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Ytterbium(III) trifluoromethanesulfonate for specific activation of *n*-pentenyl orthoesters in the presence of acid-sensitive functionalities

K. N. Jayaprakash, K. V. Radhakrishnan and Bert Fraser-Reid*

Natural Products and Glycotechnology Research Institute, Inc. (NPG), 4118 Swarthmore Road, Durham, NC 27706, USA

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Abstract—Various Lewis acids have been examined as agents which react with *N*-iodosuccinimide to release iodonium ion for activating *n*-pentenylorthoester (NPOE) donors, particularly for coupling to acceptors that have acid-labile protecting groups. Although many of the reagents do not tolerate cyclic acetals, $BF_3{\cdot}Et_2O$ does. However, the latter cleaves *p*-methoxybenzyl (PMB), making it possible to use this Lewis acid to simultaneously promote coupling of NPOEs and remove PMB groups. Of several transition metal salts investigated, ytterbium triflate is outstanding in its ability to promote NPOE coupling with complete preservation of acid-labile protecting groups.

The ability to finesse reactions of *n*-pentenyl glycosyl donors by using different sources of halonium ions was first demonstrated ten years ago, in a synthesis of a blood group tetrasaccharide.[1] Prior to that, protic acid induced reactions of *N*-halosuccinimides, long used for aromatic halogenations,[2] had been introduced for NPG activation in 1990[3] and extended to thioglycoside[4,5] counterparts shortly thereafter. This source of iodonium ion has since enjoyed widespread application.[6–9] However, the acids employed as catalysts to generate the iodonium ion can obviously threaten some commonly used protecting groups, a problem which becomes increasingly worrisome as the oligosaccharide targets becomes more and more complex.

The widespread use of Lewis Acids[10] and transition metal salts[11] in organic synthesis of acid-catalyzed reactions has demonstrated the subtlety of which these reagents are capable. It therefore occurred to us that these reagents might be capable of generating halonium ions, while permitting the survival of acid labile protecting groups. In this manuscript, we report some examples in connection with these investigations.

For our test case, we choose to examine the coupling of the *n*-pentenyl orthoester (NPOE) **1a**, and the cyclohexylidinated inositol **2**[12] (Scheme 1). Prior work had shown that use of triethylsilyltriflate or *tert* butyl dimethylsilyltriflate to activate *N*-iodosuccinimide (NIS) led to **3a**, indicating significant loss of the cyclohexylidine-protecting group[13] (Table 1, entry i). On the other hand, use of boron trifluoride etherate (Table 1, entry ii) led to excellent retention of the acetal, affording pseudodisaccharide **3b** in 95% yield.

The *p*-methoxybenzyl (PMB) protecting group, which is known to be unpredictable with respect to its stability to acids,[14] was chosen for a study in which both donor and acceptor possessed acid labile protecting groups. Thus upon treatment of the donor **1b** and acceptor **2** with $BF_3{\cdot}Et_2O$/NIS, the product **3c**, obtained in 93% yield had suffered loss of the PMB group but, notably, retention of the cyclohexylidene group (entry iii).

Under comparable conditions, use of triphenylboron or triphenylborate as Lewis acids with *N*-iodosuccinimide, led to complex mixtures (entries iv and v). Better success was had with 0.3 equiv. of *tris*pentafluorophenylboron, in that coupling was effective, giving **3d**,[15] albeit accompanied by substantial amounts of the PMB cleavage product **3c** (entry vi). We then examined scandium triflate, the virtues of which have been championed in recent reports, notably by Kobayashi.[16,17] Although use of 0.3 equiv. of the reagent resulted in moderate coupling, the result was again compromised by substantial cleavage of the PMB protecting group (entry vii).

