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Indium-mediated chemoselective deprotection and demonochlorination of 2,2,2-trichloroethyl esters

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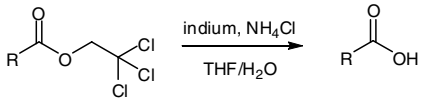
Abstract—On treatment with indium metal, the 2,2,2-trichloroethyl carboxylates smoothly undergo deprotection to carboxylic acids and reductive demonochlorination to 2,2-dichloroethyl esters, sharply depending on their structures.

A sequence of protection/deprotection procedures for functional groups is often essential for the construction of complex molecules. Among the protecting groups explored,[1] the 2,2,2-trichloroethyl moiety serves as a convenient masking unit for alcohols, amines, and carboxylic acids, as well as phosphorus compounds. The trichloroethyl moiety can be routinely cleaved with Zn/AcOH,[2] electrolysis,[3] SmI_2,[4] Se/$NaBH_4$,[5] and Cd/AcOH.[6] The alternative indium-mediated methods for its removal under mild conditions have been developed.[7,8]

In our continuous efforts to explore indium-based methodologies, indium metal has been found to be sufficiently effective to deprotect trichloroethyl benzoates. Thus, a mixture of trichloroethyl esters and indium powder, with THF/H_2O as the solvent, was heated in the presence of NH_4Cl to achieve an exclusive cleavage to benzoic acids. A variety of aromatic and aliphatic carboxylates were subjected to an indium-mediated reaction to furnish the carboxylic acids in good to excellent yields (Scheme 1). Table 1 shows the summary of the deprotection. The benzoate derivatives with electron-donating and -withdrawing substituents were smoothly deprotected to the corresponding acids (entries 2–5). Deprotection of nicotinate (entry 6) and isonicotinate (entry 7) proceeded readily as well. This method was equally applicable to the cinnamates (entries 8 and 9) and to the aliphatic carboxylates, including the olefinic ester (entries 10–12).



Scheme 1.

On the other hand, when 2,2,2-trichloroethyl carboxylates containing the benzylic methylene moiety such as phenylacetate and ω-phenylalkanoates were subjected to the indium-mediated reactions, the situation was not so simple (Scheme 2). As shown in Table 2,[9] the reaction of trichloroethyl phenylacetate (entry 1) and 3-phenylpropionate (entry 7) with an indium metal resulted in an exclusive formation of 2,2-dichloroethyl esters with negligible amounts of deprotected forms, while 4-phenylbutyrate (entry 8) and 6-phenylhexanoate (entry 9) gave a mixture of 2,2-dichloroethyl esters and free carboxylic acids in the ratio of 2.2:1. Trichloroethyl phenylacetate derivatives examined gave the reductive dechlorination products as isolable major compounds (entries 2–6), indicative of the convenient procedure from 1,1,1-trichloromethyl groups to 1,1-dichloromethyl groups, which can be considered as the equivalent of aldehydes.[10,11] When the large excess amount of indium, up to 6 equiv was used under the same condition, trichloroethyl phenylacetate and 3-phenylpropionate gave 2,2-dichloroethyl esters in 55% and 78% yields, respectively, without other major side products. Both the reactions leading to cleavage and reductive demonochlorination might proceed through dichloromethyl radicals and/or dichloromethyl anions initially generated by electron transfer from indium metal as postulated for conventional methods, although the

