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Trichloromethyltrimethylsilane, Sodium Formate, and Dimethylformamide: A Mild, Efficient, and General Method for the Preparation of Trimethylsilyl-Protected 2,2,2-Trichloromethylcarbinols from Aldehydes and Ketones

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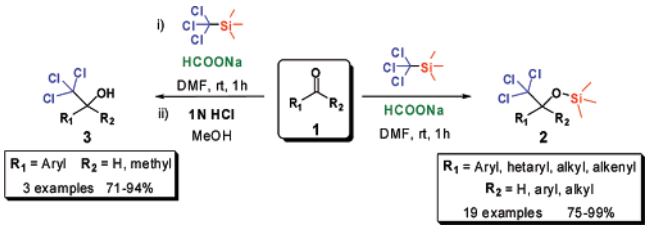

New conditions for the preparation of trimethylsilyl-protected 2,2,2-trichloromethylcarbinols **2** from aldehydes and ketones are reported. Compounds **2**, which are important intermediates in organic synthesis, were obtained in excellent yields by use of a combination of trichloromethyltrimethylsilane ($TMSCCl_3$), and a catalytic amount of sodium formate (HCOONa) in dimethylformamide (DMF). Substrates bearing highly sensitive protecting groups have been successfully subjected to our conditions. We also describe a one-pot procedure that gives direct access to 2,2,2-trichloromethylcarbinols **3**. This methodology avoids the use of strong bases usually required for the synthesis of **3** (Wyvratt et al. *J. Org. Chem*. **1987**, *52*, 944; Aggarwal and Mereu, *J. Org. Chem*. **2000**, *65*, 7211).

Trimethylsilyl-protected 2,2,2-trichloromethylcarbinols **2** are valuable intermediates in organic synthesis and are involved in a variety of transformations.[1] Indeed, they are known precursors of (*Z*)-2-chloroalk-2-en-1-ols,[1a] α-chloroketones, vinyl dichlorides, and terminal alkynes.[1b] Moreover, trimethylsilyl (TMS) deprotection of **2**[2] gives access to 2,2,2-trichloromethylcarbinols **3**, which have been subjected to numerous chemical transformations.[3] Compounds **3** have mainly been used for the formation of α-fluoro acids,[3b] α-hydroxy acids,[3c,d] α-amino acids,[3c,d] epoxides,[3e] vinyl dichlorides,[3f] and terminal alkynes.[3g] Our group reported transformation of 2,2,2-trichloromethylcarbinols **3** into 2-haloalk-2(*Z*)-en-1-ols and 1-chloro-1(*Z*)-alkenes,[3h] and more recently a ring expansion/homologation-aldehyde condensation cascade sequence with cyclic trichloromethylcarbinols.[3i]

Although trifluoromethyl group transfer to carbonyl compounds has been thoroughly studied with trifluoromethyltrimethylsilane ($TMSCF_3$, Ruppert's reagent),[4] only a few methods for the preparation of **2** by mean of a trichloromethyl-providing reagent are reported in the literature.[5] Trichloromethyltrimethylsilane ($TMSCCl_3$),[5b,c,d,g] trimethylsilyl trichloroacetate (Cl_3CCO_2TMS),[5e,f] or a combination of trimethylsilyl chloride (TMSCl) and carbon tetrachloride (CCl_4) have been used successfully.[5a] Base catalysis with various F^- sources [tris(diethylamino)sulfonium difluoromethylsilicate (TASF),[5b,c,f] potassium fluoride (KF),[5f] and tetrabutylammonium fluoride (TBAF)[5g]] or potassium carbonate (K_2CO_3)[5e] are the most efficient and widely used reaction conditions described.

