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A novel deprotection of trichloroacetamide

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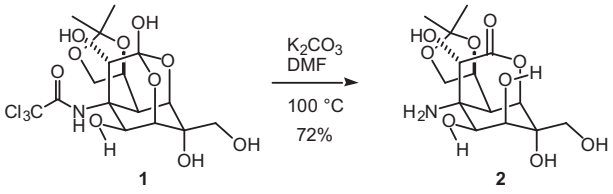
Abstract—Deprotection of trichloroacetamide was carried out with Cs_2CO_3 in DMF or DMSO at 100 °C to afford an amine in good yield. A survey of the scope and limitations revealed the utility of the deprotection condition for various functionalized substrates.

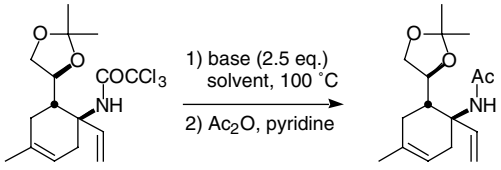
The rearrangement of allylic trichloroacetimidate to allylic trichloroacetamide, the so-called Overman rearrangement, has been widely employed to prepare nitrogen-containing compounds.[1] An improved condition developed in our laboratories has expanded the range of substrates for the rearrangement.[2] Recently, Overman and Anderson reported the catalytic asymmetric rearrangement of trichloroacetimidate.[3] On the other hand, the removal procedure of the resulting trichloroacetamide is limited to hydrolysis with aqueous NaOH or HCl solution and reduction with $NaBH_4$[4] or DIBAL-H.[5] In the course of our synthetic studies of (−)-tetrodotoxin,[6] incidentally we found that trichloroacetamide **1** was heated with K_2CO_3 in DMF to afford amine **2** (Eq. 1). This result prompted us to study the details of the reaction, and we have developed the optimum conditions for deprotection of trichloroacetamide.



1 2 (1)

We first examined the effect of an alkali metal of carbonate for the reaction using the trichloroacetamide **3**[7] as a model substrate (Table 1). When **3** was heated with Li_2CO_3 in DMF at 100 °C, no reaction was observed (entry 1). The reaction with Na_2CO_3 proceeded to afford the corresponding amine, which was isolated as acetamide **4** in 18% yield because of its volatility (entry 2). On the other hand, the reaction with K_2CO_3 gave **4** in 75% yield (entry 3). Rb_2CO_3 and Cs_2CO_3 were found to be more effective bases for the deprotection (entries 4 and 5). In these reactions, 2.5 equiv of the base was required for complete consumption of the starting material **3**. DMSO was also a suitable solvent to remove the trichloroacetamide in good yield (entry 6). From these results, we concluded that Cs_2CO_3 in DMF or DMSO at 100 °C was the best condition for removal of trichloroacetamide.[8,9]

Table 1. Optimization of the deprotection condition



3 4

Entry	Base	Solvent	Time of (1)	Yield (%)
1	Li_2CO_3	DMF	3 h	0
2	Na_2CO_3	DMF	3 h	18[a]
3	K_2CO_3	DMF	2 h	75
4	Rb_2CO_3	DMF	1 h	86
5	Cs_2CO_3	DMF	40 min	82
6	Cs_2CO_3	DMSO	30 min	86

[a] The starting material **3** was recovered in 65% yield.

Next, we examined the scope and limitations of the reaction for various substrates.[10] The results are shown in Table 2. Deprotection of simple trichloroacetamide **5**[11]

Keywords: Protecting group; Deprotection; Trichloroacetamide; Overman rearrangement.
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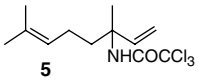
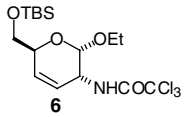
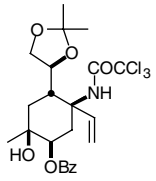
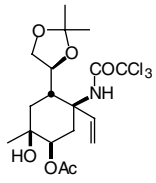
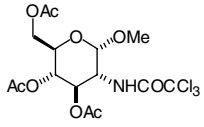
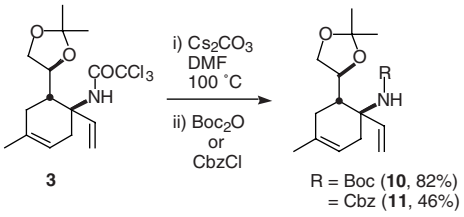
Table 2. The deprotection of trichloroacetamide[a,b]

