *Ber. Dtsch. Chem. Ges* **9**, 373 (1876).
[f] M. Servigne and E. Szarvasi, US Patent 2,843,607 (1958); *Chem. Abstr.* **52**, 20197 (1958).
[g] V. N. Ipatiev, *Ber. Dtsch. Chem. Ges* **45**, 3217 (1912).
[h] P. Chuit and J. Hausser, *Helv. Chim. Acta* **12**, 463 (1929).
[i] A. J. van Pelt, Jr. and J. P. Wibaut, *Rec. Trav. Chim.* **60**, 55 (1941).
[j] A. Streitwieser, Jr. and A. C. Waiss, *J. Org. Chem.* **27**, 290 (1962).
[k] M. Lecat, *Rec. Trav. Chim.* **46**, 240 (1927).
[l] L. Szperl, *Roczniki Chem.* 291 (1923); *Chem. Abstr.* **18**, 1290 (1924).
[m] L. F. Fieser, R. C. Clapp and W. H. Daudt, *J. Am. Chem. Soc.* **64**, 2052 (1942).
[n] E. E. Ried, *Ibid.* **39**, 124 (1917).
[o] Calcd. for $C_9H_7Br_3O_2$: C, 27·91; H, 1·81. Found: C, 27·80; H, 2·09.
[p] B. Radziszewski, *Ber. Dtsch. Chem. Ges* **7**, 141 (1874).
[q] Reaction carried out at 20°.
[r] J. Herzig and M. Schleiffer, *Liebigs Ann.* **422**, 326 (1921).

cury(II) nitrate in 60% aqueous dioxane.[11] No attempt was made, however, to determine either the optimal conditions for, or the scope and generality of, these hydrolyses.

We have found that the ease and efficiency with which alkyl bromides undergo mercury(II)-assisted hydrolysis depends markedly on the nature of the mercury salt employed. Mercury(II) nitrate is not a suitable reagent; treatment of alkyl bromides with this salt in aqueous acetone solution always resulted in formation of the corresponding nitrate ester (10–60%) in addition to the expected alcohol. Both mercury(II) bromide and mercury(II) oxide/mercury(II) bromide, on the other hand, were completely ineffective in attempted hydrolyses of n-nonyl bromide in aqueous acetone; conversion of the halide into the alcohol was less than 5% complete after 24 h. Consequently, it was evident that development of a suitable procedure necessitated use of a highly electrophilic mercury(II) salt, the anion of which should preferably be of very low nucleophilicity. Only when this latter criterion is satisfied can competition between the anion and the solvent as nucleophiles be minimised or eliminated.

Mercury(II) perchlorate is a reagent which satisfies these criteria admirably. For obvious reasons of safety, no attempt was made either to prepare or use solid mercury(II) perchlorate; instead, standard aqueous solutions of the salt were prepared by dissolving mercury(II) oxide in a mixture of 60% aqueous perchloric acid and 1,2-dimethoxyethane. Addition of an alkyl bromide to the resulting solution and stirring of the mixture at room temperature resulted in rapid and efficient hydrolysis in most of the cases studied; details of representative conversions are given in Table 4.

The scope and limitations of this hydrolysis are similar to those encountered in formation of acetate esters (*vide supra*). Thus, the reactions with cyclopentyl, -hexyl, and -heptyl bromides led to complex mixtures of products, while mercuration of sufficiently reactive aromatics and oxymercuration of olefins were again faster than halogen-hydroxyl metathesis. Finally, the CN group did not survive

