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2,2-Dichlorination of Aldehydes with the 2,6-Lutidine·HCl/Cl_2/CH_2Cl_2 System: an Environmentally Benign Process Suitable for Scale Up

Franco Bellesia,[a] Laurent De Buyck,[b] Franco Ghelfi,[a,*] Emanuela Libertini,[a] Ugo Maria Pagnoni[a] and Fabrizio Roncaglia[a]

[a]*Dipartimento di Chimica, Università degli Studi di Modena e Reggio Emilia, via Campi 183, 41100 Modena, Italy*
[b]*Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Ghent, Coupure Links 653, B-9000 Ghent, Belgium*

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Abstract—An effective and environmentally benign preparation of 2,2-dichloroaldehydes has been achieved by chlorination of aldehydes with Cl_2(g) in CH_2Cl_2, using 2,6-lutidine hydrochloride as recoverable catalyst. Remarkable qualities of the process are: easy work up, high purity products, HCl as the only 'waste' stream and inherent bias to the scale up.

Introduction

2,2-Dichloroaldehydes are a useful class of starting materials in the field of agrochemicals,[1,2] and the Cl,Cl-acetal carbon near the carbonyl group makes them valuable and very promising dissonant bifunctional substrates in synthetic organic chemistry from several varied standpoints.[3] In fact important synthons, such as α-ketoaldehydes and α-ketoacetals, can be easily prepared starting from 2,2-dichloroalkanals by treatment with alkaline alkoxides;[4] also, interesting molecules such as 2,2-dichloroaldehyde *N*-acyl hemiaminals, 2,2-disulphenylated aldehydes, 2-chloroesters, or chlorinated vinyl phosphates[1] can be attained through nucleophilic attack with primary amides,[5] sodium thiolates,[6] cyanide ion[7] or phosphites.[8]

The versatility and usefulness of 2,2-dichloroaldehydes in organic synthesis has been especially shown by a number of reactions, mainly with C-nucleophiles, to build furan derivatives,[9] (*E*)-α,β-unsaturated ketones,[10] DDT analogues,[1] pyridine derivatives[2] or chiral 4-substituited 2-oxetanones.[11] Furthermore, reactions with metals and C-electrophiles are also reported.[12,13]

The oxidation of 2,2-dichloroaldehydes to 2,2-dichloroalkanoic acids with Cl_2/2-picoline·HCl,[14] $KMnO_4$,[15,16] $K_2Cr_2O_7$[15] or H_2O_2/$NaHCO_3$,[15,16] and their reduction to 2,2-dichloroalkanols with $NaBH_4$[17,18] have recently aroused a special interest in preparative organic chemistry. These compounds are used in a variety of applications; for example, the pivotal role played by the 2,2-dichlorocarboxylic acids in a novel synthetic route to 2-pyrrolidinones.[19]

In spite of this useful reactivity and chemistry, the preparation of 2,2-dichloroaldehydes still suffers from the lack of an efficient, economic and convenient protocol. Procedures for the direct chlorination of aldehydes to produce 2,2-dichloroalkanals have in fact met with only limited success,[20] and indirect approaches exploiting the chlorination of enamines with Cl_2[21,22] or imines with *N*-chlorosuccinimide[23,24] were generally preferred.

Some years ago one of us smoothly achieved dihalogenation of alkanals with the Cl_2/DMF/HCl system,[15,16] and since then, to our knowledge, only two additional protocols for direct dihalogenation have been reported: one uses Cl_2/pyrrolidinecarboxaldehyde/HCl,[25] whereas the other uses tetraethylammonium trichloride.[26] These methods are not suited for large-scale preparation: (i) the catalysts are treated as a waste, (ii) the solvents used are either carginogenic ($CHCl_3$) or difficult to remove (DMF), and (iii) the reaction mixtures are dilute.

As a consequence of the need to minimize the amount of toxic wastes and by-products from chemical processes, and in order to work with more environmentally friendly synthetic protocols, we have recently improved the Cl_2/DMF/HCl method, by replacing DMF/HCl with 2-picoline·HCl, which is a recoverable catalyst.[14] In spite of the

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* Corresponding author. Tel.: +39-059-2055043; fax: +39-059-373543; e-mail: ghelfi.franco@unimo.it

