Trichloroacetimidate as an Efficient Protective Group for Alcohols

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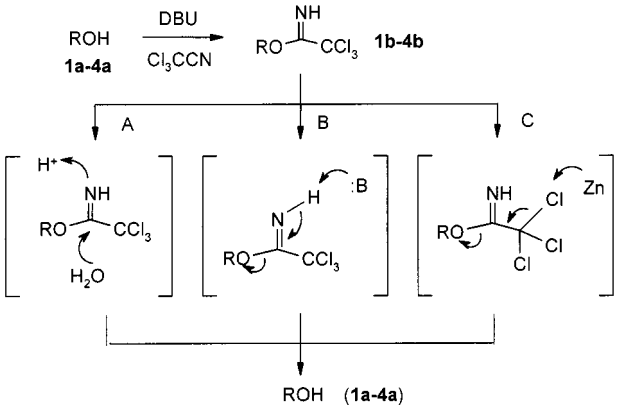
Abstract: The trichloroacetimidate is disclosed to be a general and efficient protective group for alcohols, which can be deprotected under mild acidic, basic, or neutral conditions, and has orthogonal stability with the acetate and *tert*-butyldimethylsilyl (TBS) protections.

Key words: trichloroacetimidate, protective group, alcohol

Protection of hydroxyl function is one of the main themes in the protective group chemistry, and is decisive in many synthetic works.[1] Although a very large number of protective groups for alcohols have been developed, new and efficient protection manipulation continues to be the focus of attention and will certainly open up new possibilities for performing the art of organic synthesis.[1,2] The trichloroacetimidate, which can be readily generated from an alcohol by addition with trichloroacetonitrile in the presence of a base, has widely been used for two purposes: (1) serves as an excellent leaving group to liberate a useful cation, such as in glycosyl,[3] benzyl,[4] *p*-methoxybenzyl,[5] allyl,[4b,c] *tert*-butyl,[6] and 2-phenylisopropyl trichloroacet-imidate[6b]; (2) serves as a neighboring nucleophilic nitrogen surrogate to deliver an aza-Claisen rearrangement (Overman rearrangement)[7] or an addition to a trigonal site (an epoxy[8] or a Hg^{2+} or I^{+} activated carbon-carbon double bond[9]). To the best of our knowledge, so far only two papers mentioned the use of the trichloroacetimidate as a temporary protective group for hydroxyl function.[10] Both cases involved in the course of execution of the Schmidt glycosylation;[3] therein the anomeric trichloroacetimidate at the same time was employed as a leaving group. The trichloroacetimidate protection remained intact during the glycosylation under the promotion of TMSOTf and BF_3•OEt_2, and was removed afterwards under acidic conditions (1N HCl/MeOH and 80% HOAc) in moderate to good yields (51% and 87%, respectively). Herein, we report that trichloroacetimidate can be used as a general and efficient protective group for alcohols, which can be deprotected under mild acidic, basic, or neutral conditions, and has orthogonal stability with the acetate and TBS ether protections.

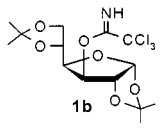
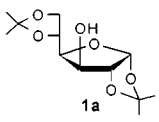
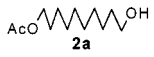
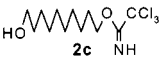
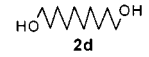
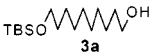
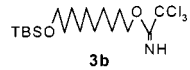
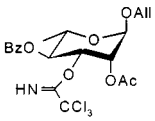
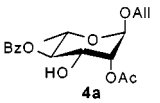
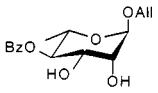
According to the intrinsic properties of the trichloroacetimidate, three types of conditions were sought to release the masking hydroxyl function (Scheme 1 and Table): (A) Acidic conditions (TsOH-H_2O, MeOH/CH_2Cl_2, rt); the same mechanism as in the acid catalyzed hydrolysis of esters proceeds. (B) Basic conditions (DBU, MeOH); a retro-reaction of the addition of an alcohol to trichloroacetonitrile involves.[11] (C) Reductive elimination conditions (neutral conditions) (Zn, NH_4Cl, EtOH); the same mechanism as in the deprotection of the 2,2,2-trichloroethoxycarbonyl (TrOC) group[12] and the 2,2,2-trichloro-ethyl ester works.[13]



Condition A: TsOH-H_2O (0.5 equiv), CH_2Cl_2/MeOH (1/1, v/v), rt, 5 min; Condition B: DBU (1.0 equiv), MeOH; Condition C: Zn, NH_4Cl, EtOH, reflux, 5 min.

