Synthesis of Bicyclic and Tricyclic Enones via Regioselective Dialkylation of Cyclic 1,3-Diketone-dimethylhydrazones with 4-Chlorobutane-2-one

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Bicyclic and Tricyclic Enones, Regioselective Annulation, Metalated Hydrazones

An efficient, regioselective synthesis of substituted bicyclo nonenes and deccenes of type (4a, b) and the tricyclic tetradeadiene (5) is described. The key step is the regioselective dialkylation of cyclic 1,3-diketone-dimethylhydrazones (1a–e) with 4-chlorobutane-2-one.

**Introduction**

In the last decade several different approaches have been applied towards the synthesis of bicyclic ketones of type A [1] and tricyclic ketones B [2]. Most of the reported syntheses of this class of enones started from the Wieland-Miescher ketone and its analogues, which are available by Robinson annulations of cyclic 1,3-diketones with methyl vinyl ketones [3].

In connection with the work on the synthesis of taxodione C [4] and quassinoids such as similikalactone D [5], we now wish to report an alternative synthesis of A and B, which involves an A → AB → ABC ring approach for the construction of the bicyclic and tricyclic systems by regioselective double alkylation of cyclic 1,3-diketones via their dimetalated dimethylhydrazones with 4-chlorobutane-2-one.

![Scheme](image)

**Results and Discussion**

As is depicted in the scheme, the cyclic 1,3-diketones 1 were converted easily to the corresponding dimethylhydrazone derivatives in excellent yields, which according to the spectroscopic data (IR, NMR) exist as their tautomeric enhydrazinones 2 shown [6, 7].

![Structures](image)

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Dimetalation with bases, such as n-butyllithium in tetrahydrofuran at −78 °C, followed by treatment with two equivalents of 4-chlorobutane-2-one as methyl vinyl ketone equivalent [8] at −78 °C, yielded after quenching with saturated ammonium chloride solution and purification by column chromatography the regioselectively double alkylated (at C-2 and C-4) products 3a–e in 40–60% theoretical yield [9].

The Robinson annulation of 3a and b with KOH/EtOH and subsequent acidic hydrolysis of hydrazones provided the bicyclic enones 4a and b in good yields.

As shown in the Scheme, the double electrophilic substitution presumably involves the regioselective trapping of the “dianion” 2′ at position 2 and 4 in agreement with our previous observations [7–10].

As shown below, a second annulation of 4a with KOH/EtOH furnished the tricyclic enone 5 in 65% yield.

In conclusion, the overall highly regioselective annulation of cyclic 1,3-diketones to bicyclic/tricyclic enones 4 and 5 described here, offers a new entry to these compounds, which are important precursors in natural product synthesis.

Experimental

1H NMR spectra were recorded on a Varian EM-390-Bruker instrument. IR spectra were taken with a Beckman Acculab 4 instrument. Mass spectra were obtained on Kratos MS-30 and MS-50 spectrometers at an ionization energy of 70 eV. The elementary analyses were carried out with a Carlo Erba 1104 instrument. For analytical TLC, Merck TLC plates (silica gel 60 F 254) were used. All solvents were dried and distilled according to standard procedures. The melting points (Buechi apparatus, system Dr. Tottoli) are uncorrected.

Hydrazones 2. General procedure

A mixture of 10 mmol 1,3-diketone and 11 mmol dimethylhydrazine were refluxed for 4 h, and then poured into dichloromethane and washed with brine. The organic layer was separated, dried over Na2SO4 and concentrated in vacuo. Purification by column chromatography (silica gel, EtOAc, n-hexane 3:1) afforded colorless or yellow solids.

1,3-Cyclohexanedione-dimethylhydrazone (2a)

Reaction of 2.8 g (25 mmol) of 1,3-cyclohexanedione and 1.8 ml (26 mmol) N,N-dimethylhydrazine according to the general procedure yielded 3.7 g (98%) of 2a as a colorless solid, m.p. 135–136 °C. The spectroscopic data were identical with those given in the literature [7].

