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THE NITRO-ALDOL REACTION OF α-KETOALDEHYDES WITH NITROALKANES YIELDS α-DIKETONES

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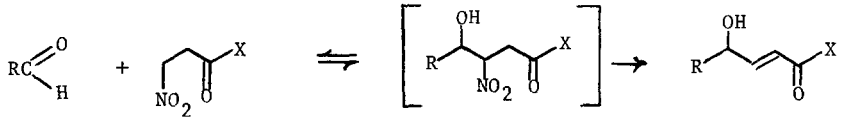
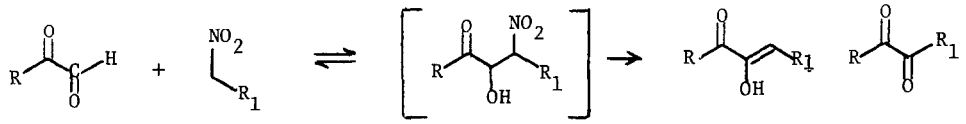
Summary: The reaction of α-ketoaldehydes with nitroalkanes at pH 9 yields nitro-aldols, which eliminate nitrite to form α-diketones.

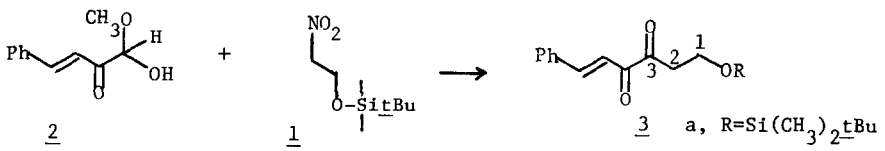
The Henry[1] nitro-aldol reaction has proved a versatile synthetic tool for carbon-carbon bond formation.[2] A special case of this reaction involves substrates in which the nitroalkane partner possesses a carbonyl function in β-position to the nitro group. In this case the reaction is driven to completion by β-elimination of nitrite to form an allylic alcohol (eq. 1)[3]

(1) 

It occurred to us that were one to place the carbonyl function on the aldehydic reaction partner, as in eq. (2), β-elimination of nitrite should give rise to α-diketones. This extension of the Henry reaction has not previously been described.

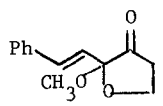
(2) 

We now wish to report that the reaction sequence (2) can indeed be realized. When the dimethyl t-butylsilyl ether of 2-nitroethanol (1)[4] was reacted with the methyl hemiacetal of styrylglyoxal (2) at 25° in THF/H_2O in the presence of methanolic trimethylamine (pH 9.0) for 12 hrs there was isolated the α-diketone 3 in better than 90% yield. The yellow diketone was characterized spectroscopically, as well as by its monomethoxime, quinoxaline (after desilylation) and the cyclic acetal 4. When the reaction time was shortened to 30 min at 0° the diastereomeric nitro-aldols could be isolated.



2 1 3 a, R=Si(CH$_3$)$_2$tBu
b, R=H

The reaction was readily extended to more complex nitrocompounds e.g., 5 (X=NO_2, R=(CH$_3$)$_2$ t-BuSi)[5] which gave rise to the diketone 6 in 55% yield. The following experiments are typical:



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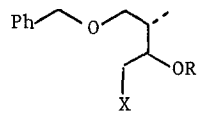

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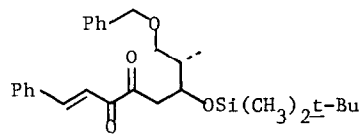

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Diketone 3a: A solution of freshly distilled styrylglyoxal (350 mg) in methanol (3 ml) was evaporated to dryness in vacuo and the residue dissolved in THF (13.5 ml) containing 2-t-butyldimethylsiloxynitroethane[4] (1, 449 mg). Water (8.5 ml) was added at 0° to incipient turbidity followed by 25% trimethylamine in methanol (517 µl) (pH ∿9). After 30 min the ice bath was removed and the reaction conducted at 25° with addition of trimethylamine in 4 hr intervals (190 and 150 µl) for a total of 12 hrs. Ice-cold 0.1 N HCl was added and the mixture extracted with ethyl acetate, furnishing the diketone 3a (656 mg, >95% pure by NMR) in 90% yield; mp ∿25°. 500 MHz NMR ($CDCl_3$, δ): 0.04 (s, 6H); 0.87 (s, 9H); 3.04 (t, J=6, 2H); 4.00 (t, J=6, 2H); 7.29 (d, J=16, 1H): 7.33-7.62 (m, 5H); 7.80 (d, J=16, 1H). IR ($CDCl_3$, cm^{-1}): 1712 (C=O), 1680 (conj. C=O), 1603 (C=C), 1100 (SiO). m/e 318 (M^+), 303 ($M-CH_3$), 261 (64%, M-tBu), 187 ($M-C_8H_7CO$), 131 (100%, C_8H_7CO). $C_{18}H_{26}O_3Si$: C, 67.92; H, 8.18. Found: C, 67.32; H, 8.54.

The diketoalcohol 3b was prepared with 0.008 M HCl in THF/H_2O for 18 hrs. Yellow cryst. mp 75-76° (EtOAc/hex.). $C_{12}H_{12}O_3$: C, 70.59; H, 5.88. Found: C, 70.30; H, 6.11.

Quinoxaline, mp 183-186° (d). m/e 276 (M^+, 100%).

3-anti-methoxime, mp 95-95.5° (hex./EtOAc); m/e: 233 (M^+, 73%). IR ($CDCl_3$): 3620, 1665, 1610. $C_{13}H_{15}O_3N$: C, 66.95; H, 6.44; N, 6.01. Found: C, 67.46; H, 6.79; N, 6.03.

The methyl hemiketal 4 was prepared from 3a (2.87 g) with p-TSA (0.5 g) in methanol (150 ml) at 25° for 1 hr in 88% yield. m/e: 218 (M^+), IR ($CDCl_3$): 1765, 1600.

Diketone 6: As for 3a but longer reaction time determined by tlc. IR: 1720, 1680, 1600, 1250. m/e: 466 (M^+), 409 (M-tBu), 335 ($M-C_8H_7CO$), 131 (C_8H_7CO).

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References and Notes

1. L. Henry, Compt. Rend. 120, 1265 (1895).
2. D. Seebach, E. W. Colvin, F. Lehr and T. Weller, Chimia, 33, 1 (1979).
3. P. Bakuzis, M. L. F. Bakuzis and T. F. Weingartner, Tetrahedron Lett. 2371 (1978).
4. Prepared from 2-nitroethanol and $(CH_3)_2$tBuSiCl with imidazole in DMF for 10 hrs.
5. Prepared from 5(X=OH, R=H) (W. J. Elliott and J. Fried, J. Org. Chem. 41, 2469 (1976)) via the tosylate 5(X=OTs, R=H), TsCl (1.15 equ.), pyridine, 0°; iodide 5(X=I, R=H), NaI, acetone, 25°, 72 hrs; iodo silyl ether 5(X=I, R=$(CH_3)_2$tBuSi), $(CH_3)_2$tBuSiCl (20 equ.) Et_3N, DMAP, DMF; nitrosilyl ether 5($X=NO_2$, R=$(CH_3)_2$tBuSi), KNO_2, 18-crown-6, DMF, 25°, 24 hrs (Zubrick et al., Tetrahedron Lett. 71 (1975).

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