One-Pot Synthesis of 1,4-Diketones from Nitroalkenes and Ketones

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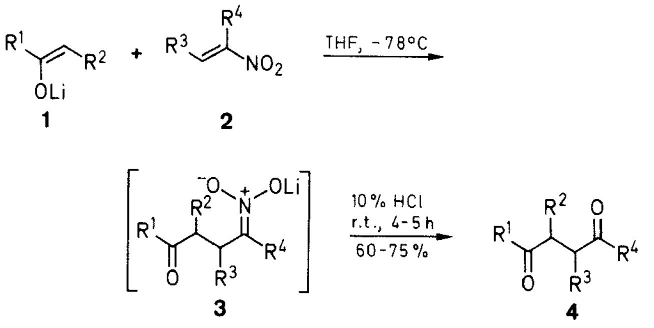
A convenient one-pot synthesis of 1,4-diketones was achieved by the conjugate addition of lithium enolates of ketones to nitroalkenes, followed by *in situ* hydrolysis of the resulting lithium salts of *aci*-nitro compounds with aqueous hydrochloric acid in tetrahydrofuran.

Nitroalkenes are potentially useful substrates in carbon–carbon bond forming reactions,[1] and have widely been used in organic synthesis.[2] We have demonstrated that they serve as excellent oxoalkylating agents of carbonyl compounds,[3] e.g., the Lewis acid promoted Michael reaction of silyl enol ethers or ketene silyl acetals with nitroalkenes gives a wide variety of 1,4-diketones and γ-keto esters, respectively, in good yield.[4] In these reactions, acidic conditions were used as nitroalkenes are highly susceptible to alkaline conditions. We now report a more convenient procedure for the synthesis of 1,4-diketones, which consists of the conjugate addition of lithium enolates **1** to nitroalkenes **2**[5] followed by *in situ* hydrolysis of the resulting lithium salt of *aci*-nitro compounds **3** with aqueous hydrochloric acid.

The enolates **1**, generated from the corresponding ketones with lithium diisopropylamide (LDA) in tetrahydrofuran at − 78 °C, react with a variety of conjugated nitroalkenes **2** to yield the Michael adducts **3**,[5] which are treated *in situ* with 10% aqueous hydrochloric acid[6] at room temperature for 4–5 h to give 1,4-diketones **4** via the Nef reaction in 60–75% yield (Table). Thus, a variety of 1,4-diketones



1	R^1	R^2	2	R^3	R^4
a	Bu	H	**a**	H	Me
b	Et	Me	**b**	H	Et
c	$-(CH_2)_4-$		**c**	Me	Me

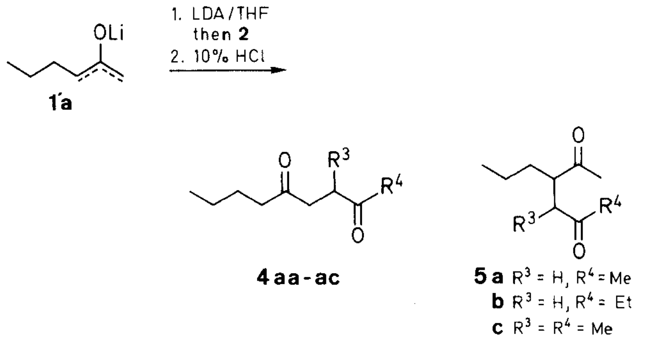
3, 4	R^1	R^2	R^3	R^4
aa	Bu	H	H	Me
ab	Bu	H	H	Et
ac	Bu	H	Me	Me
ba	Et	Me	H	Me
bb	Et	Me	H	Et
bc	Et	Me	Me	Me
ca	$-(CH_2)_4-$		H	Me
cb	$-(CH_2)_4-$		H	Et
cc	$-(CH_2)_4-$		Me	Me

Table. 1,4-Diketones **4** Prepared

Product	Yield[a] (%)	bp (°C)/Torr[b]	Molecular Formula[c] or Lit. bp (°C)/Torr	IR (neat) $\nu_{C=O}$(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS) δ, J(Hz)
4aa	65[d]	61/1	106–108/12[8]	–	–
4ab	65[e]	78/1	$C_{10}H_{18}O_2$ (170.3)	1712	0.91 (t, 3H, J = 6.5), 1.06 (t, 3H, J = 6.8), 1.0–1.8 (m, 4H), 2.2–2.7 (m, 4H), 2.70 (s, 4H)
4ac	63[f]	99/0.9	$C_{10}H_{18}O_2$ (170.3)	1709	0.88 (t, 3H, J = 6.8), 1.08 (d, 3H, J = 6.8), 1.0–2.1 (m, 4H), 2.2 (s, 3H), 2.3–3.2 (m, 5H)
4ba	64	55/1	92–95/0.02[9]	–	–
4bb	75	59/1	$C_9H_{16}O_2$ (156.2)	1710	1.04 (t, 3H, J = 7.5), 1.06 (t, 3H, J = 7.9), 1.10 (d, 3H, J = 5.8), 2.2–3.2 (m, 7H)
4bc	67[g]	80/1.2	$C_9H_{16}O_2$ (156.2)	1706	0.9–1.2 (m, 9H), 2.18 (s, 3H), 2.3–3.1 (m, 4H)
4ca	60	83/0.2	84–85/0.8[10]	–	–
4cb	64	83/0.2	115–120/0.02[11]	–	–
4cc	61[h]	84/0.2	115–120/0.02[11]	–	–