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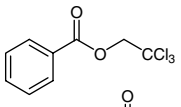
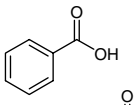
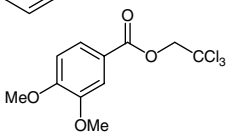
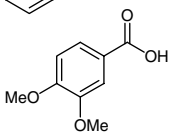
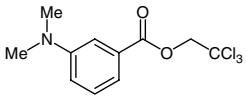
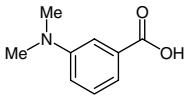
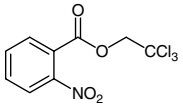
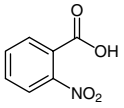
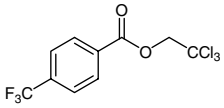
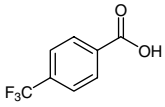
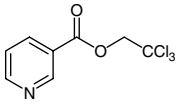
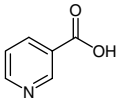
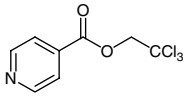
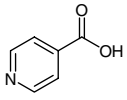
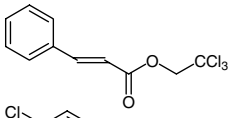
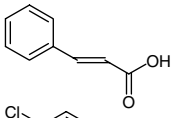
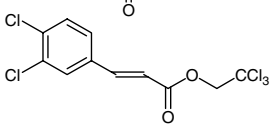
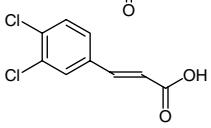
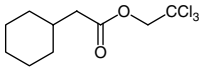
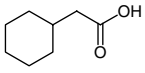
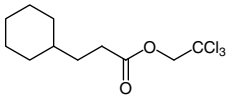
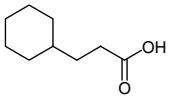
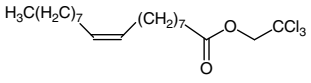
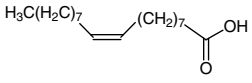
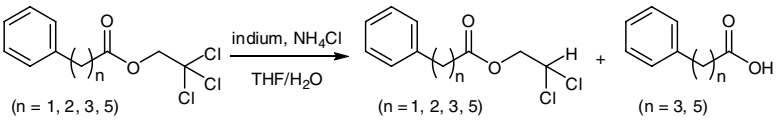
Table 1. Indium-mediated deprotection of trichloroethyl esters[a]

Entry	Substrate	Product	Time (h)	Yield[b] (%)
1			7	92
2			11	75
3			4	74
4			3.5	93
5			7	73
6			11	95
7			12	62
8			15	76
9			1.5	94
10			3	80
11			5	61
12			48	88

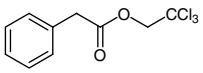
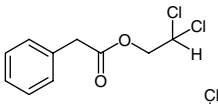
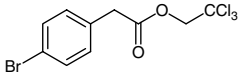
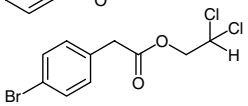
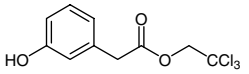
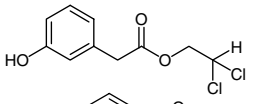
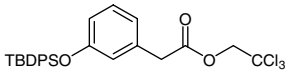
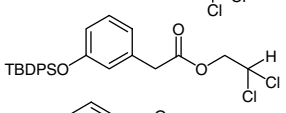
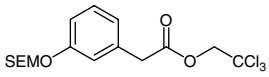
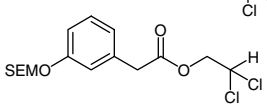
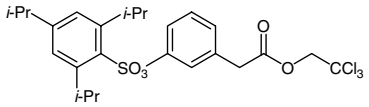
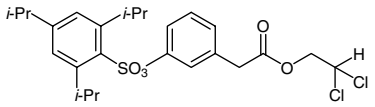
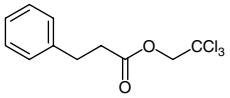
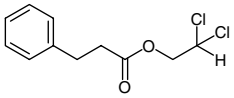
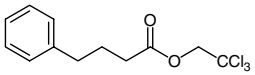
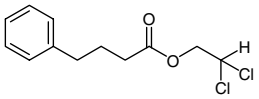
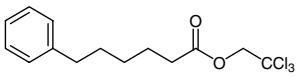
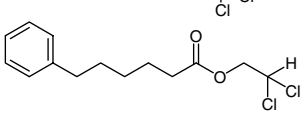
[a] All reactions were conducted at reflux using 2 equiv of indium metal, 5 equiv of NH_4Cl, and THF/H_2O (10:1) as the solvent.
[b] Isolated yields.



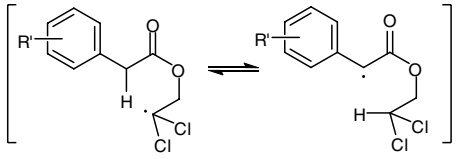
Scheme 2.

reductive stability of radicals/anions can be a factor as noted in the previous report on the dichotomy between radical and anionic dechlorination.[12] Formation of dichloroethyl esters might be rationalized by the intramolecular stabilization of the active species derived from the participation of the benzylic methylene group (Scheme 3). Further investigation is needed for a clear mechanistic elucidation.

