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Dye-Sensitized Photooxygenation of Furanosyl Furans: Synthesis of a New Pyridazine *C*-Nucleoside

Flavio Cermola,* M. Rosaria Iesce, and Gianluca Buonerba

Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, Complesso Universitario di M. Sant'Angelo, Via Cinthia 4, 80126 Napoli, Italy

cermola@unina.it

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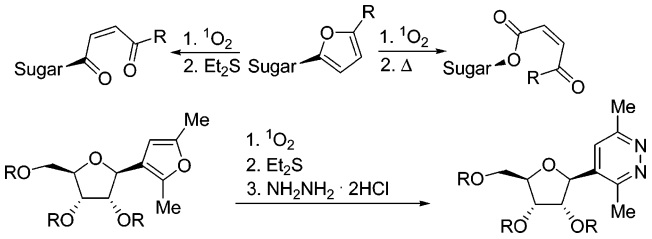
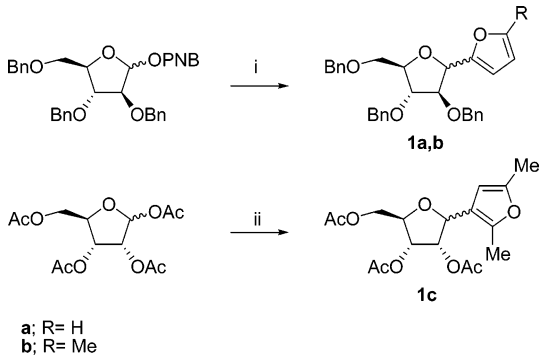


The dye-sensitized photooxygenation of furanosyl furans easily affords *C*- or *O*-glycosides with cis-α,*β*-unsaturated 1,4-dioxo aglycones. The reaction, performed on a ribofuranosyl furan, provides a useful new entry to a novel pyridazine *C*-nucleoside that can be achieved through a simple one-pot procedure.

C-Nucleosides are compounds of great interest owing to their potential biological activity together with their higher stability than nucleosides.[1−5] The research of new synthetic procedures for this compound class is a field of organic chemistry continuously explored. Generally, the synthetic approach is based on coupling reactions between a glycosyl-donor and a heterocycle as well as on the elaboration of a preexistent residue that is selectively converted into the desired aglycone.[6] In the framework of the latter strategy,[6a] the use of furan is well-known.[7,8]

Recently, we have tested the use of the dye-sensitized photooxygenation on some glucopyranosyl furans with the aim to introduce this procedure as additional methodology toward new and functionalized glycosides.[9]

SCHEME 1[a]



[a] Conditions: (i) furan (6 equiv), $SnCl_4$ (1.6 equiv), CH_2Cl_2, 4 h (for **1a**); 2-methylfuran (1 equiv), $SnCl_4$ (1.6 equiv), CH_2Cl_2, 2 h (for **1b**); (ii) 2,5-dimethylfuran (1 equiv), $SnCl_4$ (1.6 equiv), CH_2Cl_2, 1 h.

Here, we extend the procedure to five-ring sugar furans to provide a new synthetic entry for novel *C*-nucleosides. First, we verify the chemical behavior of furanosyl furans **1a**,**b** under photooxygenation conditions and, finally, we report a one-pot procedure for a novel pyridazine *C*-nucleoside.

The furanosyl furans **1**, previously unknown, were prepared starting from the 2,3,5-tri-*O*-benzyl-1-*O*-(4-nitrobenzoyl)-D-arabinofuranose (for **1a**,**b**), and from the 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose (for **1c**), all commercially available (Scheme 1).[10,11] The reactions afforded a mixture of the α and *β*-anomers of **1** (α: *β*/1:3, 1:2 and 1:8 molar ratio for **1a**, **1b** and **1c**, respectively)[12] so showing a different stereochemical trend from that observed in the synthesis of glucosyl furans[9] which were obtained in α-configuration.

Thus, we start with the methylene blue-sensitized photooxygenation in dichloromethane at −20 °C of the arabinofuranosyl furan **1a** as an α- and *β*-anomeric mixture in a 1:6 molar ratio. When the reaction was

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(10) *C*-Glycosides **1** were synthesized using 6 equiv (for **1a**,**c**) and 1 equiv (for **1a**) of the related furan. The use of a large amount of 2-methylfuran for **1b** has to be avoided. Indeed, when 6 equiv of the 2-methylfuran was used, the reaction afforded only an open-chain product deriving from a further furan addition to the furanoside ring (unpublished results).