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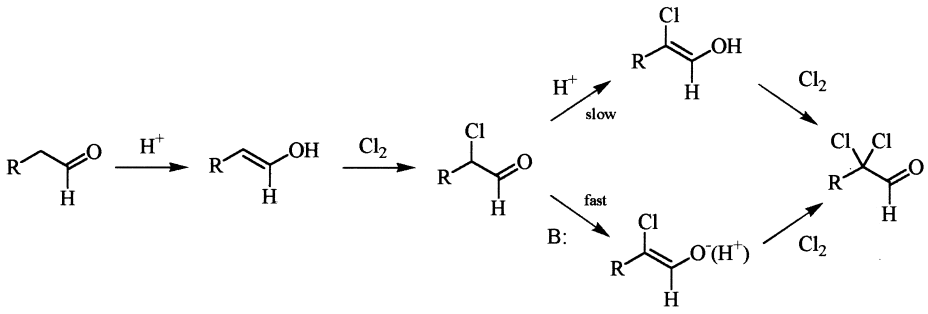


Scheme 1.

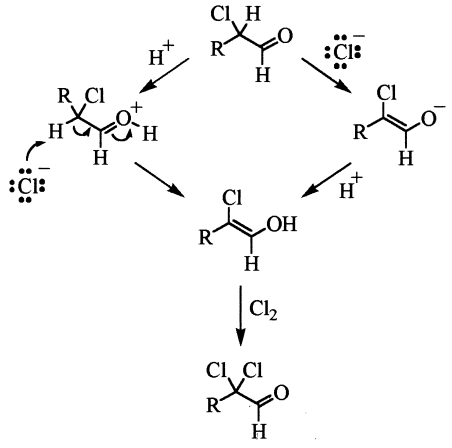
high yield obtained, the process still lacks those features that characterize an ideal plant process[27] and are requisite to the scale up: in fact (i) a harmful solvent like $CHCl_3$ is used, (ii) recycle–regeneration of 2-picoline·HCl is a lengthy and expensive process, (iii) aqueous work up decreases product specifications due to contamination with the hydrate form, and (iv) waste gas vented from the reactor is a dangerous mixture of HCl/Cl_2.

Aiming at a safer and economically and ecologically more sound process for the perchlorination of aldehydes at the C(2) site, we are now in a position to report that the previously listed drawbacks can be overcome by the halogenating system Cl_2/2,6-lutidine·HCl/CH_2Cl_2.

Results and Discussion

The 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.[15] However, the functionalization, under acid catalysis, also suffers a major disadvantage, which is the slowness of the second enolization step (Scheme 1). In fact, the basicity of the carbonyl group is decreased considerably by a 2-halogen substituent, and the applied procedure frequently yields products contaminated with substantial amounts of 2-monochloroaldehydes.

The introduction of the first chlorine substituent in the aldehydes is clearly acid-catalysed, while the second chlorination is base-catalysed or combined-acid-base-catalysed.[28] Combination of an organic nitrogen base and HCl appears to be a particularly suitable catalyst for the enolization of carbonyl compounds and 2,2-dihalogenation,[5,29] as it assures the indispensable base-catalysis, which is required for a rapid second chlorination step; indeed, it is well known that the small, symmetrical and densely charged chloride ion is a strong Brønsted base in aprotic solvents (Scheme 2).[16,30–32]



Scheme 2.

The activity of 2-picoline·HCl rests on three fundamental features: (i) solubility in the reaction medium, (ii) survival of the molecular structure during the chlorination step, and (iii) cooperative action of a proton donor and a proton acceptor. In principle, a wide choice of catalysts of this type may be identified; thus, looking for a catalyst more active and convenient than 2-picoline·HCl, a number of aromatic bases† (2-ethyl-pyridine, 2,6-lutidine, 2,4-lutidine, 3,4-lutidine, 2,4,6-collidine, 2-phenyl-pyridine, 5-ethyl-2-methyl-pyridine, 2,2′-dipyridyl) hydrochlorides (15 mol %) were tested with pentanal (0.25 mol) at 60°C in $CHCl_3$ and 35% HCl (2 ml), using the reactor **A** (Fig. 1).[14] Obviously, only the soluble hydrochlorides turned out to be active, the best result being afforded by 2-picoline·HCl, 2,6-lutidine·HCl (LHC) or 2,4,6-collidine·HCl. 2-Picoline hydrochloride must be melted and used while liquid,

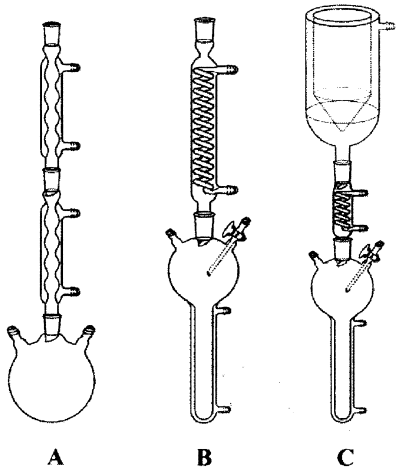


Figure 1.

