Pergamon

Tetrahedron Letters 43 (2002) 5573–5577

TETRAHEDRON LETTERS

Efficient activation of glycosyl *N*-(phenyl)trifluoroacetimidate donors with ytterbium(III) triflate in the glycosylation reaction†

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Received 8 May 2002; revised 31 May 2002; accepted 13 June 2002

Abstract—The mild, moisture-stable and cheap catalyst $Yb(OTf)_3$ activates glycosyl *N*-(phenyl)trifluoroacetimidates in the stereoselective synthesis of 1,2-*trans* and 1,2-*cis* glycosides. A suitable choice of the reaction solvent led to good yields and stereoselectivity ratios. The protocol was successfully applied to acceptors and donors both exhibiting a wide range of reactivity.
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We have very recently described[1,2] the feasible use of moisture-stable lanthanide triflates in the activation of the widely used glycosyl trichloroacetimidate[3] donors. In the course of this research we disclosed that some lanthanide triflates were efficient even in catalytic amounts, although with the less reactive disarmed donors heating was required for glycosidations to be performed.[2] On the other hand, good yields were gained using 2-*O*-alkoxycarbonyl protected donors, the undesired formation of orthoester-like coupling products being minimized.

In this paper we report the improvement and the convenient extension of the use of a cheap lanthanide triflate, $Yb(OTf)_3$, to the activation of the recently reported[4] glycosyl *N*-(phenyl) trifluoroacetimidates, that we have recently observed to provide better results than the corresponding trichloroacetimidates in an investigation which allowed us to develop another moisture-stable activation system (stoichiometric iodine/catalytic triethylsilane) for glycosyl imidates.[5] Furthermore, trifluoroacetimidate donors offer the advantages of an increased stability[6] which can be useful for their purification as well as for their storage.

In a preliminary comparative experiment the glycosylation of the acceptor **1**, carrying a poorly reactive 4-OH, was attempted with trichloro- and trifluoroacetimidate 2-*O*-alkoxycarbonylated donors **5**[2] and **6**[5] in the presence of catalytic $Yb(OTf)_3$ (0.15 equiv.) and 4 Å MS. The glycosidation of **1** with donor **5** in toluene at 50°C[2] afforded **7** in average yield (45–50%, ^{1}H NMR), while the coupling involving donor **6** furnished an improved result (55–60%) albeit a slightly higher temperature (60°C) was required. Interesting results were also obtained by coupling trifluoroacetimidate donor **6** with other secondary more reactive acceptors such as **2** and **3** at 60°C (yields 70 and 90% for **8** and **9**, respectively) (Chart 1).

At this stage, in order to avoid the recourse to high temperatures to effect the reactions, several solvent mixtures were tested in addition to the use of acid washed molecular sieves (AW 300). The utilization of these latter was found decisive to drive to completion glycosidations promoted by I_2/Et_3SiH,[5] supposedly because of the ability of ordinary molecular sieves to function as proton scavengers. This property could also be deleterious in the glycosidations promoted by $Yb(OTf)_3$, where triflic acid is reasonably generated in small amounts as a transient species apt to regenerate the lanthanide catalyst (or act itself as a promoter). Accordingly, the model acceptor **2** was coupled with trifluoroacetimidate donor **6** (1.3 equiv.) under the activation of $Yb(OTf)_3$ (0.15 equiv.) in the presence of AW 300 MS.[7] The results, reported in Table 1 (entries 1–4), showed that in all cases the reactions proceeded in a satisfactory or even good yields at room temperature or below 40°C with a variety of solvent mixtures.[8] The mixture 4:1 dichloroethane/propionitrile furnished the

Keywords: carbohydrates; glycosylation; glycosyl *N*-(phenyl)-trifluoroacetimidates; lanthanides.
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† Dedicated to Professor L. Mangoni on the occasion of his 70th birthday.

