ORGANIC LETTERS

2003
Vol. 5, No. 24
4545−4548

Glycosidation with a Disarmed Glycosyl Iodide: Promotion and Scope

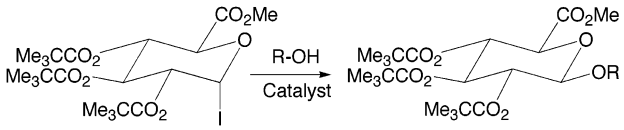
Jennifer A. Perrie,[†] John R. Harding,[‡] Clare King,[‡] Deborah Sinnott,[†] and Andrew V. Stachulski*,[†]

The Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Liverpool L 69 7 ZD, UK, and Drug Metabolism and Pharmacokinetics Department, AstraZeneca UK, Ltd., Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4 TG, UK

stachuls@liv.ac.uk

Received August 5, 2003

ABSTRACT



Catalyst: NIS/I_2, then TMSOTf **or** MX_n±I_2

Glucuronyl iodide 1 has been studied in detail as a "disarmed" glycosyl donor. In a model reaction, using *N*-iodosuccinimide (NIS) as a promoter and 2-phenylethanol as acceptor, best results were obtained using NIS with I_2, followed by trimethylsilyltrifluoromethanesulfonate (TMSOTf). When a series of primary and secondary alcohols was glycosylated using these conditions, yields of 60–83% of β-glucuronides were obtained. Various "nonheavy" metal salts also effectively catalyzed the model reaction but led to significant amounts of α-product with less reactive secondary alcohols.

Glycosidation is a fundamental process in organic chemistry,[1] and there is continuing interest in the development of new methodology in this area. Of late there has been renewed interest in glycosyl iodides as glycosyl donors, generally in the "armed" series (typically benzyl ether-protected sugars).[2,3] We recently reported[4] that the "disarmed" glycosyl iodide **1** derived from glucuronolactone was a highly stable derivative of well-defined crystal structure and commented briefly on its potential in glycosidation. We now present a detailed study of the glycosyl donor ability of **1**, using mainly iodine-based[5] reagents and excluding heavy metals. Iodosugar **1** has proved to be a good and flexible donor, reacting under mild conditions (0°−20 °C) more efficiently than the corresponding bromosugar and with a wider range of substrates, including hindered and deactivated alcohols.

Although iodine alone was a satisfactory catalyst for the glucuronidation of 3-*O*-pivaloyl morphine by **1** (55% yield),[4] this procedure proved to lack generality when applied to a range of alcohols. We investigated NIS, which had given good results with the corresponding glucuronyl bromide,[6] in the reaction of **1** with 2-phenylethanol **2** (Scheme 1) for primary evaluation.

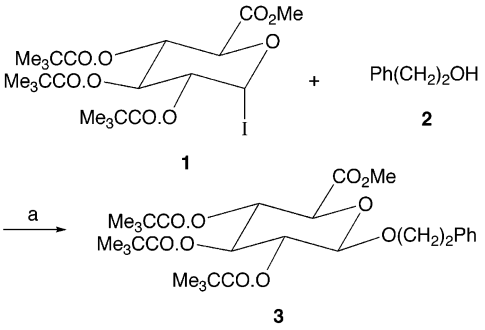
Reaction of **1** with **2** (1.5 equiv) promoted by NIS (1.1 equiv) and I_2 (0.25 equiv) in 1,2-dichloroethane at 0−20 °C in the presence of 3 Å molecular sieves[7] gave (81%) a mixture of the desired β-glucuronide **3** and ortho ester **4** upon complete reaction of **1**; in this series, such ortho esters proved to be highly stable.[8]

[†] University of Liverpool.
[‡] AstraZeneca UK, Ltd.

