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Chemical Properties of β–Triketones: Reexamination of Albizati's Tandem Aldol Process

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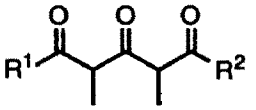
Summary: The structural revision of the product of the tandem aldol - Swern oxidation process to β–triketones is reported. Further oxidation of products leading to the corresponding diketones (*ex.* **4**, **5**) was observed. The properties of the β–triketone are also described.

β–Triketones of the general form **1**, are fundamental intermediates in polypropionate biosyntheses. Although much efforts have been done on β–diketones such as **2**, relatively fewer reports appeared about β–triketone syntheses.[1] We have come to be interested in efficient preparation of **1**, the key intermediate for our biomimetic synthesis of biologically active γ–pyrone containing-natural products.[2]



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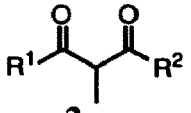

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Recently Albizati *et al.* reported the preparation of β–triketones *via* their tandem aldol protocol (Fig. 1, route a).[3] However, our synthetic β–triketone **3** prepared by acylation of the β–diketone (route b), was different from the product (**4**) they postulated as **3**. Particularly, the mass spectrum of **4** revealed its *m/z* 254 as the highest peak, whereas that of **3** agreed with its molecular weight (*m/z* 256). Their assignment of the peak at *m/z* 254 as (M^+-2) seemed to be questionable from our experience on β–triketone synthesis. We report herein structural revision of the products obtained by the tandem aldol - Swern oxidation process.

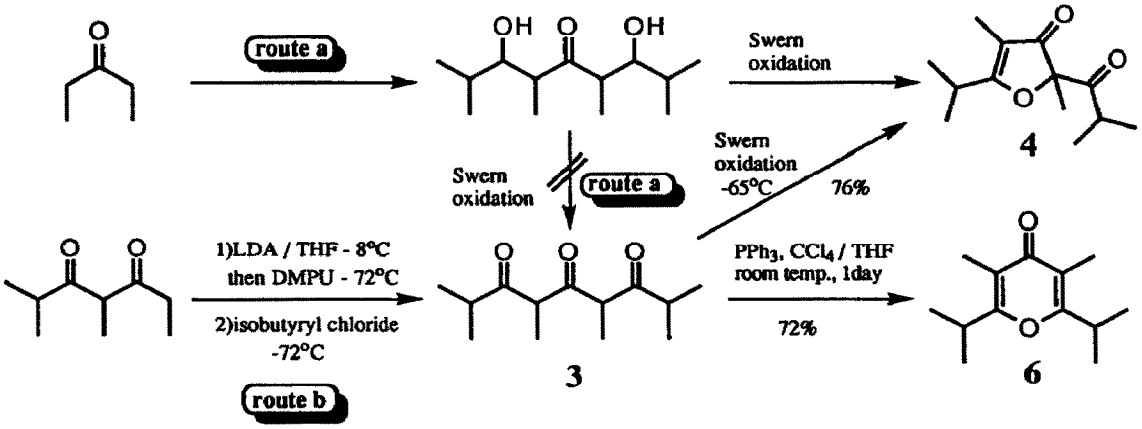


Fig.1 Synthesis of the β–triketone (3) and its cyclization products

Compound 4 prepared according to the Albizati's procedure, provided superimposable spectral data with those described in the literature.[3] The detailed examinations of ^{1}H and ^{13}C NMR technique (NOESY, COLOC, DEPT) suggested that 4 has the closely related structure with 5,[2a,4] which we had reported as the oxidation product of the corresponding β–triketone. Most importantly, NOE was observed between the two isopropyl groups of 4, and this information strongly supported the cyclic diketone structure as shown in Fig. 2.

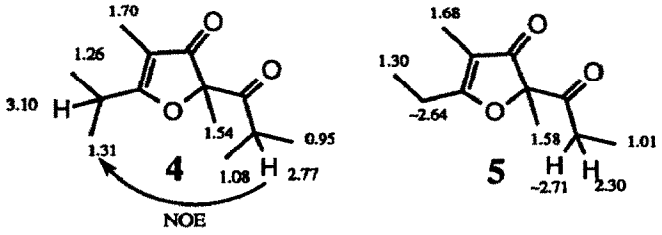
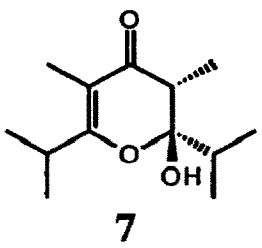


Fig. 2 Comparison of ^{1}H NMR chemical shifts for compound (4) and (5)

It is likely that the β–triketone formed in the Albizati's protocol, reacted further with the excess Swern reagent to give 4. In order to confirm this hypothesis, compound 3 was treated under Swern conditions (1.5 eq. $(COCl)_2$, 3eq. DMSO, then Et_3N at -65 °C), and indeed expected 4 was obtained in 76% yield (Fig. 1).

