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Aryl(trifluoroethyl)iodonium Triflimide and Nitrile Solvent Systems: A Combination for the Stereoselective Synthesis of Armed 1,2-*trans*-β-Glycosides at Noncryogenic Temperatures

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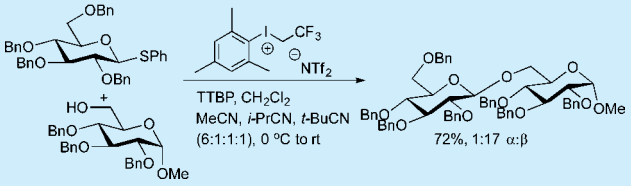
Supporting Information

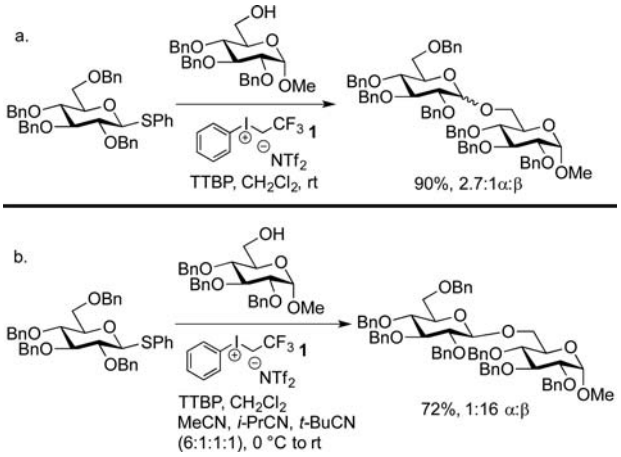
ABSTRACT: Armed thioglycosides can be activated with aryl(trifluoroethyl)iodonium triflimide in 2:1 CH_2Cl_2/pivalonitrile or a solvent combination of CH_2Cl_2, acetonitrile, isobutyronitrile, and pivalonitrile (6:1:1:1) at 0 °C for glycosylation reactions that proceed in good yield and moderate to excellent selectivity (up to 25:1 β/α). Comparison to other common glycosylation promoters reveals that both the mixed solvent and the iodonium salt promoter are required for stereoselectivity.



It has long been known that complex carbohydrates play a host of important roles in biological systems.[1] Our understanding of the molecular basis of carbohydrate function and our ability to utilize these molecules in drug discovery is still in its infancy compared to advances made with other classes of biologics. This is due in large part to the difficulties associated with the construction of homogeneous oligosaccharides.[2] Unlike other classes of biopolymers, oligosaccharides are frequently highly branched compounds, and consequently, issues of regiochemistry and stereochemistry must be taken into account when planning their synthesis.[3,4] A more fundamental challenge, however, lies in the basic nature of carbohydrate synthesis itself. Whereas peptide and nucleic acid chemistry have matured to the point where many sequences can be routinely prepared in the laboratory, the synthesis of even a relatively simple oligosaccharide still requires extensive synthetic training to successfully execute. There remains a need for efficient glycosylation chemistries that can be carried out with high stereocontrol. This has prompted calls for the development of operationally simpler carbohydrate chemistries.[5] A number of groups have responded to this call with a variety of "user-friendly" glycosylation methodologies. This includes (but is not limited to) thioglycoside activation using bismuth-based promoters,[6] stable hypervalent iodine promoters,[7,8] photochemical activation,[9] and electrochemical glycosylation.[10]

Recently, we have reported that phenyl(trifluoroethyl)-iodonium triflimide (**1**) is a remarkably stable promoter for room temperature glycosylation reactions using thioglycoside donors (Scheme 1a).[7a] Glycosylation reactions promoted by **1** are run at room temperature and do not require strict exclusion of air or moisture. While this technology is very user-friendly, the reactions promoted by **1** are unselective in the absence of C2 acetate directing groups, which can be problematic under certain circumstances.[10b,11] Indeed, a number of laboratories have recently introduced arming ethereal directing groups to address this issue.[12] Our own group is interested in developing