Table 4. Conversion of aliphatic bromides into alcohols

$RBr \rightarrow ROH$

R	Temp, °C	Time, h	Yield, %[a]	b.p., °C	Lit. b.p., °C
n-C_8H_{17}	25	3·0	98	192/760 mm	90·2/11·8 mm[b]
(n-C_4H_9)(C_2H_5)$CHCH_2$	25	1·5	94	78–9/10 mm	84–6/15 mm[c]
cyclo-$C_6H_{11}CH_2$	25	1·0	78	78–9/10 mm	83/14 mm[d]
$C_6H_5(CH_2)_2$	85	0·5	98	98–99/10 mm	99–100/10 mm[e]
$C_6H_5(CH_2)_3$	25	4·0	96	127–8/10 mm	105–7/5 mm[f]
$NC(CH_2)_3$	25	3·0	76[g]	84–5/10 mm	89/12 mm[h]
n-$C_6H_{13}CHCH_3$	25	1·0	88	175–7/760 mm	179/760 mm[i]
n-$C_7H_{15}CHCH_3$	25	1·0	91	84–6/10 mm	87·5/10 mm[j]
n-$C_8H_{17}CHCH_3$	85	1·0	79	208–9/760	210–11/760[k]
$C_6H_5CH_2CHCH_3$	25	1·0	60	95/10 mm	92–3/8 mm[l]
$C_6H_5CH_2$	25	0·5	97	203–4/760 mm	205/760 mm[m]
2,6-$Cl_2C_6H_3CH_2$	25	0·5	96	m.p. 96–97	m.p. 97–98·5[n]
2,4,6-$Br_3C_6H_2CH_2$	25	0·5	71	m.p. 130–32	[o]
3-$CH_3C_6H_4CH_2$	25	0·5	89	217/760 mm	215/740 mm[p]
4-$CH_3C_6H_4CH_2$	25	0·5	82	m.p. 58–9	m.p. 59[q]
4-$NO_2C_6H_4CH_2$	25	0·5	92	m.p. 91–2	m.p. 93[r]
4-$ClC_6H_4CH_2$	25	0·5	74	m.p. 69–71	m.p. 73[s]
4-$BrC_6H_4CH_2$	25	0·5	64	m.p. 74–5	m.p. 77[t]
$C_6H_5CHCH_3$	25	0·5	98	88–9/10 mm	93/12 mm[u]
1-adamantyl	25	3·0	92	287	288·5–290[v]
(n-$CH_3CH_2CH_2$)$_2$C($CH_2CH_2C_6H_5$)	25	1·0	60	149–50/6 mm	[w]

[a] Refers to pure, isolated material.

[b] P. E. Verkade and J. Coops, Jr., *Rec. Trav. Chim.* **46**, 903 (1927).

[c] J. von Braun and G. Mantz, *Ber. Dtsch. Chem. Ges* **67B**, 1696 (1934).

[d] E. Venus-Danilowa, *Ibid.* **61**, 1954 (1928).

[e] J. N. Street and H. Adkins, *J. Am. Chem. Soc.* **50**, 162 (1928).

[f] B. Wojcik and H. Adkins, *Ibid.* **55**, 4939 (1933).

[g] Yield refers to isolated γ-butyrolactone.

[h] S. S. G. Sircar, *J. Chem. Soc.* 898 (1928).

[i] M. Lecat, *Rec. Trav. Chim.* **45**, 620 (1929).

[j] C. Mannich, *Ber. Dtsch. Chem. Ges* **35**, 2144 (1902).

[k] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **99**, 45 (1911).

[l] C. Columbic and D. L. Cottle, *J. Am. Chem. Soc.* **61**, 996 (1939).

[m] J. F. Norris and A. A. Ashdown, *Ibid.* **47**, 837 (1925).

[n] R. N. Castle and J. L. Riebsomer, *J. Org. Chem.* **21**, 142 (1956).

[o] Calcd. for $C_7H_5Br_3O$: C, 24·38; H, 1·46. Found: C, 24·04; H, 1·85.

[p] B. Radziszewski and P. Wispek, *Ber. Dtsch. Chem. Ges* **15**, 1743 (1882).

[q] H. D. Law, *J. Chem. Soc.* **91**, 748 (1907).

[r] E. S. Davies and N. H. Hartshorne, *Ibid.* 1830 (1934).

[s] C. Mettler, *Ber. Dtsch. Chem. Ges* **38**, 1750 (1905).

[t] C. L. Jackson and W. Lowery, *Ibid.* **10**, 1209 (1877).

[u] H. Wieland, C. Shopf and W. Hermsen, *Liebigs Ann.* **444**, 40 (1925).

[v] S. Landa, S. Kriebel and E. Knobloch, *Chem. Listy* **48**, 61 (1954); *Chem. Abstr.* **49**, 1598 (1955).

