Pergamon

Tetrahedron Letters 42 (2001) 5967–5969

TETRAHEDRON LETTERS

Activation of disarmed 2-*O*-alkoxycarbonylated glycosyl trichloroacetimidates with lanthanide triflates: an efficient approach for the synthesis of 1,2-*trans* glycosides

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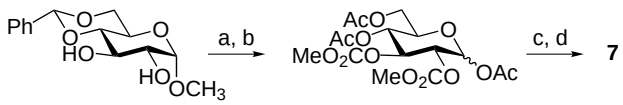
Received 23 May 2001; revised 19 June 2001; accepted 28 June 2001

Abstract—Disarmed glycosyl trichloroacetimidates can be activated by $Yb(OTf)_3$ in the synthesis of 1,2-*trans* glycosides involving primary and secondary acceptors. Concurrent formation of orthoester side products can be avoided by the use of alkoxycarbonyl groups for the protection of the donor 2-hydroxyl. © 2001 Elsevier Science Ltd. All rights reserved.

Glycosyl trichloroacetimidates are probably the most popular donors in glycoside synthesis.[1–4] Their activation is typically based on the use of catalytic amounts of Lewis acids such as TMSOTf, $BF_3{\cdot}OEt_2$, triflic acid, whose manipulation and storage requires strictly anhydrous conditions due to stability or hygroscopicity problems. Very recently we have reported the use of $Sm(OTf)_3$ as a highly efficient catalyst for glycosylations involving armed glycosyl trichloroacetimidates.[5] On pursuing our investigations, we have found that several other trivalent lanthanide triflates such as $Sc(OTf)_3$, $Tb(OTf)_3$ and $Yb(OTf)_3$ can activate perbenzylated glycosyl trichloroacetimidates under conditions analogous to those described for $Sm(OTf)_3$.[6] In addition, the use of lanthanide triflates for *O*- and *C*-glycosidation of glycals has been reported.[7–10] Trivalent lanthanide triflates are generally stable salts which can be easily stored without particular precautions. Furthermore, they can be easily dried[11] and are recyclable promoters of several organic transformations.[12]

In this paper we wish to report the feasible extension of the use of these promoters in the case of disarmed imidate donors. It is well known that the presence of an acyl protecting group on the O-2 of a glycosyl donor commonly induces the exclusive formation of a 1,2-*trans* glycoside because of a neighbouring group participation effect.[1] On the other hand, 2-*O*-acylated donors (disarmed donors) are less reactive than the corresponding 2-*O*-nonacylated counterparts[13] and sometimes they are not activated even by the mildest of promoters which work well with armed donors.[14] Actually, when we attempted the glycosylation of acceptor **1** with donors **2**–**5**, greater amounts of lanthanide triflates and higher temperatures than previously reported[5] for **6** were required to effect the activation of the donors. However, in the case of donors **2**–**4** we generally observed the formation of substantial amounts of the corresponding 1,2-orthoesters together with the desired β-linked disaccharides as well as degradation products (derived from the donors). Degradation of the donor predominated in the case of **5** which was expected to be less amenable to furnish orthoesters because of the bulky pivaloyl group present on O-2.[15] It is well known that 1,2-orthoesters can rearrange into the corresponding 1,2-*trans* glycosides by the action of a strong Lewis acid such as TMSOTf,[16] but apparently this process did not occur with the milder lanthanide triflates. A satisfying solution for this problem was found when the use of an alkoxycarbonyl as an O-2 participating group was tested. Taking advantage of our recently reported procedure for the alkoxycarbonylation of saccharide hydroxyls,[17] imidate **7** was easily prepared as shown in Scheme 1. Adopting the coupling of acceptor



Scheme 1. Synthesis of model glycosyltrichloroacetimidate **7**. (a) TMEDA (2 equiv.), $ClCO_2Me$ (3 equiv.), CH_2Cl_2, 0°C, 30 min, quant.; (b) 10:4:1 $Ac_2O/AcOH/H_2SO_4$ (conc.), 48 h, rt, 73%; (c) benzylamine (1 equiv.), THF, rt, 7 h, 77%; (d) CCl_3CN, DBU (0.1 equiv.), 0°C, 68%.