(1) For example: Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173. Boons, G. J. *Tetrahedron* **1996**, *52*, 1095−1121. Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137−2160.
(2) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961−6967.
(3) (a) Gervay, J. Glycosyl Iodides in Organic Synthesis. In *Organic Synthesis: Theory and Applications*; JAI Press, Inc.: 1998; Vol. 4, pp 121−153. (b) Gervay-Hague, J.; Lam, S. N. *Carbohydr. Res.* **2002**, *337*, 1953−1965. (c) Gervay-Hague, J.; Lam, S. N. *Org. Lett.* **2002**, *4*, 2039−2042. (d) Gervay-Hague, J.; Ying, L. Q. *Carbohydr. Res.* **2003**, *338*, 835−841.
(4) Bickley, J.; Cottrell, J. A.; Field, R. A.; Harding, J. R.; Ferguson, J. R.; Hughes, D. L.; Kartha, K. P. R.; Law, J. L.; Scheinmann, F.; Stachulski, A. V. *Chem. Commun.* **2003**, 1266−7.
(5) (a) Kartha, K. P. R.; Aloui, M.; Field, R. A. *Tetrahedron Lett.* **1996**, *37*, 8807−8810. (b) Kartha, K. P. R.; Karkkainen, T. S.; Marsh , S. J.; Field, R. A. *Synlett* **2001**, 260−262.
(6) Stachulski, A. V. *Tetrahedron Lett.* **2001**, *42*, 6611−6614.

10.1021/ol035475k CCC: $25.00
Published on Web 10/30/2003

Scheme 1. Glycosidation of 2-Phenylethanol[a]



[a] Reagents and conditions: (a) NIS, I_2, 0−20 °C, then Lewis acid; see text.

Addition of I_2 was beneficial: NIS alone gave poorer yields and significantly more degradation. Simply stirring **1** and **2** together with the sieves in DCE gave no reaction. The use of 0.8 g of 3 Å sieves per 0.2 mmol of **1** was important to reduce degradation and give clean β-product. The mixture of **3** and **4** was treated with either $BF_3{\cdot}Et_2O$ or TMSOTf to effect rearrangement of **4** to **3**; the latter proved to be slightly higher-yielding, though in either case a small amount of degradation resulted. Marginally the best procedure involved the addition of TMSOTf (0.5 equiv) from the start, followed by an additional 0.25 equiv when **1** had wholly reacted, affording **3** in 76% yield. 1,2-Dichloroethane (DCE) was clearly the best solvent: acetonitrile led mainly to degradation products.

Having established the reliability of the NIS−I_2−TMSOTf method, we then evaluated **1** as a donor for a range of alcohols, with the results summarized (Table 1: total reaction time of 6 h in all cases). In all cases, we used just 1.5 equiv of acceptor, *not* a large excess, which would be unrealistic for more complex alcohols.

Table 1. Glucuronidation of Various Alcohols[a] Using **1** + NIS/I_2/TMSOTf[b] in the Presence of 3 Å Molecular Sieves

entry	alcohol	yield (%)	β: α ratio
1	$Ph(CH_2)_2OH$	76[c]	β only
2	$PhCH_2OH$	60[d]	β only
3	c-$C_6H_{11}OH$	67	β only
4	3-pentanol	77	β only
5	epiandrosterone	65	β:α = 96:4
6	3-*O*-benzoylestradiol	70	β:α = 96:4
7	di-*O*-isopropylidene-D-galactose	83	β only
8	β-D-glucose-1,2,3,4-tetraacetate	62	β only

[a] Performed with 1.5 equiv of acceptor (alcohol) in each case. [b] NIS (1.1 equiv) and I_2 (0.25 equiv) were added at 0 °C initially, then TMSOTf (0.5 equiv) was added at −15 °C when all **1** had reacted. [c] TMSOTf added in two portions: see text. [d] Some oxidation to benzaldehyde seen.

(7) Spherical 3 Å molecular sieves of 1/16 in. diameter were used, activated by drying at 130 °C.

All yields were from 60 to 83%: the somewhat lower yield for benzyl alcohol is mainly due to some oxidation to benzaldehyde. The relative proportions of ortho ester and directly formed glucuronide varied for different alcohols, and in general it was simpler to add TMSOTf (0.5 equiv) in one portion at −15 °C upon complete reaction of **1**: rearrangement of ortho ester was complete in about 2 h in all cases. We included steroidal alcohols (entries 5 and 6) because steroidal glucuronides are of great importance in metabolism and as analytical standards.

