Conversion of Alkyl Halides into the Corresponding Alcohols Under Mild Reaction Conditions

Clare L. Ruddick, Philip Hodge, Mark P. Houghton

Chemistry Department, University of Manchester, Manchester M13 9PL, UK
Chemistry Department, University of Lancaster, Bailrigg, Lancaster LA1 4YA, UK

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Reaction of primary, cyclopentyl, allyl and arylmethyl halides, but not an acyclic secondary halide or a tertiary halide, in acetone or tetrahydrofuran with the formate form of a commercial anion-exchange resin gave formate esters in good yields. The formates were hydrolysed efficiently to the corresponding alcohols by a brief treatment with hydrochloric acid. Reaction of primary alkyl bromides or iodides, secondary alkyl bromides, cinnamyl and arylmethyl halides in tetrahydrofuran or 1,4-dioxane with the bicarbonate form of the same anion-exchange resin gave the corresponding alcohols directly in good yields. This latter reaction can be carried out successfully in the presence of ester or amide groups.

It is often necessary in organic synthesis to convert alcohols into alkyl halides, but only occasionally is it necessary to achieve the reverse conversion, i.e. the hydrolysis of alkyl halides. As a consequence relatively few reagents have been developed for this purpose. The more reactive alkyl halides, i.e. tertiary, benzy1 and allyl halides, can be hydrolysed easily by water in various solvents or by aqueous bicarbonate. However, the hydrolysis of primary alkyl halides is more difficult and has usually been achieved using alkali metal hydroxides, though in a few simple cases it has been shown that water in N-methylpyrrolidone or hexamethy1phosphoramide can achieve hydrolysis. Primary bromides and iodides have also been "hydrolysed" using bis(trIBUTY1) oxide in the presence of silver salts.

In connection with our work on the synthesis of cyclic and linear oligoesters, we wished to be able to convert primary alkyl bromide groups smoothly into hydroxyl groups under conditions that would not hydrolyse ester linkages in the same molecules. This has prompted us to look for new methods for the hydrolysis of alkyl halides and in this paper we report two new methods.

The ready availability of strong base anion-exchange resins designed for use in organic solvents has resulted in the study of a wide variety of anionic forms of such resins as polymer-supported (PS) reagents. Such resins generally contain residues I and the reagents can be considered as PS benzyltrimethylammonium salts. In addition to being easy to prepare and convenient to use, since excess and spent reagent can be removed simply by filtering off the beads, they can be used successfully in various organic solvents. Examples of reactions using these PS quaternary ammonium salts are the synthesis of esters by reaction of PS carboxylates Ib with alkyl halides in hexane or diethyl ether, and the use of PS periodate Ie to cleave 1,2-dios in dichloromethane, and to oxidise quinols in chloroform or thioethers in methanol. The present study has involved reagents of this general type, namely PS carbonate Id, PS formate Ie and PS bicarbonate If. The last of these three proved to be very effective for hydrolysing alkyl halides.

The first method we investigated for hydrolysing primary alkyl bromides was to treat them with PS carbonate Id. It has been shown before that PS carbonate Id hydrolyses allyl, benzyl and primary alkyl halides in tetrahydrofuran or benzene at reflux temperature. In the present study we treated methyl 11-bromoundecanoate (2) with PS carbonate Id. The reaction was carried out for 24 h in 1,4-dioxane at 60°C. The desired methyl 11-hydroxyundecanoate was obtained but only in trace amounts (1% yield). The main product (~70% yield) was a mixture of oligoesters. The latter presumably arise by hydrolysis of the ester group in 2 to give a PS carboxylate, then reaction of this with the alkyl bromide residues to generate new ester linkages. Consistent with this it was found that methyl undecanoate reacted with PS carbonate Id under similar conditions to give undecanoic acid (15% yield). Since the PS carbonate Id clearly hydrolyses esters at a significant rate and overall the reactions are complex, this reagent was not further investigated.

\[
\text{Br(CH}_2{\text{CH}}_2\text{CO}_2\text{CH}_3} \quad \text{(2)}
\]

