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Glycosyl trifluoroacetimidates. Part 1: Preparation and application as new glycosyl donors

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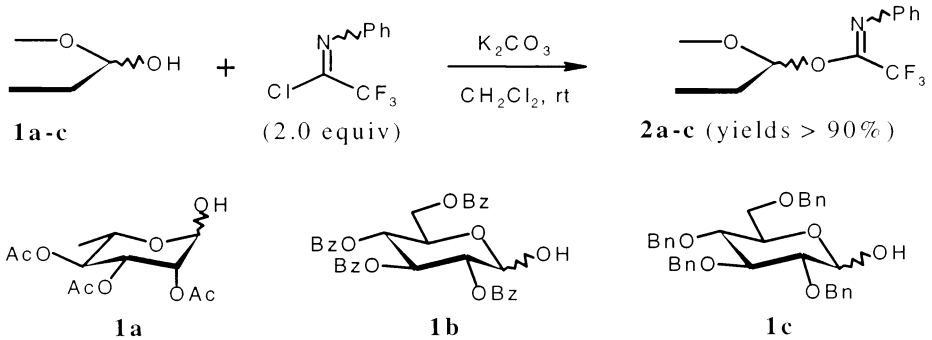
Abstract—Glycosyl (*N*-phenyl)trifluoroacetimidates, readily prepared from 1-hydroxyl sugars by treatment with (*N*-phenyl)trifluoroacetimidoyl chloride in the presence of K_2CO_3, were demonstrated to be effective glycosyl donors.

Stimulated by the recognition of the significance of oligosaccharides in many biological and pharmaceutical processes, intensive efforts have been given to the development of glycosylation methods over the last two decades.[1,2] Among the many methods now available, the leaving groups of the glycosyl donors, have been recognised as one of the most important parameters responsible for the viability of glycosylation reactions; indeed glycosylation reactions are now inevitably categorised by the leaving groups of the glycosyl donors.[1,2] Glycosyl trichloroacetimidates, introduced by Schmidt and co-workers in 1980,[3] are one of the most widely used glycosyl donors.[2] The initial use of glycosyl imidates as donors was reported by Sinaÿ in 1976.[4] However, due to the enormous structural diversity of glycosidic linkages, no single glycosylation method is generally applicable including glycosylation with trichloroacetimidate donors. For example, a disaccharide trichloroacetimidate failed to be attached to the hydroxyl group of a disaccharide macrolactone in the synthesis of Tricolorin A,[5] while an ethyl thioglycoside counterpart succeeded.[6] There are still difficulties in constructing many glycosidic linkages, therefore, the introduction of new and effective glycosylation methods is still necessary. Based on Schmidt's successful glycosyl trichloroacetimidate donors, we prepared glycosyl trifluoroacetimidates and tried their application as glycosyl donors. Some preliminary results are reported herewith.

N-Substituted trifluoroacetimidoyl halides are readily accessible from the reaction of trifluoroacetic acid with primary amines in a PPh_3–Et_3N–CCl_4 system.[7] The halogen attached to the imidoyl carbon can easily be replaced by various nucleophiles, such as carbanions, amines, and alcohols.[8] Acetyl, benzoyl, and benzyl pro-



Scheme 1.

Keywords: glycosyl trifluoroacetimidate; glycosylation; glycosyl donor.

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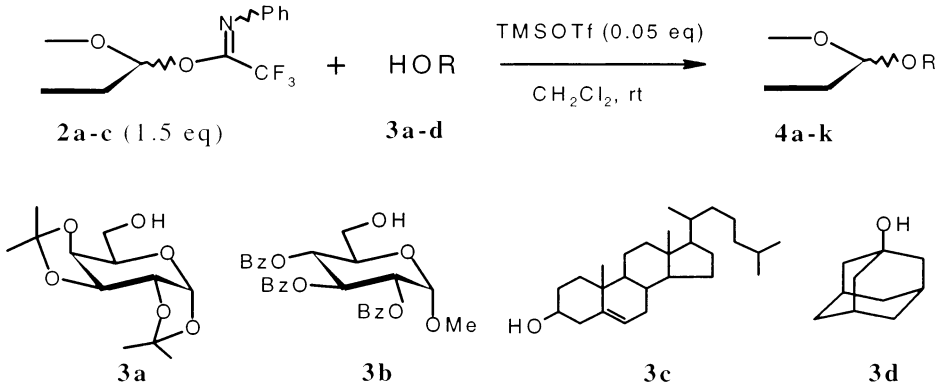


Scheme 2.