(11) NMR data for all new compounds are consistent with the assigned structures. Spectra were recorded at 500 MHz for [^{1}H] and 125 MHz for [^{13}C]. The carbon multiplicity was determined by DEPT and the proton coupling by ^{1}H−^{1}H COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC and HMBC pulse sequences.

(12) Stereochemistry was assigned on the basis of both the $^3J_{H1-H2}$ and the ^{1}H and ^{13}C chemical shifts of the anomeric-H1 and C1 and by comparison with the data reported in the literature for α- and *β*-glycoside derivatives: (a) Mizutani, K.; Kasai, R.; Nakamura, M.; Tanak, O. *Carbohydr. Res.* **1989**, *185*, 27. (b) Agrawal, P. K. *Phytochemistry* **1992**, *31*, 3307.

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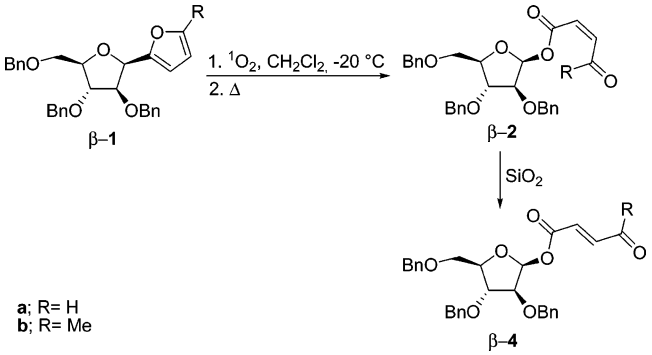
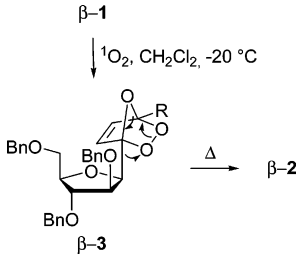
SCHEME 2



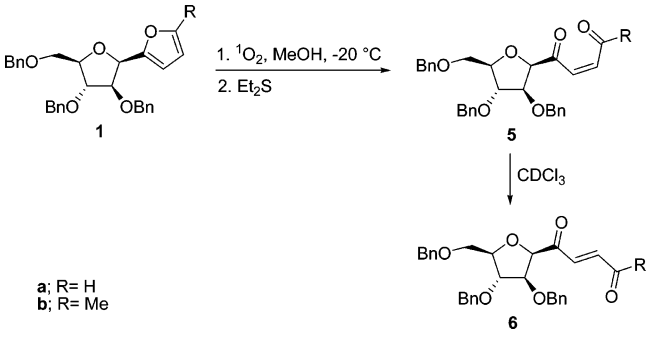
SCHEME 3



complete (90 min, TLC), the solution was warmed to rt. The ^{1}H NMR showed the presence of the only *cis-O*-furanoside **2a** (>90%) as an α,*β*-anomeric mixture in the same molar ratio as the starting **1a**. When the photooxygenation was performed under the same conditions starting from the only *β*-**1a**, only the *β*-**2a** was obtained (Scheme 2). These results showed that the intermediate endoperoxides **3** deriving from the cycloaddition of singlet oxygen to furanosyl furans undergo a selective thermal rearrangement to the corresponding O-derivatives as observed for the glucopyranosyl analogues (Scheme 3). Moreover, the stereochemical trend confirmed that the Baeyer−Villiger type-rearrangement occurs with complete retention of the configuration, as previously suggested.[9] On contact with chromatographic adsorbents, compound **2a** isomerized into *trans*-**4a**, and the extent of the isomerization strictly depended on the time employed for the analysis. Similar results were obtained starting from the 2,5-disubstitued furan *β*-**1b** (Scheme 2).

The new *C*-glycosides **5a**,**b** were obtained by carrying out the photooxygenation of *β*-**1a**,**b** in methanol[13] at −20 °C and, when each reaction was complete, by adding Et_2S to the crude mixture, kept at this temperature.