A second method investigated was the conversion of alkyl halides into formates followed by the hydrolysis of these relatively easily hydrolysed esters (Scheme). Although numerous esters have been prepared previously by reaction of alkyl halides with PS carboxylates, these esters do not include formates. PS formate Ie was prepared in two steps. First, the commercially available chloride form 1a of Amberlyst A26 was converted into the bicarbonate form If by treatment of the former with a large excess of aqueous sodium bicarbonate using a column technique. The bicarbonate form If was then neutralised with formic acid to give PS formate Ie. Suspecting that the latter would have only a modest thermal stability its decomposition was investigated by thermogravimetric analysis (TGA). This showed that PS formate Ie decomposes rapidly at temperatures above 100°C. Hence, reactions using this reagent need to be carried out at temperatures significantly lower than this. Of several reaction solvents investigated (THF, acetone, chloroform, toluene), THF and acetone proved to be the most effective.
A range of alkyl halides were, therefore, treated with 3 to 4 molar equivalents of PS formate 1e in either THF or acetone at reflux temperature. The reactions were monitored by GC and in selected cases the products were isolated. Due to the modest reaction temperatures and the modest nucleophilicity of the formate anion, in most cases reaction times of 72 h were necessary to obtain satisfactory yields. The results are summarised in Table 1, entries 1 to 11. It is evident that formates were obtained in satisfactory yields from the primary, cyclopentyl, allyl and arylmethyl halides but not from the acyclic secondary halide or the tertiary halide. The hydrolysis of the formate esters is so easy that in some cases (see entries 1, 8 and 11) they hydrolysed partially under the reaction and "workup" conditions. In selected cases the formates were hydrolysed efficiently by treating the crude reaction products with hydrochloric acid at 20°C for 15 minutes.

\[
\text{R-Ha} \xrightarrow{\text{PS HCO}_2^-} \text{R-OC-H} \xrightarrow{\text{H}^+ / \text{H}_2\text{O}} \text{R-OH}
\]

**Scheme**

One attractive feature of PS reagents is that it is possible to use two PS reagents in the same reaction system without them reacting directly together.\(^{16,17}\) In the present system it was shown (Table 1, entries 12, 13 and 14) that alkyl halides can be converted into alcohols satisfactorily in a one-pot procedure by using together PS formate 1e and Amberlyst 15, a PS sulphonic acid suitable for catalysing formate hydrolysis, in acetone containing 2% of water. As expected, with 1,2-dibromoethane reaction occurred mainly at the primary rather than the secondary position. The mixture of bromohydrins obtained could be useful as both isomers would be expected to react with base to generate the terminal epoxide.

The final method investigated, and the one which proved to be the most satisfactory, for converting alkyl halides into the corresponding alcohols was to treat the halide with PS bicarbonate 1f. This reagent, prepared as described above, was shown by TGA to begin to decompose at ca. 120°C and so reaction temperatures up to ca. 100°C are satisfactory. Tetrahydropyran (bp 88°C) and 1,4-dioxane (bp 101°C) proved to be suitable reaction solvents and various alkyl halides in one or other of these solvents were treated with 2 to 3 molar equivalents of PS bicarbonate 1f at reflux temperature for 3 to 24 h. The results are summarised in Table 2. These show that the primary alkyl bromides and ar iodide, secondary alkyl bromides, cinnamyl and arylmethyl halides all react to give good isolated yields of the corresponding alcohols. It is noteworthy that the secondary alkyl halides reacted reasonably well. The primary alkyl chloride and tertiary alkyl halide reacted but in only poor yield, the former even in the presence of PS iodide 1g as a catalyst.\(^{18}\) The particularly attractive feature of this hydrolysis procedure is that the conversion of the halide group into a hydroxyl group took place without any significant hydrolysis of ester groups (see Table 2, entries 11,13 and 14) or an amide group (Table 2, entry 12) and, in the

