**Synthesis** 2003, No. 14, pp 2173–2178

Advanced online publication: 24.09.2003


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An Efficient Route to Aliphatic 2,2-Dichloroaldehydes via Chlorination of Aldehydes or Alcohols with the System Cl₂/Quaternary Ammonium Chloride

Franco Bellesia, a) Laurent De Buyck, b) Franco Ghelfi, a) Ugo M. Pagnoni, a) Andrew F. Parsons, c) Adriano Pinetti a)

a) Dipartimento di Chimica, Università degli Studi di Modena e Reggio Emilia, via Campi 183, 41100 Modena, Italy
Fax +39(59)373543; E-mail: ghelfi.franco@unimo.it.
b) Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, 9000 Gent, Belgium
c) Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

Received 30 April 2003; revised 4 July 2003

An efficient and low waste method for preparing aliphatic 2,2-dichloroaldehydes has been achieved by halogenation of aldehydes or alcohols with Cl₂ using tetraalkylammonium chlorides as recoverable catalysts.

**Key words:** alcohols, aldehydes, halogen, halogenation, halide

Chlorine and chloro compounds are exceptionally important tools in the chemical industry, being essential for the production of a large number of substances necessary to modern life. The formation of chlorinated compounds can, however, offer some environmental risks and the development of more benign methods of chlorination is an important synthetic goal. This goal can be achieved through the design of processes that make efficient use of resources thereby minimising waste.

The preparation of aliphatic 2,2-dichloroaldehydes, which are an emerging and promising class of synthetically useful bifunctional substrates, appears as an interesting candidate. The significance of these compounds in synthetic organic chemistry is highlighted by their easy transformation into α-ketoaldehydes, α-αketoacetals, aziridines, ethyldienazonium salts, furan derivatives, (E)-α,β-unsaturated ketones, pyridine derivatives, 1,4,5,8-tetraazacyclonane, 2,5-disubstituted imidazoles, 2-chloro enolates, 2-chloro enamides, propargyl alcohols and Wynberg β-lactones. In addition, the oxidation of 2,2-dichloroaldehydes with Cl₂/2-picoline-HCl/KMnO₄, K₂Cr₂O₇, H₂O₂/NaHCO₃ or HNO₃ the versatile 2,2-dichloroalicyclic acids are afforded in high yields: noteworthy is the pivotal role of these compounds in the synthesis of 2-pyrrolidonones, 3-pyrroline-2-ones and chaetomellic A acid.

The aliphatic 2,2-dichloroaldehydes are currently obtained by α-perhalogenation of alkanals with Cl₂–DMF–HCl, Cl₂/piperidine–2-picoline–HCl, or Cl₂/6-lutidine–HCl. Although reliable, these methods are however, afflicted by one or more of the following disadvantages: i) high fraction of catalyst (which acts as the chloride-carrier) is required, ii) the catalyst is not recovered, iii) lengthy and expensive processes are required for recovering and recycling the catalyst, iv) an aqueous work up is employed which decreases product specifications due to contamination with the hydrate form of the aldehyde, and v) large amounts of aqueous and/or organic liquid waste is produced. In this paper we report a much cleaner approach to the α-perchlorination of aldehydes, which circumvents the previously listed limitations, by using chlorine and a small amount of a quaternary ammonium chloride, as an easily recoverable catalyst.

The α-dichlorination of aldehydes needs two successive enolization steps and for a successful transformation the reaction has to be performed under acid-catalysis. In fact, in an alkaline medium, the halogenation would result in oxidation and aldol condensation. After the introduction of the first Cl-function, acid-catalysis, owing to the strongly reduced basicity of the carbonyl group, is unable to promote a sufficiently rapid second chlorination step and, as a consequence, side reactions can predominate. To maintain a high level of selectivity, the intervention of an appropriate base is required to speed up the completion of the reaction (Scheme 1).

![Scheme 1](image-url)

Dick, who studied the perchlorination of propanal with Cl₂ under acid-catalysis, noticed that H⁺ alone was not able to ensure an acceptable selectivity and that chloride anions were beneficial for the transformation. The importance of this observation was fully realized by one of us: namely that base-catalysis by Cl⁻ ion is an indispensable requisite for a rapid second chlorination step. Indeed, the common feature of the existing and reliable chlorination methods is an allowance of an adequate concentration of Cl⁻ ions in the reaction environment.
It is well known that the small, symmetrical and densely charged Cl$^-$ ion is a relatively strong Bronsted base in aprotic solvents. For example the pK$_a$ of HCl rises from ~8 in water to 1.8 in DMSO. However, anions cannot deprotonate very weak acids when the acid-base equilibrium is particularly adverse, unless an irreversible reaction can push the equilibrium in this direction. This can be observed on α-dichlorination of aldehydes, as the chloride anion can increase the rate of formation of the enolic form. As soon as the enol is formed, it is promptly and irreversibly trapped by reaction with chlorine.