The steroidal results are noteworthy and should be compared with those obtained using the corresponding imidate donor. Thus, the known tetrapivaloate **5**[9] (Figure 3)

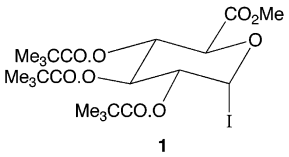


Figure 1. Chemical structure of glycosyl iodide ("donor") **1**.

was subjected to anomeric deacylation (N_2H_4−AcOH, DMF) to afford the hemiacetal **6** in 74% yield. Treatment of **6** with Cl_3CCN−K_2CO_3 in CH_2Cl_2 then gave imidate **7**[10] (87%) previously prepared via the glucuronyl bromide **8**. We employed **7** for the first time in glucuronidation of steroidal alcohols and, using 1.2 equiv **7** with TMSOTf catalysis, obtained the β-glucuronide esters derived from epiandrosterone and 3-benzoylestradiol in 36 and 65% yields, respectively; cf. Table 1, entries 5 and 6. Clearly, iodosugar **1** performs very well here and takes one step fewer to prepare than **7**.

The results with monosaccharide acceptors (Table 1, entries 7 and 8) show clear potential for oligosaccharide synthesis: in particular, the glucose tetraacetate (entry 8), regarded as a poor acceptor, still gives a very acceptable result (62%).

In contrast to glycosidation with bromide **8** + NIS,[6] secondary alcohols now react at a good rate (6 h or less in all cases studied) in highly acceptable yields *without large excesses of promoters*. For the more nucleophilic alcohols (viz. entries 1−4, 7, and 8), *no* α-anomer could be detected

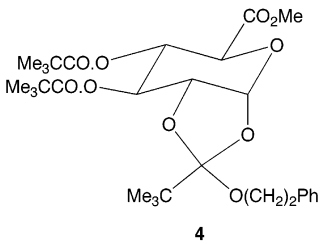
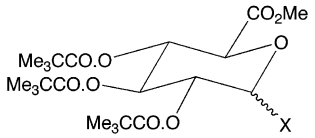


Figure 2. Chemical structure of ortho ester **4**.



X = β–OCO.CMe$_3$ (**5**)

X = α–OH (**6**)

X = α–OC(=NH)CCl$_3$ (**7**)

X = α–Br (**8**)

Figure 3. Glucuronate Intermediates.

even in the NMR of crude product: for the less reactive steroidal secondary alcohols (entries 5 and 6), about 4% of the α-product was detected.[11] As the *β*-products are anomerically stable under the reaction conditions, we attribute this small "slippage" to α/*β* glycosyl iodide exchange prior to glycosidation. Small (<5%) quantities of α-anomers are not a concern, being readily crystallized out.

We also investigated various "nonheavy" metal salts as promoters, with or without I_2 present. The use of Zn halides with a glucuronyl *bromide* but with no added I_2 had been reported previously,[12] and a few other metal salts have been used in conjunction with glucosyl bromides.[13] The results for the model reaction, Scheme 1, are summarized in Table 2.

Table 2. Glucuronidation of **2** with **1** Using $MX_n \pm I_2$ [a]

entry	promoter	I_2 equiv[b]	time, comments	yield of **3** (%)
1	$FeCl_3$	1.5	24 h, complete	79
2	$ZnCl_2$	0	24 h, complete	65
3	CuCl	1.5	5 h, complete	88
4	$NiCl_2$ [c]	1.5	26 h, complete	66
5	NiI_2 [c]	1.5	26 h, complete	62
6	$CeCl_3$ (2 equiv)	0	26 h, incomplete	58
7	$Yb(OTf)_3$	1.5	72 h, incomplete	47
8	$Sc(OTf)_3$	0	50 h, complete	43
9	MgI_2	1.5	96 h, incomplete	19
10	$LiClO_4$	1.5	72 h, incomplete	13

[a] Using 1.1 equiv of metal halide and 1.5 equiv of I_2 unless otherwise stated, in the presence of 3 Å molecular sieves (for quantity, see text) at 20 °C in DCE. [b] For entries 1, 3, 4, 5, 7, 9, and 10 the reaction *without* I_2 was impracticably slow. [c] Using 4 Å sieves (same quantity).

