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An acid-catalyzed Michael–aldol reaction

I. David Reingold,[a,*] Charles Bowerman,[a] Melissa John,[a] Robert S. Walters, Jr.,[a]
Bevin C. Daglen,[a] Anna M. Butterfield[a] and Milan Gembický[b]

[a] *Department of Chemistry, Juniata College, Huntingdon, PA 16652, USA*
[b] *Department of Chemistry, SUNY Buffalo, Buffalo, NY 14260-3000, USA*

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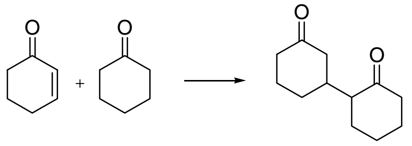
Abstract—A tricyclic ketone is formed from cyclohexanone and cyclohexenone in strong acid solutions. The structure is confirmed by X-ray crystallography.

In our efforts to understand tandem Michael–Claisen reactions,[1] we decided to look at one of the simplest Michael reactions one could imagine, the addition of cyclohexanone to cyclohexenone to make bicyclohexyl-2,3′-dione **1**.

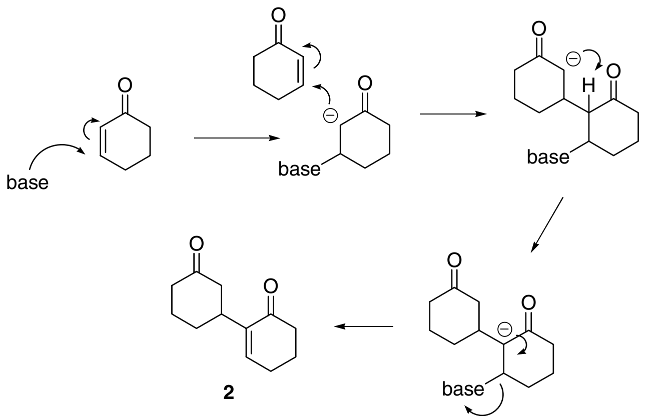


1

To our great surprise, we could not find this reaction in the literature. Compound **1** has been made from enol silyl ethers[2] and enamines,[3] but not by simple acid or base-catalyzed condensation of the free ketones. Accordingly, we set about determining whether this reaction occurs.

Mixtures of cyclohexanone and cyclohexenone were treated with a variety of bases (KO*t*-Bu, LiO*t*-Bu, NaOMe, NaOH, pyridine, Et_3N, DBU, NaH, LDA, Me_4NOH, Bu_4NOH) in a variety of solvents (*t*-BuOH, MeOH, DMSO, CH_3CN, THF, ether, DMF, none). In most cases no reaction was observed. We found no conditions that efficiently produced **1**, but several that produced **1** in combination with **2**, which results from Baylis–Hillman[4] reaction of cyclohexenone with the base.

We then investigated the acid-catalyzed reaction of cyclohexanone with cyclohexenone. As reported recently by Jung and Maderna,[5] and independently of their investigation, we also found several sets of conditions that led to **1**, and that this was transformed under the reaction conditions to **3**. While Jung and Maderna used trifluoromethane sulfonic acid, we found that trifluoroacetic acid and BF_3-etherate produced the same product, though not in quite as good a yield. Following the reaction by GC, we saw that the starting material mostly disappear and **3** appear as the sole significant peak at the end of the reaction. Nevertheless, upon workup only 24% of **3** was isolated. We interpret this to mean that the majority of the reaction mixture was intractable material that did not go through a GC.



Keywords: Michael reaction; Aldol condensation; Baylis–Hillman reaction; Tricyclic; Ketone.

[*] Corresponding author. Tel.: +1 814 641 3565; fax: +1 814 641 3685; e-mail: reingold@juniata.edu

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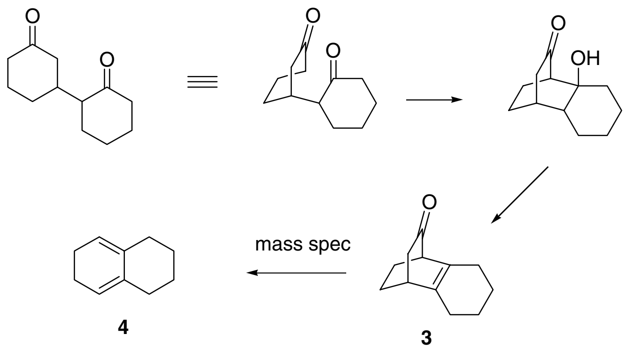
Our identification of **3** was based on its decomposition under mass spectrometer conditions to a peak of mass 134 that we identified as **4**, and by one- and two-dimensional NMR spectra, which were consistent with the proposed structure. However, many of the protons were heavily overlapped with each other, and the structure could not be established beyond doubt. Even lanthanide shift reagents failed to separate all the overlapping protons in the spectrum.