Turning our attention to ytterbium(III) triflate,[18] we found that after a reaction time of 5 min, a quantitative

* Corresponding author. Tel.: (919) 493 6113; fax: (919) 493 6113; e-mail: dglucose@aol.com

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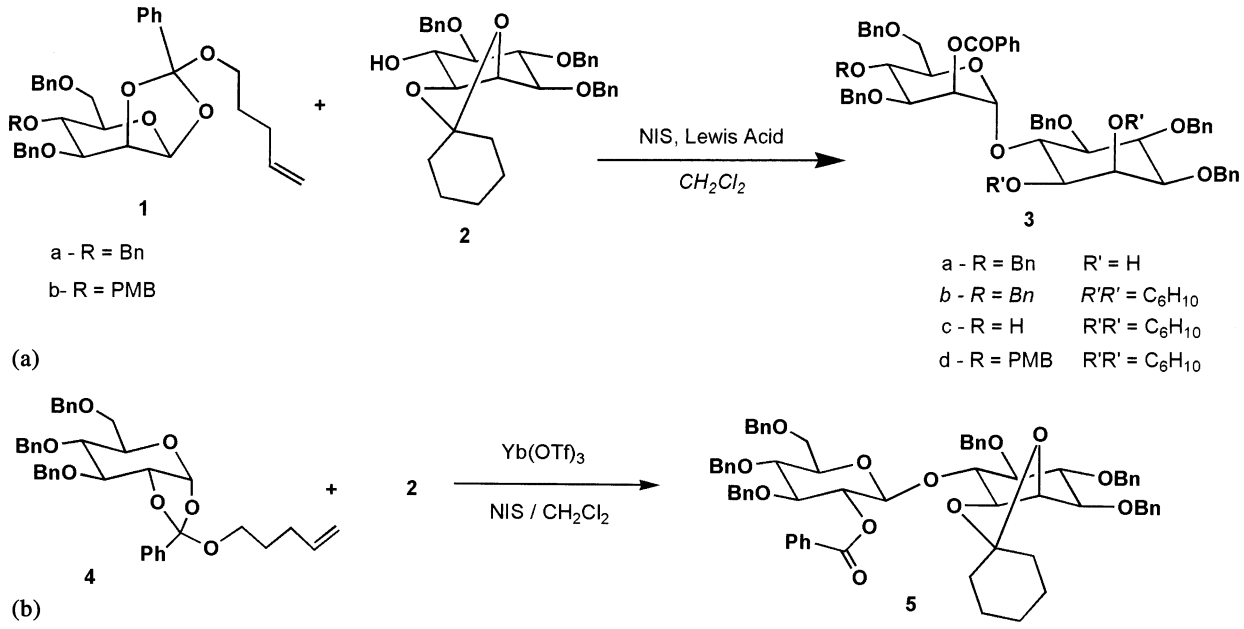

Scheme 1.

Table 1. Lewis acid-catalyzed coupling of acceptor **2** (1 equiv.) with *n*-pentenyl glycosyl donors (3 equiv.)

Entry	Donor	Lewis Acid (equiv.)	Product(s) (ratio)	Yield (%)
i	**1a**	TESOTf (0.3)	**3a**	Modest
ii	**1a**	$BF_3{\cdot}Et_2O$ (0.3)	**3b**	95
iii	**1b**	$BF_3{\cdot}Et_2O$ (0.3)	**3c**	93
iv	**1b**	Ph_3B (0.3)	Complex mixture	
v	**1b**	$(PhO)_3B$	Complex mixture	
vi	**1b**	$(C_6F_5)_3B$ (0.3)	**3d**+**3c** (7:3)	70
vii	**1b**	Sc(OTf)$_3$ (0.3)	**3d**+**3c** (7:3)	49
viii	**1b**	Yb(OTf)$_3$ (0.3)	**3d**	Quantitative
ix	**4**	Yb(OTf)$_3$ (0.3)	**5**	90

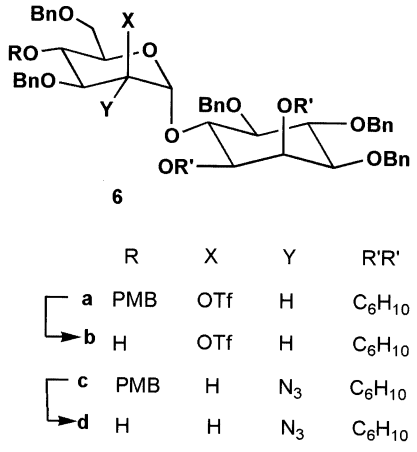

Figure 1.

yield of the product **3d** was obtained (entry viii). This excellent result prompted us to test the *gluco* NPOE **4**. Efficient coupling with acceptor **2**, in the presence of 0.3 equiv. of Yb(OTf)$_3$ gave product **5** in 90% yield (entry ix).

