The Copper(I) Catalysed [2+2] Intramolecular Photoannulation of Carbohydrate Derivatives

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This paper is dedicated to Professor A. Eschenmoser

Abstract: Carbohydrate derivatives 1a, 1b, 3a and 3b have been subjected to copper(I) catalysed photoannulation to produce tetracyclic products 2a, 2b, 4a and 4b respectively as single enantiomers. The same reaction carried out on substrates 5a and 5b leads stereoselectively to the spiro products 6a and 6b respectively. Photoannulation of substrate 7 gave an approximate 1:1 mixture of spiro products 8 and 9. A mechanistic rationalisation of these results is proposed.

Key words: annulation, carbohydrates, copper, cycloadditions, photochemistry

Synthetic chemists have used carbohydrates as polyhydroxylated chiral starting materials for many years.¹ When the chosen target molecule in these ventures is cyclic, methods for the annulation of the carbohydrate starting material are required, and there are many varied strategies to achieve this objective.² One potentially useful method for carbohydrate annulation involves a [2+2] photoannulation. To the best of our knowledge there are three applications of intramolecular enone-olefin [2+2] photoannulation in a carbohydrate example,³ in which stereoselectivity was not always observed. There are also two examples of intermolecular enone-olefin [2+2] photoannulation on sugar derivatives, one of which occurs in low yield with poor stereoselectivity.⁴ We now report the stereoselective formation of several cyclobutane carbohydrate derivatives, in good yield, via the copper(I) catalysed [2+2] photoannulation of the corresponding unactivated 1,6-dienes.

The formation of coordination complexes between copper(I) and olefins is well known.^{5, 6} Applications of these complexes in catalysed photoannulation reactions has been studied by Salomon for many years.⁷ In particular copper(I) catalysed [2+2] cycloaddition has been especially successful. Coordination of the copper(I) to both olefins produces a complex which absorbs the light and cyclizes. The product does not coordinate, and so is released from the copper, which then coordinates another molecule of diene to complete the cycle.

Continuing our interest in new methods for carbohydrate annulation⁸ we have investigated the application of the copper(I) triflate catalysed [2+2] photoannulation to this problem. We were particularly interested to see if the promising results of Salomon and Ghosh,⁹ on the stereocontrol of these reactions, could be applied in carbohydrate examples to produce single enantiomerically pure diastereoisomers.

Table 1. Summary of the results of photoannulation reactions carried out on 1,6-diene carbohydrate derivatives.



The 1,6-dienes¹⁰ **1a-b**, **3a-b**, **5a-b** and **7** were selected and the results of the photoannulation reactions are summarised in Table 1. The first photoannulation substrate was the trans glucose derivative 1a, which was irradiated at 254 nm in benzene, using a Rayonet photochemical reactor, with a catalytic amount copper(I) triflate benzene complex.11 Two diastereoisomeric products are possible in this reaction, arising from the facial selectivity of the [2+2] cycloaddition. The ¹³C NMR spectrum of the crude product showed that only one diastereoisomer was formed, and only a single peak was observed by HPLC. The six stereogenic centres in the enantiomerically pure starting material 1a would not reasonably be expected to change on irradiation, and so we conclude that product 2a, obtained in 86% isolated yield, is enantiomerically pure. The absolute configurations of the two new centres in 2a were confirmed in the X-ray crystal structure¹² by comparison with the unchanged stereogenic centres.

Similar treatment of the more hindered *trans* diene **1b** gave a modest 18% yield of product **2b**, whereas the *cis* glucose derivatives **3a** and **3b** led to single diastereoisomers **4a** and **4b** in 86% and 89% yield respectively.

To extend the range of this work we prepared two substrates **5a** and **5b** for spiro photoannulation. Irradiation under our usual conditions produced the products **6a** and **6b** as single enantiomers in moderate yield, whose structures were confirmed by X-ray crystallography.¹³ Diene **7** gave an approximate 1:1 mixture of the two possible products **8** and **9** in a 63% yield.