The β–triketone (3) itself, after silica gel chromatography, was obtained as a pale yellow oil. In positive and negative FABMS spectra, peaks appeared at *m/z* 257 (M+1) and 255 (M-1), respectively. The ^{1}H and ^{13}C NMR spectra exhibited to be consisted of a mixture of tautomeric isomers, and precise assignment of each structure was unsuccessful. The IR spectrum (film) showed three characteristic absorption bands at 1735 (br.), 1662 and 1620 cm^{-1}. These spectral properties were consistent with those of the other β–triketones that had been synthesized by us. Although a purity at this stage was not clear, β–triketone 3 could be converted to γ–pyrone 6 in 72% yield[2a,5] (PPh_3-CCl_4 / THF, room temp.).

Fortunately, crystallization of 3 from pentane - $CHCl_3$ gave colorless crystals. The disappearance of the absorption band at 1735 cm^{-1} in IR spectrum (KBr) indicated no isolated ketones existed in the crystals, and the X-ray crystallography proved that 3 only existed as the hemiacetal form (7), as can be seen in Fig. 3. The hydroxyl group and hydrogen at the adjacent carbon took *syn*-relationship.[6] A stability of 7 in $CDCl_3$ from -50 up to 25 °C was indicated by no observation of signals ascribed to other isomers in the ^{1}H NMR spectrum. However, over 50 °C or after the addition of DCl at 25 °C, the equilibrium with acyclic isomers occurred slowly (Fig. 4). The signals appeared around 4 ppm (marked with *) were attributable to a methine proton of acyclic isomers.



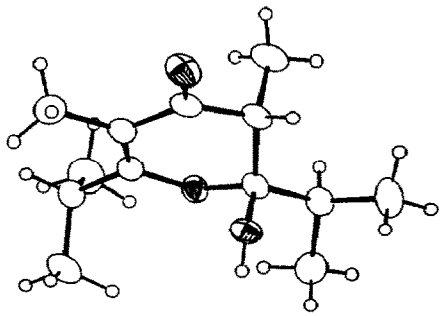


Fig. 3 ORTEP drawing of the hemiacetal (7)[8]

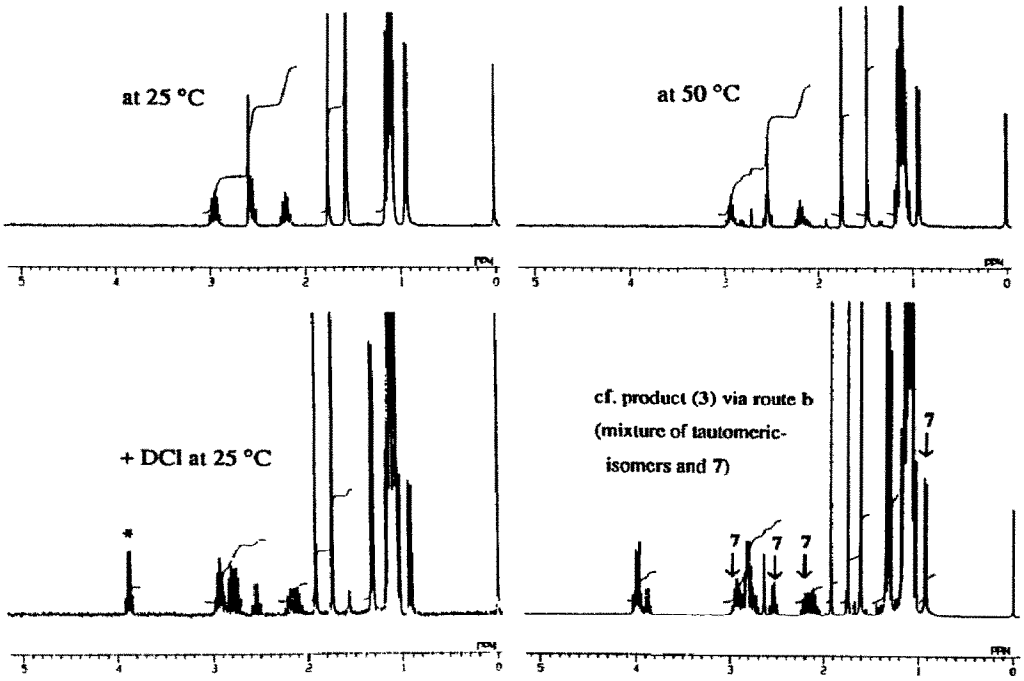
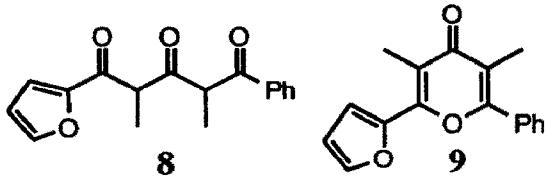


Fig. 4 ^{1}H NMR spectra (270 MHz, $CDCl_3$) of 7 at relevant temperatures

We also prepared triketone **8** by route b (acylation), starting from 2-methyl-1-phenyl-1,3-pentanedione (67% yield). Albizati *et al.* described that **8** was obtained as a chromatographically separable mixture of keto, monoenol, and dienol forms.[3a] The synthesized **8** via acylation, showed same signals as those of the Albizati's keto form in ^{1}H NMR spectrum.[7a] To confirm the triketone structure, **8** synthesized was transformed to γ-pyrone **9** in 61% yield, coupled with 19% of unreacted **8**.[7b]

In our experiments via route a (the tandem aldol process), only a complex mixture including **8** was obtained. Unfortunately the compounds which Albizati postulated as monoenol and dienol form could not be isolated, but judging from their reported analytical data,[7c] they might be overoxidized products.