**Table 1. Synthesis and Hydrolysis of Various Formates**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction Conditions(^a)</th>
<th>Yield (%)(^b)</th>
<th>From Formate(^c)</th>
<th>One-Pot Procedure(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Solvent</td>
<td>Temp. (°C)</td>
<td>Time (h)</td>
<td>Formate</td>
</tr>
<tr>
<td>1</td>
<td>butyl bromide</td>
<td>acetone</td>
<td>56</td>
<td>72</td>
<td>46(^e)</td>
</tr>
<tr>
<td>2</td>
<td>octyl bromide</td>
<td>THF</td>
<td>65</td>
<td>72</td>
<td>76(^f)</td>
</tr>
<tr>
<td>3</td>
<td>dodecyl bromide</td>
<td>THF</td>
<td>65</td>
<td>72</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>dodecyl bromide</td>
<td>acetone</td>
<td>56</td>
<td>72</td>
<td>100(^g)</td>
</tr>
<tr>
<td>5</td>
<td>2-bromo-octane</td>
<td>THF</td>
<td>65</td>
<td>72</td>
<td>3(^h)</td>
</tr>
<tr>
<td>6</td>
<td>cyclopentyl bromide</td>
<td>THF</td>
<td>65</td>
<td>72</td>
<td>72(^i)</td>
</tr>
<tr>
<td>7</td>
<td>t-butyl chloride</td>
<td>THF</td>
<td>65</td>
<td>72</td>
<td>17(^j)</td>
</tr>
<tr>
<td>8</td>
<td>cinnamyl bromide</td>
<td>acetone</td>
<td>56</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>cinnamyl bromide</td>
<td>THF</td>
<td>65</td>
<td>72</td>
<td>92(^k)</td>
</tr>
<tr>
<td>10</td>
<td>benzyl chloride</td>
<td>acetone</td>
<td>56</td>
<td>72</td>
<td>100(^l)</td>
</tr>
<tr>
<td>11</td>
<td>2-(bromomethyl)naphthalene</td>
<td>acetone</td>
<td>56</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>octyl bromide</td>
<td>acetone</td>
<td>56</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>1,2-dibromo-octane(^b)</td>
<td>acetone</td>
<td>56</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>benzyl bromide</td>
<td>acetone</td>
<td>56</td>
<td>24</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) The alkyl halide in the given solvent was treated with a 3-4 fold excess of PS formate 1e.

\(^b\) Unless indicated otherwise, yields quoted are isolated yields. See Experimental Section for full details.

\(^c\) Yield of alcohol from hydrolysis of formate. Unless indicated otherwise, hydrolysis was carried out by stirring the filtered reaction mixture with 3 M aq HCl at 20°C for 15 min. The yield is the percentage of the formate present that was hydrolysed.

\(^d\) Yield of alcohol from one-pot synthesis. See experimental for full details.

\(^e\) In a similar experiment carried out using THF as the solvent and monitored by GC, the yield of the formate was 84%.

\(^f\) Estimated by GC and/or \(^1\)H NMR spectral analysis.

\(^g\) As c, except that 1M methanolic HCl was used.

\(^h\) Starting material prepared by treating oct-1-ene in CCl\(_4\) with a molar equivalent of Br\(_2\) in CCl\(_4\) for 10 min at 20°C, followed by evaporation of the solvent.

\(^i\) By \(^1\)H NMR spectroscopy the product was a mixture of 1-hydroxy-2-bromo-octane (86%), 1-bromo-2-hydroxy-octane (4%) and octane-1,2-diol (10%).
Table 2. Hydrolysis of Alkyl Halides Using PS Bicarbonate 1f

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Yield of Alcohol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Solvent</td>
<td>Temp. (°C)</td>
</tr>
<tr>
<td>1</td>
<td>undecyl chloride</td>
<td>D</td>
<td>101</td>
</tr>
<tr>
<td>2</td>
<td>undecyl bromide</td>
<td>D</td>
<td>101</td>
</tr>
<tr>
<td>3</td>
<td>undecyl iodide</td>
<td>D</td>
<td>101</td>
</tr>
<tr>
<td>4</td>
<td>2-bromoethylbenzene</td>
<td>THP</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>2-bromooctane</td>
<td>D</td>
<td>101</td>
</tr>
<tr>
<td>6</td>
<td>cyclopentyl bromide</td>
<td>D</td>
<td>101</td>
</tr>
<tr>
<td>7</td>
<td>i-buty1 bromide</td>
<td>acetone</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>cinnamyl bromide</td>
<td>THP</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>p-bromobenzyl bromide</td>
<td>THP</td>
<td>88</td>
</tr>
<tr>
<td>10</td>
<td>2-bromomethylnaphthalene</td>
<td>THP</td>
<td>88</td>
</tr>
<tr>
<td>11</td>
<td>methyl 11-bromoundecanoate</td>
<td>D</td>
<td>101</td>
</tr>
<tr>
<td>12</td>
<td>N-butyl-11-bromoundecanoate</td>
<td>D</td>
<td>101</td>
</tr>
<tr>
<td>13</td>
<td>methyl 4-chloromethylbenzoate</td>
<td>THP</td>
<td>88</td>
</tr>
<tr>
<td>14</td>
<td>methyl undecanoate</td>
<td>D</td>
<td>101</td>
</tr>
</tbody>
</table>

