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Mitsunobu Glycosylation of Nitrobenzenesulfonamides: Novel Route to Amadori Rearrangement Products

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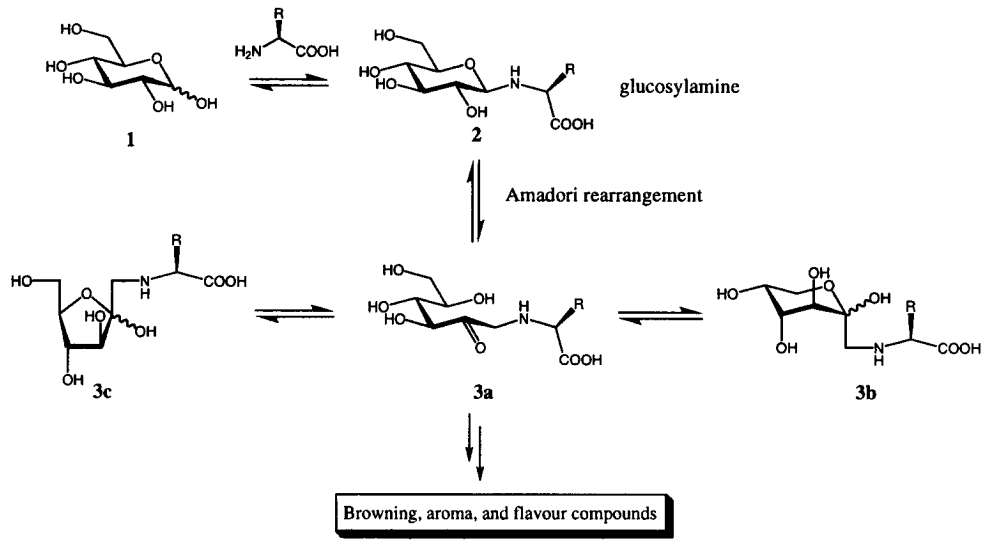
Abstract: Amino-acid derived 2-nitrobenzenesulfonamides were successfully condensed under Mitsunobu conditions with 2,3,4,6-tetra-*O*-acetyl-D-glucose to afford the fully protected glucosylamines in excellent yield. Upon total deprotection, these compounds rearranged to provide the corresponding Amadori products in good overall yield.

Keywords: Mitsunobu glycosylation, Amadori Rearrangement Products, nitrobenzenesulfonamides.

The condensation of an amino acid with the reducing end of a sugar and the many reactions that occur thereafter is known as the Maillard reaction.[1,2] This set of reactions which is sometimes referred to as "non-enzymatic browning" is of great importance in the processing of foods for the production of aroma, taste and colour. Furthermore, evidence strongly suggests that this intricate reaction cascade is involved in the pathology of diabetes and ageing.[3,4] A key intermediate in the early stages of the Maillard reaction for D-glucose is the 1-amino-1-deoxy-D-fructose **3** formed as a result of the rearrangement of the corresponding glucosylamine **2** (Scheme 1).



Scheme 1

0040-4039/99/$ - see front matter
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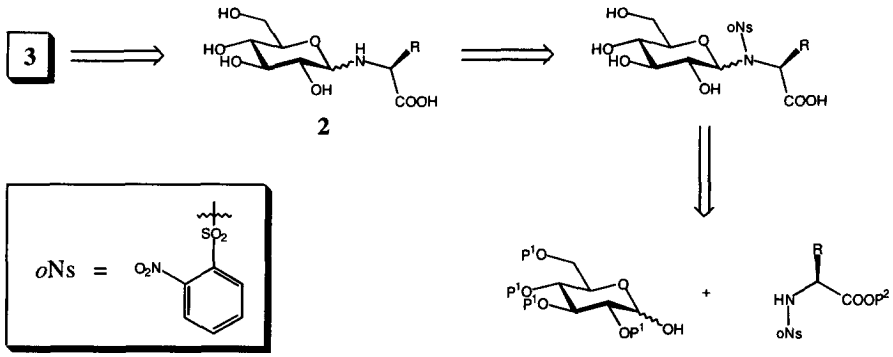
This so-called Amadori Rearrangement Product **3a** (ARP) has been shown to undergo thermal polymerisation and degradation leading to brown coloured dye formation, accompanied by the formation of various compounds associated with the aroma and flavour of foods.[5, 6] In order to study such pathways in more detail, sufficient quantities of pure ARPs are required. As a result, considerable attention has been focussed on their synthesis.[7]

Here we present a novel methodology which exploits the propensity of glucosylamines to rearrange to the corresponding Amadori products. It was envisaged that successful adaptation of Fukuyama's protocol[8] for the synthesis of secondary amines to the glycosylation of carbohydrates would, upon deprotection, yield Amadori products **3** *via* glucosylamines **2** (Scheme 2).

