Regiospecific Synthesis of α-Haloketones using α-Haloalkyllithium Reagents

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Although α-haloketones can be prepared by direct halogenation of the parent ketones\textsuperscript{1}, this method suffers from a lack of regioselectivity in cases where one of the alpha positions is not sterically hindered. Alternative methods of preparation are: (1) condensation of lithium dihalocarbenoids with carbonyl compounds followed by cyclisation of the resultant O-lithiated halohydrins to haloxydrines and isomerisation of the latter to α-haloketones\textsuperscript{2,3} or (2) coupling of dichloromethylolithium with carbonyl compounds, treatment of the resulting haloxydrins with a base, and hydrolysis\textsuperscript{4}.

We considered that the direct coupling of α-monohalocarbenoids with carboxylic acid derivatives should also lead to α-haloketones. Although α-halocyclopropylcarbenoids are well known and used in synthesis\textsuperscript{5}, the non-cyclic monohalocarbenoids have received less attention\textsuperscript{6,7}. We have now optimised the conditions of our method to give a reproducible high-yield synthesis of the reagents 3 and 4 which are unstable above \( -100 \) °C.

\[
\begin{align*}
\text{X} & \quad \text{THF/ether/pentane} & \quad \text{X} \\
1 x = \text{Cl, } R^1 = n - \text{C}_6\text{H}_5 & \quad 3 x = \text{Cl} \\
2 x = \text{Br, } R^1 = n - \text{C}_6\text{H}_5 & \quad 4 x = \text{Br}
\end{align*}
\]

Compounds 1 and 2 are easily prepared by alkylation of bromochloromethylolithium\textsuperscript{8} and dibromomethylolithium\textsuperscript{5}, respectively. Bromine/lithium exchange\textsuperscript{6,7} in 1 or 2 using \( n \)-butyllithium in tetrahydrofuran/ether/pentane at \(-115\) to \(-113\) °C gives the products 3 or 4 in 90% yield together with about 7% of the alkene \( R^1\text{-CH}-\text{CH}_2\text{-R}^1 \) resulting from C–C coupling during formation of the organometallic derivatives.

We have previously described the condensation of dichloro- and dibromomethylolithium\textsuperscript{8} with esters to give good yields of α,α-dichloromethyl ketones. The same reaction with acid chlorides gave tertiary alcohols and their derivatives\textsuperscript{10}. We have now extended these studies to the reactions of 3 and 4 with esters 5 and obtained the α-haloketones 8 regiospecifically in good yields (Table 1). The absence of tertiary alcohol products suggests (as in the case of the reactions of dihalocarbenoids) that the intermediate 6 is stable at low temperature and is converted to the ketone 8 by hydrolysis.
This reaction is directly analogous to that of the reagents 3 and 4 with methyl formate to give \( \alpha \)-haloaldehydes\(^2\), in which case the hemiacetal corresponding to 7 is also stable.

The presence of a bulky \( R^2 \) group (e.g. cyclohexyl) moderates the rate of the coupling reaction and side reactions, e.g. exchange when \( X = Br \) or metallation when \( X = Cl \) of the CHX moiety of the intermediate 6 by the reagent 3 or 4, become predominant. When \( X = Br \), a major by-product is the non-halogenated ketone 9. When \( X = Cl \), use of an increased amount of 3 should improve the yield of the \( \alpha \)-chloroketone 8.

All products obtained were characterised by \(^1\)H- and \(^1\)C-N.M.R. spectroscopy. G.L.C. analysis were performed with a Carlo Erba Fractovap 2150 chromatograph using a 2 m x 6 mm glass column packed with 10% SE 30 on chromosorb W-HMDS, 80-100 mesh. All reactions were carried out under a slight positive pressure of dry nitrogen.