† Aliphatic tertiary amine hydrochlorides were discarded because they were not resistant enough to the reaction conditions.[14]

Table 1. 2,2-Dichlorination of aldehydes carried out in reactor **B** (0.25 mol of substrate and 25 ml of CH_2Cl_2 were used)

No.	R	Catalyst (%)	35% HCl	T (°C)[a]	Conversion (%)	Yield (%)[b]
1	*n*-Propyl	2,6-Lutidine·HCl (15%)	Yes	65	100	59
2	*n*-Propyl	2,6-Lutidine·HCl (15%)	No	65	100	86
3	*n*-Propyl	2-Picoline·HCl (15%)	No	65	100	91
4[c]	*n*-Propyl	2,6-Lutidine·HCl (15%)	No	70	100	92
5	*i*-Propyl	2,6-Lutidine·HCl (15%)	No	75	100	88
6	Methyl	2,6-Lutidine·HCl (15%)	No	75	100	90
7	Benzyl	2,6-Lutidine·HCl (15%)	No	75	100	90
8	*n*-Hexyl	2,6-Lutidine·HCl (15%)	No	75	100	84

[a] Temperature of the heating fluid.
[b] Determined on isolated material.
[c] 0.50 mol of substrate and 50 ml of CH_2Cl_2 were used.

whereas other hydrochlorides can be more easily handled as solids, because the two methyl groups flanking the aromatic nitrogen strongly decrease their hygroscopicity, and since 2,6-lutidine is cheaper and less toxic than 2,4,6-collidine, the successive optimization steps were performed using its salt. The involvement of a chloride ion in the dihalogenation mechanism was clearly confirmed by the sharp efficiency loss, observed when 2,6-lutidinium tosylate (yield 58%), a poorly basic salt, replaced LHC (yield 80%).

Fluorobenzene, trifluorotoluene, ethyl acetate and CH_2Cl_2, safer solvents than $CHCl_3$, were then tested for LHC solubility and tolerance to reaction conditions. Only dichloromethane,[33] a cheap, easy recyclable, and non-carcinogenic solvent (by NTP and OSHA), largely used in pharmaceutical products synthesis, got through both tests. Unfortunately, the first runs in CH_2Cl_2 were disappointing nor the change to the more functional reactor **B** (Fig. 1) improved appreciably the performances (Table 1, item 1). A breakthrough arrived when we did not add HCl (Table 1, item 2), a modification that proved crucial also for the economy of the process, as the reaction procedure and work up were both simplified. In fact, on diluting the final reaction mixture with *n*-hexane or ether,[‡] LHC (but not the 2-picoline·HCl) salted out and was quantitatively recovered by filtration. The collected material showed no activity decline, and was confidently re-used. As no water enters in the work up step, there is no need for drying salts, nor waste waters are produced and the 2,2-dichloroaldehydes purity increase (absence of the hydrate form). Moreover, solvents can be recovered, isolated by fractional distillation and recycled. It should be noticed that even though 2-picoline·HCl is somewhat more active than LHC (Table 1, items 2 and 3), the difference disappears on a larger scale (Table 1, item 4). The optimized protocol was then applied to other aldehydes, and has worked excellently in all cases (Table 1).

To get the highest yields, substrate feeding needs to be regulated in order to maintain in some excess the steady flow of chlorine. This leads to an excessive chlorine consumption (~2 mol), with negative consequences for the environment and the process economy: the unreacted halogen adds to HCl in the waste gas stream. Taking advantage of the large difference between the boiling points of Cl_2 and HCl (−34°C and −85°C), the two compounds were separated: the halogen was kept inside the reaction chamber by fitting reactor **B** with a cold-finger condenser (Fig. 1, **C**) set at −78°C (acetone/dry ice).

This more efficient chlorine utilization made it possible to employ an almost stoichiometric amount of gas, but immediately we understood how reactor and chemistry inside it are correlated.[34] Indeed, notwithstanding a number of variations of the experimental protocol, trials to produce 2,2-dichloropentanal in **C** were unsatisfactory, since yields never went beyond 79% (Table 2, item 1). When, however, the reaction scale was risen from 0.25 to 0.5 mol, results became excellent (Table 2, items 2–4); also, under identical reaction conditions, equally good results were obtained by all the other aldehydes tested (Table 2). Maybe, operating at the top volume allowed by the reaction chamber, the reactor shape allows a more efficient Cl_2 uptake from the inner atmosphere.