To sharply decrease the amount of chloride carrier necessary for an effective aldehyde α-perchlorination (e.g. 2,6-lutidine-HCl was used at concentration of 15–30 mol%) a relatively stronger base is required, but the Cl$^-$ anion is particularly well suited for this task as it is cheap and is continuously regenerated in the reaction (Scheme 2).

Scheme 2

Since all of the reported chloride carriers are hydrohalides, they can undergo H-bonding between the Cl$^-$ anion and its counter-ion, and this can partially screen the negative charge of the anion. Following this argument, we speculated that the catalysis could be performed more effectively by quaternary ammonium chlorides. These salts, carrying a naked anion, should be more active in α-dichlorination than hydrohalides. Indeed, the beneficial effect of using quaternary ammonium chlorides rather than hydrochlorides has been reported in the literature for the alkylation of aromatic amines and for some aromatic nucleophilic substitution reactions.

Accordingly we evaluated a series of chloride carriers, CsCl, 2,6-lutidine-HCl (2,6-LHC), triethylamine-HCl (TEAHCl), tetramethylammonium chloride (TMAC), benzyltrimethylammonium chloride (BTMAC), and benzyltrimethylammonium chloride (BTEAC), in the α-chlorination of pentanal (1a). The aldehyde was added to a saturated solution of Cl$_2$ in CH$_2$Cl$_2$, containing the halide at 0 °C and after 2 hours the reaction mixture was analysed by gas-chromatography to check the amount of 2-chloropentanal (2a) and 2,2-dichloropentanal (3a). The results are reported in Table 1.

As predicted, the tetraalkylammonium halides proved to be the most effective chloride carriers. The disappointing results obtained when using CsCl (Table 1, entry 1) can be explained by the fact that this salt is completely insoluble in CH$_2$Cl$_2$ and so cannot affect the reaction course. Evidently the catalyst solubility is a critical parameter and this can also be inferred from the relatively low yield of

Following the promising result using tetraethylammonium chloride, a series of experiments, in which pentanal (1a) and Cl$_2$ were gradually added to a solution of TEAC in CH$_2$Cl$_2$, were then carried out at varying catalyst concentration, reaction temperature and delivery rate of Cl$_2$. The flow of Cl$_2$ was adjusted so as to maintain a slight excess of the halogen in the reaction mixture. To avoid possible side reactions a small stream of O$_2$ (ca 25 mL/min) was also supplied. With the best conditions in hand (Table 2, entry 1), using a remarkably low amount of TEAC catalyst (2 mol%), the method was extended to a number of alkanals. In all cases, excellent results were obtained (Table 2, entries 2–8).

The reaction work up is straightforward as the products were directly recovered by distillation of the crude reaction mixture. It should be noted however, that the distillation flask should not be heated above 120 °C, otherwise Cl$^-$ anions could induce a troublesome dehydrohalogenation of the 2,2-dichloroaldehydes. The catalyst can also be easily recovered from the distillation residue (see experimental section) by extraction with water and evaporation of the aqueous layer. The catalyst can then be reused without any noticeable change in reactivity (Table 2, entries 5 and 6). Although aliphatic ammonium carriers are less robust than pyridinium hydrochlorides, recently proposed by us, the reaction conditions are mild enough to preserve the catalyst integrity. With a view to increasing the scale of the method, the opportunity to use the 2,2-dichloroalkanal products as reaction solvents, appears particularly convenient (Table 2, entry 2).

The preparation of 2,2-dichloroaldehydes by chlorination of alcohols with the Cl$_2$/Cl$^-$ system is an appealing alternative to the chlorination of aldehydes. In comparison to aldehydes, alcohols are usually more widely available and are much less expensive. In addition, they
Table 2  Chlorination of Aldehydes with \( \text{Cl}_2/\text{TEAC} \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>TEAC</th>
<th>Conv.</th>
<th>Product</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>CH(_2)CH(_2)</td>
<td>1a</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>2*</td>
<td>CH(_2)CH(_2)</td>
<td>1a</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>CH(_3)</td>
<td>1b</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>CH(_2)(_2)</td>
<td>1c</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>(CH(_3))(_2)CH</td>
<td>1d</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>6f</td>
<td>(CH(_3))(_2)CH</td>
<td>1d</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>CH(_3)(CH(_2))(_2)</td>
<td>1e</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>PhCH(_3)</td>
<td>1f</td>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>

*Conditions: 1a–f (500 mmol), CH\(_2\)Cl\(_2\) (25 mL), Temp = 50 °C (temperature of the heating fluid); delivery rate of 1a–f = 250 mmol/h.

b GC values.
c Determined on isolated pure product.
d CH\(_2\)Cl\(_2\) was replaced by 15 mL of TEAC.
e The amount of 2a, determined by GC, is given in parentheses.
f Recycled TEAC was used.