Table 2. Reductive dechlorination by the indium-mediated reactions[a]

Entry	Substrate	Product	Time (h)	Yield[b] (%)
1			20	54
2			20	56
3			12	59
4			20	71
5			18	70
6			12	61
7			18	85
8			24	57 (+27)[c]
9			24	60 (+27)[c]

[a] All reactions were conducted at reflux using 2 equiv of indium metal, 5 equiv of NH_4Cl, and THF/H_2O (10:1) as the solvent.
[b] Isolated yields.
[c] In parentheses are the yields of the corresponding free carboxylic acids.



Scheme 3.

In conclusion, the indium-mediated modification of 2,2,2-trichloroethyl carboxylate esters highly depends on their structures, indicative of high chemoselectivity based on the benzylic methylene group. The further explorations to find the reaction utility as well as mechanistic investigations are intensely ongoing.

General experimental procedure: In a typical experimental procedure, the trichloroethyl esters (1 mmol) were dissolved in THF/H_2O (10:1, v/v, 10 mL), and indium powder[13] (2 mmol) and NH_4Cl (5 mmol) were added at room temperature. The reaction mixture was heated at reflux and monitored for completion by TLC. Flash column chromatography on silica gel furnished analytically pure products, which were confirmed by ^1H NMR, ^{13}C NMR, and mass spectroscopy.

Acknowledgment

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References and notes

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Phenylacetic acid 2,2-dichloroethyl ester (Table 2, entry 1): ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.28 (m, 5H), 5.82 (t,

1H, $J = 6.3$ Hz), 4.47 (d, 2H, $J = 6.3$ Hz), 3.71 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 133.1, 129.3, 128.6, 127.4, 68.5, 68.2, 40.8; HRMS (ESI^+) m/z: $[M+Na]^+$ calcd for $C_{10}H_{10}Cl_2O_2$, 254.9956; found, 254.9945.

4-Bromophenylacetic acid 2,2-dichloroethyl ester (Table 2, entry 2): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, 2H, $J = 8.6$ Hz), 7.17 (d, 2H, $J = 8.0$ Hz), 5.81 (t, 1H, $J = 6.3$ Hz), 4.46 (d, 2H, $J = 6.3$ Hz), 3.65 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 132.0, 131.7, 131.0, 121.4, 68.5, 68.1, 40.2; HRMS (ESI^+) m/z: $[M+Na]^+$ calcd for $C_{10}H_9BrCl_2O_2$, 334.9037; found, 334.9064.

3-Hydroxyphenylacetic acid 2,2-dichloroethyl ester (Table 2, entry 3): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (t, 1H, $J = 7.4$ Hz), 6.84 (d, 1H, $J = 7.5$ Hz), 6.76–6.74 (m, 2H), 5.81 (t, 1H, $J = 6.3$ Hz), 5.71 (s,1H), 4.47 (d, 2H, $J = 6.3$ Hz), 3.65 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 155.8, 134.5, 129.9, 121.6, 116.3, 114.5, 68.6, 68.1, 40.7; HRMS (ESI^+) m/z: $[M+Na]^+$ calcd for $C_{10}H_{10}Cl_2O_3$, 270.9905; found, 270.9930.

3-(tert-Butyldiphenylsilyloxy)phenylacetic acid 2,2-dichloroethyl ester (Table 2, entry 4): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, 4H, $J = 8.0$, 1.7 Hz), 7.45–7.42 (m, 2H), 7.38–7.36 (m, 4H), 7.02 (t, 1H, $J = 7.5$ Hz), 6.79 (d, 1H, $J = 7.5$ Hz), 6.75 (t, 1H, $J = 1.8$ Hz), 6.64 (dd, 1H, $J = 7.5$, 1.7 Hz), 5.69 (t, 1H, $J = 6.3$ Hz), 4.37 (d, 2H, $J = 6.3$ Hz), 3.52 (s, 2H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 155.7, 135.5, 134.3, 132.8, 129.9, 129.3, 127.7, 122.0,120.7, 118.6, 68.4, 68.2, 40.1, 26.5, 19.4; HRMS (ESI^+) m/z: $[M+Na]^+$ calcd for $C_{26}H_{28}Cl_2O_3Si$, 509.1083; found, 509.1076.