In the course of our studies, a general method for the preparation of **2** under mild conditions compatible with both acid- and base-sensitive substrates was needed. In this respect the reported methods showed some restrictions. Indeed, the diversity and sensitivity of the substrates, aldehydes and ketones, studied in the previous reports are limited. This observation prompted us to investigate new reaction conditions for the formation of **2** using the readily accessible $TMSCCl_3$.[6]

First, acetophenone was used as a model substrate for the screening of various bases as catalyst for the formation of **2** (Table 1). Fluorine-, phosphorus-, and oxygen-based as well as nitrogen-based Lewis bases were explored. All reactions led to the clean formation of **2**, although with variable yields. After workup the crude mixture was composed of product **2** and the starting acetophenone. It turned out that both TBAF and KF led to low conversion in dimethylformamide (DMF) (Table 1, entries 2 and 3). Phosphorus-based catalysts were inefficient (Table 1, entries 4−6). Among the different nitrogen-donor Lewis bases used, TBD was the most efficient (Table 1, entry

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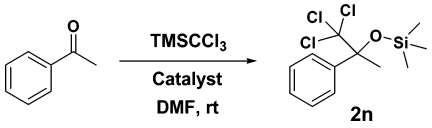
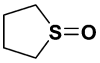
TABLE 1. Catalyst Screening for the Formation of 2n[a]



entry	catalyst	yield[b] (%)
1	none	0
2	TBAF	22
3	KF	29
4	$(Ph)_3P$	11
5	$(Ph)_3P{=}O$	5
6	$(Bu)_3P$	5
7	TBD	36
8	DBU	7[c]
9	$(i\text{-}Pr)_2EtN$	9
10	DMAP	23
11	pyridine *N*-oxide	8
12	DMPU	11
13		17
14	sodium phenolate	65
15	sodium benzoate	70
16	lithium acetate	70
17	sodium acetate	74
18	potassium acetate	61
19	sodium trichloroacetate	44
20	sodium formate	83
21	sodium formate	84[d]
22	potassium formate	80
23	cesium formate	82

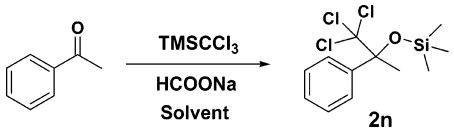
[a] Reaction conditions: acetophenone (0.5 mmol), $TMSCCl_3$ (0.6 mmol, 1.2 equiv), catalyst (0.05 mmol, 10 mol %), and DMF (1 mL), 4 h at 20 °C. [b] Isolated yields. [c] α-Trimethylsiloxystyrene formed in 35% yield. [d] Reaction for 1 h.

7). Interestingly, under the reaction conditions, DBU led to α-proton abstraction on acetophenone (Table 1, entry 8) and to the subsequent formation of the trimethylsilyl enol ether in 35% yield. Higher yields were obtained with sodium phenolate (Table 1, entry 14), and most of all with carboxylate-derived catalysts (Table 1, entries 15−23). Salts of formic acid provided comparable results (Table 1, entries 20−23), and sodium formate (Table 1, entry 21) was selected for further investigation.

Next, with sodium formate as catalyst, the reaction conditions were optimized (Table 2). Screening of different solvents revealed that only polar solvents led to the formation of **2n** (Table 2, entries 1−5); no product was observed with toluene or dichloromethane (Table 2, entries 1 and 2), probably because of sodium formate's low solubility. Variation of the substrates concentration from 0.25 to 1 mol/L (Table 2, entries 6−8) did not significantly affect the yield of the reaction. The catalyst amount, from 5 to 30 mol %, (Table 2, entries 10−12) had also a minimum impact on the product formation. However, the critical parameter appeared to be the amount of $TMSCCl_3$ (Table 2, entries 13−17). The maximum yield was reached with 1.5 equiv of $TMSCCl_3$; higher quantities of the reagent did not change the outcome of the reaction.

The optimized conditions were then applied to various aldehydes and ketones (Table 3) to establish the scope and limitations of the reaction. First we studied aldehydes reactivity. Benzaldehyde derivatives were used to analyze both the electronic and the steric effects of phenyl ring substituents (Table 3, entries 2, 3, and 6). The presence of electron-donating (entry 2) and -withdrawing groups (entry 3) as well as a sterically demanding group (entry 6) had no effect on the product

TABLE 2. Effect of Solvent, Concentration, Amount of Catalyst, and Amount of $TMSCCl_3$[a]



entry	$TMSCCl_3$ (equiv)	solvent (conditions)	time (h)	yield[b] (%)
1	1.2	toluene	14	
2	1.2	CH_2Cl_2	14	
3	1.2	THF	14	31
4	1.2	CH_3CN	14	62
5	1.2	DMSO	14	61
6	1.2	DMF (5 mL)	4	71
7	1.2	DMF (2 mL)	4	81
8	1.2	DMF (0.5 mL)	4	83
9	1.2	DMF (at 0 °C)	4	69
10	1.2	DMF (HCOONa, 5 mol %)	1	80
11	1.2	DMF (HCOONa, 20 mol %)	1	81
12	1.2	DMF (HCOONa, 30 mol %)	1	86
13	1.3	DMF	1	87
14	1.4	DMF	1	91
15	1.5	DMF	1	96
16	1.6	DMF	1	96
17	2.0	DMF	1	94