Table 3  Chlorination of Alcohols with \( \text{Cl}_2/\text{Cl}^- \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Catalyst</th>
<th>Conv.</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH(_3))(_2)CH</td>
<td>4a</td>
<td>TEAC</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)(CH(_2))(_2)</td>
<td>4b</td>
<td>TEAC</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>CH(_3)(CH(_2))(_2)</td>
<td>4c</td>
<td>TEAC</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>CH(_3)(CH(_2))(_2)</td>
<td>4d</td>
<td>TEAC</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>CH(_3)(CH(_2))(_2)</td>
<td>4d</td>
<td>TBAC</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>CH(_3)(CH(_2))(_2)</td>
<td>4d</td>
<td>TBAB</td>
<td>5</td>
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<tr>
<td>7</td>
<td>CH(_3)(CH(_2))(_2)</td>
<td>4d</td>
<td>TBPC</td>
<td>5</td>
</tr>
<tr>
<td>8f</td>
<td>CH(_3)(CH(_2))(_2)</td>
<td>4d</td>
<td>TBAC</td>
<td>10</td>
</tr>
</tbody>
</table>

*Conditions: 4a–d (125 mmol), CHCl\(_3\) (25 mL), Temp = 70 °C (temperature of the heating fluid); delivery rate of 4a–d = 62.5 mmol/h.

b GC values.
c Determined on isolated pure product.
d In all of the experiments, the \(-\) monochloroaldehydes were formed in less than 1%.
e TBAC (tetrabutylammonium chloride); TBAB (tetrabutylammonium bromide); TBPC (tetrabutylphosphonium chloride).
f Reaction on 250 mmol scale, CHCl\(_3\) (50 mL); delivery rate = 125 mmol/h.

have a longer shelf life, being unaffected, as aldehydes are, by oligomerization and autoxidation reactions. Obviously, when alcoholic feedstocks are exploited, a cascade process in two main stages must be accomplished: i) oxidation of the CH\(_2\)OH group to CHO, and ii) \( \alpha \)-perchlorination of the intermediate aldehyde (Scheme 3).

Scheme 3

The oxidation could follow different routes: e.g. by an E2 elimination of an intermediate alkyl hypochlorite 5, or a concerted reaction of the alcohol with \( \text{Cl}_2 \). At present, we are not in a position to indicate the more likely pathway under our experimental conditions.

When using the protocol described previously, the oxidation stage appeared not to be as fast as the chlorination step. As the alcohol can react with aldehydes (e.g. leading to the formation of alkyl alkanoates\(^{36} \)) some adjustments to the original procedure were required. Gratifying results were obtained by increasing the amount of catalyst to 5 mol\%, replacing CH\(_2\)Cl\(_2\) with CHCl\(_3\) (so as to increase the reaction temperature), and reducing the delivery rate of the alcohol from 250 mmol/h to 62.5 mmol/h (Table 3).

A variety of different catalysts were reacted with decanol (4d). Similar yields of products were obtained when a phosphonium chloride (Table 3, entries 5 and 7) replaced an ammonium chloride carrier. Certainly the process productivity with alcoholic feedstocks was considerably less than that with aldehydes, but this gap could be filled by increasing the percentage of catalyst to 10 mol\% (Table 3, entry 8). At this catalyst concentration, the lipophilic tetraethylammonium chloride proved to be more soluble than TEAC. Considering that the slowest step of the transformation is the oxidation of the alcohol, it appears that increasing the concentration of the chloride anion increases the rate of alcohol oxidation, a behaviour that has recently been reported by other authors.\(^{34,35} \)

Since the bromide carriers are less expensive than the chloride analogues, and on considering that the Cl\(_2\) could feed the reaction mixture with the required Cl\(^-\) anions after oxidation of the Br\(^-\) to bromine, we also attempted the oxidation-chlorination of 1-decanol using tetrabutylammonium bromide, as catalyst. The result (Table 3, entry 6), albeit not as good as with the chloride anion salts, was indeed satisfactory. This shows that the bromide carriers can be viewed as acceptable alternative catalysts for promoting the transformation of alcohols into 2,2-dichloroaldehydes.

