Synthesis of 2,3-Disubstituted Cyclopent-2-en-1-ones from 6-Methoxyindanone[1]

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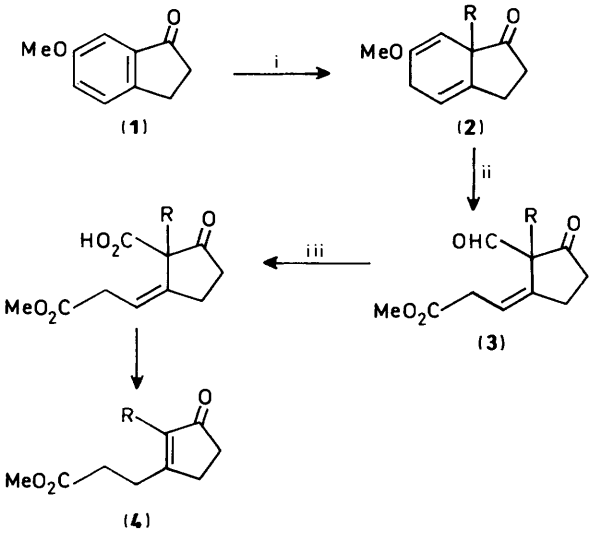
A new route to 2,3-disubstituted cyclopentenones (**4**) is described. Reductive alkylation of 6-methoxyindanone (**1**) in potassium and liquid ammonia followed by addition of lithium bromide and an alkyl halide gives dihydroindanones (**2**). Ozonolysis of the dihydroindanones results in cleavage of the vinyl ether double bond, and oxidation of the resulting aldehyde (**3**) leads to the 2,3-disubstituted cyclopentenones (**4**), after spontaneous decarboxylation of the intermediate β-keto acid.

The reduction of aromatic compounds such as alkyl- and alkoxy-benzenes with alkali-metals in liquid ammonia (Birch reduction) has found wide application in organic synthesis over many years.[2] More recently it has been shown that the reduction of the aromatic ring of aromatic esters and ketones, traditionally regarded as unsuitable substrates, is also possible, and reliable conditions for the reduction and reductive alkylation of aromatic ketones have been established for acetophenone and its methoxy derivatives.[3] We have utilised similar reductive alkylations of indan-1-ones in the synthesis of novel tricyclic [10]annulenes,[4] and we now report in detail the extensions of this work as a key step in the conversion of the readily available aromatic ketone, 6-methoxyindanone (**1**) into substituted cyclopentenones.[1]



Scheme. *Reagents:* i, K, NH_3, Bu^{t}OH, THF, −78 °C; LiBr, RX (see Table); ii, O_3, MeOH; Zn, AcOH work-up; iii, Jones reagent

Results and Discussion

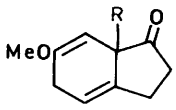
The preparation of five-membered rings remains a topic of current interest and several new methods for the construction of cyclopentenones have been devised.[5] The use of aromatic indan derivatives as precursors to cyclopentanes is not new; prostaglandin-E_1 has been prepared in >25 steps from 5-methoxyindanone.[6] Our direct approach to cyclopentenones is based on the selective ozonolysis of the dihydroindanones (**2**) obtained by reductive alkylation of the aromatic ketone (**1**) (Scheme). The optimum conditions for the Birch reduction of 6-methoxyindanone (**1**), prepared by cyclisation[7] of commercially available 3-(4-methoxyphenyl)propionic acid, involved an inverse addition procedure. Thus a mixture of the ketone (**1**) and t-butyl alcohol (2 equiv.) in dry tetrahydrofuran (THF) was added to a pre-formed blue solution of potassium in liquid ammonia at −78 °C. Subsequently, lithium bromide in THF was added in order to exchange the counter cation in the intermediate dihydroindanone enolate, and this was followed by addition of the alkylating agent, RX. Aqueous work-up gave the alkylated dihydroindanones (**2**), which without purification were ozonised in methanol. As expected, the vinyl ether double bond in (**2**) was selectively cleaved; direct oxidative work-up (ozonolysis in dichloromethane in this case) was unsatisfactory, but addition of zinc and acetic acid gave the aldehyde (**3**) which was immediately oxidised further with Jones reagent. The resulting β-keto acid spontaneously decarboxylated with concomitant movement of the exocyclic double bond into conjugation with the ketone to give the desired cyclopentenone (**4**) (Scheme and Table). Attempts to isolate and purify the intermediate 5,7a-dihydroindanones (**2**) resulted in their partial isomerisation into the 6,7a-dihydro derivatives.