[a] Reaction conditions: acetophenone (0.5 mmol), sodium formate (0.05 mmol, 10 mol % unless otherwise stated), solvent (1 mL, unless otherwise stated), 20 °C unless otherwise stated. [b] Isolated yields.

formation, as high yields were achieved in each of these examples. Aliphatic aldehyde **1d** (Table 3, entry 4) gave access to product **2d** in high yield. Starting with α,β-unsaturated aldehyde **1e** (Table 3, entry 5), product **2e** arising from the 1,2-addition was regiospecifically obtained as the single product of the reaction. The reaction works equally well with heterocyclic compounds **1g** and **1h** (Table 3, entries 7 and 8). Our reaction conditions were then applied to para-substituted benzaldehydes containing different protecting groups (Table 3, entries 9−12). Acetate-, trimetylsilyl-, and *tert*-butoxycarbonyl-protected 4-hydroxybenzaldehyde were selected as both base- and acid-sensitive groups.[7] 4-Acetoxybenzaldehyde **1i** (entry 9) gives access to product **2i** in 82% yield when a reduced amount of $TMSCCl_3$ is used (method B). The yield for the formation of **2i** dropped to 68% when the regular conditions (method A) were used due to partial phenol deprotection. Under the optimized condition, **1j** was very efficiently converted into the bis-protected product **2j** (as shown by the crude NMR). Nevertheless, the purification of **2j** proved to be difficult due to the high instability of the phenolic TMS group. Indeed, purification by column chromatography on silica gel or alumina led to complete phenol deprotection and to **2k** in quantitative yield (entry 11). Vacuum distillation was ineffective and product degradation occurred. Use of preparative HPLC with a reverse-phase column and the absence of water in the eluent was the only efficient method to purify **2j** in 75% yield (entry 10). Product **2l** bearing a carbonate group was formed in quantitative yield (entry 12). In the case of ketoaldehyde **1m**, a chemoselectivity problem had to be overcome in order to form product **2m** (entry 13). Once again, method B provided the desired product in 88% yield, whereas **2m** was obtained in 60% yield

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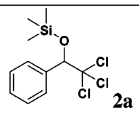
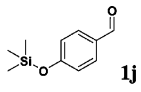
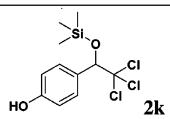
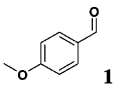
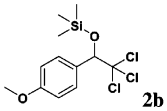
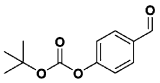
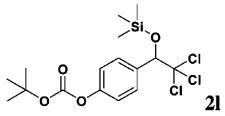
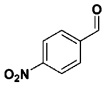
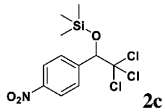
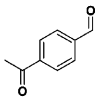
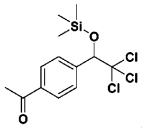
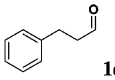
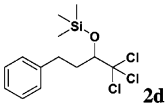
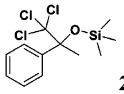
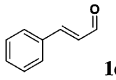
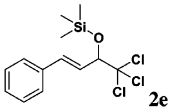
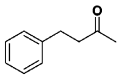
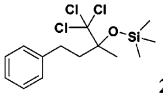
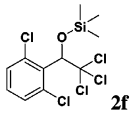
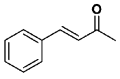
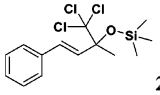
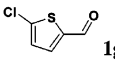
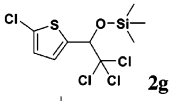
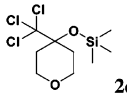
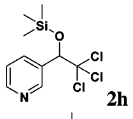
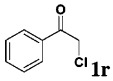
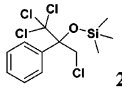
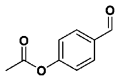
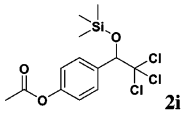
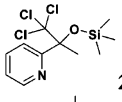
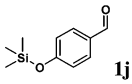
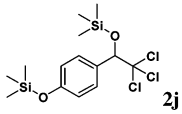
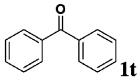
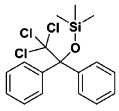
TABLE 3. Formation of Trimethylsilyl-Protected 2,2,2-Tricloromethylcarbinols 2 from Aldehydes and Ketones[a]