Treatment of **3** with excess DDQ in refluxing toluene slowly converted it into benzobicyclo[2.2.2]octanone, which is known.[6] The identification was made by the GC/MS database rather than by isolation of the product.

To confirm the identity of **3**, we attempted to grow suitable crystals of various solid derivatives. Both the oxime and the semicarbazone failed to provide X-ray quality crystals after many attempts in different solvents, but the 2,4-dinitrophenylhydrazone finally succumbed to recrystallization in acetonitrile.

The X-ray experiment[7] revealed positions of all atoms (including hydrogens) as they are depicted in Figure 1. In the later step of crystal structure refinement, observed H atoms connected to C atoms were substituted with geometrically positioned ones. All observed bonding distances show values typical for C–C, C–N, N–N, and N–O bonds. The same applies to bond angles. The 2,4-dinitrophenylhydrazone fragment is perfectly planar as expected and forms the dihedral angle of 15.5° with ethylene moiety of the bicyclooctene.

Experimental: A solution of 2.5 g (0.026 mol) of cyclohexanone, 2.5 g (0.026 mol) of cyclohexenone, and 3 mL of BF$_3$-etherate in 15 mL of chloroform was refluxed for 6 h. Water was added and the aqueous layer was extracted three times with ether. The organic layers were dried and concentrated, and the residue was chromatographed over silica gel using 5% ether in hexane. The product **3** was obtained as a pale yellow oil, 1.18 g (24%). Upon attempted distillation of previous runs we obtained small amounts of colorless **3**, bp 65 °C at 125 μm, but the distillation was accompanied by extensive decomposition and was not repeated. ^{1}HNMR (300 MHz, CDCl$_3$): δ 2.82 (t, 1H), 2.59 (t, 1H), 2.2–1.4 (14H); ^{13}CNMR: δ 213.6, 139.8, 130.3, 53.3, 41.2, 37.1, 27.1, 26.9, 25.0, 23.1, 23.01, 22.98); IR (neat) 1720 cm^{-1}; MS 176, 134, 119, 105, 91.

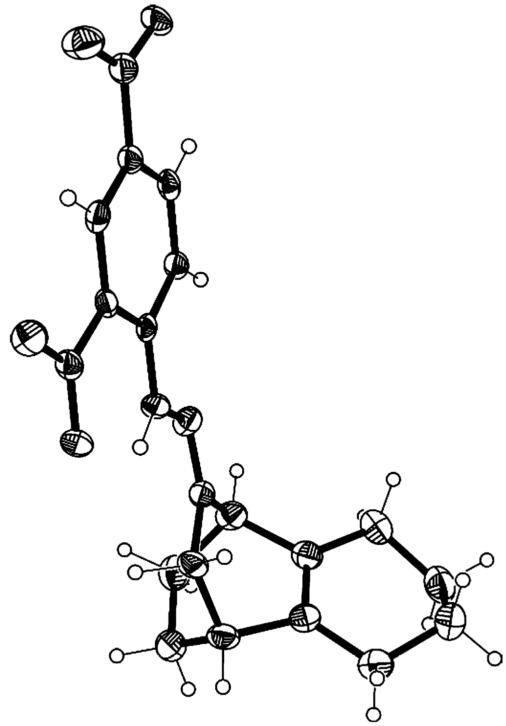


Figure 1. Molecular structure of **3** 2,4-dinitrophenylhydrazone with 50% probability ellipsoids.

Acknowledgments

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References and notes

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7. Crystal data for **3** 2,4-dinitrophenylhydrazone: $C_{18}H_{20}N_4O_4$, $M = 356.38$, $0.25 \times 0.10 \times 0.02$ mm^3, triclinic, space group P-1 (no. 2), $a = 6.9383(6)$, $b = 8.0459(7)$, $c = 15.8440(14)$ Å, $\alpha = 96.153(3)$, $\beta = 101.688(3)$, $\gamma = 101.979(3)°$, $V = 836.94(13)$ Å^3, $Z = 2$, d_c 1.414 g cm^{-3}, $\mu(\mathrm{Mo}_{K\alpha}) = 0.102$ cm^{-1}, $T = 125$ K, $2\theta_{max} = 46.52°$, 9435 reflections collected, 2393 unique ($R_{int} = 0.0295$). The refinement (235 variables, 0 restriction) based on F^2 converged with $R = 0.0442$, $R_w = 0.1065$, and GOF = 1.134 using 1920 unique reflections with $I > 2\sigma(I)$. CCDC 289332 contains the supplementary crystallographic data for this letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).