Entry	Substrate	Time (min)	Yield (%)
1	 **5**	15	78[c]
2	 **6**	20	80
3	 **7**	25	80
4	 **8**	20	49
5	 **9**	15	Trace

[a] The deprotection was carried out with Cs_2CO_3 in DMSO at 100 °C.
[b] All products were characterized by ^1H,^{13}C NMR and elemental analyses or HR-MS.
[c] The product was isolated as acetamide after acetylation.

proceeded under the optimized conditions to give the corresponding allylic amine in 78% yield (entry 1). In the reaction of **6**[2], the amine was obtained in 80% yield along with the symmetrical urea in 20% yield (entry 2).[12] Deprotection of **7** containing benzoate[13] gave the amine in 80% yield without affecting the benzoate (entry 3). However, trichloroacetamide of **8**[14] containing acetate was removed in 49% yield (entry 4) and trichloroacetamide of **9**[15] containing three acetates gave only a trace amount of the amine (entry 5). The reason for the low yields is removal of the acetates.

Furthermore, we attempted one-pot transformation of trichloroacetyl group of amine into another protecting group (Scheme 1). The reaction mixture of amine obtained from **3** under the established conditions was



Scheme 1.

treated with Boc_2O or CbzCl at room temperature to give the corresponding carbamate **10** and **11**, respectively.[16]

In summary, we have developed a novel deprotection condition of a trichloroacetamide to an amine. The condition is compatible with many functional groups such as ether, silyl ether, acetal and benzoate. We also demonstrated one-pot transformation of trichloroacetamide into the corresponding carbamate such as Boc and Cbz. These reactions would also increase the utility of the Overman rearrangement for synthesizing highly functionalized compounds.

Acknowledgements

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8. *Typical experimental procedure for deprotection of trichloroacetamide* (entry 5 in Table 1). A mixture of trichloroacetamide **3** (397 mg, 1.04 mmol) and Cs_2CO_3 (861 mg, 2.64 mmol) in DMF (12 mL) was stirred at 100 °C for 40 min. After being cooled to room temperature, the reaction mixture was poured into satd $NaHCO_3$ solution (15 mL). The mixture was extracted with AcOEt (15 mL × 3) and the resulting organic layer was washed with H_2O (45 mL × 2) and brine (45 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in pyridine (6 mL) and Ac_2O (6 mL). After stirring at room temperature for 16 h, the reaction mixture was diluted with toluene and concentrated in vacuo. The residue was purified by column chromatography (silica gel 12 g, AcOEt/hexane = 1:3 → 1:1 → 3:1) to afford acetamide **4** (237 mg, 82% in two steps). ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, s, acetonide), 1.43 (3H, s, acetonide), 1.58–1.69 (2H, m, C*H*, CH_AH_B), 1.64 (3H, br s, CH_3), 1.93–2.05 (1H, m, CH$_A$$H_B$), 1.95 (3H, s, Ac), 2.24 (1H, d quintet, J = 17, 2 Hz, CH_AH_B), 3.36 (1H, dd, J = 17, 6 Hz, CH$_A$$H_B$), 3.64 (1H, t, J = 7.5 Hz, O–CH–CH_AH_B–O), 3.97–4.08 (2H, m, O–CH–CH$_A$$H_B$–O, O–C*H*–CH$_2$–O), 5.19 (1H, d, J = 17.5 Hz, CH=CH_AH_B), 5.27 (1H, d, J = 10.5 Hz, CH=CH$_A$$H_B$), 5.37 (1H, m, C=C*H*), 5.83 (1H, dd,

J = 17.5, 10.5 Hz, C*H*=CH_2), 7.77 (1H, br s, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 24.5, 26.2, 26.6, 30.1, 36.7, 44.4, 58.7, 68.8, 76.7, 109.5, 115.2, 119.6, 130.4, 135.3, 168.9. Anal. Calcd for $C_{16}H_{25}Cl_3NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.81; H, 9.01; N, 4.82.

9. Cs_2CO_3 was chosen because of its lower price compared to that of Rb_2CO_3.
10. Although the reaction mechanism has not been completely clarified yet, we speculate that an isocyanate generated under the condition[17] may be captured by the carbonate, giving the amine.
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12. Less steric hindrance of the trichloroacetamide of **6** connected to a secondary carbon may be the reason that a significant amount of the symmetric urea was obtained only in this case.
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14. The substrate **8** was prepared in 80% yield from **3** by dihydroxylation with OsO_4[13] and acetylation.
15. The substrate **9** was prepared in 76% yield from 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside[18] by trichloroacetylation in pyridine.
16. The reaction conditions of these transformations have not been optimized.
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