In contrast to the traditional Koenigs–Knorr reaction, where Ag, Hg, and Cd are used almost exclusively, a wide range of transition metals *and even lanthanides* (normally regarded as oxophilic, not halophilic: entries 6 and 7) are now effective and give over 50% yields: the results with $FeCl_3$ (entry 1) and CuCl (entry 3) are particularly good. We emphasize that, apart from entries 1 and 3, these results are *unoptimized* but refer to pure, chromatographed product. "Harder" metal cations, as in entries 8–10, are less effective. The use of $LiClO_4$ (entry 10) in conjunction with an in situ-formed "armed" glycosyl iodide was reported before.[14]

Our early results with this method gave variable α/*β* ratios, but we discovered that on using a minimum quantity of 3 Å molecular sieves (0.8 g per 0.2 mmol of **1**), the anomer **3***β* was cleanly produced (<2% **3**α by NMR): cf. the NIS method above. No significant amounts of ortho ester were seen in this reaction mode.

The $FeCl_3$–I_2 + **1** method was then applied to the same range of acceptors as in Table 1 with the results shown in Table 3.

Table 3. Glucuronidation of Various Alcohols[a] Using **1** + $FeCl_3/I_2$ [b] with 3 Å Molecular Sieves

entry	alcohol	yield (%)	α:*β* ratio
1	$Ph(CH_2)_2OH$	79	*β* only
2	$PhCH_2OH$	76	*β* only
3	c-$C_6H_{11}OH$	67	*β* only
4	3-pentanol	70	*β* only
5	epiandrosterone	42	*β*:α = 9:1
6	epiandrosterone	64[c]	*β* only
7	3-*O*-benzoylestradiol	68	*β*:α = 9:1
8	di-*O*-isopropylidene-D-galactose	57	*β* only
9	*β*-D-glucose-1,2,3,4-tetraacetate	10[d]	*β* only
10	monosaccharide **9**	61[c]	*β* only

[a] Performed with 1.5 equiv of acceptor (alcohol) in each case. [b] $FeCl_3$ (1.1 equiv), I_2 (1.5 equiv), 20 h at 20 °C in 1,2-dichloroethane. [c] Replacing $FeCl_3$ with CuCl. [d] See text.

With primary alcohols, yields were very comparable to those seen using NIS–I_2–TMSOTf, and clean *β*-products resulted. However, when this method was used for less reactive secondary steroidal alcohols, entries 5 and 7, anomeric mixtures containing 10% α-anomer resulted. We suggest that the entrainment of halide ion by the sieves, which inhibits anomeric halide exchange, is not complete and therefore the less nucleophilic alcohols no longer give clean *β*-products.[15] The results with CuCl (entries 6 and 10) suggest that appropriate selection of metal salt may, at least in some cases, eliminate α/*β* exchange: the faster rate seen for CuCl over $FeCl_3$ in the model reaction (Scheme 1 and Table 2), however, is not maintained for the steroidal alcohols.

(8) Ortho ester derived from 2-trimethylsilylethanol and **1** was fully characterized: in particular, δ_H ($CDCl_3$) 4.29 (1 H, approximately t, 2-H) and 5.91 (1 H, d, J = 4.8 Hz, 1-H).

(9) Vlahov, J.; Snatzke, G. *Liebigs Ann. Chem.* **1983**, 570–574.

(10) (a) Kornilov, A. V.; Kononov, L. O.; Zatonskii, G. V.; Shashkov, A. S.; Nifant'ev, N. E. *Russ. J. Bioorg. Chem. (Engl.)* **1997**, *23*, 597–607. (b) Suzuki, T.; Mabuchi, K.; Fukazawa, N. *Bioorg. Chem. Med. Lett.* **1999**, *9*, 659–662.

