A New, Simple, and General Synthesis of 1,3-, 1,4- and 1,5-Diketones from Functionalized Nitroalkanes

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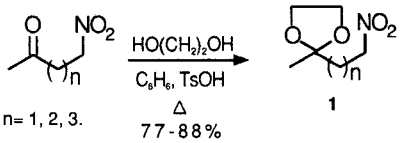
Herein is reported the utilization of protected nitro ketones, in the synthesis of 1,3-, 1,4-, and 1,5-diketones, by their condensation with aldehydes then conversion of the obtained conjugated nitroalkenes into monoprotected carbonyl derivatives which, by removal of the protecting group, gives diketones.

The chemistry and the efficient preparation of dicarbonyl compounds have attracted much interest due to their widespread application in important fields. 1,3-Diketones and related derivatives are ubiquitous in nature[1,2] and, often, represent the basic key structures in chemistry.[3] 1,4-Diketones are important intermediates for the synthesis of cyclopentenones and heterocyclic compounds such as furans, pyrroles, thiophenes, and pyridazines,[4-9] while 1,5-diketones are widely employed for the construction of six-membered carbocycles[10,11] and heterocyclic compounds.[12]

In the past, numerous methods have been reported for the synthesis of 1,3-, 1,4-, and 1,5-diketones,[3,13-21] however, most of these suffer from drawbacks such as the use of harsh conditions, employment of expensive chemicals and/or tedious procedures. Furthermore, no method is general for the synthesis of all three classes of diketones.

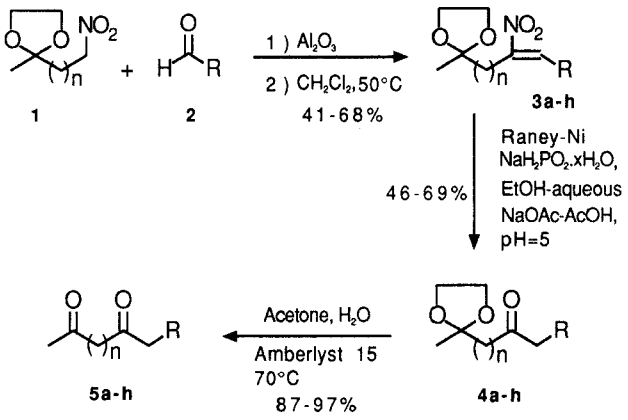
The practical use of reagents for nucleophilic introduction of alkyl groups is subject to three general conditions: (i) that the anion precursor is an inexpensive and stable compound; (ii) that the C,C-bond forming process is accomplished readily under mild conditions; (iii) that the anion stabilizing groups on the nucleophilic centre can be removed or converted into other groups without interference from the other functionalities in the molecule. In this context the nitro group has found extensive use as an activating group for the formation of C,C-bonds.[22,26] Moreover, the ease of replacement of a nitro group by hydrogen,[22b,23] as well its conversion into a carbonyl,[24,25] or other functional groups,[26] have significantly increased the synthetic potential of nitroalkane derivatives as reagents for the nucleophilic introduction of functionalized alkyl groups.

In this paper we wish to describe a new synthetic procedure for the preparation of 1,3-, 1,4-, and 1,5-diketones **5** using the easily available (Scheme 1), protected nitro ketones **1**.



Scheme 1

The nitroaldol condensation of **1** with aldehydes **2**, on an alumina surface at room temperature, followed by the addition of dichloromethane and warming at 50 °C, gave the conjugated (*E*)-nitroalkenes **3**,[27] which, using sodium hypophosphite,[25b] were directly converted into the monoprotected dicarbonyl derivatives **4**. Subsequent deprotection of the ketal, carried out in acetone–water with Amberlyst A-15 as the catalyst,[28] gave the diketones **5** (Scheme 2).



Compound	n	R
a	1	$CH_3(CH_2)_4$
b	1	$PhCH_2CH_2$
c	1	$CH_3(CH_2)_9$
d	2	$CH_3(CH_2)_4$
e	2	⬡
f	2	$CH_3(CH_2)_5$
g	3	$CH_3(CH_2)_5$
h	3	$CH_3(CH_2)_9$

Scheme 2

It is important to stress how, by this method, it is possible to obtain the monoprotected diketones **4**, which, generally, are difficult to prepare by other methods.

