ORGANIC LETTERS

2000
Vol. 2, No. 5
701−703

The Use of Diazabicyclo[2.2.2]octane as a Novel Highly Selective Dechloroacetylation Reagent

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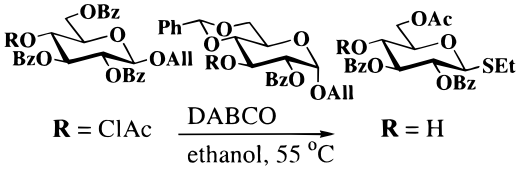
Received January 19, 2000

ABSTRACT



In a study directed toward the use of the chloroacetyl protecting group in carbohydrate synthesis, the sterically hindered tertiary amine diazabicyclo[2.2.2]octane (DABCO) was found to give complete and selective cleavage of the chloroacetyl group in the presence of other ester functions such as benzoyl and acetyl groups at primary and/or secondary positions.

The chloroacetyl group is used for the temporary protection of hydroxyl groups, as it is a very base-sensitive group that can be selectively cleaved in the presence of other acyl functions by a number of methods. In addition to, for example, aqueous ammonia[1] or hydrazine acetate,[2] the most widely used deprotection reagent is thiourea.[3] The latter reaction is easy to perform but requires relatively long reaction times. The nucleophilic sulfur of thiourea displaces the chloride atom of the chloroacetyl group, and one of the amine functions subsequently attacks the ester bond intramolecularly.[4] Deprotection using hydrazine dithiocarbonate (HDTC), introduced by van Boeckel et al.,[5] is based on the same reaction mechanism. It gives rise to fast and clean reactions but requires the preparation of the reagent just before use, since it is only stable for 15−20 min.[6] This paper reports a novel dechloroacetylation reagent, diazabicyclo-[2.2.2]octane (DABCO), which turned out to be highly selective, fast, and easy to handle.

In the course of the synthesis of oligosaccharides, we were confronted with problems in the deallylation of compound **1** to give **2** (Figure 1). The yield of the isomerization of the double bond using tristriphenylphosphine rhodium(I) chloride and DABCO (3 equiv) in refluxing ethanol was low, due to

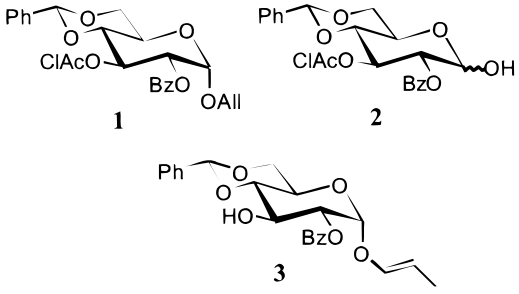


Figure 1. Deallylation of **1** (→ **2**) and the formed side product **3**.

(1) Reese, C. B.; Stewart, J. C. M.; van Boom, J. H.; de Leeuw, H. P. M.; Nagel, L.; de Rooy, J. F. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 934−942.

(2) Udodong, U. E.; Rao, C. S.; Fraser-Reid, B. *Tetrahedron* **1992**, *48*, 4713−4724.

(3) See, for example: Blatter, G.; Jacquinet, J. C. *Carbohydr. Res.* **1996**, *288*, 109−125. Naruto, M.; Ohno, K.; Naruse, N.; Takeuchi, H. *Tetrahedron Lett.* **1979**, *3*, 251−254. Glaudemans, C. P. J.; Bertolini, M. J. *Meth. Carbohydr. Chem.* **1980**, *VIII*, 271−275.

(4) Masaki, M.; Kitahara, T.; Kurita, H.; Ohta, M. *J. Am. Chem. Soc.* **1968**, *90*, 4508−4509.

(5) van Boeckel, C. A. A.; Beetz, T. *Tetrahedron Lett.* **1983**, *24*, 3775−3778.

10.1021/ol005567z CCC: $19.00
Published on Web 02/15/2000

the formation of the dechloroacetylated monosaccharide derivative **3**, as shown by ^{1}H NMR (Figure 1).[7] This observation stimulated further investigations toward the use of DABCO as a general dechloroacetylation reagent.

Complete dechloroacetylation of **1** to give **4** (Figure 2) was achieved by incubating 0.02 M **1** in ethanol in the absence of Wilkinson's catalyst with 5 equivs of DABCO at room temperature for 6 h.[8] Isomerization of the double bond without affecting the chloroacetyl group was achieved by reaction of 5 mM **1** with Wilkinson's catalyst without DABCO in refluxing ethanol or by using only a catalytic amount of DABCO in either refluxing ethanol or refluxing 1:1 ethanol−toluene, the latter solvent system slowing down the dechloroacetylation. After reaction of the intermediate with *N*-iodosuccinimide and water, **2** was obtained in 77% yield.[9]

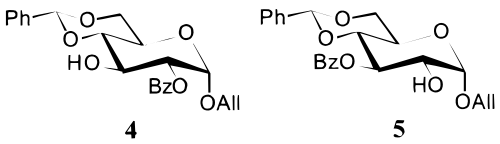


Figure 2. Dechloroacetylation of **1** afforded **4** and in some cases the migrated product **5**.