* See Experimental Section for details. D = 1,4-dioxane THP = tetrahydropryan.

^ Unless indicated otherwise yield quoted is of product isolated by distillation or column chromatography.

^ Determined by 1H NMR spectral analysis.

* Products were as starting material but with the halogen replaced by hydroxyl.
* Yield of recovered starting material.

The case of (2-bromoethyl)benzene, without significant elimination of hydrogen bromide.

In summary, three methods have been investigated for converting alkyl halides into alcohols under mild conditions. PS carbonate 1d brings about the hydrolysis of various alkyl halides but it also brings about ester hydrolysis. The two-step procedure of reacting alkyl halides with PS formate 1e followed by hydrolysis of the formate ester (see Scheme) can give good yields of alcohol but the first reaction tends to be sluggish. By using the PS formate 1e and a strong acid cation exchange resin catalyst together both the reaction steps can be carried out successfully in 'one-pot'. The most satisfactory reagent is PS bicarbonate 1f. This converts a wide variety of alkyl halides into alcohols without bringing about any significant elimination or ester or amide hydrolysis.

Unless indicated otherwise the alkyl halides, resins and solvents were purchased from either the Aldrich Chemical Company or Lancaster Synthesis and were used without further purification. Methyl 11-bromoundecanoate, methyl undecanoate, N-buty1-11-bromoundecanoate and methyl 4-chloromethylbenzoate were synthesised by known literature methods. Column chromatography was performed on silica gel 60, 230–400 mesh (Merck). Petroleum ether refers to the fraction bp 60–80 °C. GC analysis was carried out using a Perkin-Elmer model 8300 equipped with a 10% PEG A on Chrom W-AW (80–100 mesh) column, length 2 m, internal diameter 2 mm. The oven temperature was set at 180 °C, the injector port temperature at 230 °C, the detector temperature at 230 °C and the flow rate at 20 mL/min. 1H and 13C NMR spectra were recorded on a Bruker AC 300 spectrometer operating at 300 and 75 MHz, respectively, or a Varian FX 100 for 1H NMR operating at 100 MHz. Chemical shifts (δ) are quoted in ppm relative to TMS. Mass spectra were obtained with a Fisons VG TRIO 2000 spectrometer. IR spectra were recorded for evaporated films on a ATI Mattson Genesis Series FTIR spectrometer. Melting points were determined using an Electrothermal capillary apparatus and are uncorrected. Unless indicated otherwise, drying was achieved using a vacuum oven operating at 60 °C, 0.1 Torr. Elemental analyses were carried out in-house using a Carlo Erba instrument. Where reaction products were well-known compounds, such as butanol and cinnamyl alcohol, they were identified by IR and 1H NMR spectroscopy in comparison with authentic samples.

Amberlyst 15 was washed successively with dill HCl, water, acetone and Et2O, then dried by heating at 105 °C for 6 h.

PS Carbone 1d: Amberlyst A-26 in the chloride form 1a was packed into a column. It was then washed successively with water (2 volumes), sat Na2CO3 solution (10 volumes over 24 h), water until the washings were neutral, acetone (2 volumes) and finally Et2O (2 volumes). The resin was then dried at 40 °C in a vacuum oven for 48 h. By back titration using 2 N HCl, the final resin contained 3.40 mmol of carbonate per g.