In this context compounds **1** can be regarded as synthetic equivalents of the monoprotected dicarbonyl anion synthons **a**, and were easily prepared (Scheme 1) by

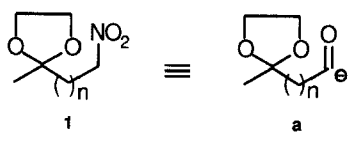


Table 1. Nitroalkenes **3a–h** Prepared

Product	Yield[a] (%)	IR (film) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	41	1510	0.88 (t, 3H, J = 7), 1.25–1.64 (m, 6H), 1.38 (s, 3H), 2.3 (t, 2H, J = 7.6), 3.13 (s, 2H), 3.88 (m, 4H), 7.15 (t, 1H, J = 7.9)
3b	50	1650 1500	1.51 (s, 3H), 2.6 (m, 2H), 2.8 (m, 2H), 3.08 (s, 2H), 3.8–3.92 (m, 4H), 7.1–7.18 (m, 6H)
3c	42	1505	0.9 (t, 3H, J = 6.7), 1.2–1.5 (m, 16H), 1.38 (s, 3H), 2.3 (m, 2H), 3.1 (s, 2H), 3.9 (m, 4H), 7.1 (t, 1H, J = 8.07)
3d	63	1500	0.9 (t, 3H, J = 7), 1.2–1.6 (m+s, 9H), 1.82 (m, 2H), 2.25 (q, 2H, J = 7.3), 2.7 (m, 2H), 3.95 (m, 4H), 7.08 (t, 1H, J = 7.9)
3e	46	1522	1.55–1.9 (m, 12H), 1.36 (s, 3H), 2.22–2.36 (m, 1H), 2.7 (m, 2H), 3.97 (m, 4H), 6.9 (d, 1H, J = 10.68)
3f	56	1500	0.9 (t, 3H, J = 6.7), 1.22–1.58 (m+s, 11H), 1.85 (m, 2H), 2.25 (m, 2H, J = 7.6), 2.7 (m, 2H), 3.95 (m, 4H), 7.1 (t, 1H, J = 7.9)
3g	54	1505	0.9 (t, 3H, J = 6.8), 1.22–1.75 (m, 12H), 1.3 (s, 3H), 2.15–2.3 (m, 2H), 2.58–2.68 (m, 2H), 3.93 (m, 4H), 7.1 (t, 1H, J = 7.9)
3h	68	1512	0.88 (t, 3H, J = 6.5), 1.2–1.75 (m, 20H), 1.3 (s, 3H), 2.25 (m, 2H), 2.63 (m, 2H), 3.93 (m, 4H), 7.11 (t, 1H, J = 7.9)

[a] Yield of pure, isolated product. Products isolated as oils.

