The Use Of Benzyl Esters in the Synthesis Of 1β-*O*-Acyl Glucuronides By Selective Acylation

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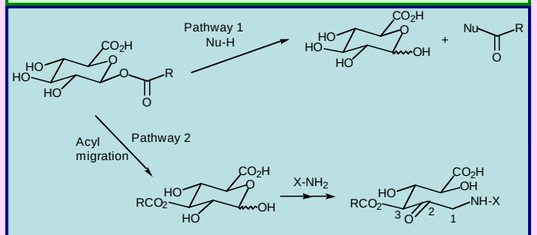
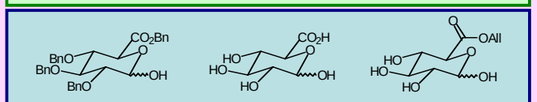
Introduction

Acyl glucuronides are key phase 2 metabolites for many carboxylic acid-containing drugs, notably of non-steroidal anti-inflammatory agents (NSAIDs).[1] It is important to synthesise acyl glucuronides in pure form, and especially as single 1β-anomers, for bioevaluation during drug discovery and development. Acyl glucuronides are reactive species: they may react by hydrolysis or displacement with other nucleophiles or by acyl migration followed by condensation with amines (Amadori rearrangement), **Scheme 1**.[2,3]



Scheme 1. Hydrolysis and rearrangement of acyl glucuronides.

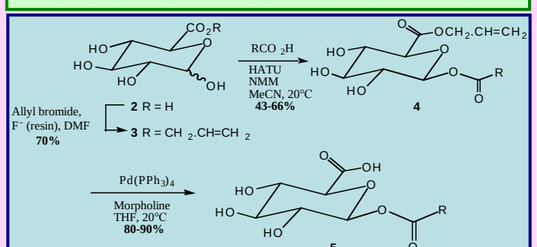
Previous acyl glucuronide syntheses were long and low-yielding. Fully protected intermediates such as **1**[4] require multi-step preparation prior to coupling to RCO$_2$H, while unprotected glucuronic acid **2** can be successfully coupled only in some special cases.[5]



1 **2** **3**

Discussion and results

We recently reported[6] a new acyl glucuronide synthesis (**Scheme 2)**, relying on selective acylation of allyl glucuronate **3** obtained from glucuronic acid **2**.[7] Previously **3** had been coupled with RCO$_2$H using the Mitsunobu reaction.[7] Although this method was satisfactory, it led to variable yields (usually 20-40%) and mixed α/β products, requiring preparative HPLC separation.



Scheme 2 Acyl glucuronide synthesis by selective acylation.

References

1 A. V. Stachulski and G. N. Jenkins, *Nat. Prod. Reports*, 1998, **15**, 173.

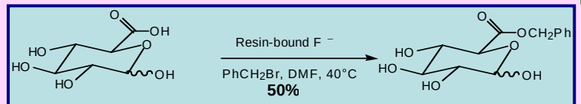
2 S. J. Vanderhoeven, J. C. Lindon, J. Troke, G. E. Tranter, I. D. Wilson and J. K. Nicholson, *Xenobiootica*, 2004, **34**, 73.

3 M. J. Bailey and R. G. Dickinson, *Chemico-Biological Interactions*, 2003, **145**, 117; M. Shipkova, V. W. Armstrong, M. Oellerich and E. Wieland, *Ther. Drug Monit.*, 2003, **25**, 1.

Selective acylation (**Scheme 2)** gave highly satisfactory yields (43-66%) of intermediates **4** with excellent β/α selectivity, 19:1 or better, for a range of carboxylic acids. In the acylation step, the strength of the base used and degree of carboxyl activation were key variables. We eventually found the HATU-NMM procedure shown to be generally suitable. In general the Pd (0) deallylation was reliable, but traces of Pd reagent sometimes persisted in the products **5**, even after chromatography. It was possible to use a resin-bound Pd (0) reagent, but a logical alternative was to employ another ester removable under very mild conditions. We therefore investigated the benzyl ester **6**.

Use of Benzyl Glucuronate

Alkylation of glucuronic acid **2** with PhCH$_2$Br using the resin-bound fluoride gave benzyl ester **6** in satisfactory yield after chromatography, **Scheme 3**. We are continuing to optimise this step. Previously **6** was obtained[8] in three steps from glucose.



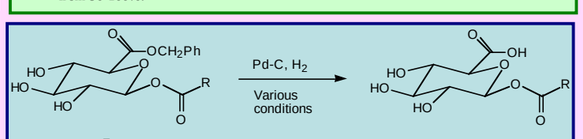
2 **6**

Scheme 3. Preparation of benzyl glucuronate.

Using **6**, the HATU-NMM method again gave good yields of the acylation products **7**, slightly higher than those obtained with **3**. (**Table 1**, reagents as **Scheme 2**).

