



## Effect of deuterated solvents toward 2,2,2-trichloroethyl esters with a benzylic methylene moiety

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### ABSTRACT

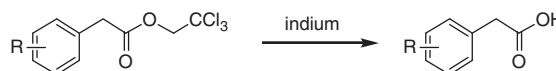
The indium-promoted chemoselective deprotection of 2,2,2-trichloroethyl esters containing a benzylic methylene was successfully achieved by employing deuterated solvents.

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A number of protecting groups have been introduced over the past few decades,<sup>1</sup> and the 2,2,2-trichloroethyl moiety has been used as a convenient protecting unit for alcohols and amines, as well as for carboxylic acids.<sup>2,3</sup> Among the many available procedures used to deprotect the 2,2,2-trichloroethoxycarbonyl (Troc) group, we have employed mild methods for its removal from alcohols<sup>4</sup> and amines<sup>5</sup> by utilizing indium powder and ammonium chloride. In addition, the 2,2,2-trichloroethyl moiety is known to be routinely cleaved from 2,2,2-trichloroethyl esters using Zn/AcOH,<sup>2</sup> electrolysis,<sup>6</sup> SmI<sub>2</sub>,<sup>7</sup> Se/NaBH<sub>4</sub>,<sup>8</sup> and Cd/AcOH.<sup>9</sup> We also have continuously explored the use of indium-mediated reactions for 2,2,2-trichloroethyl esters.<sup>10</sup> We have recently reported a mild method to deprotect 2,2,2-trichloroethyl esters and furnish the carboxylic acids in good to excellent yields. However, the method was unsuccessful for substrates wherein a benzylic methylene moiety was present, which is a limitation.

In this case, demochlorination proceeded in an exclusive formation of 2,2-dichloroethyl esters with negligible amounts of the deprotected form. To overcome this shortcoming, we have now discovered the conditions that could efficiently cleave 2,2,2-trichloroethyl esters containing a benzylic methylene moiety and yield the deprotected forms of the free carboxylic acids by using deuterated solvents (Scheme 1).

To begin, benzene, toluene, and chlorobenzene were selected as the solvents, and the reaction mixtures containing 4-tolylacetic acid 2,2,2-trichloroethyl ester and indium metal powders were heated at reflux, applying the reaction conditions from our previous work. However, none of the experimental procedures produced any chemical transformations leaving the starting material in the solution intact after 5 days, even when high boiling points of toluene and chlorobenzene were used. We then approached the problem from a different perspective. Regarding the choice of tetrahydrofuran (THF) in our previous report, THF-*d*<sub>8</sub> was considered as a promising solvent that could deprotect 2,2,2-trichloroethyl esters with a benzylic methylene moiety. Also, the reductive stability of radicals/anions was reviewed.<sup>10–12</sup> When dissociation of a C–H bond of THF is responsible for the demochlorination of 2,2,2-trichloroethyl esters, the rate of the reaction should be slowed when THF is replaced by THF-*d*<sub>8</sub>, due to the kinetic isotope effect of the corresponding C–D bond. Based on the previously mentioned study concerning reaction rates, the reaction rate involving the C–H bond is five to six times faster than that involving the corresponding C–D bond.<sup>13,14</sup>

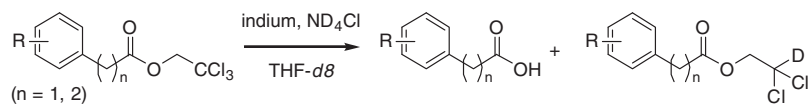


Scheme 1.

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**Table 1**  
Reactions using THF- $d_8$  as the solvent<sup>a</sup>

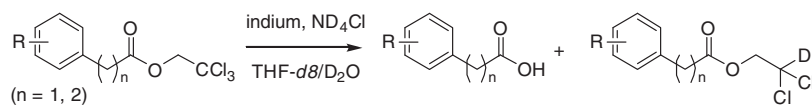


Entry	Substrate	Products and yields <sup>b</sup>	Time (h)
1		23%  67%	30
2		13%  60%	30

<sup>a</sup> All reactions were conducted at reflux using 2 equiv of In, 5 equiv of ND<sub>4</sub>Cl, and THF- $d_8$  as the solvent.