To gain insight into the factors influencing the reaction time needed for complete dechloroacetylation of **1** in ethanol, several parameters were varied. By increasing the amount of DABCO, the reaction time was shortened from 6 to 2 h (Table 1, entries 1 and 2). Furthermore, the temperature of the reaction mixture had a marked influence on the reaction rate (entries 3, 4, and 5), and thereby on the reaction time. Using 15 equiv of DABCO at 55 °C, a sufficiently short reaction time was obtained (entry 6). By increasing the concentration of **1** from 0.02 to 0.06 M (Table 1, entries 6 and 7), the reaction time was further decreased from 30 min to less than 10 min. In all cases a quantitative conversion was detected from TLC and ^{1}H NMR, after neutralization of the reaction mixtures with Dowex H^+, filtration, and concentration. No migration of the benzoyl group from O-2 to O-3 was observed. Only after 3 days of stirring, in the case of entries 1 and 2, could about 5% migration (**4** → **5**, Figure 2) be seen.[10] This migration also started to occur after more than 4 h of stirring for entries 4−6. Only in the case of entry 7 was some migration already found after 30 min. Therefore, in view of reaction time and practical ease, we preferred the reaction conditions described for entry 6.

Table 1. Effect of the Amount of DABCO, Temperature, and Concentration on the Reaction Time of the Dechloroacetylation of **1** As Carried out in Ethanol

entry	DABCO (equiv)	temp (°C)	time (min)	concn (M)
1	5	20	360	0.02
2	20	20	120	0.02
3	10	20	240	0.02
4	10	55	40	0.02
5	10	70	15	0.02
6	15	55	30	0.02
7	15	55	<10	0.06

To compare the effectiveness of DABCO with thiourea, the following experiments were performed. According to the commonly used dechloroacetylation with thiourea, 3 equiv of reagent, either thiourea or DABCO, was reacted with 0.03 M **1** in 5:1 ethanol−pyridine at 70 °C. Although in both cases excellent isolated yields were obtained, the use of DABCO resulted in much faster dechloroacetylation (Table 2, entries 1 and 2). Also following the established procedure (Table 1, entry 6), DABCO was found to give a much faster dechloroacetylation (Table 2, entries 3 and 4).

Table 2. Comparison of DABCO and Thiourea in the Dechloroacetylation of **1**

entry	reagent	solvent	time (min)	yield (%)
1	thiourea	ethanol/pyridine	90	93
2	DABCO	ethanol/pyridine	<10	95
3	thiourea	ethanol	270	97
4	DABCO	ethanol	30	94

In additional studies, two other tertiary amines, triethylamine (TEA) and *N*,*N*-diisopropylethylamine (DIPEA), were examined for their dechloroacetylating properties. Incubation of **1** with 15 equiv of TEA or DIPEA in ethanol at room temperature resulted in partial dechloroacetylation. Before the dechloroacetylation was complete, about 10% migration of the benzoyl group had occurred from O-2 to O-3, resulting in the formation of **5** (Table 3, entries 1 and 3). In dichloromethane, no reaction was observed within 1.5 h at room temperature (Table 3, entries 2 and 4). These results

Table 3. Dechloroacetylation of **1** Using the Tertiary Amines TEA or DIPEA

entry	base	solvent	temp (°C)	time (h)	yield (%)[a] of **1**:**4**:**5**
1	TEA	ethanol	20	16	25:65:10
2	TEA	Cl_2CH_2	20	1.5	no reaction
3	DIPEA	ethanol	20	16	25:65:10
4	DIPEA	Cl_2CH_2	20	1.5	no reaction

[a] Estimated from TLC.

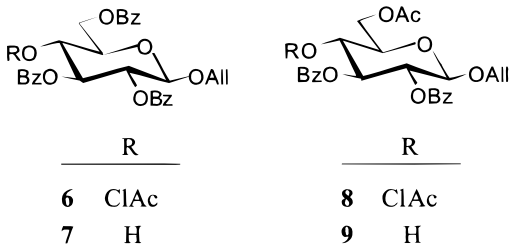
(6) Smith, A. B., III; Hale, K. J.; Vaccaro, H. A.; Rivero, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 2112−2122.