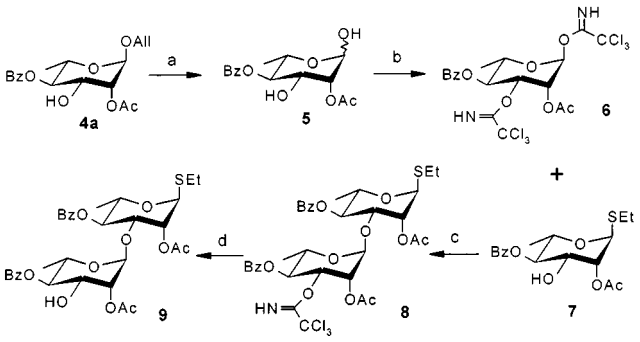
Scheme 1

Three conditions worked very well on the cleavage of the trichloro-acetimidate on a relatively robust substrate **1b** (entries 1-3).[14,15] However, treatment of **1b** with TsOH under longer time also resulted in the partial cleavage of the 4,6-isopropylidene. The trichloroacet-imidate was found to be selectively removed under acidic (condition A) and reductive elimination conditions (condition C) in the presence of an acetate counterpart (entries 4, 6). Prolonging the reaction time under Zn/NH_4Cl in ethanol (condition C) also led to the cleavage of the acetate (entry 7), which was likely effected by the eliminated fragment (i.e. HN=C=CCl_2); because it has been found that acetate remained stable under these conditions.[16] Interestingly, it was also found that the acetate was removed selectively in the presence of its trichloroacetimidate counterpart under the action of DBU in methanol (condition B, entry 5). The trichloroacetimidate in between an acetyl and benzoyl groups was also selectively removed under the action of TsOH (substrate **4b**, entry 13); while under the action of Zn/NH_4Cl in EtOH, both the trichloroacetimidate and the acetate were removed with the benzoate remained intact

Entry	Substrate[a]	Conditions[b]	Product (Yield%)[c]	
1		A		98
2		B (rt, 2h)		100
3	**1b**	C	**1a**	99
4		A	**2a**	93
5		B (rt, 2h)		91
6	**2b**	C	**2a**	90
7		C (2h)	 **2d**	100
9		A	 **3a**	92
10		B (40°C, 40h)	**3a**	94
11	**3b**	C	**3a**	99
12		D	**2c**	86
13		A	 **4a**	85
14	**4b**	C	 **4c**	73

[a] The trichloroacetimidate substrates (**1b**-**4b**) were prepared from the corresponding alcohols (Cl_3CCN, DBU, CH_2Cl_2, rt) in excellent yields. [b] Conditions A, B, and C are listed in Scheme 1; Conditions D: TBAF, THF, rt. [c] Isolated yields.

(entry 14). Moreover, it was also found that the trichloroacetimidate has excellent orthogonal stability with another commonly used protective group – TBS ether (entries 9-12): the trichloroacetimidate was selectively removed under all three conditions in the presence of an TBS counterpart (entries 9-11), while in turn the TBS ether was selectively cleaved under TBAF without affecting its trichloroacetimidate counterpart (entry 12), giving the corresponding deprotection products in excellent yields.



Reagents and conditions: (a) $PdCl_2$, MeOH, rt, 76%; (b) Cl_3CCN, DBU, CH_2Cl_2, rt, 89%; (c) BF_3OEt_2, 4 Å MS, CH_2Cl_2, -78 °C, 64%; (d) TsOH-H_2O (0.8 equiv), MeOH, CH_2Cl_2, rt, 81%.

Scheme 2

As depicted in scheme 2,[17] the use of trichloroacetimidate as a protective group for hydroxyl function is particular useful in the oligosaccharide synthesis. To prepare the disaccharide acceptor **9**, a protective group should be introduced onto the 3-OH of **4a**[18] first, which should be stable under the conditions for converting the anomeric allyl group to the trichloroacetimidate and for the subsequent glycosylation (conditions a-c), and then has to be removed afterwards without effecting the acetyl, benzoyl, anomeric thioether, and the glycosidic bond. It was not easy to find a perfect protective group to meet all these requests; nevertheless, herein the trichloroacetimidate protection was demonstrated unequivocally to be a very nice and straightforward choice.

