# TWO EFFECTIVE PROCEDURES FOR THE SYNTHESIS OF TRICHLOROMETHYL KETONES, USEFUL PRECURSORS OF CHIRAL α-AMINO AND α-HYDROXY ACIDS

E. J. Corey, John O. Link and Yang Shao

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

*Summary: Trichloroacetic acid can be converted to trichloromethyl ketones in good yield by two practical new procedures, one involving the catalyzed reaction of trichloroacetic acid with aldehydes at 23 °C followed by oxidation and the other utilizing the coupling of organozinc intermediates with trichloroacetyl chloride.*

Chiral α-trichloro- and tribromomethyl carbinols have assumed a new importance because they can be prepared in high enantiomeric purity by oxazaborolidine catalyzed (CBS) reduction of the corresponding ketones[1,2] and can be easily converted to enantiomerically pure α-amino acids and α-hydroxy acids.[3] The utility of trichloromethyl carbinols and the lack of satisfactory procedures for the production of their precursor ketones prompted us to investigate improved methods of trichloromethyl ketone synthesis. Herein we describe two simple, efficient and practical procedures for the production of a wide range of α-trichloromethyl ketones in high purity. These methods are complementary and serve as the most practical route to a wide variety of α-trichloromethyl ketones from simple precursors; the ketones 3a are formed by trichloromethide addition to aldehydes and subsequent oxidation (formation of C-C bond α), or from addition of organozinc reagents to trichloroacetyl chloride (formation of C-C bond α'). α-Tribromomethyl ketones can be prepared by parallel processes.

The first route detailed here involves a mild and efficient generation of trichloromethyl carbinols 2a from aldehydes and subsequent oxidation.[4] The usual formation of these carbinols by the reaction of chloroform and strong base to produce trichloromethide in the presence of an aldehyde[5] is unsatisfactory for aldehydes bearing α-protons, since complex mixtures result from extensive aldol side reactions.[5a] A great improvement in trichloromethyl anion generation has resulted from our finding that a 1:1 mixture of trichloroacetic acid (TCA) and sodium trichloroacetate (NaTCA) in dimethyl formamide (DMF) undergoes rapid decarboxylation even at 4-23 °C to generate the highly nucleophilic trichloromethyl anion. This anion adds to aldehydes 1 in DMF solution to form the desired trichloromethyl carbinols 2a cleanly even for highly sensitive aldehydes bearing α-protons (entries 1, 3, 5 and 6, Table 1).[6] The accompanying experimental details exemplify the simplicity of the procedure and ease of pure product isolation (*vide infra*).
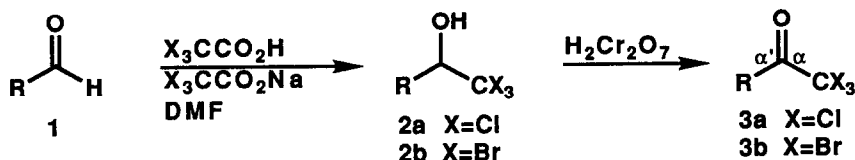
This transformation is exceptional in that a highly nucleophilic and basic carbanion is generated and reacts with a carbonyl in a C-C bond forming step in protic media. Presumably the trichloromethyl anion preferentially reacts with aldehydes in the presence of trichloroacetic acid because the carboxylic acid proton is strongly hydrogen bonded to DMF.

**Table 1.** α-**Trichloromethyl Carbinols**

| entry | aldehyde 1 | equiv each of TCA and NaTCA | temp °C | time h | yield% of carbinol 2a |
|---|---|---|---|---|---|
| 1 | hydrocinnamaldehyde | 1.5 | 23 | 0.5 | 97 |
| 2 | cinnamaldehyde | 1.5 | 23 | 0.75 | 95 |
| 3 | cyclohexanecarboxaldehyde | 1.5 | 23 | 1 | 84 |
| 4 | pivaldehyde | 9.0[a] | 23 | 9 | 76 |
| 5 | diphenylacetaldehyde | 13.5[b] | 4 | 36 | 59 |
| 6 | 3,4,5-trimethoxyphenylacetaldehyde | 10.0[a] | 4 | 12 | 74 |

[a] Half added initially, the rest added at one half the full reaction time.
[b] Two thirds added initially, the rest added at one half the full reaction time.
Chromic acid oxidation afforded the following yields of trichloromethyl ketones: Entry 1: 75%; 3: 89%; 4: 100%; 5: 87%. Swern oxidation afforded an 82% yield of trichloromethyl ketone entry 2.[4b]

Additionally, tribromomethyl carbinols **2b** can be synthesized from aldehydes treated with tribromoacetic acid (TBA) and its sodium salt (NaTBA) in DMF as shown in **Table 2**. Decarboxylation of this mixture to generate the tribromomethide occurs more rapidly than the corresponding reaction with TCA/NaTCA but is otherwise experimentally identical.