(7) ^{1}H NMR analysis showed the removal of the chloroacetyl group (δ 4.00, 3.94: 2 d, each 1 H), a shift of H-3 from 5.87 to 4.40 ppm, and the presence of a 1-propenyl group (δ 6.11: dq, 1 H, OC*H*═CHCH$_3$. 5.19: dq, 1 H, OCH═C*H*CH$_3$. 1.52: dd, 3 H, OCH═CHC*H*$_3$).

(8) Characteristic ^{1}H NMR data of **4**: δ 5.87−5.74 (m, 1 H, OCH$_2$C*H*═CH$_2$), 5.57 (s, 1 H, PhC*H*), 5.21 (d, 1 H, H-1), 5.30−5.22, 5.15−5.10 (2 m, each 1 H, OCH$_2$CH═C*H*$_2$), 5.06 (dd, 1 H, H-2), 4.40 (t, 1 H, H-3).

clearly show that the selectivity of DABCO in the dechloroacetylation of **1** does not result solely from being a tertiary amine.

To further explore the generality of the procedure, compounds **6** and **8** (Figure 3) were subjected to the



	R		R
6	ClAc	**8**	ClAc
7	H	**9**	H

Figure 3. Dechloroacetylation of **6** and **8**.

following reaction conditions:[11] (A) 0.02 M **6** or **8**, 15 equiv of DABCO, 55 °C, ethanol; (B) 0.04 M **6** or **8**, 1 equiv of DABCO, 55 °C, 5:1 ethanol−pyridine.

Dechloroacetylation of **6** was found to be complete in 45 min using method A. Using method B, which is much milder, 2 h were needed for the conversion of **6** to **7**. In both cases the isolated yield was 95%.[12] Compound **8** was dechloroacetylated in 75 min using method A and in 2.5 h using method B. The isolated yields were 95% and 97%, respectively.[13] No migration could be observed by ^{1}H NMR. Although method A is much faster than method B, method B may be used when more basic conditions are expected to cause problems.

Performing the reaction according to method B without DABCO, complete dechloroacetylation of **6** and **8** required 6 and 7 h, respectively. This observation indicates that pyridine alone is also able to affect the chloroacetyl group but that DABCO greatly accelerates the reaction. Ethylenediamine, *o*-phenylenediamine, and 2-mercaptoethylamine[14] have also been mentioned as dechloroacetylation reagents. However, those reactions were performed with a large excess of pyridine and TEA in methanol. Our findings with pyridine and TEA show that these reagents themselves might not be the actual dechloroacetylating agents.

The results clearly show that the use of DABCO as dechloroacetylating agent provides a good method in addition to the commonly used reagents. Benzoyl and acetyl groups at primary and/or secondary positions are stable under the reaction conditions employed. The procedure is fast, highly selective, and easy to perform.

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(9) Characteristic NMR data of **2**: ^{1}H, δ 5.54 (s, 1 H, PhC*H*α), 5.52 (s, 1 H, PhC*H*β), 5.88 (t, 1 H, H-3), 5.57 (d, 1 H, H-1α), 5.19 (dd, 1 H, H-2β), 5.09 (dd, 1 H, H-2α), 4.92 (d, 1 H, H-1β); ^{13}C, δ 101.5 (Ph*C*H), 95.8 (C-1α), 90.7 (C-1β), 40.4 (Cl*C*H$_2$COα), 40.3 (Cl*C*H$_2$COβ).

(10) All signals in the ^{1}H NMR spectrum were slightly shifted. Strong shifts were observed for H-3, from 4.40 to 5.61 ppm, and for H-2, from 5.06 ppm to the bulk region.

(11) Purification: after complete reaction, the mixture was diluted with ethyl acetate, poured into 0.05 M HCl, and washed. The organic layer was dried ($MgSO_4$), filtered, and concentrated.

(12) Characteristic ^{1}H NMR data: **6** δ 5.76 (t, 1 H, H-4), 4.86 (d, 1 H, H-1), 3.95 and 3.89 (2 d, each 1 H, ClC*H*$_2$CO). **7**: δ 4.81 (d, 1 H, H-1), 3.93 (dt, 1 H, H-4), 3.58 (d, 1 H, HO-4).

(13) Characteristic ^{1}H NMR data: **8** δ 5.72 (t, 1 H, H-4), 4.76 (d, 1 H, H-1), 3.97 and 3.90 (2 d, each 1 H, ClC*H*$_2$CO), 2.12 (s, 3 H, C*H*$_3$CO). **9**: δ 4.73 (d, 1 H, H-1), 3.83 (t, 1 H, H-4), 2.12 (s, 3 H, C*H*$_3$CO).

(14) Cook, A. F.; Maichuk, D. T. *J. Org. Chem.* **1970**, *35*, 1940−1943.