[‡] Less flammable *n*-heptane or *t*-butylmethyl ether are preferable on large scale production.

Table 2. 2,2-Dichlorination of aldehydes carried out in reactor **C** (0.50 mol of substrate and 50 ml of CH_2Cl_2 were used)

No.	R	Catalyst (%)	T (°C)[a]	Conversion (%)	Yield (%)[b]
1[c]	*n*-Ethyl	2,6-Lutidine (15%)	70	100	79
2	*n*-Ethyl	2,6-Lutidine (15%)	50	100	94
3	*n*-Ethyl	2,6-Lutidine (30%)	30	100	97
4	*n*-Ethyl	2,6-Lutidine (15%)	45	100	95
5	*i*-Propyl	2,6-Lutidine (30%)	30	100	91
6	*i*-Propyl	2,6-Lutidine (30%)	45	100	98
7	*i*-Propyl	2,6-Lutidine (15%)	55	100	98
8	Benzyl	2,6-Lutidine (30%)	45	100	95

[a] Temperature of the heating fluid.
[b] Determined on isolated material.
[c] 0.25 mol of substrate and 25 ml of CH_2Cl_2 were used.

Assembly **C** even has a good influence on the reactor (100 ml) output too: since no halogen is vented out, the feeding rate of the educts could be speeded up from 1 to 2 mmol/(cc·h). The chlorine flow can be easily monitored and adjusted looking at its dropping rate from the bottom of the cold-finger condenser. At 35°C, owing to the low initial acidity of the reaction mixture, the halogenation showed for all the substrates tested an induction period, which decreases to zero by increasing the reaction temperature or the catalyst amount (Table 2, items 2–4).

In conclusion, the perchlorination of aldehydes at C(2) with Cl_2/2,6-lutidine·HCl/CH_2Cl_2 here described displays several useful features: high selectivity, considerable productivity, easy recycling of the catalyst and solvent, easy work up, and HCl as the only waste. These characteristics make the process economic and environmentally safe, therefore a good candidate for scale up. Finally, the easy access to 2,2-dichloroaldehydes will certainly give new impetus to the chemistry of this interesting functional group.

Experimental

^{1}H NMR, IR and MS spectra were recorded respectively on Bruker DPX200, Philips PU 9716 and HP 5890 GC–HP 5989A MS Engine. Reagents were standard grade commercial products, purchased from Aldrich or Fluka, and used without further purification. Chlorine (99.99%) was supplied by SIAD. The reactors **A** (flask volume 250 ml), **B** (reaction chamber volume 100 ml) and **C** are sketched in Fig. 1. Chlorinations in **A** were carried out according to the literature.[14]

Preparations of aromatic base hydrochlorides

The catalysts were prepared by adding a 10% excess of 35% aq. HCl to aromatic bases and then drying at the rotavapor.

Typical procedure, reactor B

The apparatus was fitted with an efficient coil condenser (coolant temperature −12°C/−18°C) to accomplish the separation of CH_2Cl_2 from the outlet gases (Cl_2 and HCl). A solution of LHC (3.75×10^{-2} mol) in CH_2Cl_2 (25 ml) was flushed with O_2,[§] maintaining a small and steady flow for the duration of the reaction. Then a controlled flow of Cl_2 (0.6 g/min) was turned on to saturate the mixture, the apparatus wrapped with a black cloth[§] and the heating fluid (Table 1 for temperature setting) put in circulation. A few minutes later, aldehyde (0.25 mol) addition was started through a syringe pump, at such a rate sufficient to maintain some excess of Cl_2 in the reaction chamber. When the addition of aldehyde was completed (2.5 h), the Cl_2 flow was turned off after 10 min and the mixture was further stirred for another 20 min. The heating device was then switched off and the reaction mixture stripped with O_2 to remove residual Cl_2. Finally, dilution with *n*-hexane (50–100 ml) salted out the LHC, which was filtered off. The 2,2-dichloroaldehydes were isolated from the crude by distillation under reduced pressure.

Special case. With 3-phenylpropanal, ethyl ether had to replace *n*-hexane to achieve LHC precipitation.