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(14) Typical procedures for the deprotection of trichloroacetimidates. Condition A: to a solution of **1b** (120 mg, 0.30 mmol) in CH_2Cl_2-MeOH (4 mL, 1:1) at rt was added

TsOH-H_2O (28 mg, 0.15 mmol). After being stirred at rt for 5 min, the reaction was quenched by addition of Et_3N (0.2 mL), and then concentrated. The residue was purified by a silica gel column chromatography (petroleum ether-EtOAc, 2:1) to give **1a** as a white solid (76 mg, 98%). Condition B: to a solution of **1b** (49 mg, 0.12 mmol) in dry MeOH at rt was added DBU (0.02 ml, 0.12 mmol). After being stirred for 2 h, the solution was concentrated to a residue, which was purified by a silica gel column to give **1a** (32 mg, 100%). Condition C: to a solution of **1b** (83 mg, 0.21 mmol) in dry EtOH (2 mL), was added Zn powder (67 mg, 1.0 mmol) and NH_4Cl (27 mg, 1.0 mmol). After being refluxed for 5 min, the mixture was filtered. The filtrates were concentrated to a residue, which was purified by a silica gel column to give **1a** (53 mg, 99%).

(15) ^{1}H NMR of trichloroacetimidates (**1b**-**4b**) (300 MHz, $CDCl_3$).
1b: 8.55 (1H, s), 5.92 (1H, d, *J* = 3.7), 5.32 (1H, d, *J* = 2.6), 4.62 (1H, d, *J* = 3.6), 4.38 (1H, t, *J* = 6.2), 4.30 (1H, dd, *J* = 7.5, 2.5), 4.13 (1H, t, *J* = 7.2), 4.02 (1H, m), 1.53, 1.41, 1.32, 1.29 (3H each, s each).
2b: 8.20 (1H, brs), 4.27 (2H, t, *J* = 6.5), 4.03 (2H, t, *J* = 6.8), 2.03 (3H, s), 1.78 (2H, m), 1.59 (2H, m), 1.43-1.25 (12H, m);
3b: 8.21 (1H, brs), 4.27 (2H, t, *J* = 6.5), 3.59 (2H, t, *J* = 6.5), 1.76 (2H, m), 1.51-1.28 (14H, m), 0.88 (9H, s), 0.03 (6H, s).
4b: 8.45 (1H, s), 8.02-7.80 (5H, m), 5.93 (1H, m), 5.60 (3H, m), 5.32 (2H, m), 4.88 (1H, s), 4.24 (1H, dd, *J* = 12.8, 5.1), 4.10 (2H, m), 2.14 (3H, s), 1.31 (3H, d, *J* = 6.3).

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(17) ^{1}H NMR (300 MHz, $CDCl_3$) data for compounds **5**-**9**. **5**: 8.05 (2 H, m), 7.60 (1H, m), 7.46 (2H, m), 5.26 (1H, m), 5.16-5.09 (2H, m), 4.26 (2H, m), 3.23 (1H, d, J = 4.1), 2.44 (1H, d, J = 9.7), 2.19 (3H, s), 1.28 (3H, d, *J* = 6.2);
6: 8.79 (1H, s), 8.57 (1H, s), 8.01 (2H, m), 7.60 (1H, m), 7.46 (2H, m), 6.47 (1H, d, J = 1.6), 5.69-5.57 (3H, m), 4.26 (1H, m), 1.89 (3H, s), 1.32 (3H, d, *J* = 6.3);
8: 8.02 (4H, m), 7.56 (2H, m), 7.43 (4H, m), 5.48-5.26 (5H, m), 5.12 (2H, m), 4.37 (1H, dd, J = 9.7, 3.4), 4.30 (1H, m), 4.12 (1H, m), 2.66 (2H, m), 2.29 (3H, s), 1.78 (3H, s), 1.27 (9H, m);
9: 8.04 (4H, m), 7.57 (2H, m), 7.47 (4H, m), 5.41 (2H, m), 5.27 (3H, m), 4.95 (1H, d, J = 1.5), 4.32 (2H, m), 4.04 (1H, m), 3.78 (1H, m), 2.63 (2H, m), 2.23 (3H, s), 1.89 (3H, s), 1.26 (9H, m).

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