Table 1. Glycosylation with glycosyl trifluoroacetimidates **2a**–**c** as donors

Entry	Acceptor	Donor	Product	Yield (%)[a]	α:β[b]
1	**3a**	**2a**	**4a**	95	α only
2		**2b**	**4b**	94	β only
3		**2c**	**4c**	90	α mainly
4	**3b**	**2a**	**4d**	86	α only
5		**2b**	**4e**	94	β only
6		**2c**	**4f**	96	1.3: 1
7	**3c**	**2b**	**4g**	98	β only
8		**2c**	**4h**	95	1: 1
9	**3d**	**2a**	**4i**	99	α only
10		**2b**	**4j**	99	β only
11		**2c**	**4k**	94	1.5: 1

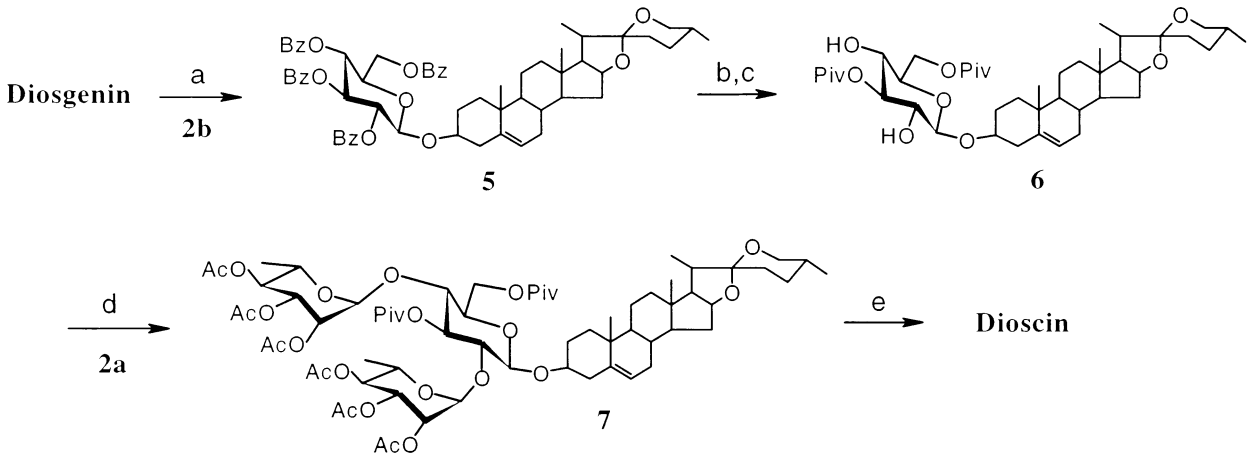
[a] Isolated yields.
[b] Determined by ^{1}H NMR analysis.

tected glycosyl trifluoroacetimidates (**2a**–**c**)[9] were therefore readily synthesised in excellent yields (>90%) by treatment of the corresponding 1-hydroxyl sugars (**1a**–**c**) with *N*-phenyl trifluoroacetimidoyl chloride in the presence of K_2CO_3 (2.0 equiv.) in CH_2Cl_2 at room temperature for 3 h (Scheme 1). The α anomers were produced predominantly due to the anomeric effect of the corresponding 1-*O*-potassium sugars. It is noteworthy that these glycosyl trifluoroacetimidates (**2a**–**c**) were stable to storage at 4°C for weeks.

The glycosyl trifluoroacetimidates (**2a**–**c**) were demonstrated to be effective donors in the presence of TMSOTf (0.05 equiv.) and 4 Å MS in CH_2Cl_2 (rt, 3 h) (Scheme 2), the typical reaction conditions for glycosylation with trichloroacetimidate donors.[2] As shown in Table 1, all the glycosylation reactions, including the tertiary alcohol, 1-adamantanol **3d**, gave the corresponding coupling products (**4a**–**k**) in very high yields. Not surprisingly, donors with neighbouring participating groups (**2a**,**b**) gave only the corresponding 1,2-*trans* products, whilst donors without a neighbouring group **2c** gave mixtures of the α and β anomers.