### 3-Bromo-2-heptanone (8a; \( R^1 = n-C_4H_{10}, R^2 = CH_3, X = Br \); Typical Procedure:

1,1-Dibromopentane (2; \( R^1 = C_2H_5, X = Br; 5.75 g, 0.025 mol \)), tetrahydrofuran (60 ml), diethyl ether (40 ml), and pentane (30 ml) are placed in a four-necked flask equipped with a mechanical stirrer, addition funnel, low temperature thermometer, and nitrogen inlet tube. 1.23 Molar \( n \)-butyllithium solution (21.1 ml) in hexane is added dropwise at -115 °C under der stirring during 20 min. The solution becomes pale yellow in colour. Methyl acetate (5; \( R^2 = CH_3; 2.22 g, 0.022 mol \)) diluted with tetrahydrofuran (10 ml) is then added at -115 to -120 °C during 10 min and the temperature is then allowed to reach -100 °C during 30 min. Hydrolysis is performed rapidly by addition of 2 normal sulfuric acid (50 ml). The organic layer is extracted with hexane (3 x 50 ml) and the extract washed with saturated aqueous sodium chloride solution (2 x 50 ml). The organic layer is dried with magnesium sulfate. The solvents are removed and the residue is distilled at reduced pressure: yield 3.1 g (64%); b.p. 87-90 °C/23 torr.

### 1-Bromo-1-chloropentane (1; \( R^1 = n-C_4H_{10}, X = Cl \);

To a mixture of diisopropylamine (62 g, 0.6 mol), tetrahydrofuran (600 ml), pentane (300 ml), and diethyl ether (150 ml) is added 1.49 normal

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### Table. \( \alpha \)-Haloketones 8 (\( R^1 = n-C_4H_{10} \)) prepared

<table>
<thead>
<tr>
<th>Product No.</th>
<th>( R^2 )</th>
<th>X</th>
<th>Yield [%]</th>
<th>b.p. [°C/torr] (n(_{20}))</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>( \delta_{\text{CHX CO}} )</th>
<th>( \delta_{\text{CO}} )</th>
<th>( \delta_{\text{CHX CO}} )</th>
<th>( \delta_{\text{CO}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>CH(_3)</td>
<td>Br</td>
<td>64</td>
<td>87-90/23 (1.4590)</td>
<td>( \text{C}<em>8\text{H}</em>{10}\text{Br} )</td>
<td>123.1</td>
<td>4.10</td>
<td>201.2</td>
<td>54.4</td>
<td></td>
</tr>
<tr>
<td>8b</td>
<td>CH(_3)</td>
<td>Br</td>
<td>60</td>
<td>97/18 (1.4559)</td>
<td>( \text{C}<em>8\text{H}</em>{10}\text{BrO} )</td>
<td>142.1</td>
<td>4.15</td>
<td>204.6</td>
<td>53.3</td>
<td></td>
</tr>
<tr>
<td>8c</td>
<td>i-C(_3H_7)</td>
<td>Br</td>
<td>32(^b)</td>
<td>103/20 (1.4580)</td>
<td>( \text{C}<em>8\text{H}</em>{11}\text{Br} )</td>
<td>158.1</td>
<td>4.25</td>
<td>199.5</td>
<td>51.6</td>
<td></td>
</tr>
<tr>
<td>8d</td>
<td>(CH(_2))(_2)-Cl</td>
<td>Br</td>
<td>70</td>
<td>96/0.7 (1.4807)</td>
<td>( \text{C}<em>8\text{H}</em>{10}\text{BrCl} )</td>
<td>183.7</td>
<td>4.15</td>
<td>201.9</td>
<td>52.3</td>
<td></td>
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<tr>
<td>8e</td>
<td>CH(_3)</td>
<td>Br</td>
<td>80</td>
<td>98/0.3 (1.5380)</td>
<td>( \text{C}<em>8\text{H}</em>{10}\text{BrO} )</td>
<td>154.1</td>
<td>5.0</td>
<td>192.5</td>
<td>47.3</td>
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<td>8f</td>
<td>2-furanyl</td>
<td>Br</td>
<td>78</td>
<td>90/0.2 (1.5301)</td>
<td>( \text{C}<em>8\text{H}</em>{10}\text{BrO} )</td>
<td>154.1</td>
<td>4.85</td>
<td>193.9</td>
<td>47.8</td>
<td></td>
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<td>8g</td>
<td>CH(_3)</td>
<td>Cl</td>
<td>62</td>
<td>69/18 (1.4368)</td>
<td>( \text{C}<em>8\text{H}</em>{10}\text{ClO} )</td>
<td>154.1</td>
<td>4.03</td>
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<td>8h</td>
<td>CH(_3)</td>
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<td>67</td>
<td>78/13 (1.4404)</td>
<td>( \text{C}<em>8\text{H}</em>{10}\text{ClO} )</td>
<td>154.1</td>
<td>4.1</td>
<td>205.8</td>
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<tr>
<td>8i</td>
<td>i-C(_3H_7)</td>
<td>Cl</td>
<td>44</td>
<td>89/14 (1.4396)</td>
<td>( \text{C}<em>8\text{H}</em>{11}\text{ClO} )</td>
<td>176.7</td>
<td>4.15</td>
<td>199.5</td>
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<td>8j</td>
<td>i-C(_3H_7)</td>
<td>Cl</td>
<td>trace</td>
<td>105/15 (1.4635)</td>
<td>( \text{C}<em>8\text{H}</em>{11}\text{ClO} )</td>
<td>176.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td>8k</td>
<td>(CH(_2))(_2)-Cl</td>
<td>Cl</td>
<td>66</td>
<td>77/0.3 (1.4653)</td>
<td>( \text{C}<em>8\text{H}</em>{10}\text{ClO} )</td>
<td>181.1</td>
<td>4.2</td>
<td>203.9</td>
<td>63.7</td>
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<td>8l</td>
<td>CH(_3)</td>
<td>Cl</td>
<td>75</td>
<td>104/0.5 (1.5224)</td>
<td>( \text{C}<em>8\text{H}</em>{10}\text{ClO} )</td>
<td>168.1</td>
<td>4.9</td>
<td>193.5</td>
<td>57.8</td>
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<tr>
<td>8m</td>
<td>2-furanyl</td>
<td>Cl</td>
<td>82</td>
<td>89/90/0.3 (1.5062)</td>
<td>( \text{C}<em>8\text{H}</em>{10}\text{ClO} )</td>
<td>168.1</td>
<td>4.85</td>
<td>192.5</td>
<td>58.4</td>
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</tbody>
</table>

