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Carbohydrates

Sequential Norrish Type II Photoelimination and Intramolecular Aldol Cyclization of 1,2-Diketones in Carbohydrate Systems: Stereoselective Synthesis of Cyclopentitols**

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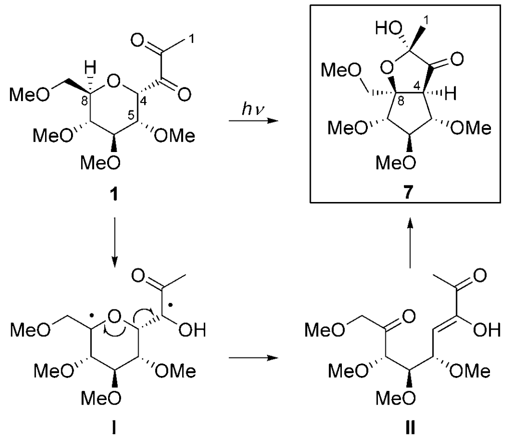
The photochemical behavior of 1,2-diketones differs considerably from that of monoketones and has received a great deal of attention from a theoretical viewpoint over the years.[1] Suitably substituted aliphatic 1,2-diketones exhibit remarkable regioselectivity of intramolecular 1,5-hydrogen-atom transfer, and the 1,4-biradical intermediate yields almost exclusively 2-hydroxycyclobutanones (Norrish–Yang photocyclization).[2] Another important difference between 1,2-diketones and monoketones is that the former compounds do not undergo Norrish type II photoelimination to a large extent.[3] In our opinion, two principal drawbacks have hampered the development of synthetic applications of this 1,5-hydrogen-atom transfer:[4] First, rate constants for the hydrogen abstraction are only about 1% as large as for monoketones.[5] Second, some aliphatic 1,2-diketones are not very stable and are difficult to prepare by standard methods, especially from sensitive substrates.

Within this context, and in connection with our ongoing research programs on the reactivity of 1,2-diketones[6] and hydrogen-atom transfer (HAT) promoted by alkoxyl radicals in carbohydrate chemistry,[7] the aim of the present study has been to explore the photochemical reactivity of nono-2,3-diuloses (e.g. **1**, Scheme 1).[8] It is generally accepted that hydrogen-atom abstraction by an excited carbonyl group closely resembles HAT by alkoxyl radicals.[1a] Therefore, in a 1,2-diketone, such as **1**, inasmuch as the hydrogen atom at C5 is blocked stereochemically, one would expect the hydrogen atom at C8 to be abstracted by the external carbonyl group via a seven-membered transition state (TS). Hydrogen-atom abstraction by the internal carbonyl group via a six-membered TS, which should lead to acyl cyclobutanones, has never been observed.



Scheme 1. Photochemistry of the nono-2,3-diulose **1**.

In contrast, earlier research by our group showed that both processes are possible with alkoxyl radicals. C-Glycosides that contained hydroxymethyl[9] and 1-hydroxyethyl[10] tethers cyclized to give 6,8-dioxabicyclo[3.2.1]octane and 2,9-dioxabicyclo[3.3.1]nonane derivatives, respectively.

Photochemical experiments were carried out with a variety of 4,8-anhydronono-2,3-diuloses (Table 1). 1,2-Diketones **1**–**6** were prepared from the corresponding non-2-ynitols by oxidation of the triple bond with ozone[11] or $RuO_2{\cdot}H_2O/NaIO_4$[12] (see the Supporting Information). 1,2-Diketones **2**–**4** with benzyl ether protecting groups were better prepared by oxidation of the triple bond with $RuO_2{\cdot}H_2O/NaIO_4$ than by oxidation with ozone. The 1,2-diketones were obtained as yellow oils and are stable for at least several months when stored at −25 °C under nitrogen in the dark. They can be purified by rapid silica-gel column chromatography, although a significant loss of material was observed. In all the 1,2-diketones, the conformation of the pyranose ring was determined to be $^4C_1$ by careful analysis of coupling constants; thus, the hydrogen atom H-C8 and the diketone tether are in a 1,3-diaxial relationship.

