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3-(Dimethylamino)-1-propylamine: A Cheap and Versatile Reagent for Removal of Byproducts in Carbohydrate Chemistry

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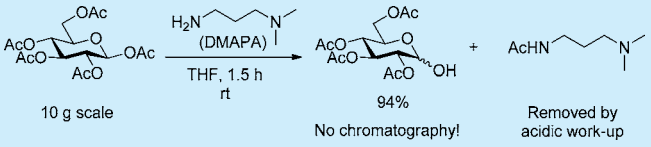
Supporting Information

ABSTRACT: Inexpensive 3-(dimethylamino)-1-propylamine (DMAPA) was found to be effective in anomeric deacylation reactions giving 1-*O* deprotected sugars in high yield as precursors for the formation of imidate glycosyl donors. DMAPA was also found to be useful for removing excess reagents such as benzoyl chloride, tosyl chloride, and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride. The deacylation reaction could be conducted in moist THF and did not require chromatographic purification since an acidic wash was sufficient to remove excess reagent and the formed byproduct.



Chemical glycobiology has for a long time been predicted to have a bright future, and much progress has been made. The field heavily depends on access to pure and uniform glycans, which are often prepared through synthetic methods. In spite of important developments in automated synthesis and click reactions, every oligosaccharide molecule is still a unique synthetic target with no general synthetic strategy available.[1] For new discoveries in chemical glycobiology, it is therefore of utmost importance to develop new and improved synthetic methods to allow for the continued demand of glycans.

Among the most successful glycosyl donors[2] for the synthesis of oligosaccharides are the trichloroacetimidates[3] and the *N*-phenyl trifluoroacetimidates,[4−6] which both use reducing 1-*O* deprotected lactols for their preparation. In addition, 1-*O* deprotected lactols can be used directly in dehydrative glycosylations[7] or be converted to glycosyl thiols[8] by treatment with Lawesson's reagent[9] for subsequent attachment to proteins.[10]

A literature survey suggests that little progress in methods leading to selective anomeric deacylations has been made since the classical method using hydrazinium acetate (H_2NNH_3-OAc)[11] in DMF was developed. This protocol still seems to be the most popular despite the apparent drawbacks of this reagent being shelf stability, price,[12] and toxicity.[13] In addition, there are also drawbacks to the use of the hazardous solvent DMF, which often complicates workup due to its physical properties. A less used and alternative protocol to hydrazinium acetate is the employment of an alkyl amine (e.g., ethylene diamine/AcOH[14] or $BnNH_2$[15]) in the less hazardous and more volatile solvent THF. Alkylamines like benzylamine, however, yield a lipophilic amide byproduct, which later needs to be removed by time-consuming column chromatography.

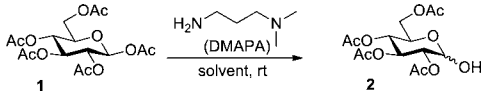
We had previously used 3-(dimethylamino)-1-propylamine (DMAPA) as a nucleophile in a Pd-catalyzed Buchwald reaction[16] and noticed its low price compared to both $BnNH_2$ and Et_3N. DMAPA is a bulk chemical used, e.g., for the synthesis of betaines in shampoos, for curing epoxy resins, and as an additive to fuels. It furthermore has a safety profile[17] comparable to both $BnNH_2$ and Et_3N.

We believed that the bifunctional nature of DMAPA could make it useful as a nucleophile for selective anomeric acylations in carbohydrate chemistry, and it could subsequently be removed easily from the reaction mixture by acidic workup due to presence of the tertiary amine functionality.[18] DMAPA has previously been found useful in cleaning reaction mixtures.[19−29]

To investigate the potential of DMAPA in anomeric deacylation, we chose β-D-glucose pentaacetate **1** as a model substrate. To our delight, DMAPA (1.5 equiv) in THF was found to cleanly provide the desired lactol **2** after acidic workup consisting of a single wash with 1 M hydrochloric acid in a separation funnel. Lowering the amount of DMAPA to 1.3 equiv resulted in incomplete reaction but increasing the amount of DMAPA to 3 or 5 equiv gave a substantially shorter reaction time and an equally selective reaction in a largely unperturbed yield (Table 1).