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\(^a\) Satisfactory microanalyse obtained: C ± 0.42, H ± 0.30, Br ± 0.31, Cl ± 0.38.

\(^b\) Formation of \( n-C_4H_{10} - ClBr \) detected by G.L.C.

\(^c\) The corresponding \( \alpha \)-bromoketone is not formed.
solution of n-butyllithium in ether (370 ml, 0.55 mol) at −30 °C. The mixture is cooled to −90 °C, bromochlormethane (104 g, 0.8 mol) is added dropwise during 10 min, and stirring is continued for 1.5 h at <−88 °C. 1-Iodobutane (73.6 g, 0.40 mol) in diethyl ether (40 ml) is then added at −100 °C, followed by addition of a mixture of hexamethylene phosphoric triamide (80 ml, 0.5 mol) and tetrahydrofuran (80 ml) with subsequent stirring at −100 °C for 2 h. The temperature of the mixture is then allowed to increase to −60 °C during 2 h. The mixture is hydrolysed by addition of 2 normal sulfuric acid (500 ml) and then extracted with technical grade hexane (3 × 150 ml). The extracts are washed with saturated sodium chloride solution (100 ml), saturated sodium thiosulfate solution (100 ml), and saturated sodium chloride solution (2 × 100 ml). The organic layer is dried with magnesium sulfate, solvents are removed under reduced pressure and the residual oil is distilled; yield: 65 g (87%); b.p. 88 °C/70 torr; nD20: 1.4060.

2-Chloro-1-phenyl-1-hexanone (8; R1 = n-C6H13, R2 = C6H5, X = Cl): 1-Bromo-1-chloropentane (1; 4.6 g, 0.025 mol) is diluted with tetrahydrofuran (60 ml), diethyl ether (40 ml), and pentane (30 ml). To this solution, cooled at −130 °C, is added dropwise a hexane solution of n-butyllithium (0.025 mol) below −115 °C. After the addition, agitation of the mixture is continued for 15 min at −115°C and then methyl benzate (5; R1 = C6H13; 3.0 g, 0.022 mol) in diethyl ether (20 ml) is added at −120 °C. After 15 min, the temperature of the mixture is allowed to reach −100 °C during 1 h. Hydrolysis is achieved by addition of 2 normal sulfuric acid (50 ml). Extraction with technical grade hexane (3 × 50 ml), washing of the extract with saturated sodium chloride solution (2 × 50 ml), and drying with magnesium sulfate are followed by evaporation of the solvents at reduced pressure. Distillation of the oily residue gives the product 8; yield 2.88 g (75%); 104 °C/0.5 torr; nD20: 1.5224.

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