Reaction of Methyl 11-Bromoundecanoato (2) with PS Carbone 1d: A mixture of ester 2 (1.9 g), PS carbonate 1d (9.18 g) and 1,4-dioxane (50 mL) was stirred and heated at 60 °C for 24 h. The mixture was then cooled and the resin filtered and washed with CHCl3. Evaporation of the combined filtrate and washings gave an oil (1.01 g, ca. 70% yield) which was shown by 1H NMR spectroscopy and gel permeation chromatography to be a mixture of oligomers 3 with n = 1 to 6, mainly Br(CH2)nCO2(CH2)nCO2Me. The resin was washed with 2 N HCl (20 mL) and the acid was extracted with CHCl3. The extracts were dried and the solvent evaporated. This gave 11-hydroxyundecanoic acid (10 mg, 1%); mp 65–66 °C, identified by IR spectroscopy in comparison with an authentic sample.

PS Bicarbonate 1f: PS bicarbonate 1f was prepared in an analogous way to the PS carbonate 1d as described above, except that NaHCO3 was used in place of Na2CO3. The final resin contained 3.45 mmol of bicarbonate per g.

PS Formate 1e: The bicarbonate form 1f of Amberlyst A-26, prepared as above, was treated with an excess of formic acid in MeOH for 18 h. It was then washed successively with deionised water to neutrality, with acetone, and finally with Et2O, and dried at 40 °C for 48 h. Given the loading of the bicarbonate form, it was calculated that the product contained 3.65 mmol of formate anion per g.
Butyl Formate; Typical Procedure:
A mixture of butyl bromide (530 mg, 386 mmol), the formate form of Amberlyst A-26 resin (1.87 g, 3.65 mmol formate per gram of resin) and acetic anhydride (30 mL) was stirred and heated at reflux temperature for 24 h. The resin was then removed by filtration and washed with acetone. The filtrate and washings were combined and the solvent evaporated to leave the crude product as a clear liquid (224 mg). This was subjected to column chromatography using petroleum ether as the eluant. Initially butyl formate (182 mg, 46%) was eluted; bp 107°C/760 Torr. (Lit.32 bp 105–106°C/760 Torr).

The crude material obtained by reacting methyl 11-bromoundecanoate (1.04 g, 3.72 mmol) with the bicarbonate form of Amberlyst

A-26 IF (3.25 g) in 1,4-dioxane (50 mL) at reflux temperature for 24 h was purified by distillation. This gave the desired compound as a colourless liquid (616 mg, 77%); bp > 200°C/15 Torr. (Lit.37 bp 168–169°C/8 Torr).

1H NMR (CDCl3, 300 MHz): δ = 3.7–3.5 (t + s, 5 H, J = 2.4 Hz, CH3-CH2-CH2OH + CH2-CO2-Me), 2.35 (t, 2 H, J = 2.4 Hz, CH2-CO2-Me), 1.60 (quint, 4 H, J = 2.4 Hz, CH2), 1.30 (s, 12 H, CH3).

MS (CI): m/z = 324 [(M + NH4)+].

IR: ν = 3700–3100 (ν br, OH, 2927) 1740 cm⁻¹ (ester C=O).

N-Butyl-11-hydroxyundecanamide:
The crude material obtained by treating N-butyl-11-bromoundecanoic acid (1.71 g, 5.34 mmol) with the bicarbonate form of Amberlyst A-26 IF (4.50 g) in tetrahydrofuran (50 mL) at reflux temperature for 24 h was recrystallised from Et2O to give the desired compound as colourless cubic crystals (1.09 g, 80%); mp 68–69°C.

1H NMR (CDCl3, 300 MHz): δ = 5.55–5.45 (br s, 1 H, NH), 3.65 (t, 2 H, J = 2 Hz, CH2-CH2OH), 3.25 (q, 2 H, J = 2 Hz, NH2CH2CH2), 2.15 (t, 2 H, J = 2 Hz, NH2CH2), 1.75–1.50 (m, 21 H, CH3), 0.90 (t, 3 H, J = 2 Hz, CH3).


MS (EI): m/z = 258 [(M + H)+].

IR: ν = 3393, 3136, 1639 cm⁻¹.

C13H27O2N 2. calc. C 70.00 H 12.06 N 5.40 found 69.97 12.13 5.43