2-Methyl-1,3-cyclohexanedione-dimethylhydrazone (2b)

Reaction of 1.26 g (10 mmol) 2-methyl-1,3-cyclohexanedione and 0.96 ml (12 mmol) N,N-dimethylhydrazine according to the general procedure yielded 1.62 g (96%) of 2b, m.p. 112–114 °C.

IR (KBr): 3240 (NH), 2950, 2850 (CH), 1620 (CO), 1580 (C=C) cm−1.

1H NMR (CDCl3): 1.8 (s, 3H, CH3), 1.9 (m, 4H, CH2, C-4.6), 2.5 (s, 6H, NMe2), 6.0 (s, 1H, NH).

13C NMR (CDCl3): 7.4 (q, CH3), 24.8 (t, C-5), 33.2 (t, C-4), 36.5 (t, C-6), 48.7 (q, NMe2), 131.4 (s, C-2), 161.4 (s, C-3), 195.5 (s, C-1).

MS, m/z (% b.p.): 168 (M+, 98), 153 (M+-CH3, 10), 44 (NMe2, 100, b.p.).

C10H16N2O (168.14)

Calcd C 64.20 H 9.58 N 16.65,

Found C 63.89 H 9.66 N 16.54.

5,5-Dimethyl-1,3-cyclohexanedione-dimethylhydrazone (2c)

Reaction of 7.0 g (50 mmol) 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and 4.0 ml (5 mmol) N,N-dimethylhydrazine according to the general procedure yielded 8.9 g (98%) of 2c as a yellow solid, m.p. 162–163 °C.

IR (KBr): 3200 (NH), 3000–2800 (CH), 1660 (CO), 1550 (C=C) cm−1.

1H NMR (CDCl3): 1 (s, 6H, 2CH3), 2.1 (s, 4H, CH2, C-4.6), 2.6 (s, 6H, NMe2), 5.5 (s, 1H, olef. H), 7.1 (s, 1H, NH).

MS, m/z (% b.p.): 182 (M+, 78), 167 (M+-CH3, 20), 44 (NMe2, 100, b.p.).

C10H16N2O (182.14)

Calcd C 65.89 H 9.95 N 15.37,

Found C 65.63 H 10.13 N 15.35.
2-Methyl-1,3-cyclopentanedione-dimethylhydrazone (2d)

Reaction of 1.12 g (10 mmol) 2-methyl-1,3-cyclopentanedione and 0.88 ml (11 mmol) N,N-dimethylhydrazine according to the general procedure yielded 1.5 g (97%) of 2d yellow solid, m.p. 138–139 °C.

IR (KBr): 3110 (NH), 2900–2800 (CH), 1600 (CO), 1560 (C=C) cm⁻¹.

¹H NMR (CDCl₃): 1.6 (s, 3H, CH₃), 2.4–2.6 (m, 4H, CH₂, C-4.5), 2.7 (s, 6H, NMe₂), 6.2 (s, 1H, NH).

¹³C NMR (CDCl₃): 6.5 (q, CH₃), 24.6 (t, C-4), 32.7 (t, C-5), 48.5 (q, NMe₂), 106.0 (s, C-2), 173.2 (s, C-3), 203.4 (s, C-1).

MS, m/z (% b.p.): 154 (M⁺, 75), 139 (M⁺−CH₃, 10), 110 (M⁺−NMe₂, 50), 44 (NMe₂, 100, b.p.).

C₁₀H₁₂N₂O (154.21)
Calcd C 62.30 H 9.15 N 18.16,
Found C 62.65 H 9.05 N 17.66.

2-Ethyl-1,3-cyclopentanedione-dimethylhydrazone (2e)

Reaction of 2.52 g (20 mmol) 2-ethyl-1,3-cyclopentanedione and 1.6 ml (20 mmol) N,N-dimethylhydrazine according to the general procedure yielded 3.3 g (99%) of 2e as a yellow solid, m.p. 162–163 °C.

IR (KBr): 3200 (NH), 3000–2800 (CH), 1650 (CO), 1570 (C=C) cm⁻¹.