In order to explain the stereochemistry of these reactions we returned to the work of Salomon and Ghosh,⁹ in which there is a preference for the formation of the *endo* product in the photobicyclisation of 1,6-heptadiene-3-ols. Applying these arguments to the photoannulation of our diene glucose derivatives we arrive at the hypotheses illustrated in Scheme 1. Coordination of the two olefins and the hydroxyl oxygen as shown in structures **10a** and **10b** means that in the products **2a** and **2b** the cyclobutane ring and the hydroxyl group are on the β -face of the molecule. In the same way the chelated structures **11a** and **11b** lead to the products **4a** and **4b** in which the cyclobutane and the hydroxyl group are on the α -face of the molecule.



Scheme 2

We propose transition states **12a** and **12b** in Scheme 2 to explain the stereochemistry of the products **6a** and **6b**. Coordination of one of the olefins and the sugar ring oxygen to the copper(I) leads only to the observed products **6a** and **6b** on irradiation.

In contrast to the stereospecific photoannulation of **5a** and **5b**, substrate **7** gave an approximate 1:1 mixture of the two possible products **8** and **9**. Clearly in compound **7** the anomeric oxygen is too far away to coordinate to the copper(I)-diene chelate. This is in agreement with the lack of selectivity observed by Mackor and Evers in the photobicyclisation of 4-hydroxy 1,6-heptadiene.¹⁴

In conclusion we have demonstrated the remarkable stereocontrol of copper(I) triflate in the photoannulation of six unactivated 1,6-diene carbohydrate derivatives.

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- (11) Typical Synthetic Procedure for the [2+2] photoannulation: All operations were performed under nitrogen. Solvents were dried by using standard methods. Yields reported refer to products purified by column chromatography.

 $(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.02 mmol) was added to a solution of diene **1a** (140 mg, 0.42 mmol) in benzene (10 mL), in a quartz photolysis tube, water-cooled by a cold finger extending into the solution. Irradiation was carried out at 254 nm, using a Rayonet photochemical reactor, for 6 hours. The reaction mixture was diluted with diethyl ether (40 mL) and washed with aqueous ammonia solution (35%, 2x20 mL). The organic layer was washed with water (20 mL), dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether (40-60°C)/diethyl ether, 3/1) to yield **2a** as a white solid (121 mg, 86%).

Sample spectroscopic data for two photoannulated products: **2a** - M.p. 101-103°C; $[\alpha]_{D}^{20} = +34.2$ (c = 4.1 in CHCl₃); $R_{f} =$ 0.36, petroleum ether (40-60°C)/diethyl ether (1/1); ¹H NMR $(400 \text{ MHz}; \text{CDCl}_3) \delta = 7.55-7.33 \text{ (m, 5 H, Ph)}, 5.59 \text{ (s, 1 H,}$ 12-H), 4.60 (s, 1 H, 1-H), 4.31 (dd, J = 4.7, 10.2 Hz, 1 H, 6eq-H), 3.88 (dd, J = 9.2, 11.0 Hz, 1 H, 4-H), 3.87 (t, J = 10.2 Hz), 1 H, overlapping, 6ax-H), 3.70 (ddd, *J* = 4.7, 9.2, 10.2 Hz, 1 H, 5-H), 3.42 (s, 3 H, OMe), 2.84-2.73 (2 H, 7-H and 10-H), 2.29-2.15 (2 H, CHH, 9-H and CHH, 11-H), 2.15 (br s, 1 H, overlapping, OH), 2.08-1.97 (3 H, CHH, 8-H and 3-H), 1.81 (m, 1 H, CHH, 9-H), 1.58 (dt, J = 5.7, 12.3 Hz, 1 H, CHH, 11-H); ¹³C NMR (100.6 MHz, CDCl₃) δ = 138.2 (C, Ph), 129.3 (CH, Ph), 128.7 (CH, Ph), 126.6 (CH, Ph), 102.9 (CH, C1), 102.3 (CH, C12), 81.9 (C, C2), 81.4 (CH, C4), 69.6 (CH₂, C6), 65.1 (CH, C5), 55.6 (CH₃, OMe), 48.0 (CH, C3), 42.7 (CH, C7), 37.1 (CH, C10), 33.6 (CH₂, C11), 29.4 (CH₂, C9), 17.2 (CH₂, C8); HRMS (FAB): *m/z*(%): 333 (15) [*M*H⁺]; calcd for C₁₉H₂₅O₅ [*M*H⁺]: 333.1702, found: 333.1703. Anal. Found: C, 68.75; H, 7.32. C₁₉H₂₄O₅ requires C, 68.66; H, 7.28%.