SCHEME 4



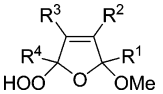
Compound **5** was configurationally unstable and in $CDCl_3$ rapidly isomerized into the corresponding *trans*-**6**, which could not be isolated by silica gel chromatography (Scheme 4).[14]

With the aim to achieve configurationally stable and more manageable *cis*-1,4-diketones as aglyconic residues, we carried out the photooxygenation of *β*-**1c** in dichloromethane at −20 °C, which was complete after 30 min (TLC). The ^{1}H NMR of an aliquot warmed to rt showed the presence of two compounds to which we tentatively assigned the structure of the diastereomeric endoperoxides *β*-**3c**.[15] The ^{1}H NMR spectrum in fact showed a complex pattern of signals among which were two singlets at *δ* 6.19 and 6.26 ppm in a 1:6 ca. molar ratio. The peroxidic nature was revealed by Et_2S addition, which quantitatively afforded the *C*-ribofuranoside **5c** (Scheme 5).[16]

As expected, the diketone **5c** was configurationally stable, and since it decomposed slightly on contact with chromatographic adsorbents, it was characterized by one- and two-dimensional NMR spectroscopy recorded on the crude mixture. Thus, after removal of the solvent, to a dry methanol solution of the crude *β*-**5c** was added hydrazine hydrochloride, and the resulting solution was kept at rt under stirring. After 3 days, the workup afforded the new pyridazine *C*-nucleoside *β*-**7c**, which was isolated by silica gel chromatography (Scheme 5). The MB-sensitized photooxygenation in methanol[13] followed by addition of Et_2S and, successively, of hydrazine hydrochloride to the crude reaction mixture provided a simple one-pot procedure for the access to the nucleoside **7** (70% from furan **1c**).

In conclusion, in this work we extended the dye-sensitized photooxygenation to five-membered-ring sugar-

(13) Methanol as a solvent is particularly attractive for α,α′-disubstituted furans, for example **1b**, since it adds to the corresponding endoperoxides leading to 5-hydroperoxy-2,5-dihydrofurans (below), which are more stable than the parent peroxides. Moreover, these hydroperoxides are readily deoxygenated by alkyl sulfides to the cis-α,*β*-unsaturated 1,4-dicarbonyl compounds, and the reduction can be carried out on the crude methanolic solution.



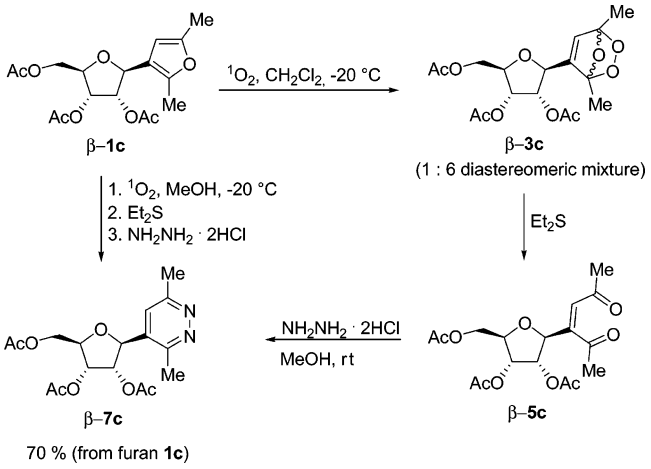
In the other cases, when alcohol addition fails, e.g., with endoperoxides of α,α′- or α-unsubstituted furans as **1a**, methanol can also be used while maintaining the temperature at low values to avoid thermal rearrangement of the endoperoxide intermediate (Iesce, M. R.; Cermola, F.; Temussi, F *Curr. Org. Chem.* **2005**, *9*, 109−139).

(14) Rapid isomerization in $CDCl_3$ was also observed in the glucoside series.[9] It is reasonable that it occurs for unsubstituted unsaturated 1,4-dicarbonyl derivatives.