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PII: S0040-4039(02)01124-3

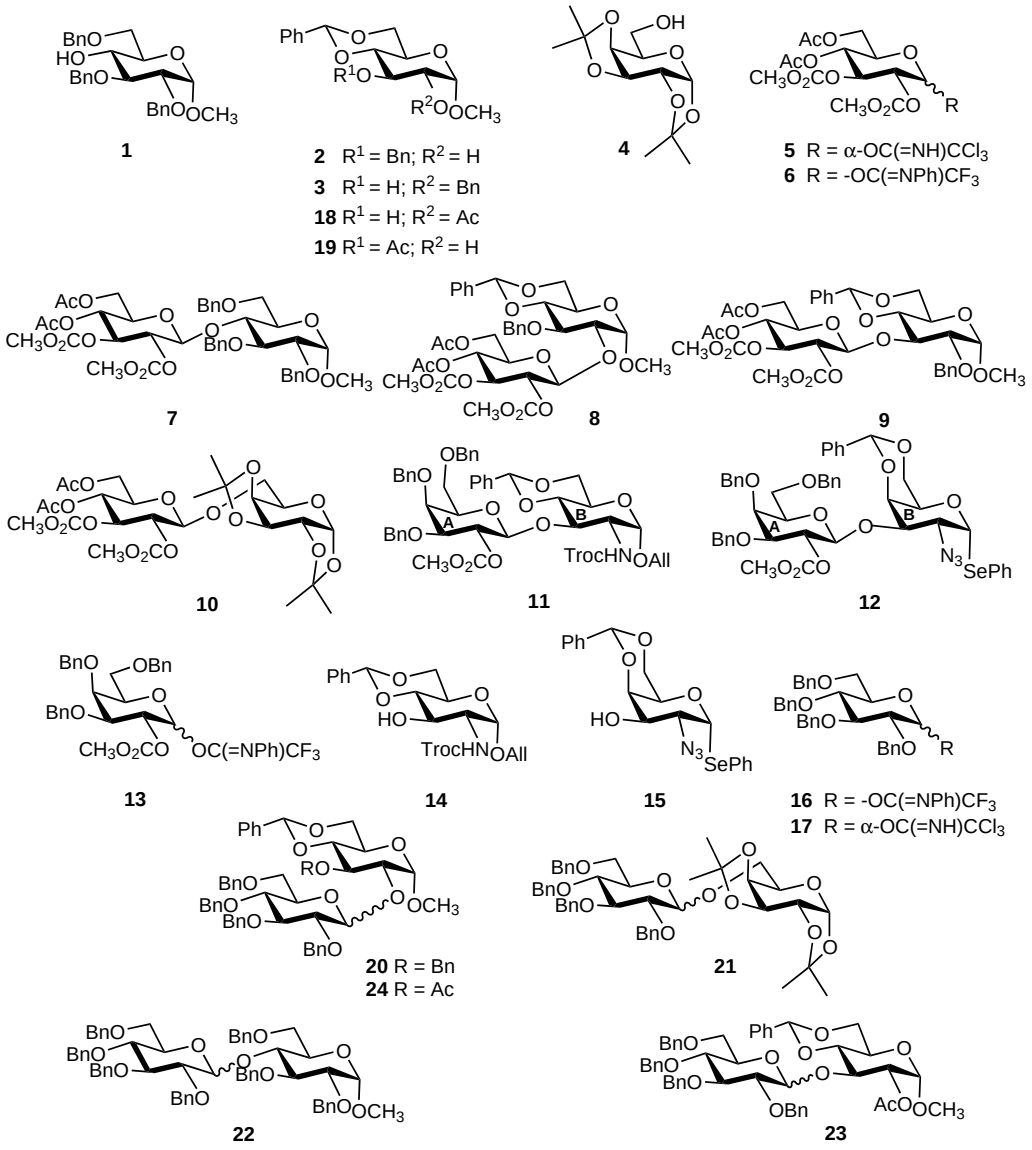


Chart 1.