[w] Calcd. for $C_{15}H_{24}O$: C, 81·82; H, 10·91. Found: C, 81·56; H, 10·82%.

the reaction conditions: 4-bromobutyronitrile gave γ-butyro-lactone in 76% yield, but reaction of 7-bromoheptanonitrile under the same conditions resulted in production of an intractable oil in low yield. Within these limitations, however, the present technique constitutes an extremely simple procedure for the conversion of alkyl bromides into alcohols under mild conditions. Again, use of an acidic medium eliminates the complications frequently encountered in base-catalysed dehydrohalogenations in unassisted hydrolyses.

Preparation of ethers (Eq 5). Direct conversion of alkyl halides into ethers is an important synthetic process for which a number of experimental procedures is available. Many excellent procedures can be used for the preparation of alkyl aryl ethers while the Williamson synthesis, which has been extensively investigated and modified since its introduction in the early part of this century, remains the most useful and general procedure for the preparation of structurally simple dialkyl ethers. A wide variety of solvent-base systems has been described and, provided that functional groups located elsewhere in the molecule can survive the strongly basic reaction conditions, good to excellent yields of ethers are normally obtained. Metal-assisted alcoholysis of alkyl halides has also been fairly intensively studied, especially with respect to silver(I) oxide, as in Purdie methylation and glycosidation with glycosyl halides.[40] The oxides and/or hydroxides of barium,[45–48] strontium[48] and thallium[49–52] have been examined as possible alternatives to silver(I) oxide, as have copper(I) oxide[53,54] and copper(I) oxide-isonitrile complexes.[55] In almost all of the

Table 5. Conversion of aliphatic bromides into ethers

$$RBr + R'OH \rightarrow ROR'$$

R	R′	Yield, %[a]	b.p., °C	Lit. b.p., °C
n-C_9H_{19}	CH_3	97	73–5/10 mm	75/10 mm[b]
n-$C_{10}H_{21}$	CH_3	97	90–92/10 mm	100·4–100·5/15·5 mm[c]
$C_6H_5CH_2CH_2$	CH_3	92	190–92/760 mm	190–95/760 mm[d]
n-$C_7H_{15}CHCH_3$	CH_3	86	186–88/760 mm	188–89/760 mm[e]
1-adamantyl	CH_3	90	115–17/10 mm	90–92/5 mm[f]
$C_6H_5CH_2$	CH_3	98	168–69/760 mm	170/760 mm[g]
4-$BrC_6H_4CH_2$	CH_3	90	106–8/760 mm	127/30 mm[h]
4-$NO_2C_6H_4CH_2$	CH_3	93	143–45/15 mm	145/15 mm[i]
2,6-$Cl_2C_6H_3CH_2$	CH_3	94	119–21/11 mm	[j]
2,4,6-$Br_3C_6H_2CH_2$	CH_3	94	m.p. 87–88	[k]
n-C_8H_{17}	CH_3CH_2	95	77–78/10 mm	74/9 mm[l]
n-C_9H_{19}	CH_3CH_2	96	88–91/10 mm	85–90/15 mm[m]
(n-C_4H_9)(C_2H_5)$CHCH_2$	CH_3CH_2	73	76–78/10 mm	53–54/5 mm[n]
$C_6H_5CH_2CH_2$	CH_3CH_2	87	192–94/760 mm	193–95/760 mm[o]
$C_6H_5CH_2$	CH_3CH_2	92	184–86/760 mm	185/760 mm[p]
2,4,6-$Br_3C_6H_2CH_2$	CH_3CH_2	98	m.p. 43·5–44·0	[q]
$C_6H_5CHCH_3$	CH_3CH_2	87	88–90/15 mm	85–90/15 mm[r]
n-C_5H_{11}	$C_6H_5CH_2$	79	110–12/15 mm	116–17/17 mm[s]
$C_6H_5CH_2CH_2$	$C_6H_5CH_2$	97	178–80/10 mm	175–78/13 mm[t]
1-adamantyl	$C_6H_5CH_2$	83	127–28/0·3 mm	123–26/0·25 mm[u]
$C_6H_5CH_2$	$C_6H_5CH_2$	83	164–66/15 mm	170/16 mm[v]
$C_6H_5CHCH_3$	$C_6H_5CH_2$	94	87–89/0·5 mm	87–94/0·5–1·0 mm[w]
$(C_6H_5)_2CH$	$C_6H_5CH_2$	74	m.p. 46–48	m.p. 50·0–50·2[x]

[a] Refers to pure, isolated material.