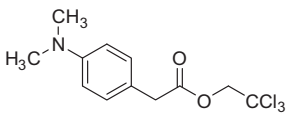
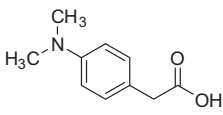
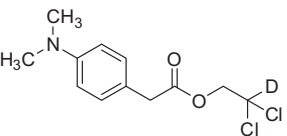
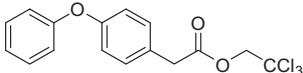
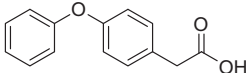
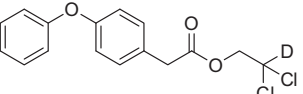
<sup>b</sup> Isolated yields and the free carboxylic acids were indicated after silica gel separation.

**Table 2**  
Reactions using THF- $d_8$ /D<sub>2</sub>O (10:1) as the solvent<sup>a</sup>



Entry	Substrate	Products and yields <sup>b</sup>	Time (h)
1		80% —  ND	40
2		72% —  ND	40
3		54%  3%	40
4		32% —  ND	24
5		70%  28%	40
6		52% —  ND	90
7		85%  6%	40
8		81%  8%	40
9		76%  14%	40

Table 2 (continued)

Entry	Substrate	Products and yields <sup>b</sup>	Time (h)
10		 63%  8%	22
11		 70%  8%	110

<sup>a</sup> All reactions were conducted at reflux using 2 equiv of In, 5 equiv of ND<sub>4</sub>Cl, and THF-*d*<sub>8</sub>/D<sub>2</sub>O (10:1) as the solvent.

<sup>b</sup> Isolated yields and the free carboxylic acids were indicated after silica gel separation.

To determine the applicability of THF-*d*<sub>8</sub> as the solvent, several substrates having representative structures were tested with an indium-mediated reaction using deuterated ammonium chloride (Table 1).<sup>15</sup> Although the reaction conditions were very mild, and some improvement was found, the obtained results were quite unsatisfactory, furnishing deuterated forms as the major products and deprotected free carboxylic acids as the minor. Since the total yields, as shown in Table 1, were not inferior, a modification of the reaction conditions was envisioned. After experimental study, the addition of deuterium oxide was found to effectively smooth the deprotection of 2,2,2-trichloroethyl esters with a benzylic methylene unit. The results are summarized in Table 2<sup>16</sup> and include various substrates possessing diverse functionalities. The compounds with representative structures were reevaluated (Table 2, entries 1 and 2). The reaction conditions were mild, and dramatic improvement was observed. In both cases, the free carboxylates were furnished exclusively in good yields. A silyl protection of the *tert*-butyldiphenylsilyl (TBDPS) group was resistant to the reaction conditions, although 28% of the deuterated form of demono-chlorination was generated (Table 2, entry 5) with an evident <sup>1</sup>H NMR spectra, by comparison with our previous data.<sup>10</sup> Meanwhile, derivatives with protected hydroxyl groups (Table 2, entries 5 and 6) displayed higher yields than the unprotected substrate (Table 2, entry 4). Among phenyl acetic acid derivatives, those with electron donating units, such as alkyl groups (Table 2, entries 7–9), showed high yields of the corresponding carboxylates, whereas those with electron-withdrawing groups, such as halogen and sulfonyloxy groups (Table 2, entries 3 and 6), displayed medium yields. In the case of 4-phenoxy derivative, the reaction furnished 70% of the corresponding carboxylate. It should be noted that separation of these two products, free carboxylates and 2-deuterio-2,2-dichloroethyl esters, was easily performed through ordinary silica gel flash chromatography.

In summary, by using deuterated solvents, we have substantially improved the mild indium-mediated deprotection of 2,2,2-trichloroethyl esters with a benzylic methylene moiety. We also have determined the applicability with respect to various substrates possessing diverse functionalities. Even when a small amount of 2-deuterio-2,2-dichloroethyl esters were formed, these minor products were easily separated. The deprotection of 2,2,2-trichloroethyl esters with a benzylic methylene moiety is now a simple process. To our knowledge, it represents the first attempt to utilize deuterated solvents in this type of chemical transformation. Research on further applications and utility is now being conducted.

**General experimental procedure:** The trichloroethyl esters (1 mmol) were dissolved in THF-*d*<sub>8</sub>/D<sub>2</sub>O (10:1, w/w, 11 g), and indium powder<sup>17</sup> (2 mmol) and ND<sub>4</sub>Cl (5 mmol) were added at room temperature. The reaction mixture was heated at reflux and monitored for completion by TLC. Flash column chromatogra-

phy on silica gel furnished analytically pure products, which were confirmed by spectroscopy.