Table 2. Monoprotected Dicarbonyl Derivatives **4a–h** Prepared

Product	Yield[a] (%)	IR (film) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
4a	69	1710	0.88 (t, 3H, J = 6.7), 1.2–1.6 (m, 8H), 1.42 (s, 3H), 2.5 (t, 2H, J = 7.47), 2.75 (s, 2H), 3.95 (m, 4H)
4b	55	1700	1.4 (s, 3H), 1.9 (m, 2H, J = 7.6), 2.55 (t, 2H, J = 7.3), 2.62 (m, 2H, J = 4.3), 2.72 (s, 2H), 3.95 (m, 4H), 7.13–7.32 (m, 5H)
4c	58	1710	0.88 (t, 3H, J = 6.6), 1.2–1.6 (m, 18H), 1.42 (s, 3H), 2.5 (t, 2H, J = 7.25), 2.77 (s, 2H), 3.97 (m, 4H)
4d	60	1720	0.88 (t, 3H, J = 6.7), 1.21–1.65 (m, 8H), 1.31 (s, 3H), 1.98 (t, 2H, J = 7.6), 2.4 (t, 2H, J = 7.5), 2.47 (t, 2H, J = 7.6), 3.94 (m, 4H)
4e	46	1711	0.82–1.93 (m, 11H), 1.31 (s, 3H), 1.95 (m, 2H), 2.28 (d, 2H, J = 6.7), 2.47 (t, 2H, J = 7.6), 3.93 (m, 4H)
4f	65	1700	0.88 (t, 3H, J = 6.7), 1.18–1.58 (m, 10H), 1.32 (s, 3H), 1.95 (t, 2H, J = 7.9), 2.4 (t, 2H, J = 7.3), 3.93 (m, 4H)
4g	48	1710	0.88 (t, 3H, J = 6.9), 1.2–1.7 (m, 14H), 1.32 (s, 3H), 2.4 (m, 4H), 3.95 (m, 4H)
4h	60	1708	0.88 (t, 3H, J = 6.8), 1.2–1.7 (m, 22H), 1.3 (s, 3H), 2.3–2.5 (m, 4H), 3.92 (m, 4H)

[a] Yield of pure, isolated product. Products isolated as oils.

acid-catalyzed (TsOH) ketalization, with ethylene glycol in refluxing benzene, of 1-nitrobutan-3-one,[29] 1-nitropentan-4-one,[30] and 1-nitrohexan-5-one.[31]

We would like to point out that the diketone **5d** has been conveniently utilized for the synthesis of dihydrojasmone.[7]

In summary this procedure is general for the preparation of 1,3-, 1,4-, and 1,5-diketones and since the starting materials **1** and **2** are easily accessible this method is preferable to other methods which employ organometallic reagents.

Melting points were determined with a Buchi apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. All ^1H NMR spectra were recorded, in $CDCl_3$ as solvent, at 300 MHz on a Varian VXR 300. Chemical shifts were recorded relative to internal TMS, and J values are given in Hz. The liquid products were monitored by GC, performed on a Carlo Erba Fractovap 4160 using a capillary column of Duran glass (0.32 mm × 25 m), stationary phase OV1 (film thickness 0.4–0.45 nm). Elemental analyses were performed using an Analyzer Model 185 from Hewlett Packard. Compounds **1**, **3**, **4** and **5** gave satisfactory microanalyses: C ± 0.27, H ± 0.22, N ± 0.24 (**Caution!** Overheating of nitro derivatives may cause thermal decomposition[32])

Protected Nitro Ketones; General Procedure:
The corresponding nitro ketone (36 mmol) was placed in a 100 mL three-necked flask equipped with a Dean–Stark apparatus and condenser. Benzene (50 mL), ethylene glycol (17 g, 274 mmol) and *p*-TsOH (0.085 g, 0.5 mmol) were added and the solution was refluxed for 24 h with continual removal of water. The mixture was cooled and sat. aq $NaHCO_3$ solution (300 mL) added. The organic layer was separated and washed with sat. aq NaCl solution (3 × 30 mL). The inorganic phase was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic layers dried (Na_2SO_4). The solvent was removed at reduced pressure to *leave a crude product* which, after distillation, afforded pure **1**.

4-Nitro-2-butanone Ethylene Acetal **(1, n = 1):** Yield 5.04 g (87%); bp 83–89 °C/0.8 mmHg; analytical data are in agreement with those previously reported.[29]

5-Nitro-2-pentanone Ethylene Acetal **(1, n = 2)**: Yield 5.54 g (88%); bp 65 °C/0.15 mmHg.

IR (film): ν = 1540 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.32 (s, 3H), 1.65–1.80 (m, 2H), 2.08–2.20 (m, 2H), 3.85–4.00 (m, 4H), 4.23 (t, 2H, J = 7.08 Hz).

6-Nitro-2-hexanone Ethylene Acetal **(1, n = 3)**: Yield 5.24 g (77%); bp 70 °C/0.06 mmHg.

IR (film): ν = 1540 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.3 (s, 3H), 1.4–1.75 (m, 4H), 1.95–2.15 (m, 2H), 3.93 (m, 4H), 4.38 (t, 2H, J = 7.12 Hz).