2,2-Dichloro-pentanal. Colourless liquid, bp 140–143°C. ^{1}H NMR ($CDCl_3$): δ 1.04 (3H, t, J=7.3 Hz), 1.56–1.88 (2H, m), 2.16–2.43 (2H, m), 9.27 (1H, s). IR (film) 1747 (C=O) cm^{-1}. MS (EI, *m*/*z*): 125 (30, M^+-29), 112 (24), 89 (62), 55 (100). Anal. Calcd for $C_5H_8Cl_2O$: C, 38.74; H, 5.20. Found: C, 38.60; H, 5.20.

2,2-Dichloro-3-methyl-butanal. Colourless liquid, bp 137–141°C. ^{1}H NMR ($CDCl_3$): δ 1.68 (6H, d, J=6.6 Hz), 2.60 (1H, hept, J=6.6 Hz), 9.27 (1H, s). IR (film) 1745 (C=O) cm^{-1}. MS (EI, *m*/*z*): 154 (1, M^+), 125 (78), 112 (70), 89 (57), 55 (100). Anal. Calcd for $C_5H_8Cl_2O$: C, 38.74; H, 5.20. Found: C, 38.7; H, 5.1.

2,2-Dichloro-propanal. Colourless liquid, bp 83–85°C. ^{1}H NMR ($CDCl_3$): δ 2.17 (3H, s), 9.27 (1H, s). IR (film) 1746 (C=O) cm^{-1}. MS (EI, *m*/*z*): 126 (6, M^+), 97 (33), 91 (46), 62 (100). Anal. Calcd for $C_3H_4Cl_2O$: C, 28.38; H, 3.18. Found: C, 28.3; H, 3.3.

3-Phenyl-2,2-dichloro-propanal. Colourless liquid, bp 75–82°C/0.05 mmHg. ^{1}H NMR ($CDCl_3$): δ 3.66 (2H, s), 7.40 (5H, bs), 9.32 (1H, s) 1745 (C=O) cm^{-1}. MS (EI, *m*/*z*): 206 (1, M^+), 173 (1), 167 (6), 103 (9), 91 (100). Anal. Calcd for $C_9H_8Cl_2O$: C, 53.23; H, 3.97. Found: C, 53.2; H, 4.0.

2,2-Dichloro-octanal. Colourless liquid, bp 81–86°C/11 mmHg. ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, t, J=6.4 Hz), 1.21–1.53 (6H, m), 1.54–1.80 (2H, m), 2.22–2.38 (2H, m), 9.27 (1H, s). IR (film) 1748 (C=O) cm^{-1}. MS (EI, *m*/*z*): 167 (M^+-29, 4), 131 (25), 112 (33), 100 (46), 95 (100). Anal. Calcd for $C_8H_{14}Cl_2O$: C, 48.75; H, 7.16. Found: C, 48.6; H, 7.1.

2,2-Dichloro-butanal. Colourless liquid, bp 113–116°C. ^{1}H NMR ($CDCl_3$): δ 1.22 (3H, t, J=7.2 Hz), 2.34 (2H, q, J=7.2 Hz), 9.28 (1H, s). IR (film) 1746 (C=O) cm^{-1}. MS (EI, *m*/*z*): 140 (1, M^+), 111 (20), 76 (19), 75 (26), 41 (100). Anal. Calcd for $C_4H_6Cl_2O$: C, 34.07; H, 4.29. Found: C, 34.1; H, 4.2.

Typical procedure, reactor C

When the short coil and cold-finger condensers were cooled respectively to −20 and −78°C, the previously prepared mixture of LHC (7.5×10^{-2} mol) in CH_2Cl_2 (50 ml) was flushed with O_2 (a small and steady flow was maintained for the duration of the reaction) and saturated with Cl_2 until a fast dropping rate of liquid halogen from the cold-finger bottom was observed. The Cl_2 flow was then turned off, the apparatus wrapped with a black cloth and the heating fluid (Table 2 for temperature setting) put in circulation. After five minutes, aldehyde (0.5 mol) addition through a syringe pump was begun and, as soon as the reaction got under way,[‖] the Cl_2 flow was restarted, at a rate sufficient to

[§] To avoid by-products from radical chlorination.

[‖] If the halogenation does not start, the aldehyde addition must be shut off and the temperature increased step by step until reaction clearly begins (evident chlorine uptake).

maintain some excess of Cl_2 in the reaction chamber (evident dropping). The addition of aldehyde was completed in 2.5 h. The same work up procedure reported for reactor **B** was followed.

Special case. With 3-phenylpropanal, ethyl ether had to replace *n*-hexane to achieve LHC precipitation.

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