Table 1. Glycosylation of saccharidic acceptors (1 equiv.) with disarmed imidates **5**, **6** and **13** (1.3 equiv.) in the presence of $Yb(OTf)_3$ (0.15 equiv.) and AW 4 Å MS

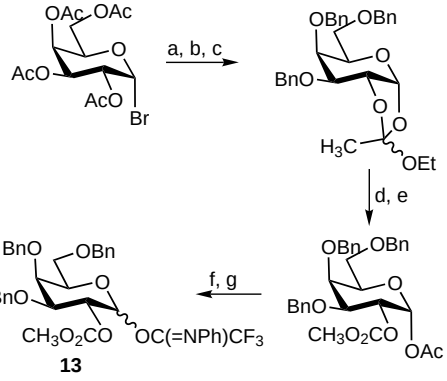
Entry	Donor	Acceptor	Solvent	Temperature, time	Product	Yield[a]
1	**6**	**2**	4:1 toluene/dioxane	rt, 4 h	**8**	70
2	**6**	**2**	4:1 toluene/MeCN	rt, 4 h	**8**	66
3	**6**	**2**	4:1 toluene/EtCN	rt, 2 h+40°C, 1 h	**8**	75
4	**6**	**2**	4:1 $(ClCH_2)_2$/EtCN	rt, 4 h	**8**	80
5	**6**	**1**	4:1 $(ClCH_2)_2$/EtCN	rt, 2 h+40°C, 2 h	**7**	65
6	**5**	**1**	4:1 $(ClCH_2)_2$/EtCN	rt, 3 h+35°C, 2 h	**7**	60
7	**6**	**3**	4:1 $(ClCH_2)_2$/EtCN	rt, 1 h+40°C, 2 h	**9**	87
8	**6**	**4**	4:1 MeCN/EtCN	rt, 4 h	**10**	77
9[b]	**13**	**14**	4:1 $(ClCH_2)_2$/EtCN	0°C, 2 h+rt, 1 h	**11**	71
10	**13**	**15**	4:1 CH_2Cl_2/EtCN	−15°C, 1 h	**12**	51

[a] Isolated yield.
[b] 0.1 equiv. of promoter were used.

best results (Table 1, entry 4), so that it was used for the coupling of donor **6** with the secondary saccharidic acceptors **1** and **3** to furnish the desired disaccharides in good yields (Table 1, entries 5 and 7).[10]

Also under these milder conditions the coupling of acceptor **1** with trifluoroacetimidate **6** proceeded in better yield than with the corresponding trichloroacetimidate **5** (entries 5 and 6).

The coupling of acceptor **4** with trifluoroacetimidate **6** (Table 1, entry 8) required a more polar solvent mixture (4:1 CH_3CN/propionitrile) to reduce the formation of an 1,2-orthocarbonate as an undesired coupling product.[11] Encouraged by these results, we tested the efficiency of this activation protocol in the synthesis of the biologically interesting disaccharide building blocks **11** and **12**, precursors of the Lewis A trisaccharide and the antigen T disaccharide,[12] respectively, and potentially elongable through the position 2 of the galactose residue. For this purpose the tri-*O*-benzylated galactose imidate **13** was easily prepared from acetobromogalactose in 7 steps (Scheme 1). Donor **13** was then coupled with the readily obtained acceptors **14**[13] and **15**[14,15] to furnish the β-linked disaccharides **11** and **12** (Table 1, entries 9 and 10).[16] Activation of **13** was expectedly achieved under milder conditions (low reaction temperature and minor amounts of catalyst) than **6**. Interestingly, in the coupling of **13** with **15** the undesired phenylselenyl transfer from the acceptor to the donor[14,15] was minimized, while with the use of the corresponding less reactive 3,4,6-tri-*O*-acetylated donor this undesired aglycon transfer was the preponderant process.



Scheme 1. Synthesis of donor **13**. (a) EtOH (2 equiv.), TBABr (0.5 equiv.), lutidine (1.3 equiv.), DCM, reflux, 5 h; (b) NaOMe, MeOH, rt, 1 h; (c) BnBr (5 equiv.), DMF, then NaH (4 equiv.), 62% over three steps; (d) 95:5 AcOH/H_2O, rt, 30 min; (e) $ClCO_2CH_3$ (1.5 equiv.), TMEDA (1 equiv.), DCM, 0°C, 30 min; (f) $BnNH_2$ (1.3 equiv.), THF, rt, 16 h, 65% over three steps; (g) DIPEA (3.5 equiv.), *N*-(phenyl)-trifluoroacetimidoyl chloride (3.0 equiv.), DCM, rt, 16 h, 70%.