Nitroalkenes (3); General Procedure:
A solution of nitroalkane **1** (25 mmol) and aldehyde **2** (25 mmol) was mechanically stirred for 10 min. at 0 °C, cooling with an ice bath. After the addition of chromatographic basic alumina (activity I, 5 g) and stirring for 1 h at 0 °C, the mixture was allowed to stand at r.t. for 9–15 h (the reaction was monitored by TLC). The mixture was filtered and the alumina was washed with CH_2Cl_2 (3 × 30 mL). The organic layer was evaporated and purified by flash chromatography with EtOAc/cyclohexane (1.5:8.5) as eluent, to give the pure nitroalkene **3**.

Monoprotected Dicarbonyl Derivatives (4); General Procedure:
To a solution of **3** (16.5 mmol) and sodium hypophosphite (16.5 g) in EtOH–aq NaOAc–AcOH (300 mL, 2:1), pH = 5.0, a suspension of Raney-Nickel (50% H_2O, 3.3 mL) was added in several portions at r.t. After maintaining the mixture with stirring at 50 °C for 3 h, the catalyst was filtered off, water added (150 mL) and the solution extracted with Et_2O (3 × 50 mL) and dried (Na_2SO_4). Evaporation of the solvent afforded **5** which was purified by flash chromatography (EtOAc/cyclohexane = 8:2).

Table 3. Diketones **5a–h** Prepared

Product	Yield[a] (%)	bp or mp (°C)/Torr	Lit. Data	IR (film) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
5a	92	oil	148–150/17[33]	3387, 1707, 1618	0.88 (m, 3H), 1.2–1.75 (m, 8H), 2.05 (s, 3H), 2.25 (m, 2H), 5.5 (s, 2H), 15.5 (s, 1H, enol form)
5b	87	oil	–	3450, 1700, 1605	1.65 (m, 2H), 2.05 (s, 3H), 2.3 (m, 2H), 2.6 (m, 2H), 5.5 (s, 2H), 7.3 (m, 5H), 15.5 (m, 1H, enol form)
5c	90	33–34	31[34]	1717, 1616	0.86 (t, 3H, J = 6.7), 1.2–1.7 (m, 18H), 2.05 (s, 3H), 2.25 (t, 2H, J = 7.6), 5.5 (s, 2H), 15.5 (s, 1H, enol form)
5d	97	33–34	–	1710	0.88 (t, 3H, J = 7.0), 1.2–1.7 (m, 8H), 2.2 (s, 3H), 2.43 (t, 2H, J = 7.5), 2.68 (m, 4H)
5e	95	oil	–	1705	0.8–1.94 (m, 11H), 2.18 (s, 3H), 2.33 (d, 2H, J = 6.6), 2.65 (m, 4H)
5f	94	39–40	38[35]	1710	0.87 (t, 3H, J = 6.7), 1.2–1.6 (m, 10H), 2.18 (s, 3H), 2.43 (t, 2H, J = 7.5), 2.7 (m, 4H)
5g	90	56–57	58[21]	1700	0.88 (t, 3H, J = 6.9), 1.2–1.6 (m, 10H), 1.85 (m, 2H, J = 7.2), 2.13 (s, 3H), 2.32–2.5 (m, 6H)
5h	95	73–74	74[20]	1700	0.87 (t, 3H, J = 6.8), 1.2–1.6 (m, 18H), 1.83 (m, 2H, J = 7.05), 2.12 (s, 3H), 2.32–2.5 (m, 6H)

[a] Yield of pure, isolated product.

Regeneration of Diketones (5); General Procedure:
To a solution of **4** (6 mmol) in acetone (25 mL) containing water (2 mL) was added Amberlyst-15 (0.5 g) and the mixture was refluxed, with stirring, for 10–20 h (reaction monitored by GC). The resin was filtered and the filtrate evaporated to give **5**. The essentially pure products were further purified by distillation or flash chromatography (EtOAc/cyclohexane = 9:1).

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