A New Simple Synthesis of 5-Aryl-4-methoxycarbonyl-3-methyl-2-cyclohexenones*

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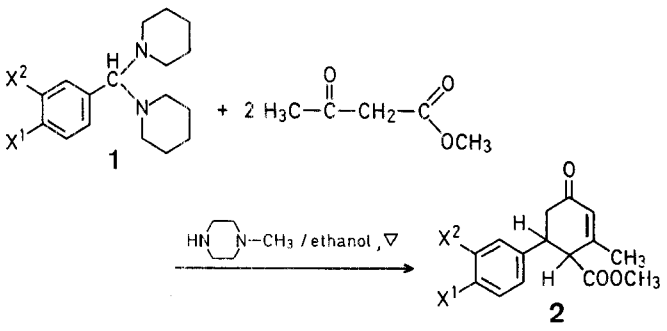
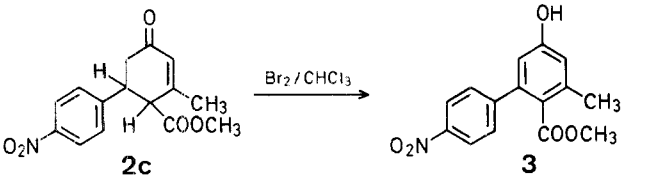
The synthesis of 5-alkyl-4-methoxycarbonyl-3-methyl-2-cyclohexenones has been reported[1,2] whereas the analogous 5-aryl derivatives could not be obtained[2]. Only a few corresponding free carboxylic acids, 5-aryl-4-carboxy-3-methyl-2-cyclohexenones, have been prepared by a three-step sequence in low overall yield[3] but the available spectral data are inadequate to support the claimed structures. We now present a new simple synthesis of 5-aryl-4-methoxycarbonyl-3-methyl-2-cyclohexenones (**2**; methyl 6-aryl-2-methyl-4-oxo-2-cyclohexene-1-carboxylates).

Reaction of the benzaldehyde aminals **1** (*N,N'*-benzylidenedipiperidines; obtained from benzaldehydes and piperidine[4]) with methyl acetoacetate in boiling ethanol in the presence of 1-methylhexahydropyrazine and column-chromatographic isolation affords the title compounds **(2)** in 60–70% yields within 90 minutes. Compounds **2** are obtained as mixtures of *cis*- and *trans*-isomers with the *trans*-isomer predominating. The *trans*-isomer can be purified by fractional crystallization with only 2–5% loss of the original *cis/trans* mixture.



The ^{1}H-N.M.R. spectra of compounds **2a–d,** purified by column chromatography followed by fractional crystallization from appropriate solvents **(2b–d),** indicate the presence of methine protons at C-4 and C-5 of the 2-cyclohexenone ring by the complex multiplets of signals over the range $\delta = 3.1$–3.7 ppm. On the other hand, the spectrum of compound **2e** shows a doublet at $\delta = 3.30$–3.41 ($J = 10$ Hz) which is assignable to the methine proton at C-4 and which indicates the *trans* stereochemistry. By analogy, the purified compounds **2a–d** are assumed to have also the *trans* structure.

The assigned structures of compounds **2** were proven by the aromatization of a representative cyclohexenone **(2c)** to the corresponding 5-hydroxybiphenyl-2-carboxylic ester **(3).**



Microanalysis and spectral data of compound **3** agree well with the assigned structure.

1-Dipiperidinomethyl-3,4-methylenedioxybenzene **(1b)** is prepared according to Ref.[4] while the other benzaldehyde aminals **1** are prepared using the following modified procedure.

Dipiperidinomethylbenzenes (1, *N,N'*-Benzylidenedipiperidines); General Procedure:

A mixture of the appropriate benzaldehyde (0.01 mol), piperidine (0.02 mol), and ethanol/water (1/1; 30 ml) is stirred at room temperature (25 °C) for 30 min. The separated solid is isolated by suction, washed with ethanol, and recrystallized from chloroform/hexane.

Aminal **1a,** $X^1 = X^2 = H$; yield: 95%; m.p. 78 °C.

Aminal **1c,** $X^1 = NO_2$, $X^2 = H$; yield: 85%; m.p. 70–71 °C.

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Table 1. 2-Cyclohexenones **2** prepared

2	X^1	X^2	Yield [%]	m.p. [°C]	Molecular formula[a]
a	H	H	70	oil	$C_{15}H_{16}O_3$ (244.2)
b	—O—CH_2—O—		68	95°	$C_{16}H_{16}O_5$ (288.3)
c	—NO_2	H	62	109–110°	$C_{15}H_{15}NO_5$ (289.2)
d	—NH—CO—CH_3	H	69	173–174°	$C_{17}H_{19}NO_4$ (301.3)
e	—NH—CO—CH_3	—NO_2	70	209–210°	$C_{17}H_{18}N_2O_6$ (346.3)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.39; H, ±0.34; N, ±0.09. Exception: **2d**; C, −0.45; N, −0.43.

