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Microwave-assisted, tin-mediated, regioselective 3-*O*-alkylation of galactosides

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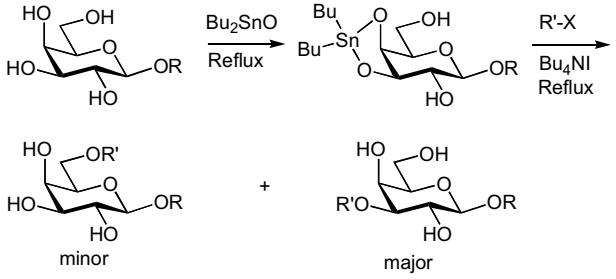
Abstract—A rapid, efficient and versatile microwave-assisted dibutylstannylene-mediated 3-*O*-alkylation method for galactosides was established. The alkylation reaction was significantly enhanced by microwave irradiation and allowed the use of an alkylating agent too unstable for incorporation using conventional heating.

The use of microwave irradiation is rapidly increasing within the various domains of organic chemistry.[1] However, its use in carbohydrate synthesis is clearly underexplored.[2] So far it has been limited to Ferrier rearrangements,[3] protecting group manipulations,[4] aglycon introductions,[5] and only very recently has the prospect of its use in glycosylation reactions been explored.[6] In the light of the acute need for new carbohydrate functionalization methods that minimize the employment of protecting groups, tin acetal-mediated regioselective functionalization of galactosides are of great interest.[7–11] While the action of microwave irradiation on acylation reactions have been reported,[12,13] no such examples exist involving alkylation. In this paper we report on the 3/6-*O*-regioselective tin-mediated microwave-assisted alkylation of different galactosides.

In non-microwave procedures dibutylstannylene acetals are generated by heating the unprotected carbohydrates along with Bu_2SnO under reflux (Scheme 1). These reactions take several hours in either methanol, benzene or toluene until a clear solution indicates completion. The subsequent acylation or alkylation in DMF or toluene, in some cases in the presence of tetrabutylammonium salts, takes up to 16 h to complete.[14] Even though this method can be successfully employed for simple regioselective acylations/alkylations of glycosides, high-temperatures and long reaction times limit the scope of the reaction. Less stable alkylating agents cannot be employed.



Scheme 1. Tin-mediated alkylation of galactosides.

Our initial microwave-assisted experiments were concerned mainly with the alkylation of two different galabiose and lactose building blocks (Scheme 2). These were part of ongoing efforts to synthesize different multivalent sugar-containing structures that can inhibit bacterial adhesion to human cells with enhanced activity.[15] Reactions were run with controlled microwave irradiation (MW) under sealed vessel conditions.[16] In the optimized 3-*O*-alkylation reaction, the unprotected galactoside (100 mg) was suspended in a dry benzene/acetonitrile mixture (5:1, 3 mL). After addition of Bu_2SnO (1.1 equiv) the mixture was exposed to microwave radiation in a sealed vessel at a controlled

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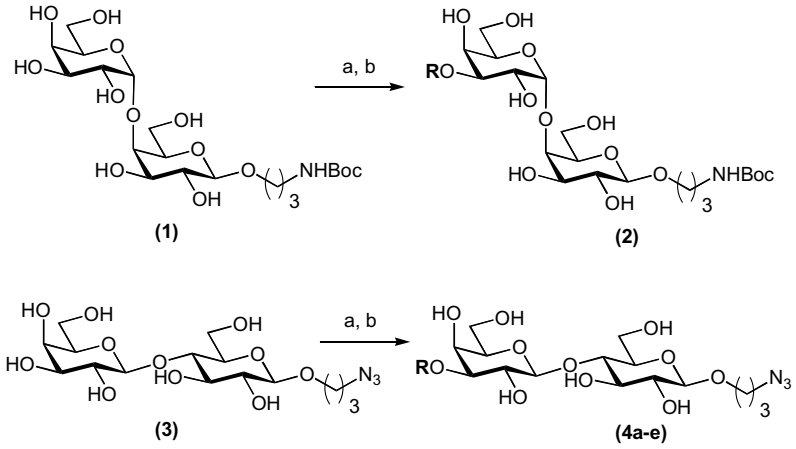
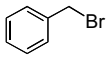
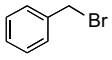
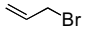
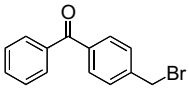
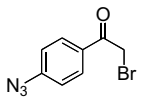
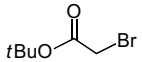


Scheme 2. Tin-mediated alkylation of galactosides. Reagents and conditions: (a) Bu_2SnO, benzene/CH_3CN (5:1), MW, 150 °C, 5 min; (b) Bu_4NI, R–Br, MW.

temperature of 150 °C for 5 min. A homogenous colourless solution was obtained indicating completion of the tin–acetal formation. After addition of the alkylating agent (5 equiv) and Bu_4NI (2.5 equiv) the mixture was irradiated again for the specific times and temperatures shown in Table 1.[17] The results for the alkylation reactions using several alkylating agents are summarized in Table 1. Good yields (75–86%) of alkylated products were obtained both with the lactose derivative **1** and the galabiose derivative **3**. The short reaction times clearly indicated the beneficial effect of heating by microwave irradiation. Compound **4d** was formed in lower yield due to the heat-sensitive nature of the alkylating agent. However, the benefit of microwave irradiation is also evident here as the corresponding conventionally heated reaction did not yield any product. The products derived from **1** and **3** were acetylated and characterized by ^1H, ^{13}C, 2D-COSY NMR and mass spectrometry. While the reactions invariably yielded the $1\rightarrow3$ linked isomer as the major product, a second regioisomer, the 6-*O*-alkylated galactoside could be observed by TLC as a minor spot. Typically the ratio between the isomers was around 8:1 ($1\rightarrow3$ vs $1\rightarrow6$).