Mioskowski recently described the \( \alpha \)-perchlorination of octanal using tetrabutylammonium trichloride at \(-78 ^\circ \text{C}.\)\(^{36} \) Therefore, the simultaneous presence of Cl\(_2\) and Cl\(^-\) species in the reaction mixture could conceivably imply the involvement of the polyhalide Cl\(_3^-\). However, the instability of the trichloride anion\(^7\) and the relatively high reaction temperature, 50–70 °C, may oppose this eventuality.

As aliphatic 2,2-dichloroaldehydes are of growing importance in synthetic organic chemistry, the development of

Chlorination of Aldehydes 1a–f; Typical Procedure

The reactor was fitted with an efficient coil condenser (coolant temperature −12 °C/−18 °C) to accomplish the separation of the reaction solvent from the outlet gases (O₂, Cl₂, and HCl). A solution of tetraethylammonium chloride (1.04 g, 12.5 mmol) in CH₂Cl₂ (25 mL) was flushed with O₂, and a small and steady flow of this gas was maintained for the duration of the reaction (ca 25 mL/min). The apparatus was wrapped with a black cloth, the heating fluid (at 70 °C) was maintained for the duration of the reaction mixture. After 15–20 min the flow of chlorine was stopped. After a further 30 min the heating device was switched off, and the mixture was purged with O₂. 2,2-Dichloropentanal (3a) was isolated (72.1 g, 93%) from the crude product by distillation under reduced pressure. The distillation residue (ca 4 mL) was diluted with CH₂Cl₂ (4 mL) and extracted with H₂O (2×2 mL). Then the aq phases were collected and evaporated. Finally, the recovered salt was regenerated by dehydration at 70 °C under vacuum (0.5 mmHg).

2.2-Dichloro-pentanal (3a)

Colorless liquid; bp 38–40 °C/13 mmHg.
IR (film): 747 (C=O) cm⁻¹.
1H NMR (CDCl₃): δ = 1.04 (t, 3 H, J = 7.3 Hz), 1.56–1.88 (2 H, m), 2.16–2.43 (2 H, m), 9.27 (1 H, s).
MS (EI): m/z (%) = 55 (100), 89 (62), 112 (24) (M⁺ – 29).


2.2-Dichloro-propanal (3b)

Colorless liquid; bp 75–82 °C/0.04 mmHg.
IR (film): 1745 (C=O) cm⁻¹.
1H NMR (CDCl₃): δ = 0.93 (t, 3 H, J = 6.4 Hz), 1.21–1.53 (6 H, m), 1.54–1.80 (2 H, m), 2.22–2.38 (2 H, m), 9.27 (1 H, s).
MS (EI): m/z (%) = 95 (100), 100 (46), 112 (33) 131 (25), 167 (4) (M⁺ – 29).


2.2-Dichloro-octanal (3c)

Colorless liquid; bp 88–90 °C/11 mmHg.
IR (film): 1748 (C=O) cm⁻¹.
1H NMR (CDCl₃): δ = 3.66 (2 H, s), 7.40 (5 H, br s), 9.32 (1 H, s).
MS (EI): m/z (%) = 41 (100), 75 (26), 76 (19), 111 (20), 140 (1) (M⁺).


Chlorination of Alcohols 4a–d; Typical Procedure

The reactor was fitted with an efficient coil condenser (coolant temperature −12 °C/−18 °C) to accomplish the separation of the reaction solvent from the outlet gases (O₂, Cl₂, and HCl). A solution of tetraethylammonium chloride (1.04 g, 12.5 mmol) in CHCl₃ (25 mL) was flushed with O₂, and a small and steady flow of this gas was maintained for the duration of the reaction (ca 25 mL/min). The apparatus was wrapped with a black cloth, the heating fluid (at 70 °C) was circulated and the solution sat. with Cl₂. A few minutes later, pentanal (1a) (43.1 g, 500 mmol) was added slowly through a syringe pump (62.5 mmol/h), and the flow of Cl₂ was regulated so that there was always a slight excess of the halogen. On completion of the aldehyde addition (2 h), the Cl₂ stream was reduced, but a small surplus of the halogen was maintained in the reaction mixture. After 15–20 min the flow of Cl₂ was stopped. After a further 30 min the heating device was switched off, and the mixture was purged with O₂. 2,2-Dichloropentanal (3a) was isolated (72.1 g, 93%) from the crude product by distillation under reduced pressure. The distillation residue (ca 4 mL) was diluted with CH₂Cl₂ (4 mL) and extracted with H₂O (2×2 mL). Then the aq phases were collected and evaporated. Finally, the recovered salt was regenerated by dehydration at 70 °C under vacuum (0.5 mmHg).

