Amidine-Promoted Addition of Chloroform to Carbonyl Compounds

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Trihalocarbinols are useful intermediates in organic synthesis as they can be readily converted into α-amino, α-hydroxy, and α-thio acids.[1,2] They are usually prepared by base-promoted addition of chloroform to aldehydes/ketones, but to date relatively strong bases have been employed.[3] Potassium *tert*-butoxide in liquid ammonia at −78 °C,[3a] sodium in liquid ammonia,[3b] or powdered potassium hydroxide in various solvents[3c−d,4] are the most commonly used conditions. However, in all these reactions low temperatures were required to minimize the extent of the Cannizzaro reaction, which gave the main side product.[3c] Perhaps the best method to date for preparing trichloromethyl carbinols is due to Wyvratt, who found that when using methanolic KOH in DMF at −5 °C, essentially no Cannizzaro reaction occurred and good yields of the desired carbinols were obtained, although only a limited range of examples was reported.[4] Corey has also reported the decarboxylation of sodium trichloroacetate and subsequent addition to carbonyl compounds as an alternative route to trichloromethyl carbinols that avoids the use of strong base.[5]

In this paper we describe our discovery that the reaction between chloroform and carbonyl compounds can be promoted under milder conditions, in high yields, using less basic catalysts such as cyclic amidines.[6]

After screening a broad range of amines (most of which were ineffective), we discovered that amidines and guanidines were extremely active promoters of the reaction between chloroform and benzaldehyde (Table 1).

Using 1 equiv of DBU or DBN with a slight excess of $CHCl_3$ without solvent provided a quantitative yield of the trichlorocarbinol **3** [entry 1 (optimum condition) and entry 4]. Using a larger excess of chloroform **2** resulted in longer reaction times, but similar yields could be achieved (entry 2). Catalytic amounts of DBU or DBN were much less effective, suggesting that some decomposition/protonation of the amidine had occurred (entries 3, 5). Guanidine **6** was also an effective catalyst for this transformation (entry 6). In none of these cases were there any products derived from the Cannizzaro reaction, even from those employing electron-withdrawing aromatics (these are particularly prone to such side reactions) (Table 2, entries 5,6).

Table 1. Amidine Catalyzed Addition of Chloroform to Benzaldehyde[a]

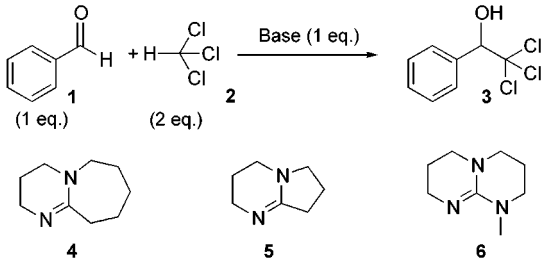
entry	catalyst	equiv	time (h)	yield (%)[c]
1	DBU	1	3	98
2	DBU[b]	1	36	95
3	DBU	0.1	2	12
4	DBN	1	3	98
5	DBN	0.1	24	4
6	guanidine **6**	1	3	98

[a] Reaction performed in absence of solvent using a PhCHO:$CHCl_3$ ratio of 1:2. [b] PhCHO:$CHCl_3$ = 1:10. [c] Isolated yields.

Table 2. DBU-Catalyzed Addition of Chloroform to Carbonyl Compounds[a]

entry	carbonyl compounds	time (h)	yield (%)[b]
1	benzaldehyde	3	98
2	2-chlorobenzaldehyde	4	94
3	2-anisaldehyde	6	95
4	4-anisaldehyde	6	95
5	2-nitrobenzaldehyde	10 min	98
6	4-nitrobenzaldehyde	10 min	98
7	mesitaldehyde	1	25[c]
8	propanaldehyde	2	80
9	isobutyraldehyde	2	80
10	cyclohexanecarboxaldehyde	7	98
11	trimethylacetaldehyde	2	30[c]
12	acetone	24	75[c]
13	cyclohexanone	24	84[c]

[a] Reactions performed in absence of solvent using a carbonyl compound:$CHCl_3$:DBU ratio of 1:2:1. [b] Isolated yields. [c] Remainder is starting material. Longer reaction times did not improve yield.