Scheme 1. (a) Iodonium Salt-Promoted Glycosylations in CH_2Cl_2 and (b) Results of This Work



glycosylation reactions where selectivity can be achieved in the absence of directing groups. In this study, we investigated the compatibility of aryl(trifluoroethyl)iodonium triflimide-promoted glycosylation reactions with the documented β-directing effect of nitrile solvents (Scheme 1b).[13]

While most reports of the use of nitrile solvents to control selectivity have required temperatures below −30 °C, we decided to perform our preliminary investigations at room temperature and 0 °C to match our previously established reaction condition.[7a] Our initial efforts focused on screening nitrile solvents having varying α-carbon substitution patterns and seeing how these affected glycosylations promoted by **4** (which possesses reactivity similar to that of **1** but offers greater solubility in reaction solvents; see Table S2 and Scheme S1 in the

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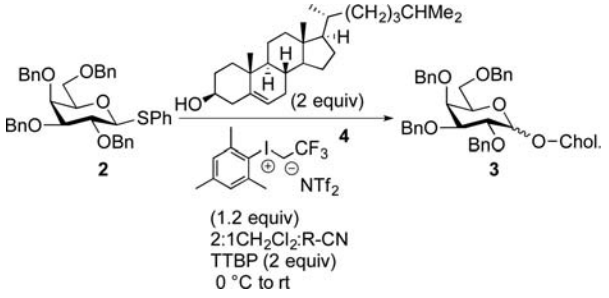
Table 1. Effects of Different Nitrile Solvents on Reactions Promoted by 4



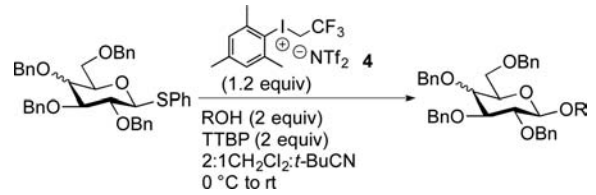
entry	R	yield (%)	α/β
1	Me	86	1:4.9
2	Et	81	1:5.6
3	*i*-Pr	87	1:7.5
4	*t*-Bu	78	1:9
5	TMS-H_2C-	48	1:9.6

Supporting Information) in the presence of non-nucleophilic base 2,4,6-tri-*tert*-butylpyrimidine (TTBP). After preliminary screens (Table 1; see Tables S1 and S2), we concluded that a reaction temperature of 0 °C with the solvent combination of 2:1 CH_2Cl_2/pivalonitrile provided the optimal reaction outcome (Table 1, entry 4). Accordingly, we then sought to examine the scope of the reaction under these optimized conditions.

Donor **2** reacted with primary acceptor **6** in good yield and selectivity (Table 2, entry 1). The more hindered acceptor **7** also provided the product in good yield, albeit with lower selectivity (Table 2, entry 2). The reaction between the less reactive thioglucoside **5**[14] and cholesterol again provided the desired product **10** in both good yield and high β-selectivity (Table 2, entry 3). This was expected because in our initial studies we did not observe any significant difference in the reactivity of **2** and **5**.[7a] It was therefore surprising to find that the carbohydrate acceptors **6** and **7** reacted with **5** to afford the desired products **11** and **12** in much lower yields (Table 2, entries 4 and 5). This is in stark contrast to when these acceptors were used with promoter **1** in the absence of nitrile solvents. Attempts to improve the yield and selectivity using adamantyl thioglycosides[11b,15] were partially successful. In the presence of **4**, **13** reacted with all three acceptors in increased yield (Table 2, entries 6–8). While this donor was particularly effective with secondary acceptors under these conditions, the yield with primary acceptor **6** indicated that there was room for further improvement (Table 2, entry 7).

