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# Novel Selectivity in Carbohydrate Reactions, IV: DABCO-Mediated Regioselective Primary Hydroxyl Protection of Carbohydrates

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# Novel Selectivity in Carbohydrate Reactions, IV: DABCO-Mediated Regioselective Primary Hydroxyl Protection of Carbohydrates

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**Abstract:** An efficient procedure for the regioselective tritylation of primary hydroxyl group of aldohexopyranosides and nucleosides using trityl chloride in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in dichloromethane has been developed. Subsequent acetylation of the tritylated products in the same pot has been made possible, thereby providing an efficient route to the fully protected carbohydrate derivatives that can be discriminated chemoselectively.

**Keywords:** DABCO-mediated alkylations, pyridine/DMF-free tritylation, regioselective tritylation

## INTRODUCTION

In continuation of our previous research,[1] a mechanochemical method for the regioselective primary hydroxyl protection of hexosides and nucleosides was recently reported from this laboratory.[2] The method is solvent-free, thus eliminating the need for often-used solvents such as pyridine and dimethylformamide (DMF).[3] However, we felt that until the mixer mills like the planetary ball mill used in that work become a

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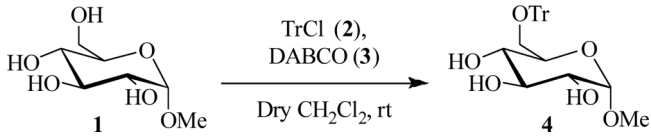
common feature of chemical laboratories worldwide, finding an more environmentally favorable alternative to pyridine and DMF as solvent for this reaction was needed. Moreover, some of the standard protocols that have been in use by chemists and biochemists worldwide for the tritylation reaction in pyridine often suffer from long reaction times and by-product formation in addition to the requirement for above-ambient reaction temperature.[4] Also, most of the frequently used systems, such as triphenylmethylium perchlorate and 2,4,6-tri-*tert*-butylpyridine,[5] trityl chloride and 4-*N,N*-dimethyl aminopyridine,[6] DBU,[7] and *N*-trityl pyridiniumfluoroborate,[8] for this class of reactions are somewhat expensive and are often required in stoichiometric proportions or in excess. Therefore, investigations of a relatively cheaper reagent such as 1,4-diazabicyclo[2.2.2]octane (DABCO) as an alternative to these would also be desirable. With these points in mind, an examination of the suitability of some of the other common organic solvents for regioselective tritylation in the presence of bases such as DABCO was carried out.

## RESULTS AND DISCUSSION

Based on our observation that regioselective 6-*O*-tritylation of methyl α-D-glucoside (**1**) was most effective when conducted using 2.5 mol equiv of each of TrCl (**2**) and DABCO (**3**) in the ball mill and from the fact that the tritylated product obtained in the reaction possessed good solubility in dichloromethane (DCM), our initial focus was on wet chemistry experiments involving glucoside **1** as the substrate in the presence of **3** in DCM. Thus, when glucoside **1** was treated with **2** and **3** under the optimized conditions for the solvent-free reactions in the ball mill in DCM at rt, the tritylation reaction proceeded smoothly (as judged by thin-layer chromatography (TLC): eluent, DCM–MeOH, 9:1). Complete consumption of **2** occurred in 2 h, leading to the formation of the expected 6-*O*-trityl glucoside **4** in virtually quantitative yield as a crystalline solid (entry 1, Table 1) upon isolation by chromatographic filtration (silica gel; eluent, EtOAc–*n*-hex, 4:1). The structure was confirmed by comparison of the physical constants and spectral data obtained for the product with those of authentic **4**. As expected, no reaction was observed in the absence of the base (entry 2, Table 1). Encouraged by these results, the optimization of the reagent requirement for the reaction to proceed at high efficiency was carried out (entries 3–7, Table 1). Thus, 1.5–2.0 mol equiv each of TrCl and DABCO were found to be sufficient for the tritylation product **4** to be obtained in yields of 90–98%.

The reaction using 2.0 mol equiv each of **2** and **3** as described previously was then repeated in the presence of 10 mol% of DMAP to