6a - M.p. 141.5-143°C; $[\alpha]_D^{12} = +36.6 (c = 3.3 \text{ in CHCl}_3); R_f$ = 0.26, petroleum ether $(40-60^{\circ}C)/diethyl ether (1/1);$ ¹H NMR (250 MHz; CDCl₃) δ = 7.55-7.30 (m, 5 H, Ph), 5.50 (s, 1 H, 12-H), 4.67 (s, 1 H, 1-H), 4.24 (dd, J = 4.4, 10.1 Hz, 1 H, 6eq-H), 3.98-3.80 (3 H, CHH, 11-H and 5-H), 3.70 (t, J = 10.1 Hz, 1 H, 6ax-H), 3.49 (s, 3 H, OMe), 3.49 (m, 1 H, overlapping, 4-H), 3.16-2.93 (2 H, 7-H and 10-H), 2.22 (m, 1 H, CHH, 9-H), 2.01 (m, 2 H, CHH, 8-H), 1.87 (m, 2 H, CHH, 3-H), 1.67 (m, 1 H, CHH, 9-H); ¹³C NMR (62.9 MHz, CDCl₃) δ = 137.8 (C, Ph), 129.5 (CH, Ph), 128.7 (CH, Ph), 126.6 (CH, Ph), 102.3 (CH, C12), 99.6 (CH, C1), 83.8 (C, C2), 77.4 (CH, C4), 73.1 (CH₂, C11), 69.9 (CH₂, C6), 64.1 (CH, C5), 55.4 (CH₃, OMe), 45.6 (CH, C7), 39.1 (CH, C10), 32.7 (CH₂, C3), 24.1 (CH₂, C9), 19.6 (CH₂, C8); HRMS (FAB): *m/z*(%): 333 (56) [*M*H⁺]. Anal. Found: C, 68.53; H, 7.27. C₁₉H₂₄O₅ requires C, 68.66; H, 7.28%.

- (12) **Crystal data for 2a**: crystal dimensions 0.54 x 0.24 x 0.12 mm, triclinic, space group P1, a = 8.467(2), b = 10.304(3), c = 10.464(5)Å, $\alpha = 90.40(3)$, $\beta = 109.34(3)$, $\gamma = 101.30(2)^{\circ}$, V = 842.2(5) Å³, Z = 2, $\rho_{calcd} = 1.311$ g cm⁻³, $2\theta_{max} = 48^{\circ}$, Mo-K $_{\alpha}$ radiation ($\lambda = 0.7107$ Å), ω scan, 190K, 2512 reflections, 2368 independent reflections used for refinement. The data were corrected for Lorentz and polarisation effects but not for absorption ($\mu = 0.094$ mm⁻¹, min/max transmission = 0.963/0.991). The structure was solved by direct methods and refined *F*² (SHELXTL/PC ver 5.0), 2 unique molecules in the asymmetric unit with different orientation of the phenyl group at C12, hydroxyl H atoms were located from difference Fourier maps, all other H atoms were included in calculated positions (C-H = 0.96Å) using a riding model. R1 = 0.063 [I>2\sigma(I)], *wR*2 = 0.169 for all data, for 313 parameters, maximum $\Delta \rho = +0.26$, -0.31 e Å⁻³.
- (13) Crystallographic data for compounds 2a, 6a and 6b in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition numbers CCDC-110883, 110884 and 110885 respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(1223)-336-033; E-mail: deposit@ccdc.cam.ac.uk).
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