The activation of armed trifluoroacetimidates was next investigated using 2,3,4,6-tetra-*O*-benzyl *N*-(phenyl)-trifluoroacetimidate **16** as a model donor. As **16** was prevailingly obtained as β anomer,[17] the exploitation of a SN2 based glycosidation was considered in order to achieve stereoselective synthesis of α-glucosides (not attainable through vicinal participation strategy). Model acceptors **3** and **4** were thus coupled with **16** in a solvent of low polarity such as toluene in the presence catalytic $Yb(OTf)_3$ (0.1 equiv.) at low temperature (−10°C). In both cases the stereoselectivity result was quite disappointing, but the overall glycosidation yields were impressively high (Table 2, entries 1 and 2). Having previously established that a mixture of ethyl ether and dioxane afforded the best α-selectivity in the $Sm(OTf)_3$ promoted glycosidation with armed glucosyl trichloroacetimidates[1] (e.g. 2,3,4,6-tetra-*O*-benzyl trichloroacetimidate **17**) we examined the behaviour of the ternary solvent mixture toluene/ethyl ether/dioxane in order to reconcile the achievement of high yields with a good control of α-stereoselectivity.

Adopting the solvent mixture 1:1:1 toluene/ethyl ether/dioxane (entry 3, Table 2), the best α-selectivity was achieved, but with the mixture 4:1:1 toluene/ethyl ether/dioxane the highest yield for the α-linked disaccharide could be obtained due to a marked increase of the overall glycosidation yield (entry 4). Consequently, this latter solvent was adopted in the following experiments in which the reactivity of poorly reactive secondary acceptors **1**, **18** and **19** was examined. In all cases a very good yield was achieved along with a good control of stereoselectivity (entries 8, 9, 11). In contrast, a disappointing α-selectivity was attained with the more reactive primary acceptor **4**, even in the absence of toluene

Table 2. Activation of donor **16** (1.3 equiv.) for the synthesis of 1,2-*cis* glycosides promoted by $Yb(OTf)_3$ (0.10 equiv.) (−10°C for 2–4 h, 4 Å AW 300 MS)

Entry	Acceptor	Solvent	Product[a]	Yield[b]	α/β
1	**3**	toluene	**20**	97	1.7:1
2	**4**	toluene	**21**	97	1.3:1
3	**3**	1:1:1 toluene/Et_2O/dioxane	**20**	76	3.8:1
4	**3**	4:1:1 toluene/Et_2O/dioxane	**20**	97	3.1:1
5	**4**	4:1:1 toluene/Et_2O/dioxane	**21**	93	1.1:1
6	**4**	4:1 Et_2O/dioxane	**21**	86	1.7:1
7[c]	**4**	4:1 Et_2O/dioxane	**21**	81	1:1
8	**1**	4:1:1 toluene/Et_2O/dioxane	**22**	75	3.5:1
9	**18**	4:1:1 toluene/Et_2O/dioxane	**23**	93	4:1
10[d]	**18**	dichloromethane	**23**	76	1.8:1
11	**19**	4:1:1 toluene/Et_2O/dioxane	**24**	80	3.5:1

[a] All disaccharides were identified by ^1H and ^{13}C NMR.
[b] Isolated yield.
[c] Donor **17** was used with 0.03 equiv. of promoter.
[d] TMSOTf (0.05 equiv.) was used as the promoter (from 0°C to rt) in the presence of 4 Å MS.[4]

Table 3. Activation of donor **16** (1.3 equiv.) for the synthesis of 1,2-*trans* glycosides promoted by $Yb(OTf)_3$ (0.1 equiv.) in the presence of 4 Å AW MS