Changing the reaction medium to CH_2Cl_2 (entry 5, Table 1) resulted in a slightly lower yield and a significantly prolonged

Table 1. Optimization Results



entry	solvent	DMAPA (equiv)	time (h)	yield[a] (%)
1	THF	1.3	72	*b*
2	THF	1.5	24	95
3	THF	3	3	88
4	THF	5	1.5	92
5	CH_2Cl_2	5	3	83

[a]Yield after acidic workup without chromatographic purification. [b]Reaction did not go to completion according to TLC analysis.

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reaction time. A range of other solvents including 2-methyltetrahydrofuran were also investigated but did not provide improved results compared to THF and CH_2Cl_2 (see the Supporting Information). Regardless of the reaction medium, the reaction product was identical by ^1H NMR analysis. Some effort was invested in trying to understand what the yield-diminishing and water-soluble byproduct(s) could be, but without success. NMR spectra of the water-soluble byproducts identified only *N*-acetyl-DMAPA and unreacted DMAPA. One could speculate on imine formation between the reducing sugar and DMAPA, which could lead to Amadori rearrangement.

For comparison, the same reaction as mentioned above was explored with the often used hydrazinium acetate in DMF (1.5 and 5 equiv) and $BnNH_2$ in THF (1.5 and 5 equiv) at ambient temperature. Here, hydrazinium acetate gave a faster reaction than DMAPA, whereas $BnNH_2$ reacted more sluggishly. Reaction yields from both reagents were slightly lower than those found for DMAPA (see the Supporting Information).

We then investigated the workup procedure by exchanging hydrochloric acid for other acids, which resulted in slightly eroded isolated yields (see the Supporting Information).

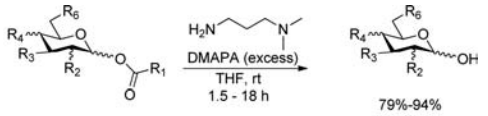
After establishing useful reaction conditions, we moved on to test the reaction on a range of different acetyl- and benzoyl-protected carbohydrates (Table 2). Given the price of DMAPA and the low reaction time, it was decided to continue with 5 equiv of the reagent. First, the influence of anomeric configuration was investigated by reaction of α-acetate **3** with DMAPA. Both reaction time and yield were found to be largely unaffected by a change in C-1 stereochemistry. In addition, other per-acetylated monosaccharides including those of galactose (**4**), mannose (**6**), 2-deoxy-2-azidoglucose (**8**), and GlcNAc (**10**) successfully underwent anomeric deacylation with DMAPA, providing the corresponding lactols in 82−86% yield. Chloroform, however, had to be used in the workup procedure for GlcNAc derivative **11** to avoid losing the lactol product in the aqueous phase and obtain an acceptable isolated yield. It is well known that the solubility of acetamido-2-deoxysugars can be problematic in practice.[30]

Octaacetyl lactose (**12**) gave similar results ($1^1/_2$ h, 89%) as found for the monosaccharides described above.