### Acknowledgment

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- Experimental data for Table 1.  
*Phenylacetic acid 2-deuterio-2,2-dichloroethyl ester* (Table 1, entry 1): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.36–7.27 (m, 5H), 4.46 (s, 2H), 3.70 (s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 170.6, 133.1, 129.3, 128.6, 127.3, 68.4, 68.2 (t, J = 27.8 Hz), 40.8.  
*Phenylpropionic acid 2-deuterio-2,2-dichloroethyl ester* (Table 1, entry 2): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.30–7.27 (m, 5H), 4.42 (s, 2H), 2.97 (t, 2H, J = 7.6 Hz), 2.71 (t, 2H, J = 7.6 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 172.0, 140.1, 128.7, 128.4, 126.5, 68.5, 68.3 (t, J = 27.8 Hz), 35.5, 30.8.
- Experimental data for Table 2.  
*4-Bromophenylacetic acid 2-deuterio-2,2-dichloroethyl ester* (Table 2, entry 3): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.46 (d, 2H, J = 8.6 Hz), 7.17 (d, 2H, J = 8.6 Hz), 4.40 (s, 2H), 3.59 (s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 170.1, 132.0, 131.8, 131.0, 121.5, 68.5, 68.1 (t, J = 27.8 Hz), 40.2.  
*3-(tert-Butyldiphenylsilyloxy)phenylacetic acid 2-deuterio-2,2-dichloroethyl ester* (Table 2, entry 5): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.72–7.71 (m, 4H), 7.45–7.42 (m, 2H), 7.38–7.36 (m, 4H), 7.03 (t, 1H, J = 8.1 Hz), 6.80–6.76 (m, 2H), 6.64 (dd, 1H, J = 8.1, 2.3 Hz), 4.36 (s, 2H), 3.52 (s, 2H), 1.10 (s, 9H); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>): δ 170.0, 156.6, 136.2, 135.6, 133.5, 130.6, 130.0, 128.7, 122.9, 121.5, 119.3, 68.9 (t, J = 27.5 Hz), 68.6, 41.0, 27.0, 20.0.  
*4-Tolylacetic acid 2-deuterio-2,2-dichloroethyl ester* (Table 2, entry 7): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.18 (d, 2H, J = 8.0 Hz), 7.15 (d, 2H, J = 8.0 Hz), 4.45 (s, 2H), 3.66 (s, 2H), 2.34 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 170.8, 137.0, 130.1, 129.3, 129.1, 68.4, 68.0 (t, J = 27.7 Hz), 40.4, 21.1.  
*4-Isopropylphenylacetic acid 2-deuterio-2,2-dichloroethyl ester* (Table 2, entry 8): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.21–7.19 (m, 4H), 4.45 (s, 2H), 3.66 (s, 2H), 2.89 (sept, 1H, J = 6.8 Hz), 1.24 (d, 6H, J = 7.0 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 170.8, 148.0, 130.4, 129.2, 126.7, 68.4, 68.0 (t, J = 27.8 Hz), 40.4, 33.7, 23.9.  
*2,4,6-Trimethylphenylacetic acid 2-deuterio-2,2-dichloroethyl ester* (Table 2, entry 9): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.86 (s, 2H), 4.43 (s, 2H), 3.71 (s, 2H), 2.29 (s, 6H), 2.26 (s, 3H); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>): δ 170.4, 137.5, 137.0, 129.7, 128.7, 69.0 (t, J = 27.8 Hz), 68.5, 35.2, 21.3, 20.6.

4-Dimethylaminophenylacetic acid 2-deuterio-2,2-dichloroethyl ester (Table 2, entry 10):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.15 (d, 2H,  $J = 8.5$  Hz), 6.99 (d, 2H,  $J = 8.5$  Hz), 4.44 (s, 2H), 3.59 (s, 2H), 2.94 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.3, 149.9, 129.9, 120.8, 112.7, 68.4, 68.1 (t,  $J = 27.5$  Hz), 40.6, 39.9.

4-Phenoxyphenylacetic acid 2-deuterio-2,2-dichloroethyl ester (Table 2, entry 11):

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.32 (m, 2H), 7.27–7.24 (m, 2H), 7.11 (t, 1H,  $J = 7.5$  Hz), 7.02–6.96 (m, 4H), 4.47 (s, 2H), 3.67 (s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.7, 157.0, 156.6, 130.6, 129.7, 127.8, 123.4, 118.94, 118.92, 68.4, 68.0 (t,  $J = 27.5$  Hz), 40.1.

17. Indium powder, 99.99%. Aldrich Chemical Company, Catalog # 277959.