Noting that less hindered nitriles provided the product in slightly higher yield, we reasoned that the lower yield of **11** may be due to a solubility issue. We therefore chose to examine mixed nitrile solvents in the hope of taking advantage of a synergy to provide the product in useful yields and selectivity. To this end, running the reaction between **5** and **6** in a mixture of 4:1:1 CH_2Cl_2/isobutyronitrile/pivalonitrile improved the yield to 68% accompanied by a slight increase in selectivity to 12.5:1 β/α (Table 3, entry 1). A further increase in yield to 77% with little loss in selectivity was achieved with the combination of 4:1:1 CH_2Cl_2/acetonitrile/pivalonitrile (Table 3, entry 2). Since pivalonitrile led to higher selectivities and isobutyronitrile and acetonitrile led to higher yields, we decided to examine the use of a quaternary solvent mixture composed of 6:1:1:1 CH_2Cl_2/acetonitrile/isobutyronitrile/pivalonitrile. Under these conditions, **4** promoted glycosylations between **5** and **6**, and there was a dramatic improvement in yields and selectivity (72%, 17–25:1 β/α, two runs, Table 3, entry 3).[16]

Table 2. Scope of the Reaction in Pivalonitrile/CH_2Cl_2



entry	donor	acceptor	product	yield (%)	α/β
1	**2**	**6**	**8**	82	1:8.5
2	**2**	7	**9**	71	1:5.5
3	**5**	Chol	**10**	70	1:12.6
4	**5**	**6**	**11**	46	1:10.2
5	**5**	7	**12**	65	1:5.9
6	**13**	Chol	**10**	92	1:14
7	**13**	**6**	**11**	65	1:10.7
8	**13**	7	**12**	85	1:6.5

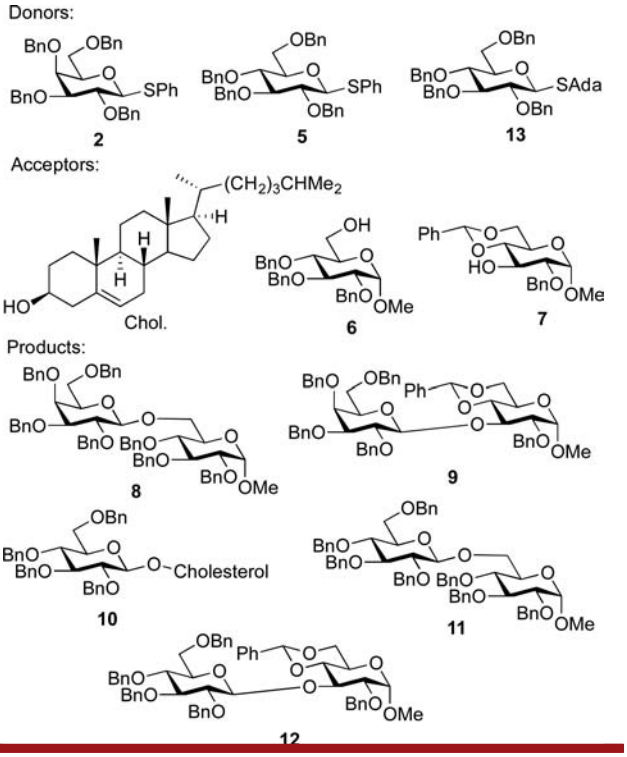
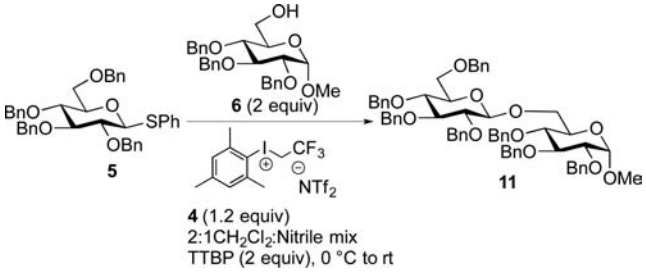