For both trichloro- and tribromomethyl carbinols oxidation with chromic acid[4a] affords the desired trihalomethyl ketones cleanly and in high yield as detailed in **Tables 1** and **Table 2**. Swern oxidation conditions can also be employed for compounds unstable to oxidation with chromic acid.[4b]

**Table 2.** α-**Tribromomethyl Carbinols**

| entry | aldehyde 1 | equiv TBA | equiv NaTBA | temp °C | time h | yield% of carbinol 2b |
|---|---|---|---|---|---|---|
| 1 | hydrocinnamaldehyde | 4.5 | 1.5 | 4 | 4 | 77 |
| 2 | cinnamaldehyde | 3.0 | 3.0 | 23 | 24 | 55 |
| 3 | cyclohexanecarboxaldehyde | 1.5 | 1.5 | 23 | 6 | 80 |

Chromic acid oxidation afforded the following yields of tribromomethyl ketones: Entry 1: 81%; 3: 82%.

The second procedure described here is a one-step preparation of trichloromethyl ketones by coupling organozinc reagents **5** with trichloroacetyl chloride, and complements the foregoing procedure under circumstances where the aldehyde precursor **1** is not readily available. For example, in our enantioselective reduction studies[3] we required access to two benzylic-α-trichloromethyl ketones. Since several steps are required to synthesize α-aryl acetaldehydes, the first route detailed here would have proven lengthy. In contrast many benzylic bromides are readily available, making the second route to these ketones expedient as follows: the organozinc was generated by the slow addition[7] of bromide **4** in toluene to lithium dispersion and $ZnCl_2$ in toluene/THF at 0 °C with sonication.[8] Trichloroacetyl chloride was then added to the reaction mixture to afford the trichloromethyl ketone **3a** directly. The reaction of alkylzinc reagents with acyl chlorides is generally

sluggish, often requiring Pd$^{II}$ catalysis[9a] or addition of CuCN.[9b] Yet, the increased electrophilicity of trichloroacetyl chloride allows its coupling with organozinc reagents to proceed rapidly at 23 °C. The following scheme details two examples of trichloromethyl ketone syntheses by this direct method.
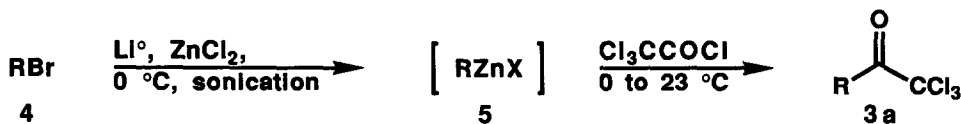


**Yield of ketones 3:** R= β-naphthyl–CH$_2$; 82%   R= 4-(phenyl)phenyl–CH$_2$; 85%

In conclusion, two complementary and practical procedures for the synthesis of trihalomethyl ketones have been developed. The following experimental procedures illustrate the simplicity of this methodology.

**4-Phenyl-1,1,1-trichloro-2-butanol.** To a solution of hydrocinnamaldehyde (1.0 g, 7.45 mmol) in 10 mL of reagent grade DMF was added trichloroacetic acid (2.0 g, 11.2 mmol) and sodium trichloroacetate (1.85 g, 11.2 mmol) with stirring while the temperature was maintained with a 23 °C water bath. Initially rapid evolution of CO$_2$ was observed, and after 30 min the mixture was diluted with 25 mL of 9 : 1 ether-hexane, washed three times with sat. NaHCO$_3$ and once with brine. The organic extract was dried (MgSO$_4$), concentrated and eluted with 3 : 2 hexane-toluene through a short plug of silica gel (sg) to afford 4-phenyl-1,1,1-trichloro-2-butanol as an oil (1.83 g, 97%); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.26 (m, 5H), 3.99 (ddd, $J$ = 1.7, 5.1, 10.0 Hz, 1H), 3.01 (ddd, $J$ = 4.8, 9.1, 13.8 Hz, 1H), 2.78 (dt, $J$ = 8.4, 13.8 Hz, 1H), 2.39 (dt, $J$ = 8.4, 13.8 Hz, 1H), 2.0 (m, 1H); FTIR (film) 3400, 1455 cm$^{-1}$; HRMS: calcd. for C$_{10}$H$_{11}$Cl$_4$O [M+ Cl]$^+$: 288.9535; found: 288.9517.