entry	substrate	product	yield (%)[b]	entry	substrate	product	yield (%)[b]
1	 **1a**	 **2a**	95	11	 **1j**	 **2k**	99[e]
2	 **1b**	 **2b**	92	12	 **1l**	 **2l**	99
3	 **1c**	 **2c**	99	13	 **1m**	 **2m**	88[c]
4	 **1d**	 **2d**	87	14	 **1n**	 **2n**	96
5	 **1e**	 **2e**	98	15	 **1o**	 **2o**	98
6	 **1f**	 **2f**	96	16	 **1p**	 **2p**	99
7	 **1g**	 **2g**	99	17	 **1q**	 **2q**	85
8	 **1h**	 **2h**	85	18	 **1r**	 **2r**	97
9	 **1i**	 **2i**	82[c]	19	 **1s**	 **2s**	95
10	 **1j**	 **2j**	75[d]	20	 **1t**	 **2t**	94

[a] Reaction conditions for method A: carbonyl derivative (0.5 mmol), $TMSCCl_3$ (0.75 mmol, 1.5 equiv), sodium formate (0.05 mmol, 10 mol %), and DMF (1 mL), 1 h at 20 °C. [b] Isolated yields. [c] Method B: same as method A, except $TMSCCl_3$ (0.6 mmol, 1.2 equiv). [d] Partial TMS deprotection occurred during the purification by preparative HPLC. [e] TMS deprotection occurred during the purification by flash chromatography on silica gel.

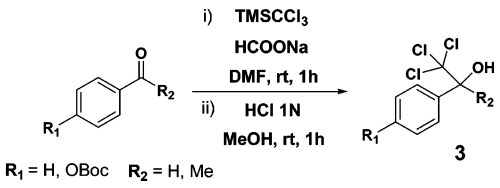
only along with the bisaddition product **2m′** (30%) when method A was used. Excellent yields were also obtained with the different ketones studied (Table 3, entries 14−20): hindered (entries 18 and 20), aliphatic (entry 15), α,β-unsaturated (entry 16), heterocyclic (entry 19), and cyclic ketones (entry 17) gave the desired product **2** with yields superior to 75%.

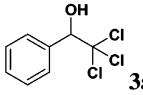
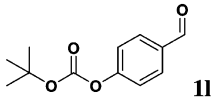
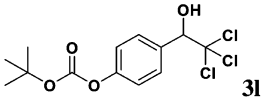
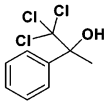
Finally we investigated the one-pot formation of 2,2,2-trichloromethylcarbinol **3** from aldehydes **1a** and **1l** and ketone **1n** by combining the $TMSCCl_3$/HCOONa methodology with a mild TMS deprotection procedure. Compounds **3** are usually prepared by base-promoted addition of chloroform to aldehydes or ketones.[8a,b] Even the latest reported methodologies involve relatively strong bases (KOH[8a] or DBU[8b]), which narrows their scope of application. We thought that the use of the one-pot process would represent an interesting alternative route for the synthesis of **3**. Table 4 summarizes the results obtained on three substrates for the two-step one-pot synthesis of compound **3**. Starting from aldehydes (Table 4, entries 1 and 2), the desired products **3** were obtained in high yields. Boc-protected aldehyde **1l** was used in order to test the stability of an acid-sensitive group under our reaction conditions and no deprotected product was observed. Nevertheless, ketone **1n** was less reactive (Table 4, entry 3), and both higher temperature and longer reaction time were required for satisfactory conversion.