Deprotection

- Intermediates **7** can be debenzylated using catalytic transfer hydrogenation (CTH) or conventional hydrogenation, **Scheme 4**.
- Using CTH and phenylacetic acid as a model (R = PhCH$_2$ in **7**), 10% Pd-C and cyclohexa-1,4-diene at 60°C in EtOH-THF or Pr^{i}OH-THF give complete reaction in 1h. Cyclohexene requires 80°C for a reasonable rate.
- Compatible with Ar-Cl (4-chlorobenzoic acid **10**); the trisubstituted C=C in mycophenolic acid **13** is unaffected. Ar-Br (in 4-bromobenzoic acid **8)** is lost. Yields are from 90-100%.



7

Scheme 4. Deprotection of benzyl esters.

Conditions: **1**. H$_2$(g), EtOH or Pr^{i}OH; **2**. Cyclohexene, Pr^{i}OH, 80°C; **3**. Cyclohexa-1,3-diene, Pr^{i}OH, 60°C.

4 R. R. Schmidt and G. Grundler, *Synthesis*, 1981, 1885.

5 A. B. Barua, C. A. Huselton and J. A. Olson, *Synth. Commun.*, 1996, **26**, 1355.

6 J. A. Perrie, J. R. Harding, D. W. Holt, A. Johnstone, P. Meath and A. V. Stachulski, *Org. Lett.*., 2005, **7**, 2591.

7 H. Juteau, Y. Gareau and M. Labelle, *Tetrahedron Lett.*, 1997, **38**, 1481.

8 M. Polakova, D. Joniak and D. Juris, *Monatsch. Chem.*, 2000, **131**, 1197.

9 S. J. Vanderhoeven, , J. Troke, G. E. Tranter, I. D. Wilson, J. K. Nicholson and J. C. Lindon, *Xenobiotica*, 2004, **34**, 889.

Illustrative Examples

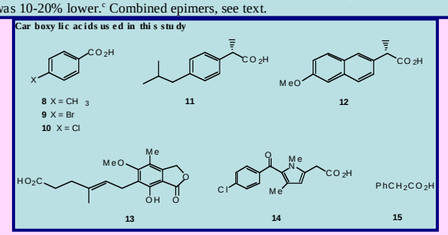
- Benzoic acids **8-10** all couple well. Slower reaction observed for acid **8** with electron-donating group.[9] 2-Br benzoic acid also couples in good yield. [6]
- From the 2-arylpropionyl class of NSAIDs, ibuprofen **11** and naproxen **12** react well. (2R, 2S)-Epimers are separable by chromatography; **11** is known to racemise at physiological pH. [10]
- Mycophenolic acid **13**[11] was satisfactorily coupled without phenol protection. Previously obtained by enzymic synthesis and prep. HPLC separation.[12]
- Zomepirac **14**, [13] whose acyl glucuronide has a half-life at physiological pH of < 30mins, was successfully prepared by our method.
- Phenylacetic acid **15** affords a good model example, and to date has given the best coupled yield of any carboxylic acid studied.

Table 1. Acyl glucuronides **7** synthesised by selective acylation of benzyl glucuronate **6**[a].

Carboxylic Acid	Equiv. HATU,[b] NMM	Yield %	Yield % with 3
8	1,3	**58**	
9	1,2	**62**	**59**
10	1,3	**62**	
11	1,3	**68**[c]	**65**
12	1,2	**67**[c]	
13	1,3	**55**	**44**
14	1,2	**59**	**52**
15	1,3	**82**	**66**

[a] In all cases the α: β ratio of the product was at least 19:1 (1H NMR). [b] Using TBTU (1 eq.), rather that HATU, yield was 10-20% lower. [c] Combined epimers, see text.

Carboxylic acids used in this study



Comments and Conclusions

- **The selective acylation method is again shown to be a good method for the synthesis of acyl glucuronides of a variety of carboxylic acids.**
- **The use of benzyl glucuronate allows mild deprotection by conventional or transfer hydrogenation. Compared to allyl esters (requiring Pd(0) deprotection), Pd residues are minimised and workup greatly simplified.**
- **Relevant drug examples are included in the examples studied: we are now in a position to evaluate rearrangement kinetics and prote in interaction of key acyl glucuronides *as single 1β-isomers*.**

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10 S.Ikegawa, N. Murao, J. Oohashi and J. Goto, *Biomed. Chromatogr.*, 1998, **12**, 317.

11 H. W. Florey, K. Gilliver, M. A. Jennings and A. G. Sanders, *Lancet*, 1946, (i), 46; M. Shipkova, A. Voland and H. J. Grone, *Ther. Drug Monit.*, 2003, **25**, 206.

12 M. Kittlemann, U. Rheinegger, A. Espigat, L. Oberer, R. Aichholz, E. Francotte and O. Ghisalba, *Adv. Synth. Catal.*, 2003, **345**, 825.

13 D. B. Levy and E. C. Vasilomanolakis, *Drug Intelligence and Clinical Pharmacy*, 1984, **18**, 983.