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[k] Calcd. for $C_8H_7Br_3O$: C, 26·74; H, 1·95. Found: C, 26·48; H, 2·25%.

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cases investigated, however, both yields and selectivities were inferior to those obtained with silver oxide.

As far as we are aware the only applications of mercury(II) salts to the preparation of ethers are in the carbohydrate field. Silver(I) oxide and carbonate are commonly employed in the Koenigs–Knorr synthesis of glycosides,[10] but it has been claimed that mercury(II) oxide in the presence of a trace of mercury(II) bromide is equally effective, less expensive and easier to use in this type of reaction.[6] Mercury(II) acetate[19,35,36,56,57] and cyanide[7,9] have also been employed in glycoside synthesis, but yields are generally lower than with the above techniques, especially in the case of complex glycosides and disaccharides.

Attempts to extend the Koenigs–Knorr synthesis to the preparation of simple ethers were unsuccessful: solutions of 1-bromo-nonane and -decane in methyl and ethyl alcohol were treated with the above mercury salts under standard Koenigs–Knorr conditions, but in each case the starting materials were recovered unchanged. These results are not surprising: mercury(II) bromide, acetate and cyanide are poorly electrophilic, and are useful in the Koenigs–Knorr glycoside synthesis only because of the high reactivity of α-halo ethers. Consequently, it was obvious that, as in the case of halogen-hydroxyl metathesis, a viable ether synthesis could only be effected by use of a highly electrophilic mercury salt, and mercury(II) perchlorate again proved to be the reagent of choice. Solutions of this salt in acidic methyl, ethyl and benzyl alcohol were found to be stable at room temperature, and addition of alkyl bromides to these solutions led to smooth formation of the corresponding ethers in good to excellent yields. Data for representative transformations are summarised in Table 5. As in the other transformations, certain limitations were observed with the method: halides containing olefinic and activated aromatic groups underwent preferential oxymercuration and mercuration respectively; a low yield of a mixture of the nitrile and the corresponding methyl ester was obtained from attempted preparation of 3-cyanobenzyl methyl ether from 3-cyanobenzyl bromide; and reaction of cyclo-pentyl, -hexyl and -heptyl bromides under the standard conditions used for the preparation of benzyl ethers (Experimental) led to complex mixtures of products. However, in contrast to the Williamson and related syntheses, the present method provides a simple and efficient route for the preparation of a wide variety of dialkyl ethers in which, due to the aqueous acidic reaction medium employed, there is no necessity for use of strictly anhydrous reagents and reaction conditions. As with the other conversions described above, there is little, if any, elimination of hydrogen halide during reaction.

EXPERIMENTAL

M.ps were determined on a Kofler hot-stage melting point apparatus, and are uncorrected. Microanalyses were performed by Mr. A. R. Saunders of the University of East Anglia. Where appropriate, identity of compounds was confirmed by comparison of IR spectra, determined by the usual Nujol mull and liquid film techniques on a Perkin-Elmer Model 257 Grating Infrared Spectrophotometer, and NMR spectra, determined as solns in either CCl_4, $CHCl_3$ or $CDCl_3$ on a Perkin-Elmer R12 60 MHz Spectrometer, using TMS as internal standard.

Starting materials. All of the alkyl halides used were either commercially available or were prepared by standard literature procedures.