Entry	Acceptor	Solvent	Temperature, time	Product[a]	Yield[b]	β/α
1	**18**	MeCN	−10°C, 2 h	**23**	82	1.4:1
2[c]	**18**	MeCN	−25 to 0°C, 2 h	**23**	78	1.4:1
3	**18**	3:2 toluene/MeCN	−10°C to rt, 6 h	**23**	97	1:1.1
4	**18**	1:4 toluene/MeCN	−10°C, 6 h	**23**	85	1.4:1
5	**18**	EtCN	−10°C, 12 h	**23**	84	1.4:1
6	**18**	4:1 EtCN/MeCN	−10°C to rt, 7 h	**23**	93	1.3:1
7	**18**	1:4 EtCN/MeCN	−10°C, 3 h	**23**	90	1.5:1
8	**1**	1:4 EtCN/MeCN	−10°C to rt, 5 h	**22**	77	3.3:1
9	**4**	1:4 EtCN/MeCN	−10°C, 1 h	**21**	93	6:1
10	**19**	1:4 EtCN/MeCN	−10°C, 2 h	**24**	86	3.8:1

[a] All disaccharides were identified by ^1H and ^{13}C NMR.
[b] Isolated yield.
[c] Donor **17** was used with 0.03 equiv. of promoter.

(entries 5–7). It should be noted that in the case of the secondary model acceptor **18**, lower yield and stereoselectivity were obtained when the described[4] glycosidation conditions were adopted (compare entries 9 and 10).

The $Yb(OTf)_3$ promoted glycosidation was also investigated in nitrile solvents that are known[18] to favour β-selectivity even in the absence of a participating group at the donor C-2. Several mixtures were tested in the glucosidation of acceptor **18** (which had provided low yields and β-selectivities in our previous investigation concerning the $Sm(OTf)_3$ activation of armed glycosyl trichloroacetimidate **17**)[1] (Table 3, entries 1–7). Although the selectivity was always modest, very high yields could be obtained with a wide range of solvents. The 4:1 acetonitrile/propionitrile mixture (entry 7) furnished the best compromise in terms of yields, selectivity and rapidity. Use of this mixture with other acceptors turned out to be quite satisfying even in the stereoselectivity (entries 8–10).

In conclusion, the results reported here complement our previous findings well in the development of a general glycosidation protocol based on the use of mild, moisture-stable and cheap catalysts. We have shown that both armed and disarmed *N*-(phenyl)-glycosyl trifluoroacetimidates can be conveniently adopted for the glycosylation of several saccharidic acceptors under the catalytic action of $Yb(OTf)_3$. Use of acid washed molecular sieves also allows the reactions with disarmed donors to be performed at lower temperature than previously reported.[2] Furthermore, a suitable choice of the reaction solvents allows a simplification of the procedure being the catalyst added as a solution.[8,10,19] Both yields and stereoselectivities were gratifying in all cases, with only few exceptions being observed as for as the latter issue.

Acknowledgements

This work was supported by MIUR (Progetti di Interesse Nazionale) and by a grant (to M.S.) from Università Federico II di Napoli (Progetto Giovani Ricercatori).

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8. The use of polar cosolvents avoided the necessity to add the donor and the acceptor by cannula to the promoter, that is sparingly soluble in the reaction solvent (toluene). Actually, this procedure was time consuming as it implied the drying of the weighed amount of lanthanide catalyst (overnight heating at 200°C under vacuum)[9] every time a reaction had to be performed. On the other hand, it should be noted that every attempt to glycosylate secondary acceptors at 50°C with trichloroacetimidate donors adopting cosolvents useful for the addition of the catalyst as a solution resulted in a sensible decrease in yields.[2]
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10. Solutions of freshly dried $Yb(OTf)_3$ in propionitrile or dioxane, stored in an essicator in the presence of P_2O_5,

turned out to be efficient in promoting glycosidations even after 1 week from their preparation.