Keywords: glycosidation; lanthanides.

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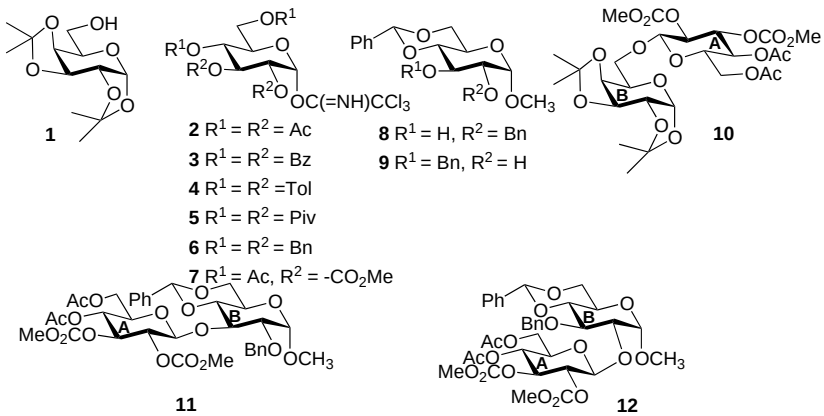
PII: S0040-4039(01)01158-3

Table 1. Glycosidations with donor **7** promoted by $Yb(OTf)_3$

Entry	Acceptor	$Yb(OTf)_3$ (% mol)	Solvent	Temperature (°C)	Product[a]	Yield[b] (%)
1	**1**	50	CH_3CN	0–rt	**10**	70
2	**1**	50	Toluene	rt	**10**	64
3	**1**	15	CH_3CN	50	**10**	61
4	**1**	15	Toluene	50	**10**	58
5	**1**	5	CH_3CN	80	**10**	85
6	**1**	5	Toluene	80	**10**	51
7	**8**	50	CH_3CN	0–rt	**11**	39
8	**8**	15	CH_3CN	50	**11**	35
9	**8**	15	Toluene	50	**11**	82
10	**9**	15	Toluene	50	**12**	69

[a] All disaccharides were identified by ^1H and ^{13}C NMR spectroscopy.[20]
[b] Isolated yield.



1 (1 equiv.) with donor **7** (1.3 equiv.) in acetonitrile as a model glycosidation, we found that 0.5 equivalents of $Sm(OTf)_3$, $Tb(OTf)_3$ or $Yb(OTf)_3$ could promote the glycosidation at room temperature.[18] Smaller amounts of activators resulted in the partial recovery of the unreacted imidate even after an extractive work up. Interestingly, the desired β-linked disaccharide **10** was the only coupling product observed, while undesired orthoester-like products were not detected. At this stage the cheaper $Yb(OTf)_3$ was used for subsequent experiments and we found that smaller amounts of catalyst could be employed when the reaction temperature was raised. For example, 0.15 equiv. of promoter were sufficient at 50°C to guarantee a complete activation of the donor while 0.05 equiv. were sufficient at 80°C (entries 1, 3 and 5 of Table 1). After a further screening of solvents, toluene was found to be superior to CH_3CN in the glycosylation of secondary acceptors **8** and **9** (entries 8–10 of Table 1). In all cases the reactions proceeded in satisfying yields adopting a slight excess of the donor (1.3 equiv.) and in short reaction times (2 hours) (Table 1).[19]

In conclusion, we have demonstrated that $Yb(OTf)_3$ catalytically promotes the activation of disarmed trichloroacetimidates under suitable conditions. Use of donors equipped with a methoxylcarbonyl protecting group on the O-2 is critical in avoiding the formation of undesired orthoester-like products which are generated with other acyl protecting groups. These orthoester intermediates do not rearrange in situ into the desired 1,2-*trans* glycosides by the action of the mild lanthanide triflates. The extension of the use of 2-*O*-alkoxycarbonylated donors to other mild glycosylation approaches is under investigation.