(11) For example, the α-product in the epiandrosterone series can be distinguished by δ_H ($CDCl_3$), inter alia, 4.40 (d, J = 9.9 Hz, 5-H), 4.78 (dd, J = 9.8 and 3.9 Hz, 2-H), and 5.57 (t, J = 9.8 Hz).

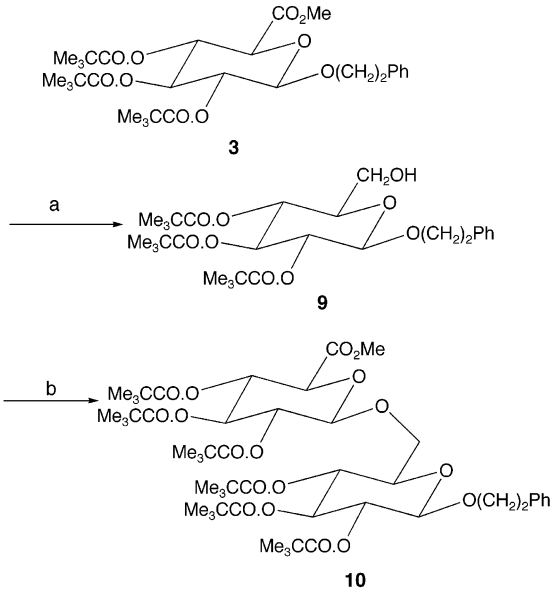
(12) Rukhman, I.; Nisnevich, G.; Gutman, A. L. *Tetrahedron* **2001**, *57*, 1083–1092.

(13) (a) ZnO (or a preformed Zn alkoxide): Gurudutt, K. N.; Rao, L. J. M.; Rao, S.; Srinivas, S. *Carbohydr. Res.* **1996**, *285*, 159–165. (b) $InCl_3$: Mukherjee, D.; Ray, P. K.; Chowdhury, U. S. *Tetrahedron* **2001**, *57*, 7701–7704. (c) $Sn(OTf)_2$: Lubineau, A.; Malleron, A. *Tetrahedron Lett.* **1985**, *26*, 1713–1716.

(14) Schmid, U.; Waldmann, H. *Tetrahedron Lett.* **1996**, *37*, 3837–3841.

(15) A referee suggested that the α-anomers may be formed by rearrangement from the ortho ester stage.

Scheme 2. Disaccharide Synthesis, Anomeric Glycoside[a]



[a] Reagents and conditions: (a) $NaBH_4$, THF, MeOH, 0 °C, 3 h, 81%; (b) **1**, CuCl, I_2, 3 Å MS, $(CH_2Cl)_2$, 0−20 °C, 24 h, 61%.

The NIS/I_2/TMSOTf method is therefore on balance our procedure of choice, as it affords essentially clean β-products and slightly superior yields to the metal halide procedure, in shorter reaction times.

The low yield obtained with glucose 1,2,3,4-tetraacetate, Table 3, entry 9, is the result of anomeric ester exchange and related side reactions ($ZnCl_2$ gave a similar result). However, the conditions are quite compatible with an anomeric *glycoside* as shown in Scheme 2 (using CuCl−I_2), which also illustrates a useful selective C(6)-reduction of glucuronides of type **3**. Here again, the disaccharide yield is unoptimized but the β-selectivity is complete, affording <2% α-anomer as indicated by ^{1}H NMR; the NIS−I_2−TMSOTf procedure was equally effective here: cf. Table 1, entry 8.

It is well-known that glucuronates, ceteris paribus, have the lowest donor reactivity of all pyranose sugars.[16] By inference, disarmed glycosyl iodides of other pyranoses are likely to show good donor ability. We believe that glycosyl iodide **1** shows considerable potential as a donor and will be of interest to other workers in the field.

Acknowledgment. We thank the EPSRC and Astra Zeneca for maintenance grants (to J.A.P. and D.S.), as well as Prof. R. A. Field (University of East Anglia) and Dr. R. Whyman (University of Liverpool) for valuable comments.

OL035475K

(16) Mueller, T.; Schneider, R.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *35*, 4763−4766.