The reaction was applied to a range of aromatic and aliphatic aldehydes and ketones (Table 2). High yields were obtained using stoichiometric amounts of DBU in all cases except those involving exceptionally hindered carbonyl groups (entries 7, 11). In these cases, and reactions with ketones, a significant amount of the carbonyl compound remained. The high yields with aliphatic aldehydes and ketones bearing enolizable protons are noteworthy (entries 8−10, 12, 13) as the use of chloroform and strong base results in extensive aldol side reactions in such cases.[5] The mild conditions were further exemplified in the reaction of the highly base sensitive substrate *p*-acetoxybenzaldehyde **7**, which certainly cannot be employed using the conventional treatment with strong base. This substrate reacted cleanly to give the intermediate tricarbinol, but this was rapidly acylated by the starting aldehyde to give **8** in 50% yield together

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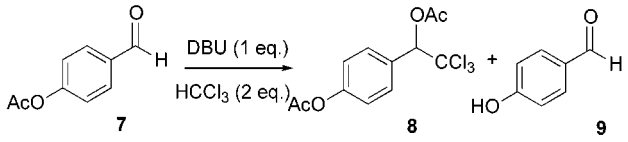
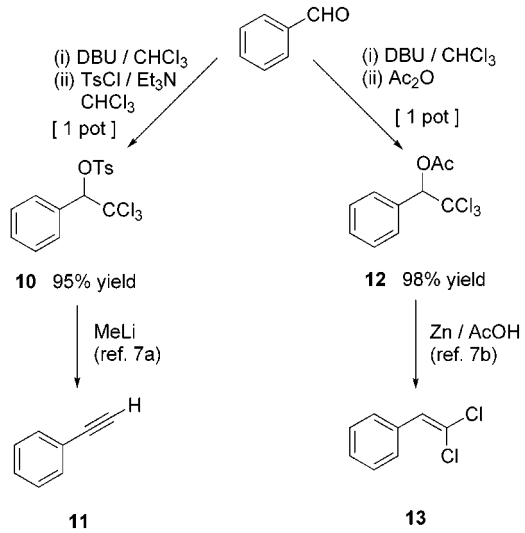
Scheme 1



Scheme 2



with 4-hydroxybenzaldehyde **9** (Scheme 1). None of the intermediate trichlorocarbinol was detected, indicating that an extremely fast in situ acylation occurred.

Trichlorocarbinols have recently been used as intermediates in the synthesis of acetylenes[7a] and vinyl dichlorides,[7b] thus extending their utility. In each case the trichlorocarbinol, which was derived from the corresponding aldehyde, was first converted into the corresponding tosylate or acetate, followed by treatment with MeLi or Zn/AcOH.[7] We have found that the DBU-promoted method for formation of the trichlorocarbinol can also be coupled with tosylation or acylation, leading to a highly efficient one-pot synthesis of intermediates **10** and **12** (Scheme 2). Thus, aldehydes can now be converted into acetylenes and vinyl dichlorides in two steps using mild conditions which, in particular, are amenable to scale-up.

The reaction protocol for formation of the trichlorocarbinols is exceptionally simple: reactions are conducted at ambient temperature and pressure, and in the absence of solvent. Washing with water removes the amidine and gives the product in high yield, which in many cases is pure by ^{1}H/^{13}C NMR. This probably represents the simplest and best method to date to prepare these useful compounds.

Experimental Section

Reagents. DBN and guanidine **6** were used as purchased from Aldrich. DBU, chloroform, and all the aldehydes and ketones were distilled prior to use except for 4-nitrobenzaldehyde, which was used as supplied.

General Procedure, α-(Trichloromethyl)benzyl Alcohol. To a mixture of benzaldehyde (200 μL, 1.97 mmol) and chloroform (310 μL, 3.94 mmol) was added dropwise under nitrogen 1 equiv of DBU (300 μL, 1.97 mmol). The reaction was stirred for 2 h and then diluted with chloroform (20 mL) and washed with 2 N HCl (3 × 10 mL) to remove the catalyst. The organic phase was then dried (Na_2SO_4) and evaporated to yield the trichlorocarbinol (430 mg, 98% yield).

2-Acetoxy-2-(4-acetoxyphenyl)-1,1,1-trichloroethane (8). ^{1}H NMR ($CDCl_3$) 2.21 (3H, s), 2.30 (3H, s), 6.38 (1H, s), 6.90−7.15 (2H, m), 7.59−7.66 (2H, m); ^{13}C NMR 20.8, 21.2, 81.8, 95.1, 101.2, 121.2, 130.5, 130.9, 151.7, 168.6, 169.7; MS *m*/*z* (EI+) 324 [M^+(3 × ^{35}Cl), 25%, Cl_3 isotope pattern], 165 (75), 123 (100) (Found M^+, 323.9711. $C_{12}H_{11}O_4Cl_3$ requires M^+, 323.9722) (Found C, 44.34; H, 3.49. $C_{12}H_{11}O_4Cl_3$ requires C, 44.27; H, 3.41).