In conclusion, 1) depending on reaction conditions or substrates employed, Albizati's procedure provided diverse product distribution and/or cyclic diketones by over-oxidation. 2) Contrary to the Albizati's description, β–triketones were obtained as a chromatographically inseparable mixture of both tautomeric and hemiacetal isomers. Crystalline hemiacetal **7** obtained, exhibited no equilibrium to its epimer or acyclic isomers, at least, under neutral conditions at ambient temperature.

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4. **3**: tautomeric mixture; IR (film) 3440, 1735 (br.), 1662, 1620, 1465 cm^{-1}. **5**: HREIMS *m/z* (obs.) 196.1103 (M^+), calc. for $C_{11}H_{16}O_3$ 196.1099 ; IR (film) 1730, 1693, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (3H, t, J = 7.1 Hz), 1.30 (3H, t, J = 7.8 Hz), 1.58 (3H, s), 1.68 (3H, s), 2.30 (1H, dq, J = 18.8, 7.1 Hz), 2.64 (2H, complex), 2.71(1H, m); ^{13}C NMR ($CDCl_3$) δ 5.8, 7.2, 10.4, 19.8, 22.3, 30.1, 93.9, 108.6, 189.0, 199.7, 202.0. **6**: HREIMS *m/z* (obs.) 208.1473 (M^+), calc. for $C_{13}H_{21}O_2$ 208.1463; IR (film) 1655, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (12H, d, J = 6.9 Hz), 1.96 (6H, s), 3.13 (2H, complex); ^{13}C NMR ($CDCl_3$) δ 9.2, 19.8, 30.1, 116.6, 166.5, 180.2. **7**: m.p. 67 - 68 °C; IR (KBr) 3380, 3300, 1640, 1608, 1510(w), 1465 cm^{-1}.
5. Albizati *et al.* described a brief argument on the reasons why no γ–pyrone was directly obtained by the tandem aldol process.[3] They only considered reaction temperature and reaction period. We must point out that the reaction should be carried out *without* Et_3N at around -20 °C , in order to get γ–pyrones with $(COCl)_2$-DMSO system.
6. It is worth noticing that this stereo-relationship is unfavorable for usual anti-dehydration to γ-pyrones. This observation is of interest in connection with the formation of γ–pyrones by our protocol. Detailed elaboration of the mechanism is in progress, and would be published elsewhere.
7. a) Small amounts of isomer were observed in ^1H NMR spectrum. Characteristic signals of the isomer were at δ 1.42 (d, J = 6.93 Hz), 7.17 (d, J = 3.63 Hz) and 7.31 (br. d, J = 4.29 Hz).
   b) **9**: HREIMS *m/z* (obs.) 266.094 (M^+), calc. for $C_{17}H_{14}O_3$ 266.0941; IR (film) 1645, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (3H, s), 2.34 (3H,s), 6.57 (1H, dd, J = 1.65, 3.30 Hz), 6.92 (1H, d, J = 3.30 Hz), 7.50 (3H, complex), 7.61 (2H, complex), 7.62 (1H, overlapped with the peak at 7.61); ^{13}C NMR ($CDCl_3$) δ 10.0, 11.7, 111.7, 113.4, 117.7, 119.4, 128.4, 128.81, 129.97, 133.1, 114.5, 147.3, 150.9, 159.4, 180.5.
   c) The *m/z*'s of these two isomers were reported two mass units lower than molecular weight (M.W. 284). Also, they did not have characteristic absorption bands of enol hydroxyl group in the IR spectra.
8. CRYSTALLOGRAPHIC DATA; $C_{13}H_{22}O_3$, MW 226.3, monoclinic, $P2_1/c$, a = 8.353(2), b = 9.345(2), c = 17.759(2) Å, β = 101.44(1)°, V = 1358.7(4) $Å^3$, Z = 4, λ(Mo Kα) = 0.71073 Å, μ = 0.072 mm^{-1}, Dx = 1.11 Mg m^{-3}. The X-ray intensities up to 2θ = 50° were measured on a Rigaku AFC-5 four-circle diffractiometer with graphite-monochromatized Mo Kα radiation. Non-hydrogen atoms were refined with anisotropic thermal parameters. Final R is 0.051 for 1633 reflections. Tables of atomic parameters, bond lengths and bond angles have been deposited with the Cambridge Crystallographic Data Center.

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