In a preliminary experiment, the 1,2-diketone **1** was irradiated with a daylight lamp[13] at 30 °C until the yellow color faded. The bicyclic compound **7** was formed as a single diastereoisomer, and no other isomers were detected by ^1H NMR spectroscopy of the crude reaction mixture

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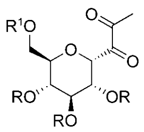
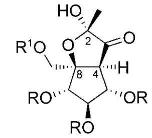
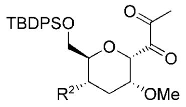
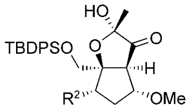
Table 1: Sequential Norrish type II photoelimination and intramolecular aldol cyclization.[a]

Entry	Diketone	*t* [h]	Product	Yield [%]
				
1	**1** R = R^1 = Me	3	**7** R = R^1 = Me	52
2	**2** R = R^1 = Bn	2	**8** R = R^1 = Bn	58
3	**3** R = Bn, R^1 = TBDPS	3	**9** R = Bn, R^1 = TBDPS	65[b]
4	**4** R = Bn, R^1 = Ac	1	**10** R = Bn, R^1 = Ac	67[c]
				
5	**5** R^2 = TBDPSO	4.5	**11** R^2 = TBDPSO	75
6	**6** R^2 = H	5	**12** R^2 = H	61

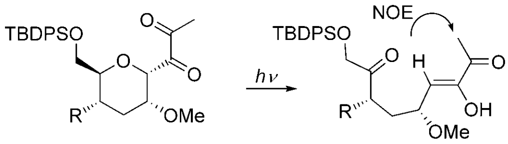
[a] A solution of the 1,2-diketone in C_6D_6 or $CDCl_3$ in a NMR tube was irradiated with a daylight lamp (Philips master PL electronic, 23W/865) placed at 2 cm. [b] Compound **9** was obtained as a 5:1 mixture of isomers at C2. [c] Compound **10** was obtained as a 1:1 mixture of isomers at C2. Bn = benzyl.

(Scheme 1). The photoreaction was completely inhibited by pyrene as triplet quencher: No reaction was observed upon irradiation at 30 °C for 12 h. Compound **7** is a crystalline solid whose structure and stereostructure were elucidated by extensive NMR spectroscopic studies and confirmed unambiguously by X-ray crystallographic analysis.[14] The configuration at the quaternary carbon atom of the hemiacetal is stabilized by an intramolecular hydrogen bond between the hydroxy group of the hemiacetal and the oxygen atom at C9, as indicated by the X-ray crystal structure. We propose a sequential mechanism for this transformation: A Norrish type II photoelimination of the biradical intermediate **I** leads to the photoenol **II**, which undergoes an intramolecular enolexo aldol reaction (Scheme 1).[15] Finally, but probably very importantly for the overall yield of the reaction, the acetalization of the regenerated diketone moiety avoids the possible absorption of visible light by the product.[16] The hydrogen atom at C8 in **1** may be extracted by the external carbonyl group to produce a 1,5-biradical, which rearranges to the 1,4-biradical **I** by a well-known reaction of α-hydroxy radicals,[17] or may be extracted directly by the internal carbonyl group. The Norrish type II photoelimination of 1,2-diketones is an extremely rare reaction. We found a single example in the literature in which the hydrogen atom appears to be abstracted by the internal carbonyl group.[3b] Curiously, the stereocenters at C4 and C8 destroyed in the photoreaction are regenerated diastereoselectively with inversion of configuration in the aldol-cyclization step.