Acknowledgements

Financial support by MURST (PRIN 2000-2001), CNR and Università di Napoli (Progetto Giovani Ricercatori) is acknowledged. NMR spectra were performed at the Centro di Metodologie Chimico-Fisiche dell'Università di Napoli.

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18. $Sc(OTf)_3$ displayed low reactivity toward **7**.
19. For a typical procedure: donor **7** (18 mg, 0.034 mmol) and the acceptor **8** (10 mg, 0.027 mmol) were dissolved in toluene (0.6 mL) in the presence of 4 Å molecular sieves and the resulting solution was added under argon to a flask containing $Yb(OTf)_3$ (2.5 mg, 0.004 mmol) and 4 Å molecular sieves. The reaction mixture was stirred at 50°C. After 2 hours the mixture was diluted with dichloromethane and washed with water. Concentration of the organic phase afforded a crude mixture purified by preparative layer (silica gel, 0.5 mm, eluent: 7:3 toluene:ethyl acetate) to afford disaccharide **11** (16 mg, 82%).
20. Selected ^{1}H NMR ($CDCl_3$, 300 MHz) signals for **10**: δ 2.08 and 2.03 (2×s, acetyl CH_3), 3.76 and 3.79 (2×s, 2×CO-OCH_3), 4.66 (1H, d, $J_{1,2}=7.7$ Hz, H-1 residue A), 5.49 (1H, d, $J_{1,2}=4.8$ Hz, H-1 residue B). Selected ^{13}C NMR signals: δ 20.5 and 20.7 (2×acetyl CH_3), 24.2, 25.0, 25.9, 25.9, (2×-C(CH_3)$_2$), 55.2 (3×-OCH_3), 108.7 and 109.4 (2×-C(CH_3)$_2$), 96.1 and 100.9 (anomeric carbons), 154.5 and 155.0 (2×-O-CO-OCH_3), 169.4 and 170.7 (acetyl CO).
Selected ^{1}H NMR ($CDCl_3$, 400 MHz) signals for **11**: δ 1.98 and 2.01 (2×s, acetyl CH_3), 3.35 (s, 1-OCH_3), 3.77 and 3.79 (2×s, 2×CO-OCH_3), 4.22 (1H, d, $J_{1,2}=7.2$ Hz, H-1 residue A), 4.45 (1H, d, $J_{1,2}=3.8$ Hz, H-1 residue B), 5.56 (1H, s, benzylidene CH). Selected ^{13}C NMR signals: δ 20.7 (2×acetyl CH_3), 55.3 (3×-OCH_3), 101.2, 98.7 and 100.5 (benzylidene and anomeric CH), 169.4 and 170.7 (acetyl CO), 154.9 and 155.1 (2×-O-CO-OCH_3).
Selected ^{1}H NMR ($CDCl_3$, 300 MHz) signals for **12**: δ 2.04 and 2.08 (2×s, acetyl CH_3), 3.41 (3H, s, 1-OCH_3), 3.69 and 3.78 (2×s, 2×3H, 2×CO-OCH_3), 4.82 (1H, d, $J_{1,2}=3.8$ Hz, H-1 residue B), 4.91 (1H, d, $J_{1,2}=8.2$ Hz, H-1 residue A), 5.56 (1H, s, benzylidene CH). Selected ^{13}C NMR signals: δ 20.6 and 20.7 (2×acetyl CH_3), 55.2, 55.3, and 55.4 (3×-OCH_3), 100.1, 100.3 and 100.4 (benzylidene and anomeric CH), 154.6 and 155.1 (2×-O-CO-OCH_3), 169.4 and 170.5 (2×acetyl CO).