**Table 1.** Regioselective tritylation of methyl-α-D-glucopyranoside (**1**): Optimization of reaction condition[a]




| Entry | Reaction condition | | | Yield of **4** (%, isolated) |
|---|---|---|---|---|
| | Base (mol equiv) | TrCl (**3**) (mol equiv) | Time (h) | |
| 1 | DABCO (2.5) | 2.5 | 2.0 | 98 |
| 2 | None | 2.5 | 24 | No reaction |
| 3 | DABCO (1.1) | 1.1 | 24 | 50 |
| 4 | DABCO (1.5) | 1.5 | 24 | 90 |
| 5 | DABCO (2.0) | 2.0 | 3.5 | 98 |
| 6 | DABCO (1.5) | 2.0 | 3.5 | 96 |
| 7 | DABCO (2.0) | 1.5 | 6.5 | 90 |
| 8 | DABCO (2) + DMAP (**5**, 0.1) | 2.0 | 3.5 | 98 |
| 9 | DMAP (2.0) | 2.0 | 50 | 5–10 |
| 10 | DMAP (2.0) + TEA (5) | 2.0 | 120 | 5–10 |
| 11 | DBU (2.0) | 2.0 | 24 | 80 |
| 12 | Collidine (2.0) | 2.0 | 24 | 84 |

[a]All reactions were carried out using 1 mmol of glucoside **1** in $CH_2Cl_2$ (4 mL) at rt.

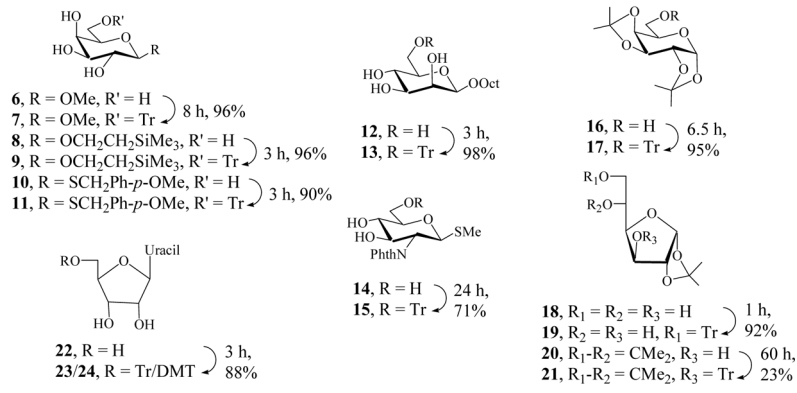
study its effect, if any, on the reaction time (entry 8, Table 1) and no perceivable rate-enhancement was observed. Also, dimethylaminopyride (DMAP) either alone or in combination with triethylamine (TEA) was also ineffective for the reaction (entries 9 and 10, Table 1). Other hindered bases such as DBU and collidine gave good yields of the product but were not as efficient as DABCO (entries 11 and 12, Table 1). Further, common inorganic bases such as sodium hydroxide (NaOH) and potassium hydroxide (KOH) were found to be completely ineffective (no reaction was observed; results not shown).

As the solvent could be expected to influence the rate and outcome of the reaction, the reactions were subsequently tried using various solvents. Acetonitrile possesses better solubilization characteristics toward both the expected product as well as its precursor and was found to be highly efficient, giving the 6-*O*-tritylated product **4** in 96% yield in 2 h at rt. Aromatic solvents such as toluene (no perceivable reaction up to 40 h at rt) and oxygenated solvents such as $Et_2O$ (5–10% yield of **4** in 72 h

at rt), THF (5–10% yield of **4** in 72 h at rt), dioxane (18% yield of **4** in 40 h at rt), and EtOAc (5–10% yield of **4** in 72 h at rt) were unsuitable for the reaction, as was seen from the very low yields obtained in the respective cases. The 6-*O*-tritylation of glucoside **1** was also done in DMF, the conventional solvent, in the presence of DABCO, and it was found that although the desired product could be isolated in reasonably good yield (79% yield of **4** in 50 h at rt), the alkylation was characteristically slow, requiring more than 2 days for the reaction. Thus, the greatest and best yields were obtained when the tritylation was carried out in MeCN or DCM.

Several aldohexose derivatives were subsequently subjected to tritylation reaction under the conditions optimized as before, and excellent results were obtained in all cases. Thus, although the *O*-/*S*-galactosides **6**, **8**, and **10** as well as the mannoside **12** and the acetonides **16** and **18** reacted with TrCl in DCM in the presence of DABCO to afford the respective tritylated products **7**, **9**, **11**, **13**, **17**, and **19** in 90–98% yields in 1–8 h at rt, the glucosamine derivative **14** required 24 h to give the corresponding 6-*O*-tritylated product **15** in 71% of isolated yield. See Scheme 1. As expected, the secondary OH group in the di-*O*-isopropylidene derivative **20** was extremely sluggish toward tritylation at rt, and only 23% of the tritylated product **21** could be obtained after allowing the reaction to take place for 60 h, thereby proving the high degree of regioselectivity observed in other instances. The reaction of uridine (**22**) with **3** as well as dimethoxytrityl (DMT) chloride in DCM in the presence of DABCO was also highly successful, yielding the respective 5′-*O*-ethers **23** and **24** in good yields after purification.