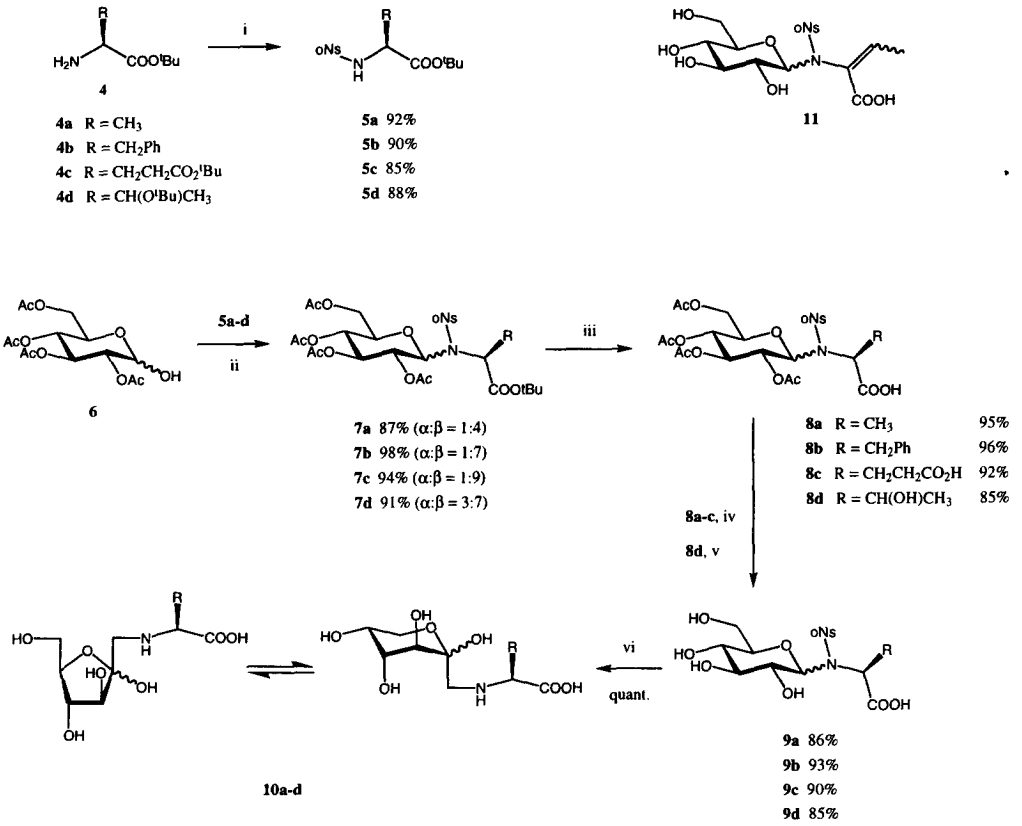


Scheme 2

Due to the notorious instability of unprotected amino-acid derived glucosylamines,[9] it would be necessary to make the cleavage of the nitrobenzenesulfonyl group the last step of the synthesis. Therefore, the protecting group strategy employed would naturally have to take this into consideration. Discounting the benzyl group whose cleavage would be incompatible with the nitrobenzenesulfonyl group, the choice of readily available anomerically free protected glucose derivatives is limited to ester functionality. However, it is well documented that treatment of α-amino acid esters with base results in racemisation[10] and, in the case of threonine, can lead to elimination of the β-hydroxyl.[11] This does not occur when the carboxyl group is free, hence an orthogonal approach using acid labile protection for the functional groups in the amino acid moiety was deemed to be the best solution. Accordingly, the known *tert*-butyl protected amino acids **4a-d** were reacted with *ortho*-nitrobenzenesulfonyl chloride and pyridine in dichloromethane to provide the corresponding sulfonamides **5a-d** in good yield (Scheme 3).[12] Each of these were condensed with 2,3,4,6-tetra-*O*-acetyl-D-glucose **6** under Mitsunobu conditions[13] at –80 °C to give the fully protected glucosylamines **7a-d** in excellent yield. The anomeric configuration of **7a-d** varied, with threonine derived **7d** providing the least selectivity. Further investigation revealed that the stereochemical outcome could be improved by keeping the reaction at low temperature for longer periods although this does result in a slight decrease in yield (e.g. **7d** 77%; α:β = 1:9, 4.5h at –80 °C then r.t.).

With fully protected glucosylamines **7a-d** in hand, treatment with neat TFA cleaved the *tert*-butyl groups in excellent yield, giving compounds **8a-d** which after purification were subjected to 1.1 eq KO^{t}Bu /MeOH (2.1 eq for the glutamic acid derivative). With compounds **8a-c**, this proceeded without problems however with threonine derivative **8d**, the product was accompanied by significant elimination (**11** = 25%) which could not be separated from the desired product. This problem could be avoided by replacement of

KO^{t}Bu with K_2CO_3 which totally suppressed formation of the elimination product giving compound **9d** in 85% isolated yield.



Reagents and conditions: (i) *o*NsCl, pyridine, CH_2Cl_2, r.t., (ii) Ph_3P, DEAD, THF, -80°C, (iii) trifluoroacetic acid, r.t, (iv) KO^{t}Bu, MeOH, r.t., (v) K_2CO_3, MeOH, r.t., (vi) PhSH, DIPEA, DMF, r.t.