3-(2-Trimethylsilylethoxymethoxy)phenylacetic acid 2,2-dichloroethyl ester (Table 2, entry 5): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (dd, 1H, $J = 8.6$, 7.5 Hz), 6.97–6.95 (m, 2H), 6.92 (d, 1H, $J = 7.5$ Hz), 5.82 (t, 1H, $J = 6.3$ Hz), 5.21 (s, 2H), 4.46 (d, 2H, $J = 6.3$ Hz), 3.75 (t, 2H, $J = 8.6$ Hz), 3.66 (s, 2H), 0.96 (t, 2H, $J = 8.6$ Hz) 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 157.6, 134.5, 129.6, 122.6, 117.2, 115.1, 92.8, 68.5, 68.2, 66.2, 40.8, 18.0, −1.4; HRMS (ESI^+) m/z: $[M+Na]^+$ calcd for $C_{16}H_{24}Cl_2O_4Si$, 401.0719; found, 401.0726.

3-(2,4,6-Triisopropylphenylsulfonyloxy)phenylacetic acid 2,2-dichloroethyl ester (Table 2, entry 6): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (dd, 1H, $J = 8.0$, 7.5 Hz), 7.20 (s, 2H), 7.18 (d, 1H, $J = 7.5$ Hz), 7.01 (t, 1H, $J = 1.7$ Hz), 6.90 (dd, 1H, $J = 8.0$, 1.8 Hz), 5.79 (t, 1H, $J = 6.3$ Hz), 4.43 (d, 2H, $J = 6.3$ Hz), 4.07 (sept, 2H, $J = 6.9$ Hz), 3.63 (s, 2H), 2.94 (sept, 1H, $J = 6.9$ Hz) 1.23 (d, 6H, $J = 6.9$ Hz), 1.19 (d, 12H, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 154.3, 151.2, 149.5, 134.9, 129.70, 129.66, 127.9, 123.9, 123.6, 121.3, 68.5, 68.1, 40.4, 34.2, 29.8, 24.6, 23.5; HRMS (ESI^+) m/z: $[M+Na]^+$ calcd for $C_{25}H_{32}Cl_2O_5S$, 537.1245; found, 537.1260.

3-Phenylpropionic acid 2,2-dichloroethyl ester (Table 2, entry 7): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.27 (m, 2H), 7.21–7.18 (m, 3H), 5.77 (t, 1H, $J = 5.8$ Hz), 4.42 (d, 2H, $J = 5.7$ Hz), 2.96 (t, 2H, $J = 7.5$ Hz), 2.70 (t, 2H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 139.9, 128.5, 128.2, 126.4, 68.3, 68.1, 35.3, 30.6; HRMS (ESI^+) m/z: $[M+Na]^+$ calcd for $C_{11}H_{12}Cl_2O_2$, 269.0112; found, 269.0134.

4-Phenylbutyric acid 2,2-dichloroethyl ester (Table 2, entry 8): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.30 (m, 2H), 7.24–7.20 (m, 3H), 5.85 (t, 1H, $J = 5.8$ Hz), 4.46 (d, 2H, $J = 6.0$ Hz), 2.70 (t, 2H, $J = 7.4$ Hz), 2.43 (t, 2H, $J = 7.5$ Hz), 2.01 (quint, 2H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 141.0, 128.44, 128.38, 126.0, 68.4, 68.1, 34.9, 33.1, 26.3; HRMS (EI^+) m/z: $[M]^+$ calcd for $C_{12}H_{14}Cl_2O_2$, 260.0371; found, 260.0342.

6-Phenylhexanoic acid 2,2-dichloroethyl ester (Table 2, entry 9): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.29 (m, 2H), 7.22–7.19 (m, 3H), 5.83 (t, 1H, $J = 6.3$ Hz), 4.46 (d, 2H, $J = 6.3$ Hz), 2.64 (t, 2H, $J = 7.5$ Hz), 2.40 (t, 2H, $J = 7.5$ Hz), 1.74–1.64 (m, 4H), 1.44–1.38 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 142.3, 128.3, 128.2, 125.6, 68.4, 68.0, 35.6, 33.7, 30.9, 28.5, 24.6; HRMS (EI^+) m/z: $[M]^+$ calcd for $C_{14}H_{18}Cl_2O_2$, 288.0684; found, 288.0668.

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