¹H NMR (CDCl₃): 0.9 (t, 3H, CH₃), 1.8–2.5 (m, 6H, CH₃ from C₅H₅, CH₂, C-4.5), 2.6 (s, 6H, NMe₂), 5.6 (s, 1H, NH).

MS, m/z (% b.p.): 168 (M⁺, 100, b.p.), 153 (M⁺−CH₃, 40), 44 (NMe₂, 160).

C₁₀H₁₂N₂O (168.24)
Calcd C 64.25 H 9.58 N 16.56,
Found C 64.23 H 9.61 N 16.82.

Hydrazones 3. General Procedure

A solution of n-butyllithium in n-hexane (2.2 eq. 1.6 M) was added dropwise with a syringe to a solution of hydrazones 2a–e in tetrahydrofuran under argon at −78 °C and stirred for 3 h and then at −20 °C for 1 h. The mixture was cooled to −78 °C and 4-chlorobutane-2-one was added. Stirring was continued at this temperature for 2 h, after which the mixture was allowed to warm up to 0 °C within 8–12 h. The mixture was then poured into a saturated aqueous ammonium chloride solution and extracted three times with ether. After drying the organic layer (Na₂SO₄) and concentrating in vacuo, the crude oily product was purified by column chromatography on silica gel (ether).
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2.4-Bis(2-oxobut-4-yl)-2-ethyl-3-N,N-dimethylhydrazono-cyclopentanediene-1,3 (3d)

Reaction of 1.68 g (10 mmol) 2e and 2.0 g (20 mmol) 4-chlorobutane-2-one according to the general procedure yielded 1.77 g (59%) of 3d as colorless oil, b.p. 118 °C, 0.02 Torr. IR (KBr): 3000-2790 (CH), 1710 (CO), 1680, 1650 cm⁻¹.

'H NMR (CDCl₃): 1.2 (s, 3H, CH₃), 2.1—2.2 (2x, 6H, CH₂ from oxobutyl), 2.5 (s, 6H, NMe₂), 1.5—2.6 (m, 11H, CH₂' s from oxobutyl), 2.6 (s, 1H, olef. H), 3.7 (s, 1H, olef. H).


General procedure: Ketones 4

A solution containing the hydrazone (3—5 mmol) and 3 ml of 3 M ethanolic potassium hydroxide according to the general procedure yielded 0.57 g (82%) of 4b as yellow oil. IR (Film): 2920-2820 (CH), 1740 (CO), 1700, 1680, 1650, 1600 cm⁻¹.

'H NMR (CDCl₃): 1.1 (s, 3H, CH₃), 1.9 (s, 3H, CH₃ from butoxy), 1.3—2.4 (m, 13H, CH₂'s, CH), 6.1 (s, 1H, olef. H).

MS, m/z (% b.p.): 234 (M⁺, 32), 191 (M⁺—CH₃CO, 48), 43 (H₂C=NMMe₂, 100, b.p.).


3.7-Dioxo-6-methyl-8-(2-oxo-but-4-yl)-bicyclo[4.3.0]octadecadien-1 (4a)

A solution containing 0.24 g (1 mmol) 4a and 4 ml of 4 M ethanolic potassium hydroxide solution was refluxed for 4 h (during which time the reaction was monitored with TLC). The solution was poured into brine, and the product was isolated with ether. The purification by PTLC (silica gel, ethylacetate-n-hexane, 3:1) afforded 0.14 g (65%) of 5 as a yellow oil. IR (Film): 3000—2840 (CH), 1740 (CO), 1700 (CO), 1570 (C=C) cm⁻¹.

'H NMR (CDCl₃): 1.2 (s, 3H, CH₃), 1.2—2.7 (m, 13H, CH₂'s, CH), 5.7 (s, 1H, olef. H), 6.0 (s, 1H, olef. H).

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**References**


[9] Changing the solvent to diethylether and toluene and the metalation temperatures (-20 °C, -30 °C) did not give better yields, the corresponding aldol products were never isolated under the reaction conditions.

[10] We assume that 4-chlorobetane-2-one react via an β-elimination/Michael addition mechanism, and not via S₂, because 1-chloropropane-2-one and 5-chloropropane-2-one did not react with the dianion under the same conditions.