1,1,1-(Trichloromethyl)benzene Methanol 4-Methylbenzenesulfonate (10).[7a] To a mixture of benzaldehyde (500 μL, 4.92 mmol) and chloroform (790 μL, 9.84 mmol) was added dropwise under nitrogen 1 equiv of DBU (740 μL, 4.92 mmol). The reaction was stirred for 3 h and cooled to 0 °C, and a solution of *p*-toluenesulfonyl chloride (1.125 g, 5.9 mmol) and triethylamine (680 μL, 4.92 mmol) in chloroform (20 mL) was added dropwise. After 12 h the reaction was diluted with ether (50 mL) and washed with saturated NH_4Cl (3 × 30 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated to give a solid which was purified by chromatography (petrol-60/80:ether = 8:1, R_f = 0.3) to give 1,1,1-(trichloromethyl)benzene methanol 4-methylbenzenesulfonate as a white solid (1.8 g, 95% yield): ^{1}H NMR ($CDCl_3$) 2.38 (3H, s), 5.85 (1H, s), 7.15 (2H, d, J = 8.3 Hz), 7.18−7.32 (3H, m), 7.42 (2H, d, J = 8.3 Hz), 7.60 (2H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) 21.9, 88.8, 99.0, 127.8, 128.4, 128.8, 129.0, 129.3, 1296.

2-Acetoxy-2-phenyl-1,1,1-trichloroethane (12).[7b] To a mixture of benzaldehyde (500 μL, 4.92 mmol) and chloroform (790 μL, 9.84 mmol) was added dropwise under nitrogen 1 equiv of DBU (740 μL, 4.92 mmol). The reaction was stirred for 3 h and cooled to 0 °C and acetic anhydride (490 μL, 5.2 mmol) was added dropwise. After 2 h, the reaction mixture was diluted with ethyl acetate (50 mL) and washed with 2N HCl (3 × 30 mL) and aqueous saturated Na_2CO_3 (3 × 30 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated to give 2-acetoxy-2-phenyl-1,1,1-trichloroethane (1.28 g, 98% yield) pure by NMR: ^{1}H NMR ($CDCl_3$) 2.22 (3H, s), 6.37 (1H, s), 7.3−7.45 (3H, m), 7.50−7.70 (2H, m); ^{13}C NMR ($CDCl_3$) 20.8, 82.7, 99.5, 128.1, 128.3, 129.8, 133.2, 168.6; MS *m*/*z* (EI+) 266 (M^+, 15%), 149 (55), 107 (100) (Found M^+, 265.9657. $C_{10}H_9O_2Cl_3$ requires M^+, 265.9668).

Registry Numbers (provided by the authors). α-(trichloromethyl)benzyl alcohol, 2000−43−3; 2-chloro-α-(trichloromethyl)benzyl alcohol, 10291−39−1; 2-methoxy-α-(trichloromethyl)-benzyl alcohol, 58369−59−8; 4-methoxy-α-(trichloromethyl)benzyl alcohol, 14337−31−6; 2-nitro-α-(trichloromethyl)benzyl alcohol, 62798−94−1; 4-nitro-α-(trichloromethyl)benzyl alcohol, 54075−25−1; 2,4,6-trimethyl-α-(trichloromethyl)benzyl alcohol, 172649−86−4; 1,1,1-trichloro-2-butanol, 6111−61−1; 1,1,1-trichloro-3-methyl-2-butanol, 32766−45−3; 2,2,2-trichloro-1-cyclohexylethanol, 57741−12−5; 1,1,1-trichloro-3,3-dimethyl-2-butanol, 41262−30−0; 1,1,1-trichloro-2-methyl-2-propanol, 57−15−8; 1-(trichloromethyl)-1-cyclohexanol, 3508−84−7; 2-acetoxy-2-(4-acetoxy-phenyl)-1,1,1-trichloro-ethane, 83671−16−3.

Supporting Information Available: Spectral data for all listed compounds including spectra (^{1}H/^{13}C) for compounds **8**, **10,** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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