In conclusion, after the screening of various Lewis bases, we found that sodium formate was an efficient catalyst for the formation of trimethylsilyl-protected 2,2,2-trichloromethylcarbinols **2**. Optimized reaction conditions were applied to a collection of aldehydes and ketones, and products **2** were formed in high yields. Finally, a one-pot $TMSCCl_3$ addition/TMS deprotection process was described leading to 2,2,2-trichloromethylcarbinols **3**. An asymmetric version of this reaction is currently under investigation in our laboratory.

(8) (a) Wyvratt, J. M.; Hazen, G.; Weinstock, L. M. *J. Org. Chem*. **1987**, *52*, 944−945. (b) Aggarwal, V. K.; Mereu, A. *J. Org. Chem*. **2000**, *65*, 7211−7212.

TABLE 4. One-Pot Formation of 2,2,2-Trichloromethylcarbinols 3[a]



entry	substrate	product	yield (%)[b]
1	 1a	 3a	94
2	 1l	 3l	85
3	 1n	 3n	71[c]

[a] Reaction conditions: (i) carbonyl derivative (0.5 mmol), $TMSCCl_3$ (0.75 mmol, 1.5 equiv), sodium formate (0.05 mmol, 10 mol %), and DMF (1 mL), 1 h at 20 °C; (ii) 1 N HCl (1 mL, 2 equiv) and MeOH (1 mL), 1 h at 20 °C. [b] Isolated yields. [c] (ii) 12 h at 50 °C.

Experimental Section

General Procedure for the Formation of Trimethylsilyl-Protected 2,2,2-Tricloromethylcarbinols 2. To a DMF solution (1 mL) of $TMSCCl_3$ (0.144 g, 0.75 mmol) were added the carbonyl derivative (0.5 mmol) and HCOONa (3.4 mg, 0.05 mmol). The reaction mixture was stirred at room temperature for 1 h and then poured into a half-saturated NH_4Cl solution (20 mL), and the product was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude residue was purified by silica gel flash chromatography (cyclohexane/CH_2Cl_2 or EtOAc) to afford the pure product.

General Procedure for the One-Pot Formation of 2,2,2-Trichloromethylcarbinols 3. To a DMF solution (1 mL) of $TMSCCl_3$ (0.144 g, 0.75 mmol) were added the carbonyl derivative (0.5 mmol) and HCOONa (3.4 mg, 0.05 mmol). The reaction mixture was stirred at room temperature for 1 h. MeOH (1 mL) and a 1 N HCl solution (1 mL, 1 mmol) were added, the reaction mixture was stirred at room temperature for 1 h and then poured into a half-saturated NH_4Cl solution (30 mL), and the product was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude residue was purified by silica gel flash chromatography (cyclohexane/EtOAc 8:2) to afford the pure product.

[2,2,2-Trichloro-1-(4-nitrophenyl)ethoxy]trimethylsilane (2c). Yield 99% as a light yellow solid, purification by flash chromatography (cyclohexane/CH_2Cl_2 95:5); mp 74−75 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25−8.21 (m, 2H), 7.81−7.78 (m, 2H), 5.20 (s, 1H), 0.13 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 148.3, 144.0, 130.4, 122.7, 101.5, 84.0, −0.1; IR (neat) 2963, 1520, 1348, 1255, 1100, 889, 844, 778, 761, 753 cm^{-1}; Elemental analysis calcd for $C_{11}H_{14}Cl_3NO_3Si$: C, 38.55; H, 4.12; N, 4.09. Found: C, 38.64; H, 4.04; N, 3.99.

tert-Butyl 4-(2,2,2-trichloro-1-hydroxyethyl)phenyl carbonate (3l). Yield 85% as a white solid after purification by flash chromatography (cyclohexane/ethyl acetate 8:2); mp 150−151 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61−7.58 (d, J = 8.7 Hz, 2H), 7.20−7.17 (d, J = 8.7 Hz, 2H), 5.15 (s, 1H), 3.52 (s, 1H), 1.56 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 151.67, 151.63, 132.3, 130.3, 120.6, 102.9, 83.9, 83.8, 27.6; IR (neat) 3447, 2986, 1726, 1370, 1316, 1222, 1154, 1084, 808, 781, 621 cm^{-1}; Elemental analysis calcd for $C_{13}H_{15}Cl_3O_4$: C, 45.71; H, 4.43. Found: C, 45.69; H, 4.47.

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Supporting Information Available: General information, analytical data, and ^1H and ^{13}C spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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