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Glucuronidation of alcohols using the bromosugar–iodonium reagent method[†]

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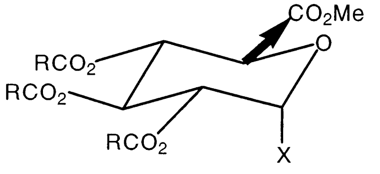
Abstract—The glycosidation method introduced by Field, employing bromosugars as donors in conjunction with iodine, has been evaluated for glucuronidation. Despite the low donor ability of glucuronates, β-glucuronides were obtained in 70–85% yield from a number of primary alcohols, and in 50–65% from two secondary alcohols, using the pivaloyl compound **11** with NIS as promoter. By contrast, the use of IBr or ICl as promoter gave mainly the α-glucuronides. © 2001 Elsevier Science Ltd. All rights reserved.

Glucuronidation of medicines and xenobiotics in vivo is a crucial means of detoxification in phase II metabolism.[1,2] Chemical synthesis of glucuronides, particularly *O*-glucuronides, is therefore important for the preparation of analytical standards and toxicology of new drugs: in addition, glucuronides may have significant bioactivity in their own right, as with morphine-6-glucuronide.[3] The strongly electron-withdrawing character of the 6β-methoxycarbonyl group in any activated glucuronate such as **1** makes such species notoriously poor donors;[4] the importance of quantifying the relative reactivity of donor and acceptor components in glycosidation is being increasingly recognised.[5]



1 R = alkyl, X = leaving group

2 R = Me, X = OC(=NH)CCl$_3$

3 R = *i*-Pr, X = OC(=NH)CCl$_3$

Methods of glucuronidation have been reviewed:[2] although the trichloroacetimidates **2** and **3** frequently perform well in the glucuronidation of a range of alcohols and phenols,[6,7] and thioglycosides have been employed,[8] new methods of glucuronidation are welcome. Field and co-workers have described the use of acetobromo aldopyranoses in conjunction with iodine as a good alternative to the traditional Koenigs–Knorr procedure for glycosidation of a range of alcohols and also the use of I_2 as a promoter for thioglycoside donors.[9,10] It was therefore of great interest to evaluate this method for glucuronidation.

The reaction of bromosugar **4** with benzyl alcohol **5** promoted by I_2 in acetonitrile or 1,2-dichloroethane (DCE) gave only a 10% yield of **6** on complete reaction of **4**. By-products included benzyl acetate and benzyl iodide; in this series added DDQ[9,10] gave no improvement. Reaction of isobutyryl bromosugar **7**[11] with **5** led to an improved yield (31%) of conjugate **8** (MeCN or DCE, I_2). A further improvement was seen using the more 'iodonium-like' *N*-iodosuccinimide (NIS) in place of I_2: thus, reaction of **7** with $Ph(CH_2)_2OH$ **9** (1.1 equiv. NIS, DCE) afforded a 57% yield of **10**. In the case of benzyl alcohol more side reactions were observed, notably oxidation to benzaldehyde when using NIS. All the runs cited up to this point employed just 1.5 equiv. of acceptor.

The most significant improvement, however, came on switching to the pivaloyl bromosugar **11** first described by Snatzke.[12] This gave an excellent yield (85%) of the conjugate **12** from **9** (1.1 equiv. NIS, DCE) in 20 h at 20°C. Other primary and secondary alcohols **13**–**16** were reacted similarly using NIS, IBr or ICl catalysis (here I_2 itself was impracticably slow) with the results summarised in Table 1.

Keywords: glucuronidation; iodine; pivaloate; bromosugars.

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[†] The work described was carried out entirely at the Ultrafine Laboratories.

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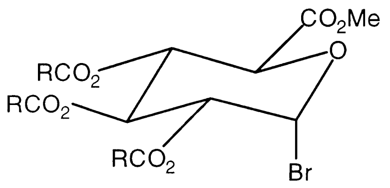
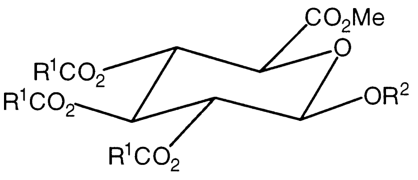
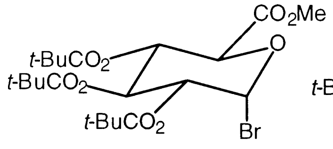


4 R = Me
7 R = *i*-Pr

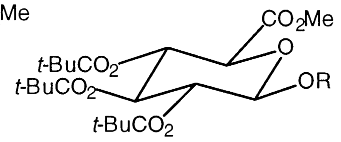


6 R^1 = Me, R^2 = CH_2Ph
8 R^1 = *i*-Pr, R^2 = CH_2Ph
10 R^1 = *i*-Pr, R^2 = $(CH_2)_2Ph$

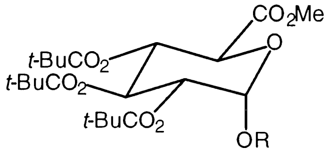
$PhCH_2OH$ **5**
$Ph(CH_2)_2OH$ **9**
n-C_4H_9OH **13**
n-$C_5H_{11}OH$ **14**
i-C_3H_7OH **15**
c-$C_6H_{11}OH$ **16**



11



12 R = $(CH_2)_2Ph$



17 R = $(CH_2)_2Ph$

Table 1. Glucuronidation of primary and secondary alcohols using pivaloyl bromosugar **11** with iodine reagents