(15) Thermal stability of endoperoxides of 2,5-dialkylfurans has been reported: Graziano, M. L.; Iesce, M. R.; Scarpati, R. *J. Chem. Soc., Chem. Commun.* **1981**, 720. On the other hand, the lack of the *O*-glycoside starting from **1c** was expected; indeed the Baeyer−Villiger-type rearrangement is reported not to occur for endoperoxides of 2,5-dialkylfurans. It has been demonstrated only for monosubstituted endoperoxides with an acyl group at C1 (Bloodworth, A. J.; Eggelte, H. J. In *Singlet Oxygen*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. II, p 165) or with $-CH_2OCOR$ groups (Kuo, Y.-H.; Shih, K.-S.; Lee, S.-M. *J. Photochem. Photobiol., A: Chem.* **1988**, 97). Thus, as for the *C*-glucoside analogues, the formation of **2** is probably due to the electrophilicity of the anomeric carbon of the sugar, which promotes this pathway also for both mono- and disubstitued **1a**,**b**.

(16) When Et_2S was added to an aliquot in $CDCl_3$, the ^{1}H NMR spectrum showed the disappearance of these two signals together with the appearance of the signals of **5c**. The cis relationship of the carbonyl groups in **5c** was unambiguously related to the bicyclic structure of the parent endoperoxides **3c**.

SCHEME 5



furans. The results confirm both the high diastereoselectivity of the reaction, affording only the cis-unsaturated aglycones, and the stereospecificity of the sugar moiety migration in obtaining *O*-glycosides. Moreover, a simple one-pot procedure for a new pyridazine *C*-nucleoside is reported. Compound **7c** is structurally related to pharmacologically active analogues,[17] and only a few synthetic approaches to this compound class are reported in the literature. Hence, this work demonstrates the use of dye-sensitized photooxygenation of a glycosyl furan moiety as an additional methodology in the field of glycoside organic synthesis. Work is under progress to extend the procedure to a variety of *C*-nucleoside derivatives.

Experimental Section

The ^1H and ^{13}C NMR spectra, DEPT experiments, $^1H-^1H$ COSY experiments, and heteronuclear chemical shift correlations (HMQC and HMBC pulse sequences) were run on a 500 NMR spectrometer in $CDCl_3$.

General Procedure of Dye-Sensitized Photooxygenation. A 0.02 M solution of **1** (0.25 mmol) in dry CH_2Cl_2 was irradiated at −20 °C with a halogen lamp (650 W) in the presence of methylene blue (MB, 1×10^{-3} mmol), while dry oxygen was bubbled through the solution. The progress of each reaction was checked by periodically monitoring (TLC, or ^1H NMR) the disappearance of **1**. When the reactions were complete (ca. 60−90 min), the solutions were heated to rt (entry **a**) or 40 °C (entry **b**). Then, after removal of the solvent, each residue was taken up in Et_2O; the suspension was filtered to remove the insoluble sensitizer (MB), and the filtrate was evaporated to give *cis*-**2** (yields > 90%). The addition of silica gel to the crude photooxygenated mixtures and, after 60 min, the removal of silica gel and MB by filtration afforded trans compound **4** in ca. 70% yields.

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***cis*-β-2a:** ^1H NMR δ = 3.61 (dd, J = 10.3, 5.1 Hz, 1 H, H-5_A), 3.64 (dd, J = 10.3, 5.1 Hz, 1 H, H-5_B), 4.03 (m, 1 H, H-3), 4.13 (s, 1 H, H-2), 4.40 (q, J = 5.1 Hz, 1 H, H-4), 4.50 (s, 2 H, PhCH_2), 4.54 (d, J = 11.6 Hz, 1 H, PhCH_2), 4.57 (s, 2 H, PhCH_2), 4.63 (d, J = 11.6 Hz, 1 H, PhCH_2), 6.35 and 6.36 (s + dd, J = 11.4, 7.3 Hz, 2 H, H-1 and H-2′), 6.59 (d, J = 11.4, 1 H, H-3′), 7.23−7.38 (m, 15 H, 3 x Ph), 10.53 (d, J = 7.3 Hz, 1 H, H-1′); ^{13}C NMR δ = 69.5 (t, C-5), 72.10 (t, PhCH_2), 72.2 (t, PhCH_2), 73.4 (t, PhCH_2), 83.3 (d, C-3), 84.2 (d, C-4), 86.7 (d, C-2), 101.5 (d, C-1), 127.8, 127.9, 128.1, 128.3, 128.4 and 128.5 (d, CH of Ph), 133.0 (d, C-3′), 137.0, 137.3, 137.8 (s, C_q of Ph), 141.0 (d, C-2′), 163.1 (s, CO_2), 192.2 (d, C-1′).