Table 1. Microwave assisted tin-mediated alkylation of galactosides

Start. mat.	R–Br	Product	Time (min)	*T* (°C)	Yield[a] (%)
1		**2**	10	150	80
3		**4a**	6	170	84
3		**4b**	6	170	86
3		**4c**	10	150	75
3		**4d**	20	110	45
3		**4e**	15	170	85

[a] Isolated yields.

In summary we have developed a convenient microwave assisted one-pot protocol for the preparation of different 3-*O*-alkylated galactosides, using stannylene acetal chemistry. The action of microwave irradiation dramatically shortened the reaction times and allowed the use of an alkylating agent, too unstable for incorporation using conventional heating as shown in the synthesis of **4d**.

Acknowledgements

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References and notes

1. (a) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 314–320; (b) Perreux, L.; Loupy, L. *Tetrahedron* **2001**, *57*, 9199; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
2. Corsaro, A.; Chiacchio, U.; Pistara, V.; Romeo, G. *Curr. Org. Chem.* **2004**, *8*, 511.
3. (a) Sowmya, S.; Balasubramanian, K. K. *Synth. Commun.* **1994**, *24*, 2097; (b) de Oliveira, R. N.; de Freitas Filho, J. R.; Srivastava, R. M. *Tetrahedron Lett.* **2002**, *43*, 2141; (c) Shanmugasundaram, B.; Bose, A. K.; Balasubramanian, K. K. *Tetrahedron Lett.* **2002**, *43*, 6795; (d) Das, S. K.; Reddy, K. A.; Abbinemi, C.; Roy, J.; Rao, K. V. L. N.; Sachwani, R. H.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 4507.
4. (a) Babtistella, L. H. B.; Neto, A. Z.; Onaga, H.; Godoi, E. A. M. *Tetrahedron Lett.* **1993**, *34*, 8407; (b) Limousin, C.; Cléophax, J.; Loupy, A.; Petit, A. *Tetrahedron* **1998**, *54*, 13567; (c) Söderberg, E.; Westman, J.; Oscarson, S.

J. Carbohydr. Chem. **2001**, *20*, 397; (d) Bailliez, V.; de Figueiredo, R. M.; Olesker, A.; Cléophax, J. *Synthesis* **2003**, *7*, 1015; (e) Kobayashi, S.; Yoneda, A.; Fukuhara, T.; Hara, S. *Tetrahedron Lett.* **2004**, *45*, 1287; (f) Limousin, C.; Olesker, A.; Cléophax, J.; Petit, A.; Loupy, A.; Lukacs, G. *Carbohydr. Res.* **1998**, *312*, 23.

5. (a) Limousin, C.; Cléophax, J.; Petit, A.; Loupy, A.; Lukacs, G. *J. Carbohydr. Chem.* **1997**, *16*, 327; (b) Nüchter, M.; Ondruschka, B.; Lautenschläger, W. *Synth. Commun.* **2001**, *31*, 1277; (c) Mohan, H.; Gemma, E.; Ruda, K.; Oscarson, S. *Synlett* **2003**, *9*, 1255.
6. Mathew, F.; Jayaprakash, K. N.; Fraser-Reid, B.; Mathew, J.; Scicinski, J. *Tetrahedron Lett.* **2003**, *44*, 9051.
7. Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 17.
8. David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
9. Morcuende, A.; Ors, M.; Valverde, S.; Herradón, B. *J. Org. Chem.* **1996**, *61*, 5264.
10. Kaji, E.; Shibayama, K. *Tetrahedron Lett.* **2003**, *44*, 4881.
11. Leigh, D. A.; Martin, R. P.; Smart, J. P.; Truscello, A. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1373.
12. Morcuende, A.; Valverde, S.; Herradón, B. *Synlett* **1994**, 89.
13. Herradón, B.; Morcuende, A.; Valverde, S. *Synlett* **1995**, 455.
14. David, S.; Thieffry, A.; Veyrières, A. *J. Chem. Soc., Perkin. Trans. 1* **1981**, 1796.
15. Autar, R.; Khan, A. S.; Schad, M.; Hacker, J.; Liskamp, R. M. J.; Pieters, R. J. *Chem. Bio. Chem.* **2003**, *4*, 1317.
16. Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624.
17. The slightly yellow solution obtained was then concentrated to dryness and the resulting solid was suspended in acetone and sonicated. The solids were removed by filtration and the mother liquor was concentrated again and loaded onto silica for column chromatography (20:1 → 10:1, CH_2Cl_2/MeOH).