**4-Phenyl-1,1,1-trichloro-2-butanone.** To a mixture of 4-phenyl-1,1,1-trichloro-2-butanol (1.00 g, 3.96 mmol) in 8 mL of glacial acetic acid was added a premixed solution of Na$_2$Cr$_2$O$_7$ (708 mg, 2.38 mmol) and H$_2$SO$_4$ (520 μL, 9.52 mmol) in 12 mL of glacial acetic acid with vigorous stirring. After 1 h isopropanol (1 mL, 13 mmol) was added to consume excess oxidant with stirring for 10 min. The mixture was diluted with 100 mL of CH$_2$Cl$_2$ and washed with 50 mL of brine, sat. NaHCO$_3$ (2 x 50 mL), and 50 mL of brine, dried (MgSO$_4$), concentrated, and eluted through a short sg plug with 10:1 hexane–ethyl acetate to afford 4-phenyl-1,1,1-trichloro-2-butanone as an oil (747 mg, 75%); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.27 (m, 5H), 3.31 (t, $J$ = 7.4 Hz, 2H), 3.05 (t, $J$ = 7.4 Hz, 2H); FTIR (film) 1751 cm$^{-1}$; HRMS: calcd. for C$_{10}$H$_9$Cl$_4$O [M+ Cl]$^+$: 286.9379; found: 286.9372.

**β-Naphthyl-1,1,1-trichloro-2-propanone.** A solution of freshly fused zinc chloride (1.95 g, 14 mmoL) in 7.6 mL of THF was added by cannula to hexane-washed lithium (384 mg, 25% dispersion in oil, Na content 0.5%, 12.5 mmol) in a dry flask fitted with a septum under argon containing 11.5 mL of toluene. β-Naphthyl bromide (1.27 g, 5.7 mmol, azeotropically dried with 3 mL toluene) in 8.5 mL of toluene was added over 40 min[7] to the sonicated (40 watt bath sonicator) zinc chloride–lithium mixture at 0 °C with occasional agitation to prevent clumping of the lithium metal. Trichloroacetyl chloride (1.56 g, 8.6 mmol) was added in one portion with stirring, and the cooling bath was removed. After 1 h the homogeneous solution was diluted with 80 mL of ethyl acetate and washed sequentially with 10 mL each of sat. KH$_2$PO$_4$, sat. NaHCO$_3$, and brine, dried over MgSO$_4$, and concentrated *in vacuo* to afford β-naphthyl-1,1,1-trichloro-2-propanone as a yellow solid unstable to flash sg chromatography. Recrystallization from toluene–hexane afforded pure β-naphthyl-1,1,1-

trichloro-2-propanone as a colorless solid (1.35 g, 82%, 2 crops); mp 87-88 °C; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.9–7.4 (m, 7H), 4.45 (s, 2H); IR (neat) 1760, 1747 cm$^{-1}$; EIMS 286 [M]$^+$; HRMS: calcd. for [C$_{13}$H$_9$Cl$_3$O]$^+$: 285.9719; found: 285.9741.[10]

## References and Notes

1. (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Letters* **1990**, *31*, 611; (b) Corey, E. J.; Cheng, X.-M.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Letters* **1991**, *32*, 6835; (c) Corey, E. J.; Cheng, X.-M.; Cimprich, K. A. *Tetrahedron Letters* **1991**, *32*, 6839. A number of α-chloroketones have also been reduced enantioselectively to form synthetically useful chlorohydrins, see (d) Corey, E. J., Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861; (e) Corey, E. J.; Link, J. O. *Tetrahedron Letters* **1990**, *31*, 601; (f) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442.

2. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, E. J., Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *ibid.* **1987**, *109*, 7925; (c) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209.

3. (a) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906; (b) Corey, E. J.; Link, J. O. preceding paper.

4. (a) Gallina, C.; Giordano, C. *Synthesis* **1989**, 466; (b) Swern oxidation of the alcohol in entry 2, **Table I** was performed as described by Mancuso, A. J.; Huang, S.-L; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480; except that oxalyl chloride (4 equiv), dimethylsulfoxide (8 equiv) and triethylamine (20 equiv) were used and the reaction mixture was filtered directly through a short plug of silica gel with 5 : 1 hexane–ether and concentrated *in vacuo*.

5. (a) Wyvratt, J. M.; Hazen, G. G.; Weinstock, L. M. *J. Org. Chem.* **1987**, *52*, 944; (b) Reeve, W.; Fine, L. W. *J. Org. Chem.* **1964**, *29*, 1148; (c) Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 3010.

6. Although trichloroacetic acid and tribromoacetic acid alone decompose in dimethyl sulfoxide solution; (see (a) Atkins, P. J.; Gold, V. *J. Chem. Soc. Chem. Comm.* **1983**, 140; (b) Atkins, P. J.; Gold, V.; Wassef, W. N. *J. Chem. Soc. Chem. Comm.* **1983**, 283); these conditions are not satisfactory for the general synthesis of trihalomethyl carbinols from aldehydes.

7. Addition times of less than 30 min gave significant amounts of Wurtz coupling products from benzylic bromides. Slow addition (>30 min, 0 °C) resulted in ratios of ketone to Wurtz product of >30 : 1.

8. (a) Petrier, C.; Luche, J.-L.; Dupuy, C. *Tetrahedron Letters* **1984**, *25*, 3463; (b) de Souza Barboza, J. C.; Petrier, C.; Luche, J.-L. *Tetrahedron Letters* **1985**, *26*, 829.

9. (a) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Letters* **1983**, *24*, 5181; (b) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2392.

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