With respect to acid-labile protecting groups, entry viii shows that Yb(OTf)$_3$ allows survival of both PMB and cyclohexylidene groups, while $BF_3{\cdot}Et_2O$ cleaved the former, but not the latter (entries i and ii). In this connection, the ready and **selective** cleavage of the PMB group with $BF_3{\cdot}Et_2O$ (Fig. 1) deserves to be noted in light of the recent report by Hinkling and Kiessling on a novel procedure for effecting this process, involving reaction with polymer supported sulfonamides.[19] For example treatment of **6a** and **6c** with $BF_3{\cdot}Et_2O$[20] removed the PMB groups, giving **6b** and **6d**, respectively, in ~90% yields.

In conclusion, careful choice of a transition metal salt or a Lewis acid permits exquisite control over the reactions of *n*-pentenyl donors, without affecting certain acid labile protecting groups. The excellent results from the use of Yb(OTf)$_3$ for the NPOE reaction in Scheme 1 is a promising observation which is under further development in our labs.

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15. The acceptor **2** (1 equiv.) and the glycosyl donor **1** (3.0 equiv.) were dissolved in a small quantity of toluene, azeotroped to dryness and the mixture dried under vacuum overnight. The mixture was dissolved in CH_2Cl_2 (5 ml) at 0°C under an argon atmosphere. *N*-Iodosuccinimide (4 equiv.) was added to the solution, after stirring for 5 min, Lewis acid was added. The reaction was quenched after 20 min with 10% aqueous sodium thiosulphate and saturated aqueous sodium bicarbonate, extracted with CH_2Cl_2, and purified by chromatography. Compounds **3a**, **3b** and **3c** were characterized by their respective ^1H and ^{13}C NMR spectra. NMR data for **3d**: ^1H NMR (400 MHz): δ ($CDCl_3$) 8.10 (d, 2H, $J=7$ Hz), 7.56 (t, 1H, $J=7$ Hz), 7.4–7.0 (m, 29H), 6.82 (d, 2H, $J=8$ Hz), 5.73 (t, 1H, $J=2$ Hz), 5.48 (d, 1H, $J=1.6$ Hz), 4.9–3.9 (m, 19H), 3.81 (s, 3H), 3.79–3.0 (m, 4H), 1.8–1.2 (m, 10H); ^{13}C NMR (100 MHz): δ ($CDCl_3$) 165.94, 159.23, 139.03, 138.74, 138.48, 138.36, 138.17, 133.26, 131.36, 130.30, 130.02, 129.77, 128.74, 128.66, 128.63, 128.50, 128.48, 128.29, 128.23, 128.16, 128.06, 127.90, 127.76, 127.69, 127.55, 113.76, 111.18, 96.55, 81.18, 78.85, 78.20, 78.01, 77.62, 75.69, 75.12, 75.01, 74.01, 74.31, 74.28, 73.44, 73.35, 71.96, 71.52, 69.38, 69.16, 55.54, 37.46, 35.22, 25.25, 24.14, 23.91. Mol. mass (calcd) for $C_{68}H_{72}O_{13}$ 1096.50, found 1096.502 (M+H).
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20. A solution of compounds **6a** and **6c** in CH_2Cl_2 treated with $BF_3{\cdot}Et_2O$ (0.3 equiv.) at 0°C, the reaction was completed in an hour. All the compounds were characterized by ^1H and ^{13}C NMR spectra.