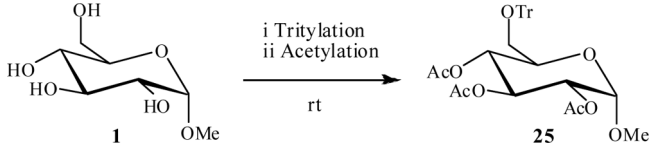
**Chemical structures 6-24:**




***Scheme 1.*** Chemical structures **6–24**.

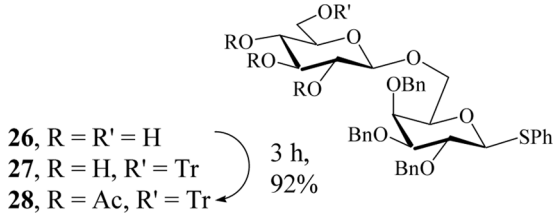
As the overall objective was to develop an alternate procedure for the fully acetylated 6-*O*-trityl-aldosides that did not require the use of pyridine/DMF for the reaction, the one-pot tritylation–acetylation protocol was subsequently attempted on glucoside **1**, and the results are summarized in Table 2. As $CH_3CN$ was proved best suited for the initial tritylation step in the two-step sequence, its suitability for the sequential reaction was first investigated. Thus, after completion of the initial tritylation, the acetylation reaction was allowed to take place by adding $Ac_2O$ (2 mol equiv per OH group) and DMAP (0.1 mol equiv) to the reaction mixture. Complete acetylation was achieved in 6 h at rt as was shown by TLC (EtOAc–*n*-hex, 1:3). Aqueous workup and purification on a silica-gel column (eluent, EtOAc–*n*-hex, 1:4) afforded the expected product **25** in 85% yield (entry 1, Table 2). A similar reaction carried out in DCM (entry 2, Table 2), on the other hand, resulted in the formation of **25** in nearly quantitative yield (98%). The acetylation reaction thus proceeded significantly faster when DCM was employed as the solvent. Reducing the amounts of DABCO and $Ac_2O$ (for the consecutive steps) from 2 mol equiv to 1.5 mol equiv resulted in increased time for the acetylation reaction as could be expected, although the product was obtained in $\geq$96% yield (entries 3 and 4, Table 2) after extractive isolation and

**Table 2.** One-pot tritylation–acetylation: Optimization of reagent concentration[a]




| | Reaction condition, step 1 | | | | Reaction condition, step 2 | | | |
|---|---|---|---|---|---|---|---|---|
| Entry | TrCl (**2**, mol equiv) | DABCO (**3**, mol equiv) | Solvent | Time (h) | DMAP (**5**, mol equiv) | $Ac_2O$ (mol equiv) | Time (h) | Yield (**25**, %) |
| 1 | 2.0 | 2.0 | MeCN | 2.0 | 0.1 | 6.0 | 6 | 85 |
| 2 | 2.0 | 2.0 | DCM | 3.5 | 0.1 | 6.0 | 1 | 98 |
| 3 | 2.0 | 1.5 | DCM | 3.5 | 0.1 | 6.0 | 4 | 96 |
| 4 | 2.0 | 2.0 | DCM | 3.5 | 0.1 | 4.5 | 10 | 98 |
| 5 | 2.0 | 2.0 + **5** (0.1) | DCM | 3.5 | — | 6.0 | 1 | 98 |

[a]All reactions were performed using 1 mmol of the glucoside **1** in the respective solvent (4 ml) at rt.




***Scheme 2.*** Chemical structures **26–28**.



chromatographic purification. By the addition of DMAP (10 mol%) at the beginning of the initial step, the subsequent acetylation could be effected without having to add any additional quantities of DMAP (entry 5, Table 2). Under the optimized conditions, the disaccharide substrate **26** could be converted first to the 6′-*O*-trityl ether **27** and further to the tri-*O*-acetate **28** in 92% overall yield. See Scheme 2.

In conclusion, a simple, highly efficient, and convenient protocol for the regioselective tritylation of aldohexose derivatives has been developed. The subsequent global acetylation (in the same pot) of any remaining hydroxyl groups in the molecule has been proved practical by the current method, thereby making chemoselective discrimination of hydroxyl groups in such molecules possible. The method eliminates the need for the use of hazardous solvents such as pyridine and DMF for such reactions.