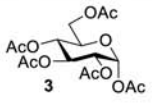
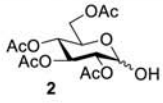
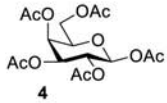
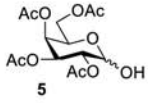
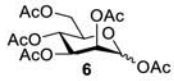
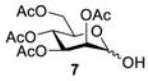
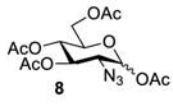
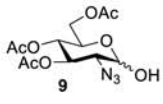
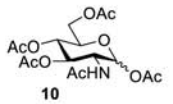
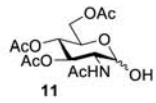
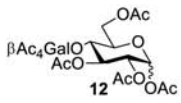
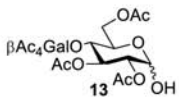
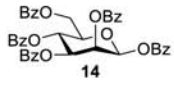
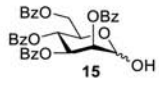
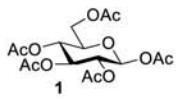
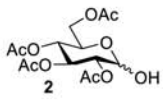
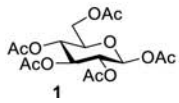
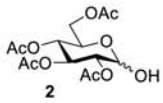
Another frequently used protecting group of the hydroxyl function in carbohydrate chemistry is the benzoyl ester, which is known to be more robust than the acetyl group. Benzoylated β-mannose derivative **14** required a longer reaction time and needed 6 equiv of DMAPA to obtain a satisfactory result. As anticipated, the anomeric benzoyl of **14** was less prone to aminolysis, but still the product was obtained in a satisfying 79% yield (Table 2, Entry 7). Until this point, all reactions had been carried out using dried solvents from a purification system (water content <42 ppm). To investigate whether the presence of water in THF would have a measurable effect on the reaction outcome, solvent from a bottle kept in the laboratory was used (water content: 425 ppm). As can be seen from Table 2, entry 8, no significant effect could be observed on either reaction time or yield for β-glucose pentaacetate (**1**) in undried THF. Finally, a 10 g scale (26 mmol) deacetylation was conducted on **1** in undried THF, which again gave a similar outcome as found for those described for a smaller scale (Table 1, entry 4, and Table 2, entry 8). This demonstrated the robustness of the present protocol and that it is suitable for large-scale preparation.

The above-mentioned results demonstrate a vast improvement of commonly used protocols for selective anomeric deacylation since it uses a cheap and relatively harmless chemical and omits the need for column-chromatographic purification of

Table 2. Anomeric Deacylations with DMAPA



R_1 = CH_3 or C_6H_5; R_2 = OAc, OBz, NHAc or N_3; R_3 = OAc or OBz
R_4 = OAc, OBz or 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl
R_6 = OAc or OBz

Entry	Substrate	Product	Time	Yield[a]
1	 **3**	 **2**	1½ h	90%
2	 **4**	 **5**	1½ h	84%
3	 **6**	 **7**	1½ h	86%
4	 **8**	 **9**	2 h	82%
5	 **10**	 **11**	2 h	83%
6	 **12**	 **13**	1½ h	89%
7	 **14**	 **15**	18 h	79%
8	 **1**	 **2**	1½ h	88%[b]
9	 **1**	 **2**	1½ h	94%[b,c]

[a]Yield after acidic workup without chromatographic purification. [b]Reaction performed in undried THF. [c]Reaction performed on 10 g scale.

the lactol product. Consequently, we next speculated whether the successful protocol also could be used as the first step in a two-step, one-pot approach to prepare a useful glycosyl trichloroacetimidate directly from an acylated sugars. Since trichloroacetonitrile/DBU was found to react very sluggishly with a lactol in THF, the one-pot strategy was explored in CH_2Cl_2 instead. To the acylated sugar of choice was added DMAPA, and upon reaction completion as judged by TLC analysis, trichloroacetonitrile (10 equiv) and a catalytic amount

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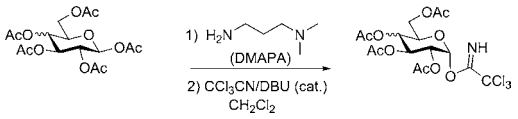
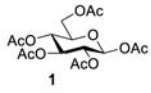
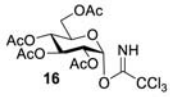
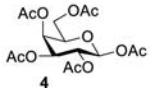
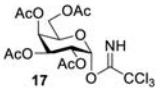
of DBU were added. The formation of the imidate product was easily monitored by TLC analysis, and the crude product could be purified by passing it through a short path silica column. In the presence of trichloroacetonitrile, the DMAPA base itself was found to be insufficient to promote the formation of imidate product, and the addition of DBU was hence necessary. As seen from Table 3, entries 1 and 2, the one-pot approach successfully produced the desired trichloroacetimidate glycosyl donor directly from the 1-*O*-acyl compounds **1** and **4** in good yields (78−82%).