***trans*-β-4a:** ^1H NMR ($CDCl_3$) δ = 3.62 (m, 1 H, H-5_A and 5_B), 4.00 (d, J = 5.1 Hz, H-3), 4.11 (s, 1 H, H-2), 4.40 (q, J = 5.1 Hz, 1 H, H-4), 4.49 (s, 2 H, CH of Ph), 4.52 (d, J = 12.2 Hz, 1 H, CH of Ph), 4.54 (s, 2 H, PhCH_2), 4.63 (d, J = 12.2 Hz, 1 H, CH of Ph), 6.35 (s, 1 H, H-1), 6.68 (d, J = 16.5 Hz, 1 H, H-3′), 6.97 (dd, J = 16.5, 7.2 Hz, 1 H, H-2′), 7.20−7.40 (m, 15 H, 3 x Ph), 9.76 (d, J = 7.2 Hz, H-1′); ^{13}C NMR ($CDCl_3$) δ = 69.5 (t, C-5), 72.1 (t, PhCH_2), 72.2 (t, PhCH_2), 73.4 (t, PhCH_2), 83.4 (d, C-3), 84.1 (d, C-4), 86.7 (d, C-2), 101.6 (d, C-1), 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5 (d, CH of Ph), 137.0, 137.4, and 137.8 (s, C_q of Ph), 138.6 (d, C-3′), 141.0 (d, C-2′), 163.8 (s, CO_2), 192.1 (d, C-1′).

One-Pot Synthesis of 7c. A 0.02 M solution of **1c** (1 mmol) in dry MeOH was photooxygenated as reported in the general procedure. When the reaction was complete (30 min), 1.2 equiv of Et_2S was added to the crude methanol solution, and the resulting mixture was kept at rt under stirring for 60 min. Then, 1.2 equiv of hydrazine hydrochloride was added. After 3 days, the solvent was removed under reduced pressure, and the residue, dissolved in ethyl acetate, was extracted with a HCl solution 1 M (3 × 30 mL). The aqueous solution was neutralized with a NaOH solution until a basic condition was achieved and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with brine, dried with $MgSO_4$, and filtered. Silica gel chromatography ($CHCl_3$/MeOH 95:5 v/v) afforded the pyridazine *C*-nucleoside β-**7c**: yield 70%; oil; ^1H NMR[18] δ = 2.10 (s, 3 H, CH_3CO), 2.11 (s, 3 H, CH_3CO), 2.14 (s, 3 H, CH_3CO), 2.67 (s, 3 H, Me-3′), 2.69 (s, 3 H, Me-6′), 4.36 (m, 2 H, H-4 and H-5_A), 4.45 (dd, J = 9.8, 3.8 Hz, 1 H, H-5_B), 5.11 (m, 2 H, H-1 and H-2), 5.25 (t, J = 5.2 Hz, 1 H, H-3), 7.41 (s, 1 H, H-5′); ^{13}C NMR δ = 19.7 (q, Me-3′), 20.4 (q, *C*H_3CO), 20.5 (q, *C*H_3CO), 20.8 (q, *C*H_3-CO), 22.1 (q, Me-6′), 63.0 (t, C-5), 70.8 (d, C-3), 75.7 (d, C-2), 77.6 (d, C-1), 79.7 (d, C-4), 123.0 (d, C-5′), 136.5 (s, C-4′), 155.2 (s, C-3′), 158.7 (s, C-6′), 169.2 (s, CO_2), 167.6 (s, CO_2), 170.4 (s, CO_2).

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Supporting Information Available: General procedures, spectral and/or physical data for new compounds, ^1H and ^{13}C NMR spectra, DEPT experiments, $^1H-^1H$ COSY experiments, and heteronuclear chemical shift correlations by HMQC and HMBC pulse sequences for the pyridazine **7c,** together with mass spectra (EI) of compounds **1c**, **5c**, and **7c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) ^1H NMR signals of the pyridazine **7c** undergo large shifts when the concentration of the $CDCl_3$ solution is changed. This is probably due to strong nonbonded intermolecular interactions between one of the heterocyclic nitrogens with the sufficiently acidic hydrogen at C5′ (δ = 7.41 ppm).