Table 3. Effects of Mixed Nitrile Solvents on Selectivity



entry	nitrile mix	yield (%)	α/β
1	*i*-PrCN/*t*-BuCN (1:1)	68	1:12.5
2	MeCN/*t*-BuCN (1:1)	77	1:10
3	MeCN/*i*-PrCN/*t*-BuCN (1:1:1)	72	1:17–25

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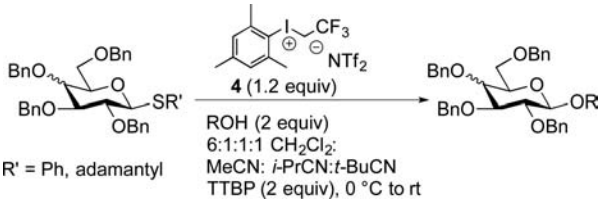
Table 4. Scope of the Reaction with a Quaternary Solvent System



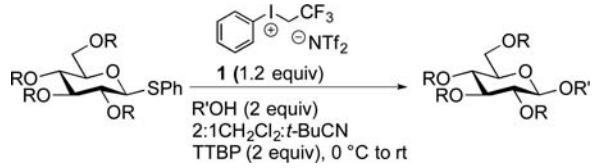
entry	donor	acceptor	product	yield (%)	α/β
1	5	Chol	10	91	1:18
2	5	7	12	82	1:6.2
3	2	Chol	3	91	1:9.2
4	2	6	8	80	1:9.5
5	2	7	9	85	1:5.1
6	13	Chol	10	92	1:15.2
7	13	6	11	84	1:11
8	13	7	12	85	6.3

Examining the scope of the reaction with different donors showed that this solvent system led to an increase in the yield of reactions between **5** and all acceptors examined (Table 4). These conditions also led to an increase in selectivity when cholesterol was used as an acceptor, whereas little change in selectivity was observed with acceptor **7** over the use of pivalonitrile alone (Table 4, entries 1 and 2). Attempts to further improve the selectivity using high-dilution conditions[17] only resulted in a decrease in yield. These optimized conditions also resulted in an increase in yield in the reaction between donor **13** and acceptor **6** (Table 4, entry 7). The impact on the yield or selectivity in reactions between **13** and other acceptors, or when donor **2** was used in the reaction, was trivial (Table 4, entries 3–8).

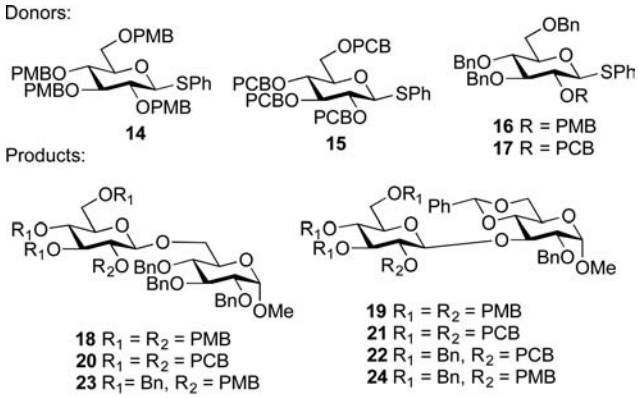
In an effort to further increase the selectivity of the reaction, we turned our attention to modulating the electronics of the C2 protecting group. Our motivation for this study arose from Mong's report,[18] where the selectivity in the nitrile effect may be enhanced by participation of the C2 oxygen into the α-nitrilium ion intermediate, resulting in the formation of a transient oxazolinium ion. To this end, we chose to examine a series of donors possessing electron-donating or -withdrawing benzyl ether groups at C2 (Table 5). Of the different donors examined, only globally PMB-protected **14** provided products with higher levels of β-selectivity than perbenzylated **5** (Table 5, entries 1 and 2). Glycosylations with **14** proceeded in much lower yield, however, and were accompanied by significant decomposition of the starting material. Given that the electronics of the protecting groups did not have a significant impact on selectivity, coupled with the fact that we were able to take advantage of the nitrile effect at much higher temperatures than has been previously reported, we began to consider that **1** and **4** were not activating the thioglycoside through a classical oxocarbenium cation pathway. To further test this idea, we chose to examine the effect of different promoters on the stereochemical outcome of the reaction.