Table 2. Spectral Data of Compounds **2**

2	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	1660 (C=O); 1720 ($COOCH_3$)	1.86 (s, 3H, 3-CH_3); 2.4–2.7 (m, 2H, CH_2); 3.46 (s, 3H, $COOCH_3$); 3.2–3.6 (m, 2H, 4-H, 5-H); 5.90 (s, 1H, 2-H); 7.10 (br s, 5H_{arom})
b	1660 (C=O); 1715 ($COOCH_3$)	1.85 (s, 3H, 3-CH_3); 2.4–2.62 (m, 2H, CH_2); 3.50 (s, 3H, $COOCH_3$); 3.3–3.65 (m, 2H, 4-H, 5-H); 5.78 (s, 2H, O—CH_2—O); 5.88 (s, 1H, 2-H); 6.52 (s, 3H_{arom})
c	1340, 1515 (NO_2); 1660 (C=O); 1720 ($COOCH_3$)	2.00 (s, 3H, 3-CH_3); 2.48–2.7 (m, 2H, CH_2); 3.52 (s, 3H, $COOCH_3$); 3.1–3.7 (m, 2H, 4-H, 5-H); 5.92 (s, 1H, 2-H); 7.22–7.32 (d, 2H, 2 *o*-H_{arom}, J=9 Hz); 8.0–8.1 (d, 2H, 2 *m*-H_{arom})
d	1670 (C=O); 1700 (—NH—CO—CH_3); 1710 ($COOCH_3$)	1.85 (s, 3H, 3-CH_3); 2.00 (s, 3H, NH—CO—CH_3); 2.4–2.62 (m, 2H, CH_2); 3.48 (s, 3H, $COOCH_3$); 3.3–3.6 (m, 2H, 4-H, 5-H); 5.90 (s, 1H, 2-H); 6.9–7.0 (d, 2H_{arom}, J=9 Hz); 7.28–7.36 (d, 1H_{arom}); 8.30 (s, 1H_{arom})
e	1340, 1510 (NO_2); 1665 (C=O); 1705 (—NH—CO—CH_3); 1725 ($COOCH_3$)	1.88 (s, 3H, 3-CH_3); 2.10 (s, 3H, NH—CO—CH_3); 2.2–2.56 (m, 2H, CH_2); 3.10–3.24 (d, 1H, 4-H, J=14 Hz); 3.62 (s, 3H, $COOCH_3$); 3.4–3.65 (m, 1H, 5-H); 5.89 (s, 1H, 2-H); 7.42–7.52 (dd, 1H, 2-H_{arom}, J_o=9 Hz, J_m=2 Hz); 7.86 (d, 1H, 6-H_{arom}, J_m=2 Hz); 8.0–8.1 (d, 1H, 3-H_{arom}, J_o=9 Hz)[a]

[a] In acetone-d_6.

Aminal **1d**, X^1=—NH—CO—CH_3, X^2=H; yield: 90%; m.p. 127–128 °C.

Aminal **1e**, X^1=—NH—CO—CH_3, X^2=NO_2; yield: 88%; m.p. 177–178 °C.

5-Aryl-4-methoxycarbonyl-3-methyl-2-cyclohexenones (2, Methyl 6-Aryl-2-methyl-4-oxo-2-cyclohexene-1-carboxylates); General Procedure:

A solution of the appropriate aminal **1** (0.01 mol), methyl acetoacetate (2.33 g, 0.02 mol), and 1-methylhexahydropyrazine (3.01 g, 0.03 mol) in ethanol (20 ml) is refluxed for 1–1.5 h. The solvent is then removed and the residue extracted with chloroform (2×40 ml). The organic solution is dried with sodium sulfate, concentrated, and filtered through silica gel using benzene (for **2a, b**) or chloroform/ethyl acetate (3/1; for **2c, d, e**) as eluent. Compounds **2b, c, d** were crystallized from diethyl ether and **2e** from ethyl acetate.

Methyl 5-Hydroxy-3-methyl-4′-nitrobiphenyl-2-carboxylate (3):

A solution of bromine (1.01 ml, 0.018 mol) in chloroform (20 ml) is slowly added to a stirred solution of 4-methoxycarbonyl-3-methyl-6-(4-nitrophenyl)-2-cyclohexenone (**2c**; 1 g, 0.003 mol) in chloroform (20 ml) at 10 °C. Stirring is continued at room temperature for 1 h, the solvent is then distilled off, and the residue redissolved in chloroform (20 ml). The solvent is again removed and the operation (dissolving and evaporating) is repeated thrice altogether. The residue so obtained is finally column-chromatographed on silica gel using chloroform/ethyl acetate (9/1) as eluent; yield: 0.54 g (55%); m.p. 183–185 °C.

$C_{15}H_{13}NO_5$	calc.	C 62.71	H 4.56	N 4.87
(287.2)	found	62.45	4.51	4.68

I.R. (KBr): ν=1350, 1510 (NO_2); 1695 ($COOCH_3$); 3350 cm^{-1} (OH).

^{1}H-N.M.R. ($CDCl_3$/DMSO-d_6/TMS_{int}): δ=2.22 (s, 3H, 3-CH_3); 3.39 (s, 3H, $COOCH_3$); 6.46–6.60 (d, 2H, 4-H_{arom}, 6-H_{arom}); 7.2–7.3 (d, 2H, 2′-H_{arom}, 6′-H_{arom}, J_o=9 Hz); 7.95–8.05 ppm (d, 2H, 3′-H_{arom}, 5′-H_{arom}, J_o=9 Hz).

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