[a] Yield of pure isolated product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.44, H ±0.30.
[d] A 88 : 12 mixture of **4aa** and **5a**.
[e] A 92 : 8 mixture of **4ab** and **5b**.
[f] A 91 : 9 mixture of **4ac** and **5c**.
[g] A 65 : 35 stereoisomeric mixture.
[h] A 88 : 12 stereoisomeric mixture.

4 including cyclic ones, are easily obtainable in an one-pot operation, although an unsymmetrical ketone, e.g., **1a** produces approximately a 90 : 10 mixture of regioisomers **4aa–ac** and **5a–c** due to the generation of isomeric enolates **1'a**.[7]



The present method is more convenient than the previous one,[4] since the experimental manipulation is simple and ketones can be used directly as substrates without transformation into silyl enol ethers. Since various nitroalkenes are readily available from nitroalkanes via aldol condensation with aldehydes or ketones (Henry reaction), the present method provides a facile entry into 1,4-diketones.

IR spectra were recorded on a JASCO A-3 spectrophotometer. ^{1}H-NMR spectra were measured at 90 MHz using a JEOL FX-90Q spectrometer.

1,4-Diketones 4; General Procedure:

To a solution of LDA (1.2 mmol) in THF, prepared from BuLi (1.6 M solution in hexane, 0.8 mL, 1.2 mmol) and diisopropylamine (121 mg, 1.2 mmol) in THF (3 mL) at – 78 °C, is added dropwise a solution of a ketone **1** (1 mmol) in THF (1 mL) over 10 min at the same temperature under Ar. After stirring for 30 min, a solution of a nitroalkene **2** (1.5 mmol) in THF (0.5 mL) is added dropwise over 5 min and the resulting mixture is stirred for an additional 2 h at – 78 °C, then warmed to 0 °C. 10% HCl (3.5 mL) is added and the mixture is stirred for 4–5 h at r.t. The mixture is partitioned between Et_2O (30 mL) and water (20 mL), and the aqueous layer is extracted with Et_2O (2 × 15 mL). The combined organic layers are washed with brine (30 mL), and evaporated to dryness. The crude 1,4-diketone **4** is purified by distillation or flash column chromatography on silica gel using EtOAc/hexane (1 : 3) as eluent (Table).

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(1) Padeken, H.G.; von Schickh, O.; Segnitz, A., in *Houben-Weyl*, 4th ed., Vol. 10/1, Georg Thieme Verlag, Stuttgart, 1971, pp 372–397.
(2) Seebach, D.; Colvin, E.W.; Weller, T. *Chimia* **1979**, *33*, 1.
Varma, R.S.; Kabalka, G.W. *Heterocycles* **1986**, *24*, 2645.
Barrett, A.G.M.; Graboski, G.G. *Chem. Rev.* **1986**, *86*, 751.
(3) Yanami, T.; Kato, M.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1975**, 726.
Yanami, T.; Ballatore, A.; Miyashita, M.; Kato, M.; Yoshikoshi, A. *Synthesis* **1980**, 407.
Miyashita, M.; Yamaguchi, R.; Yoshikoshi, A. *Chem. Lett.* **1982**, 1505.
Miyashita, M.; Yamaguchi, R.; Yoshikoshi, A. *J. Org. Chem.* **1984**, *49*, 2857.
Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284.
(4) Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1984**, *106*, 2149.
(5) A variety of lithium enolates have been found to react smoothly with nitroolefins at – 70 to – 100 °C.
Seebach, D.; Leitz, H.F.; Ehrig, V. *Chem. Ber.* **1975**, *108*, 1924.
Ehrigh, V.; Seebach, D. *ibid.* **1975**, *108*, 1961. See also Refs. 2 and 3.
(6) Treatment of these lithium nitronates with acetic acid instead of HCl inevitably forms a mixture of nitro ketones, cyclic nitronic esters, and 1,4-diketones.
(7) Isomeric ratios were 88 : 12 (R^3 = H, R^4 = Me), 92 : 8 (R^3 = H, R^4 = Et), and 91 : 9 (R^3 = R^4 = Me), respectively.
(8) Stetter, H.; Kullmann, H. *Tetrahedron Lett.* **1974**, 4505.
(9) Jacobson, R.M.; Raths, R.A.; McDonald III, J.H. *J. Org. Chem.* **1977**, *42*, 2545.
(10) Miyashita, M.; Yanami, T.; Yoshikoshi, A. *Org. Synth.* **1981**, *60*, 117.
(11) Jacobson, R.M.; Abbaspour, A.; Lahm, G.P. *J. Org. Chem.* **1978**, *43*, 4650.