General procedure for the preparation of nitrate esters. A mixture of 0·01 mole of the aliphatic bromide and 0·01 mole of mercury(I) nitrate (2·80 g; the salt was dried *in vacuo* for 48 h over NaOH pellets prior to use) in 20 ml of dry 1,2-dimethoxyethane was either stirred at room temp, or heated gently under reflux with stirring for 0·16–3 h, until the reaction was complete (TLC, see Table 2). The cooled mixture was filtered, diluted with distilled water, extracted with light petroleum (b.p. 40–60°), and the organic layer washed with distilled water and dried ($MgSO_4$). Evaporation of the solvent gave the crude nitrate ester. Solid samples were purified by crystallization, and the purity of liquid nitrate esters checked by examination of their IR and NMR spectra. For diesters, the same procedure was followed except that 0·02 mole (5·60 g) of mercury(I) nitrate was used.

General procedure for the preparation of aliphatic acetates. A soln of 0·01 mole of the aliphatic bromide and 0·01 mole (3·2 g) of mercury(II) acetate in 20 ml of glacial AcOH was heated under reflux with stirring for 0·25–3·0 h (Table 3). The mixture was cooled to room temp, diluted with distilled water, extracted with either light petroleum (b.p. 40–60°) or diethyl ether, and the organic layer washed with sat $NaHCO_3$ aq, distilled water, and dried ($MgSO_4$). Filtration and evaporation provided the crude acetate, which was purified by distillation or crystallization. For diacetate esters, the same procedure was followed except that 0·02 mole (6·4 g) of mercury(II) acetate was used.

General procedure for the preparation of alcohols. Mercury(II) oxide (2·15 g, 0·01 mole), was added to a mixture of 25 ml of 1,2-dimethoxyethane and 2·5 ml of 60% aqueous perchloric acid, and heated gently (40–60°) on a water bath with occasional swirling until almost all of the mercury(II) oxide had dissolved (10–20 min). The soln was cooled to room temp and 2 ml of distilled water, followed by 0·01 mole of the aliphatic bromide, were added. The reaction mixture was either stirred at room temp, or heated under reflux with stirring for 0·5–4·0 h (Table 4). After being cooled to room temp if necessary, the mixture was diluted with distilled water, extracted with either light petroleum (b.p. 40–60°) or diethyl ether, and the organic layer separated, dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to give the crude alcohol. Distillation or crystallization gave the pure product. In the case of water-soluble products (γ-butyrolactone and α-hydroxyethylbenzene) the same procedure was followed except that the product was isolated from the mixture by continuous extraction with ether for 24 h.

General procedure for the preparation of methyl and ethyl ethers. To a soln of 0·01 mole (2·15 g) of mercury(II) oxide in 3 ml of 60% aqueous perchloric acid, prepared by heating a mixture of the two reagents at 40–60° for 1–5 min, was added 40 ml of MeOH or EtOH, and, if a highly hydrophobic substrate was employed, 5 ml of 1,2-dimethoxyethane.

The appropriate aliphatic bromide (0·01 mole) was then added, and the mixture stirred at room temp for 10–12 h. Subsequent partitioning between light petroleum (b.p. and sat NaCl aq, washing of the organic layer 3 times with distilled water, drying ($MgSO_4$), filtration and evaporation of the solvent provided the crude ether. Distillation or crystallisation gave the pure product.

General procedure for the preparation of benzyl ethers. Treatment of 0·01 mole of the appropriate aliphatic halide with a soln of 0·01 mole (2·15 g) of mercury(II) oxide in 3 ml of 60% aqueous perchloric acid (prepared in the same manner as that employed for the preparation of methyl and ethyl ethers), 10 ml of 1,2-dimethoxyethane, and 25 ml of benzyl alcohol at room temp for 12 h, with subsequent partitioning between 1:10 benzene/light petroleum (b.p. 60–80°) and sat NaCl aq, washing of the organic phase 10–12 times with distilled water to insure removal of excess benzyl alcohol, drying ($MgSO_4$), filtration, and removal of the solvent provided the crude ether. Distillation or crystallization gave the pure product.

Removal of mercury salts from isolated products. In a few instances, adherence to the above procedures did not result in complete removal of mercury salts during product isolation. This difficulty was conveniently overcome either by solution of the isolated product in 20–30 ml of light petroleum (b.p. 40–60°, or, for some higher molecular weight products, b.p. 60–80°), addition of 5–10 g of Gelite, filtration, and evaporation of the solvent, or by interpolation of a wash with 0·1M aqueous EDTA soln prior to isolation of the crude product.

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