Scheme 3

With all the compounds at the penultimate stage, attention was focussed on the final deprotection step. In order to obtain the Amadori compounds in their free form it was necessary to deviate from the standard Fukuyama nitrobenzenesulfonyl cleavage conditions. Wuts *et al.*[14] have recently reported that DIPEA is an efficient substitute for K_2CO_3, therefore deprotection optimisations were performed using this system (DIPEA/PhSH/DMF). Disappointingly, using the conditions described therein (3 eq DIPEA, PhSH 1.2 eq, DMF), cleavage was unacceptably slow (c.a. 50% after 3 days). However, it was found that total cleavage could be effected using excess PhSH with respect to DIPEA (typically 5 eq PhSH/4 eq DIPEA in DMF overnight at r.t). If complete cleavage was not observed, the amount of reagents could be increased in the aforementioned ratio providing the Amadori products **10a-d** in essentially quantitative yield, as verified by mass spectrometry and NMR spectroscopy.[15] Significantly, it was observed that the same amount of thiophenol, but with an excess of base in the ratio described for conventional conditions resulted in a very slow reaction which was incomplete even after 5 days.

At this juncture, it should be noted that we experienced problems with the *para*-nitrobenzenesulfonyl group similar to those reported by the groups of Miller[16] and Wuts,[14] namely that cleavage was dramatically slower than the corresponding *ortho* derivative. Due to this observation the use of the former was discontinued.

In conclusion, we have successfully synthesised pure Amadori compounds using a novel Mitsunobu glycosylation procedure as the key step in good overall yield. The methodology described herein is currently being extended to other sugars and details of this will be published in due course.

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References and notes

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[12] All new compounds were obtained in an analytically pure form and fully characterised by spectroscopic techniques (^{1}H/^{13}C-NMR, MS). Selected data: **7c**β: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.29-7.51 (m, 4H, C<u>H</u>*o*Ns), 5.88 (m, 1H, H_2), 5.33-5.14 (m, 2H, H_4 and H_3), 5.02 (d, 1H, *J* 9.0Hz, H_1), 4.50-4.45 (m, 1H, $H_\alpha$glu), 4.33-4.05 (m, 2H, H_6), 3.75-3.73 (m, 1H, H_5), 2.42-1.84 (m, 16H, 2xCH_2 and 4xCH_3), 1.45 (s, 9H, ^{t}Bu), 1.22 (s, 9H, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.1, 170.2, 170.0, 169.0, 168.5, 168.3, 148.7, 134.0, 132.6, 131.9, 130.9, 123.1, 84.3, 82.1, 80.5, 74.2, 69.9, 67.1, 61.0, 58.9, 31.4, 27.8, 27.3, 27.1, 20.5, 20.4, 20.3. MS: *m/z* 797.3 $[M+Na]^+$. **9c**β: ^{1}H-NMR (600MHz, D_2O): δ 8.22-7.79 (m, 4H, C<u>H</u>*o*Ns), 5.16 (d, 1H, *J* 9.1 Hz, H_1), 4.43-4.41 (m, 1H, $H_\alpha$glu), 3.83 (d, 1H, *J* 12.4, H_6), 3.65-3.59 (m, 2H, H_2 and H_6), 3.55-3.52 (m, 1H, H_3), 3.47-3.45 (m, 1H, H_5), 3.38-3.35 (m, 1H, H_4), 2.48-2.16 (m, 4H, 2xCH_2). ^{13}C-NMR (150 MHz, D_2O): δ 178.5, 148.4, 136.0, 133.5, 132.0, 131.6, 125.2, 88.3, 79.1, 77.1, 70.7, 70.2, 61.9, 61.8, 32.4, 27.3. MS: *m/z* 517.2 $[M+Na]^+$. Characteristic data: **7d**β: ^{1}H-NMR (300MHz, $CDCl_3$): δ 5.64 (d, 1H, *J* 9.6Hz, H_1), 4.53 (d, 1H, *J* 2.3Hz, $C_\alpha$thr), 4.33-4.27 (m, 1H, $C_\beta$thr), 4.11-3.98 (m, 2H, C_6). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 86.1 (C_1), 81.6 (C_q, ^{t}Bu), 74.0 (C_q, ^{t}Bu), 69.4 ($C_\beta$thr) 65.0 ($C_\alpha$thr), 61.7 (C_6), 28.7 (CH_3, ^{t}Bu), 27.8 (CH_3, ^{t}Bu), 19.9 ($C_\gamma$thr). MS: *m/z* 769.4 $[M+Na]^+$. **9a**β: ^{1}H-NMR (200MHz, D_2O): δ 5.03 (d, 1H, *J* 8.8Hz, H_1), 4.62 (q, 1H, *J* 7.7Hz, $C_\alpha$ala), 1.62 (d, 3H, *J* 7.7Hz, CH_3). ^{13}C-NMR (50MHz, D_2O): δ 87.8 (C_1), 61.5 (C_6), 56.7 ($C_\alpha$ala), 17.9 (CH_3). MS: *m/z* 459.1 $[M+Na]^+$.

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