Alcohol	Promoter (equiv.)	Solvent	Time (h)	Yield (%)	α:β Ratio
5	NIS (1.1)	DCE	21	71	β only
5	IBr (1.5)	DCM[a]	16	58	α:β = 5:1
9	NIS (1.1)	DCE	16	85 (**12**)	β only
9	IBr (1.5)	DCM[a]	60	82 (**17**)	α:β = 7:1
9	ICl (1.5)	DCE	20	80	α:β = 7:1
13	NIS (1.1)	DCE	40	80	β:α = 19:1
14	NIS (1.1)	DCE	40	73	β:α = 9:2
14	NIS (1.1)[b]	DCE	27	82	β only
14	NIS (1.1)[b]	MeCN	20	48	β only
15[c]	NIS (2)	DCE	72	53	β:α = 19:1
16[c]	NIS (2)[b]	DCE	72	25	α:β = 3:2
16[c]	NIS (2)[b]	MeCN	18	59	β:α = 19:1

NIS, *N*-iodosuccinimide; DCE, 1,2-dichloroethane; DCM, dichloromethane.

[a] IBr added in DCM solution to reagents in DCE

[b] I_2 (0.5 equiv.) added.

[c] 4 equiv.; in all other runs 1.5 equiv. of acceptor were employed.

It is clear that NIS gave good to excellent yields (70–85%) for all the primary alcohols and that β-glucuronides analogous to **12** were the sole or greatly predominant products (95–100% of total conjugate).[13] Oxidation of **5** to PhCHO was again observed, but the yield of conjugate (71%, pure β) was still highly acceptable. For the less reactive *n*-butanol **13** and *n*-pentanol **14**, addition of I_2 (0.5 equiv.) decreased the reaction time and improved the β:α ratio. Secondary alcohols **15** and **16** reacted more sluggishly, but acceptable yields of isopropyl and cyclohexyl glucuronides were obtained using 2 equiv. of NIS and 4 equiv. of acceptor. Satisfactory reaction of **16** required the use of MeCN for a reasonable reaction rate; the β:α ratio was still very high at 19:1. In DCE the α-glucuronide was the major product and the reaction was very much slower.

On the other hand, the use of IBr or ICl in the reaction of **9** with **11** in DCE gave mainly the α-glucuronide **17**,[14] and **5** similarly gave mainly the α-product when using IBr, the α:β ratios in these runs ranging from 5:1 to 7:1. These very interesting results suggest the operation of alternative mechanisms; it may well be that when IBr or ICl are used, a more reactive β-halide is formed in situ and reacts principally by an S_N2 mechanism. Certainly there is no evidence for α/β equilibration under these conditions.

In conclusion, the combination of pivaloyl bromosugar **11** and NIS offers a good method for the β-glucuronidation of a range of primary and secondary alcohols. By contrast, when IBr or ICl is used as a promoter with **11**, primary alcohols give very largely the α-glucuronide.

Acknowledgements

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12. Vlahov, J.; Snatzke, G. *Liebigs Ann. Chem.* **1983**, 570. Bromosugar **11** is a highly crystalline material of good stability and shows no decomposition after storage in a Nalgene bottle at 20°C for 6 months.
13. **Typical procedure**: 2-Phenylethanol **9** (0.091 g, 0.75 mmol) and bromosugar **11** (0.262 g, 0.5 mmol) were stirred together over freshly activated 4 Å molecular sieves in DCE (2 cm^3) with exclusion of light for 1 h. After cooling to 0°C, *N*-iodosuccinimide (0.125 g, 0.55 mmol) was added and stirring was continued for 16 h, the temperature being allowed to rise to 20°C. The reaction was diluted with EtOAc (15 cm^3) and washed with 10% aq. sodium thiosulfate (10 cm^3), satd aq. $NaHCO_3$, water, brine, dried (Na_2SO_4) and evaporated to give a crude product (0.307 g, white solid). Chromatography on silica, eluting with 10% EtOAc–isohexane, gave highly pure product **12** (0.241 g, 85%), mp 101–102°C (from 5% EtOAc–isohexane) (found: C, 63.9; H, 7.8. $C_{30}H_{44}O_{10}$ requires C, 63.8; H, 7.8%); δ_H (250 MHz, $CDCl_3$) 1.11, 1.13, 1.15 (27H, 3 s, 3×Me_3C), 2.89 (2H, m, $ArCH_2C$), 3.65–3.80, 4.05–4.15 (2H, 2 m, CH_2CH_2O), 3.75 (3H, s, CH_3O), 4.07 (1H, d, *J* 9.8 Hz, 5-H), 4.60 (1H, d, *J* 8 Hz, 1-H), 5.10 (1H, dd, 2-H), 5.26 (1H, t), 5.37 (1H, t) and 7.15–7.35 (5H, m, ArH); *m*/*z* (C. I., NH_3) 582 (MNH_4^+, 82%) and 480 (MNH_4^+–*t*-$BuCO_2H$, 10%).

    On a larger scale, the product could be isolated simply by crystallisation of the crude product from 5% EtOAc–isohexane.
14. The α-anomer **17** was distinguished by δ_H (220 MHz, $CDCl_3$) inter alia: 2.90 (2H, m, $ArCH_2C$), 3.70 (3H, s, CH_3O), 4.00 (1H, d, *J* 9.8 Hz, 5-H), 4.85 (1H, dd, 2-H), 5.15 (1H, d, *J* 3.5 Hz, 1-H), 5.28 (1H, t) and 5.57 (1H, t).