## EXPERIMENTAL

### General Procedure for Tritylation

The sugar to be tritylated was suspended (or dissolved as the case may be) in anhydrous DCM (2 ml/100 mg of substrate), and DABCO (2 mol equiv) and TrCl (2 mol equiv) were added. The mixture was stirred at rt (approximately 30°C) until the reaction was complete (as monitored by TLC; eluent, $CH_2Cl_2$–MeOH, 9:1, or another suitable solvent system depending upon the nature of the substrate). The solvent was then removed by evaporation under reduced pressure, and the product was isolated by column chromatography (silica gel; eluent, EtOAc–*n*-Hex, 4:1, or another as appropriate depending upon the compound). All the compounds, except **27** and **28**, reported here have been reported previously.[2] Many are commercially available, and therefore analytical data for compounds **27** and **28** only have been listed here. The physical constants obtained for the known compounds agreed with the literature data, and their spectral data were in agreement with the values expected for

their respective structures. Compound **27** was prepared by the general procedure described previously in 94% yield as a colorless solid; mp 88–90°C; $[\alpha]_D = -26.52$ (C 1 in $CHCl_3$); $\delta_H$ ($CDCl_3$, 300 MHz) 7.54–7.15 (m, 20H, ArH), 4.93–4.89 (d, 1H, $CH_2Ph$, $J$ 11.5 Hz), 4.80–4.77 (d, 1H, $J$ 10.2 Hz, $CH_2Ph$), 4.74–4.70 (d, 1H, $J$ 10.2 Hz, $CH_2Ph$), 4.67 (s, 2H, $CH_2Ph$), 4.67–4.63 (d, 1H, $J_{1,2}$ 9.6 Hz, H-1), 4.61–4.57 (d, 1H, $J$ 11.5 Hz, $CH_2Ph$), 4.27–4.24 (d, 1H, $J_{1',2'}$ 7.6 Hz, H-1′), 3.94–3.80 (m, 4H, H-2, H-4, H-3′, H-4′), 3.65–3.62 (t, 1H, $J$ 5.7 Hz, H-5′), 3.58–3.54 (dd, 1H, $J_{2,3}$ 9.6 Hz, $J_{3,4}$ 5.7 Hz, H-3), 3.51–3.27 (m, 6H); MALDI-TOF MS $C_{58}H_{58}O_{10}S$ $[M]^+$ calcd. m/z 947.140; found m/z 970.154 $(M + Na^+)$, 986.160 $(M + K^+)$, and 243.122 $(Tr^+)$.

## General Procedure for One-Pot Tritylation-Acetylation

The initial tritylation reaction was carried out as described previously. When the reaction was complete, acetic anhydride (2 mol equiv per −OH group) and DMAP (0.1 mol equiv) were added, and the stirring was continued until completion of acetylation as judged by TLC (eluent, EtOAc–n-hex, 1:3). The mixture was then diluted with DCM and washed successively with cold dilute aqueous HCl, dilute aqueous $Na_2CO_3$ solution, and water. The organic layer was then dried and concentrated to dryness, and the residue was purified on a column of silica gel (eluent, EtOAc–*n*-hex, 1:9) to obtain the desired product (see Table 2). Compound **28** was prepared by the general procedure described previously in 92% yield as a colorless solid; mp 79–80°C; $[\alpha]_D = 14.01$ (C 1 in $CHCl_3$); $\delta_H$ ($CDCl_3$, 300 MHz) 7.55–7.17 (m, 20H, ArH), 5.21–5.15 (dd, 1H, $J_{3',4'}$ 9.1 Hz, $J_{2',3'}$ 8.6 Hz, H-3′), 5.11–5.05 (dd, 1H, $J_{4',5'}$ 9.3 Hz, $J_{3',4'}$ 9.1 Hz, H-4′), 5.02–4.96 (dd, 1H, $J_{2',3'}$ 8.6 Hz, $J_{1',2'}$ 7.5 Hz, H-2′) 4.96–4.92 (d, 1H, $J$ 12.0 Hz, $CH_2Ph$), 4.84–4.73 (2d, 2H, $J$ 10.2 Hz, $CH_2Ph$), 4.68 (s, 2H, $CH_2Ph$), 4.68–4.63 (m, 2H, $CH_2Ph$, H-1), 4.54–4.51 (d, 1H, $J_{1',2'}$ 7.5 Hz, H-1′), 3.95–3.85 (m, 3H, H-2, H-4, H-6a), 3.72–3.65 (dd, 1H, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 2.7 Hz, H-3), 3.65–3.58 (m, 2H, H-6b, H-6′a), 3.47–3.44 (m, 1H, H-5), 3.31–3.28 (d, 1H), 3.08–3.03 (dd, H-6′b), 1.99, 1.91, 1.73 (3s, 9H, $3 \times COCH_3$); MALDI-TOF MS $C_{64}H_{64}O_{13}S$ $[M]^+$ calcd. m/z 1073.250, found m/z 1096.581 $(M + Na^+)$, 1112.593 $(M + K^+)$, and 243.122 $(Tr^+)$.

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