The present glycosyl trifluoroacetimidate donors were also successfully applied to a synthesis of a trisaccharide saponin, dioscin[10] (Scheme 3). Glycosylation of diosgenin with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trifluoroacetimidate **2b** under the promotion of a catalytic amount of TMSOTf (0.05 equiv.) gave the corresponding glycoside **5** in 92% yield. Removal of the benzoyl groups followed by selective protection of the 6-OH and 3-OH with pivaloyl groups provided diol **6** in 60% yield. Glycosylation of diol **6** with 2,3,4-tri-*O*-acetyl-L-rhamnopyranosyl trifluoroacetimidate **2a** under similar glycosylation conditions afforded the trisaccharide **7** in 64% yield, equal to a per glycosylation yield of 80%. Removal of the acyl protecting groups using aqueous NaOH completed the synthesis of the target saponin, dioscin.

In summary, glycosyl trifluoroacetimidates are readily prepared and were used as glycosyl donors. Their accessibility, stability, and activity were shown to be comparable with those of the corresponding glycosyl trichloroacetimidate donors. Nevertheless, the easy installation of various *N*-substituted groups might provide an additional element for tuning the reactivities of the glycosyl trifluoroacetimidate donors. This is our purpose for developing glycosyl trifluoroacetimidate donors, and these attempts will be published in due course.



Scheme 3. *Reagents and conditions*: (a) TMSOTf (0.05 equiv.), 4 Å MS, CH_2Cl_2, rt, 3 h, 92%; (b) NaOMe, HOMe, rt; (c) PivCl, pyridine, 0°C, 60%; (d) conditions similar to (a), 64%; (e) NaOH, MeOH/H_2O/THF (1:1:1), 90%.

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9. Analytical data for **2a–c**. **2a** (α): $[\alpha]_D^{25}=-39.5$ (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 7.31 (t, 2H, $J=7.6$ Hz), 7.12 (t, 1H, $J=7.4$ Hz), 6.83 (d, 2H, $J=7.7$ Hz), 6.16 (br., 1H, H-1), 5.47 (br, 1H, H-2), 5.36 (dd, 1H, $J=10.2$, 3.5 Hz, H-3), 5.17 (t, 1H, $J=10.0$ Hz, H-4), 4.03 (m, 1H, H-5), 2.17, 2.09, 2.02 (s each, 3H each, Ac), 1.28 (d, 3H, $J=6.2$ Hz, H-6). EIMS (*m*/*z*, %): 273 (100), 213 (26), 189 (3.5), 171 (18), 153 (90), 111 (32). Anal. calcd for $C_{20}H_{22}F_3NO_8$: C, 52.06; H, 4.81; N, 3.04. Found: C, 52.33; H, 5.04; N, 3.18. **2b** (α): $[\alpha]_D^{25}=60.3$ (*c* 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 8.10–7.00 (m, 25H), 6.82 (br, 1H, H-1), 6.25 (t, 1H, $J=9.9$ Hz), 5.82 (t, 1H, $J=9.9$ Hz), 5.62 (dd, 1H, $J=9.9$, 3.4 Hz), 4.67 (m, 2H), 4.52 (dd, 1H, $J=12.0$, 4.5 Hz). EIMS (*m*/*z*, %): 579 (30), 457 (1), 335 (3), 231 (13), 105 (100). Anal. calcd for $C_{42}H_{32}F_3NO_{10}$: C, 65.71; H, 4.20; N, 1.82. Found: C, 65.40; H, 4.25; N, 1.83. **2c** (α): $[\alpha]_D^{25}=58.5$ (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 7.19–7.04 (m, 23H), 6.74 (d, 2H, $J=7.7$ Hz), 6.54 (br., 1H, H-1), 5.00–4.43 (m, 8H), 4.05 (t, 1H, $J=9.4$ Hz), 3.99 (m, 1H), 3.82–3.69 (m, 4H). Anal. calcd for $C_{42}H_{40}F_3NO_6$: C, 70.87; H, 5.67; N, 1.97. Found: C, 70.96; H, 5.69; N, 1.86.
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