We monitored the reaction by ^{1}H NMR spectroscopy but were unable to detect any of the photoenol **II** under these reaction conditions (30 °C). Nevertheless, at 0 °C we observed two signals assignable to the transient photoenol: a doublet at $\delta = 5.56$ ppm ($J = 9$ Hz) and a broad singlet at $\delta = 6.73$ ppm due to a hydrogen atom exchangeable with D_2O.[18] Upon warming of the reaction mixture to room temperature, these signals disappeared rapidly and completely. The cyclized product **7** was the only observable product after a few minutes.

The reaction does not seem to be influenced greatly by the steric demand of the substituents, at least in this stereochemical environment (Table 1, entries 1–4). Although the reaction yield increased slightly when the 6-deoxy derivative **5** was used as the substrate, it decreased with the apparently less-hindered 6,7-dideoxy derivative **6** (Table 1, entries 5 and 6). The polarity of the substituent at C9 was also found to have relatively little effect on the yield of the reaction (Table 1, entries 3 and 4).

The most unexpected results were observed for the deoxy compounds **5** and **6**, which were transformed into photoenols **13** and **14** upon irradiation at between 15 and 30 °C (Scheme 2).[19] Compounds **13** and **14**, which are surprisingly stable at room temperature for prolonged periods, could be isolated without significant contamination by either the starting material or the respective cyclized product. The oily crude residues did not withstand chromatographic purification, but were pure enough to enable complete analytical and spectroscopic characterization (see the Supporting Information). An NOE interaction between the methyl ketone and the vinyl hydrogen atom is indicative of a *Z* configuration of the double bond (Scheme 2). Both photoenols cyclized upon heating in benzene with protection from light: **13** at 40 °C and **14**, which is considerably more stable, at 60 °C. The aldol reaction proceeded with a high degree of diastereoselectivity to give the *syn* aldols **11** and **12** as single diastereoisomers, as expected from *Z*-configured enolates.[20]



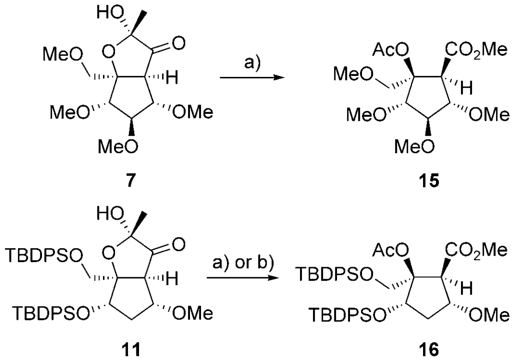
5 R = TBDPSO
6 R = H

13 R = TBDPSO
14 R = H

Scheme 2. Synthesis of photoenols **13** and **14**. TBDPS = *tert*-butyldiphenylsilyl.

Oxidative degradation of the masked 1,2-diketone can be realized with H_5IO_6 in MeOH. The oxidation of compounds **7** and **11** under these conditions and subsequent treatment with diazomethane afforded **15** and **16**, which represent a new type of cyclopentitol (Scheme 3).[21] In the case of compound **11**, better results were obtained by β fragmentation induced by the alkoxyl radical formed at the hydroxy group of the hemiacetal in the presence of the reagent system $PhI(OAc)_2/I_2$.[22]

We believe that the examples shown in Table 1 demonstrate the general efficiency and usefulness of this methodology for the diastereoselective synthesis of densely functionalized cyclopentitols of this new type from the pyranose series of carbohydrates. The irradiation of nono-2,3-diuloses with visible light results in a sequential rearrangement involving unprecedented processes: a very unusual Norrish type II



Scheme 3. Synthesis of cyclopentitols: a) 1) $H_5IO_6\cdot 2H_2O$, MeOH, room temperature, 2 h; 2) CH_2N_2, Et_2O, 0 °C; b) 1) $PhI(OAc)_2/I_2$, *hν*, room temperature, 1 h; 2) CH_2N_2, Et_2O, 0 °C.

fragmentation and a highly diastereoselective and hitherto unknown *syn* aldol cyclization in which a *Z* photoenol acts as a preformed enolate.

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