To this end, three commonly used thiophilic promoters were used to glycosylate **11** with either **6** or **7** in the optimal 6:1:1:1 CH_2Cl_2/acetonitrile/isobutyronitrile/pivalonitrile mixed solvent system (Table 6). All reactions were initiated at 0 °C and allowed to warm to room temperature in order to provide a direct comparison to **1**. Otherwise, reactions were conducted exactly as previously described in the literature. It was found that NIS (1 equiv) and TfOH (0.1 equiv) in the presence of 4 Å MS[19]

Table 5. Effect of C2 Ether Group on Selectivity

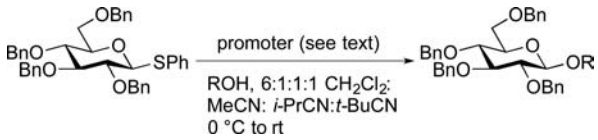


entry	donor	acceptor	product	yield (%)	α/β
1	**14**	**6**	**18**	29	β only
2	**14**	**7**	**19**	28	β only
3	**15**	**6**	**20**	67	1:7.8
4	**15**	**7**	**21**	55	1:3.5
5	**16**	**6**	**22**	70	1:7.3
6	**16**	**7**	**23**	68	1:4
7	**17**	**7**	**24**	55	1:3.5



PCB = 4-chlorobenzyl

Table 6. Comparison of 4 with Common Glycosylation Promoters



entry	promoter	equiv of TTBP	acceptor (equiv)	product	yield (%)	α/β
1	**4**	2	**6** (2)	**11**	**72**	1:17–25
2	**4**	2	**7** (2)	**12**	**82**	1:6.2
3	NIS/TfOH	0	**6** (1.2)	**11**	**95**	1:1.4
4	NIS/TfOH	0	**7** (1.2)	**12**	**93**	2:1
5	BSP/Tf_2O	3	**6** (2)	**11**	**45**	1:1.3
6	BSP/Tf_2O	3	**7** (2)	**12**	**48**	1.7:1
7	NBS	0	**6** (2)	**11**	**44**	1.3:1
8	NBS	0	**7** (2)	**12**	**45**	1.5:1

provided the products in excellent yields but with poor selectivities (Table 6, entries 3 and 4). By comparison, both 1-benzenesulfinyl piperidine (BSP, 2.8 equiv)/Tf_2O (1.4 equiv) in the presence of TTBP (3 equiv)[20] and *N*-bromosuccinimide (NBS, 1.2 equiv)[21] gave diminished yields, again with very low stereoselectivity (Table 6, entries 5–8). In the case of BSP/Tf_2O, this low yield was due to decomposition of the substrates at room temperature, while NBS was not able to completely activate the donor for glycosylation. These results indicate that **1** and **4** are indeed activating the thioglycosides through a different, more selective, pathway than other commonly used promoters.

In conclusion, we show that the use of a combination of aryl(trifluoroethyl)iodonium triflimide and either a 2:1 CH_2Cl_2/pivalonitrile or a 6:1:1:1 CH_2Cl_2/acetonitrile/isobutyronitrile/

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pivalonitrile solvent mixture permits glycosylations using armed thioglycoside donors with moderate to excellent selectivity (up to 25:1 β/α). The reaction is conducted at 0 °C to room temperature, which is a much higher temperature than normally required to take advantage of the nitrile effect. Importantly, both the solvent system and iodonium salt promoter are required for selectivity. Given the operational simplicity of the process, coupled with the stability of all of the reagents involved, we believe that this process will help lay the groundwork for technologies that will permit experimentalists with minimal synthetic training to produce their own oligosaccharide target structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03282.

Supporting studies, detailed experimental procedures, compound characterization, and ^{1}H and ^{13}NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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