2.2-Dichloro-pentanal (3a)

Colorless liquid; bp 38–40 °C/13 mmHg.
IR (film): 747 (C=O) cm⁻¹.
1H NMR (CDCl₃): δ = 1.04 (t, 3 H, J = 7.3 Hz), 1.56–1.88 (2 H, m), 2.16–2.43 (2 H, m), 9.27 (1 H, s).
MS (EI): m/z (%) = 55 (100), 89 (62), 112 (24) (M⁺ – 29).


2.2-Dichloro-propanal (3b)

Colorless liquid; bp 75–82 °C/0.04 mmHg.
IR (film): 1745 (C=O) cm⁻¹.
1H NMR (CDCl₃): δ = 3.66 (2 H, s), 7.40 (5 H, br s), 9.32 (1 H, s).
MS (EI): m/z (%) = 41 (100), 75 (26), 76 (19), 111 (20), 140 (1) (M⁺).


Chlorination of Alcohols 4a–d; Typical Procedure

The reactor was fitted with an efficient coil condenser (coolant temperature −12 °C/−18 °C) to accomplish the separation of the reaction solvent from the outlet gases (O₂, Cl₂, and HCl). A solution of tetraethylammonium chloride (1.04 g, 12.5 mmol) in CHCl₃ (25 mL) was flushed with O₂, and a small and steady flow of this gas was maintained for the duration of the reaction (ca 25 mL/min). The apparatus was wrapped with a black cloth, the heating fluid (at 70 °C) was circulated and the solution sat. with Cl₂. A few minutes later, a solution of 1-octanol (4c) (16.3 g, 125 mmol) in CHCl₃ (25 mL) was added through a syringe pump (62.5 mmol/h), and the flow of Cl₂ was regulated so that there was always a slight excess of the halogen. On completion of the alcohol addition (2 h), the stream of Cl₂ was reduced, but a small surplus of the halogen was maintained in the reaction mixture. After 15–20 min the flow of Cl₂ was stopped. After a further 30 min the heating device was switched off, and the mixture was purged with O₂. 2,2-Dichloropentanal (3a) was isolated (72.1 g, 93%) from the crude product by distillation under reduced pressure.

2.2-Dichloro-heptanal (3g)

Colorless liquid; bp 88–90 °C/20 mmHg.
IR (film): 1747 (C=O) cm⁻¹.
1H NMR (CDCl₃): δ = 0.91 (t, 3 H, J = 6.4 Hz), 1.26–1.46 (4 H, m), 1.54–1.72 (2 H, m), 2.22–2.33 (2 H, m), 9.25 (1 H, s).

MS (EI): m/z (%) = 41 (100), 75 (26), 76 (19), 111 (20), 140 (1) (M⁺).


Chlorination of Alcohols 4a–d; Typical Procedure

The reactor was fitted with an efficient coil condenser (coolant temperature −12 °C/−18 °C) to accomplish the separation of the reaction solvent from the outlet gases (O₂, Cl₂, and HCl). A solution of tetraethylammonium chloride (1.04 g, 12.5 mmol) in CHCl₃ (25 mL) was flushed with O₂, and a small and steady flow of this gas was maintained for the duration of the reaction (ca 25 mL/min). The apparatus was wrapped with a black cloth, the heating fluid (at 70 °C) was circulated and the solution sat. with Cl₂. A few minutes later, a solution of 1-octanol (4c) (16.3 g, 125 mmol) in CHCl₃ (25 mL) was added through a syringe pump (62.5 mmol/h), and the flow of Cl₂ was regulated so that there was always a slight excess of the halogen. On completion of the alcohol addition (2 h), the stream of Cl₂ was reduced, but a small surplus of the halogen was maintained in the reaction mixture. After 15–20 min the flow of Cl₂ was stopped. After a further 30 min the heating device was switched off, and the mixture was purged with O₂. 2,2-Dichloropentanal (3a) was isolated (72.1 g, 93%) from the crude product by distillation under reduced pressure.
MS (EI); m/z (%): 81 (100), 86 (62), 89 (41), 91 (39), 112 (51), 117 (60), 153 (3) (M⁺ – 29).

2.2-Dichloro-decanal (3h) 16c
Colorless liquid; bp 61–63 °C/0.03 mmHg.

Acknowledgment
We thank Dr. Fabrizio Roncaglia for the useful suggestions, the Ministero della Università e della Ricerca Scientifica e Tecnologica (MURST) and the Belgian N.F.W.O. and I.W.T. for financial assistance.

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