Table 3. One-Pot Deacylation and Trichloroacetimidate Formation



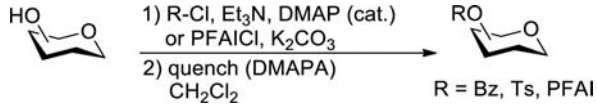
Entry	Substrate	Product	Time	Yield
1	 1	 16	4 h	78%
2	 4	 17	4 h	82%

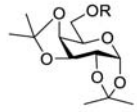
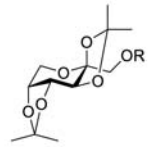
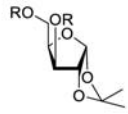
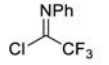
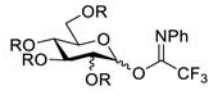
Lastly, the possibility of removing excess of reagents commonly used in carbohydrate chemistry or organic chemistry in general with DMAPA was investigated. Excess of the three reagents, benzoyl chloride, tosyl chloride, and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (PFAI-Cl), was explored in this context. All reactions were performed in CH_2Cl_2, which is commonly accepted as a rather cheap solvent that is less harmful than, e.g., pyridine or chloroform. Quenching the reagent excess in, e.g., benzoylation and tosylation reactions with water to obtain an easily removable salt can be difficult due to the immiscibility of water and CH_2Cl_2.

As substrates for benzoylations and tosylations, isopropylidene -protected D-galactose, D-fructose, and D-xylose were chosen. Excess (4 equiv) of either benzoyl chloride or tosyl chloride was used per alcohol together with triethylamine and DMAP (see Table 4). Upon reaction completion as judged by TLC analysis, DMAPA (1 equiv per chloride reagent) was added. After the reaction was stirred with DMAPA for 30 min, the reaction was washed with hydrochloric acid to remove the amines from the mixture. After drying and evaporation of the organic solvent, the purity of the product was determined with ^{1}H NMR (see the Supporting Information). We were delighted to see that the expected product had formed in excellent yield and that the acidic workup had removed unwanted byproducts. (Table 4, entries 1−3). When the reactions were quenched with water, on the other hand, extended mixing times were necessary and the products were shown to be not pure but contaminated with anhydrides and unreacted reagents, underscoring the power of DMAPA.

2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose, 2,3,4,6-tetra-*O*-benzoyl-D-mannopyranose, and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose were chosen for the reaction with 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride. In these reactions, 2 equiv of 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride and 2 equiv of K_2CO_3 were reacted with the reducing sugars. The reactions were quenched by addition of DMAPA (1.5 equiv), and the reaction

Table 4. Removing Excess BzCl, TsCl, and PFAI-Cl with DMAPA



Entry	Chloride and time	Product	Yield[a]
1	BzCl, 1.5 h or TsCl, 2 h.		R = Bz: 99% R = Ts: 99%
2	BzCl, 2 h or TsCl, 2 h.		R = Bz: 100% R = Ts: 96%
3	BzCl, 2 h or TsCl, 24 h.		R = Bz: 98% R = Ts: 96%
4	 Ac, Bz 4 h or Bn 24 h		R = Ac: 93% R = Bn: 92% R = Bz: 77%

[a]Yield after acidic workup without chromatographic purification.

was stirred for another 10 min. After washing with hydrochloric acid, drying, and evaporation of the organic solvent, the product mixture was analyzed by NMR showing that 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride was removed. Trace amounts of *N*-phenyltrifluoroacetamide were observed in the ^{1}H NMR spectra of the crude reaction mixture, which otherwise was found to only contain the expected glycosyl donor product as an α/β-*E*/*Z* mixture. This again demonstrates the usefulness of DMAPA in carbohydrate chemistry or organic chemistry in general.

In conclusion, we have shown that the inexpensive reagent, DMAPA, provides excellent yields in anomeric deacylation reactions without the need for chromatographic purification. Acidic washing of the crude reaction mixture was found to be sufficient to remove reaction byproducts. It was also demonstrated that the resulting lactol obtained after anomeric deacylation could be used in a one-pot procedure to provide a glycosyl trichloroacetimidate upon addition of trichloroacetonitrile and DBU.

DMAPA could furthermore be used to remove benzoyl chloride, tosyl chloride, and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride.

Given the low cost and utility of DMAPA, it can be recommended that it becomes a standard laboratory chemical to ease reaction workup procedures in organic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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