11. This reaction in less polar mixtures afforded appreciable amounts of a dimeric side product whose NMR spectrum ($CDCl_3$) displays the anomeric proton of the glucose residue at $\delta = 5.75$ (doublet, $J_{1,2} = 5.4$ Hz) and an upfield shift for one of the two methoxy protons signals ($\delta = 3.81$ and 3.54, singlets). Other significative signals at δ 5.52 (1H, d, $J_{1,2} = 5.2$ Hz, H-1 Gal), 5.19 (1H, dd, H-3 Glc), 5.01 (1H, dd, H-4 Glc), 4.45 (1H, dd, H-2 Glc), 2.07 (6H, overlapped singlets, 2×$COCH_3$), 1.52, 1.44, 1.32, 1.32 (12H, 4×s, acetonides CH_3).
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16. Selected ^{1}H NMR ($CDCl_3$, 400 MHz) signals of **11**: δ 5.52 (1H, s, benzylidene CH), 5.11 (1H, dd, $J_{1,2} = 7.8$ Hz, $J_{2,3} = 10.0$ Hz, H-2 A), 4.92 (1H, d, $J_{1,2} = 3.6$ Hz, H-1 B), 4.55 (1H, d, H-1 A), 3.81 (3H, s, -OCH_3), 3.44 (1H, dd, $J_{2,3} = 9.8$ Hz, $J_{3,4} = 2.6$ Hz, H-3 A). Selected ^{13}C NMR signals of **11**: δ 155.0 and 154.1 (CO), 138.5, 137.8, 137.8, 137.4 (aromatic quaternary carbons), 133.2 (-OCH_2-*C*H=CH_2), 128.8–126.0 (aromatic CH), 118.3 (-OCH_2-CH=*C*H_2), 101.4, 101.0 and 97.1 (benzylidene CH and anomeric carbons), 54.7 (-CO-O*C*H_3). Selected ^{1}H NMR ($CDCl_3$, 400 MHz) signals of **12**: δ 6.05 (1H, d, $J_{1,2} = 5.2$ Hz, H-1 B), 5.47 (1H, s, benzylidene CH), 5.23 (1H, dd, $J_{1,2} = 7.6$ Hz, $J_{2,3} = 10.0$ Hz, H-2 A), 5.05–4.54 (4H, 2×-CH_2Ph), 4.72 (1H, d, H-1 A), 4.42 (2H, s, -CH_2Ph), 4.35 (1H, dd, $J_{2,3} = 10.0$ Hz, H-2 B), 3.73 (3H, s, -OCH_3). Selected ^{13}C NMR signals of **12**: δ 155.0 (-*C*O-OMe), 138.3, 137.7, 137.7, 137.6 and 133.8 (aromatic quaternary carbons), 129.1–126.1 (aromatic CH), 102.3 and 100.5 (benzylidene CH and C-1 residue A), 85.4 (C-1 residue B), 54.9 (-CO-O*C*H_3).
17. The preparation of **16** was achieved by reacting 2,3,4,6-tetra-*O*-benzyl glucopyranose with trifluoroacetimmidoyl chloride in the presence of sodium hydride (dichloromethane, 0°C, 2 h, 90% yield) to furnish an anomeric mixture largely enriched of the β-anomer (β/α 5:1). In our hands milder bases were found quite inefficient.[4] The synthesis of glycosyl trichlororacetimidates promoted by strong bases generally yields the nearly exclusive formation of thermodynamically favoured α-anomers due to the reversibility of the addition to the electron deficient nitrile.[3] In the case of *N*-(phenyl)trifluoroacetimidates the presence of a phenyl group on the nitrogen atom in place of a hydrogen prevents the reversibility of the addition (via base-induced β-elimination) and the kinetically favoured β-anomer can be preponderantly formed.
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19. Typical procedure: donor **6** (23 mg, 0.042 mmol) and acceptor **2** (12 mg, 0.032 mmol) were dissolved in dichloroethane (480 μL) in the presence of acid washed 4 Å molecular sieves (Fluka Chemie AG, AW 300 MS) under argon. A solution of freshly dried $Yb(OTf)_3$ in EtCN (0.04 M, 120 μL, 4.8 μmol) was then added at room temperature. After 4 h Et_3N was added and the mixture was diluted with dichloromethane and washed with water. The organic phase was concentrated and the residue was chromatographed on a short silica gel column eluted with 7:3 hexane/ethyl acetate to afford disaccharide **8**[2] (19 mg, yield 80%).