Table. Overall yield of cyclopentenones (**4**) from 6-methoxyindanone (**1**)

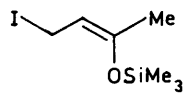
	R	Alkylating agent, RX	Yield (%)
(**4a**)	Me	MeI	11
(**4b**)	Et	EtI	9
(**4c**)	$H_2C{=}CHCH_2$	$H_2C{=}CHCH_2I$	30
(**4d**)	$EtC{\equiv}CCH_2$	$EtC{\equiv}CCH_2I$	29[a]
(**4e**)	$C_5H_{11}C{\equiv}CCH_2$	$C_5H_{11}C{\equiv}CCH_2Br$	25
(**4f**)	$PhCH_2$	$PhCH_2Br$	44
(**4g**)	EtO_2CCH_2	EtO_2CCH_2Br	21

[a] Yield reduced to 23% when corresponding bromide used.

The reaction sequence is general for a range of alkyl halides (Table), and gives 2,3-disubstituted cyclopentenones (**4**) in moderate overall yield from 6-methoxyindanone. The overall yield is dependent on the reactivity of the alkylating agent, reactive (allylic, benzylic) halides giving the higher yields. Several other electrophiles were also tried in the 'alkylation' stage of the Birch reduction, but all, after completion of the reaction sequence, failed to give the corresponding cyclopentenone. Attempts to isolate the intermediate dihydroindanones (**5a**) and (**5b**) resulting from addition of water and benzaldehyde respectively were also unsuccessful. Similarly, although there is precedent for the alkylation of Birch reduction intermediates by conjugate addition of methyl acrylate,[8] similar reactions on 6-methoxyindanone (**1**) using methyl acrylate or methyl but-2-ynoate as electrophiles failed to give any of the required dihydroindanones. Finally use of the iodide (**6**) as a



(5a) R = H
(5b) R = CH(OH)Ph



(6)

vinyl ketone equivalent[9] in our Birch reduction/alkylation sequence was also unsuccessful.

Nevertheless, despite the limitations of electrophiles that successfully participate in the reductive alkylation reaction, a range of 2,3-disubstituted cyclopentenones (**4**) is available in just three operations comprising 5 reaction steps from 6-methoxyindanone.

Experimental

I.r. spectra were recorded as thin films or as solutions in chloroform on a Perkin-Elmer 298 spectrophotometer, and calibrated against polystyrene. ^{1}H N.m.r. were recorded on a Bruker WM250 (operating at 250 MHz), on a Perkin-Elmer R32 (operating at 90 MHz), or on a Varian EM360 spectrometer (operating at 60 MHz). Mass spectra were recorded on a VG Micromass 707B mass spectrometer operating at 70 eV using a direct insertion probe. Silica gel (Merck type 60H) was used for column chromatography. Ether refers to diethyl ether and light petroleum refers to the fraction b.p. 40—60 °C. Tetrahydrofuran (THF) and ether were dried with potassium and sodium respectively, using the benzophenone ketyl radical as indicator, and t-butyl alcohol was distilled from calcium hydride. Other solvents were dried by standard procedures. All organic solutions from extractions were dried over anhydrous magnesium sulphate unless otherwise stated. Ozone was produced by passing oxygen through a Wallace and Tiernan BA 023012 ozonator at 120 V, and with a flow rate of 60 l h^{-1}.

6-*Methoxyindan*-1-*one* (**1**). Prepared by the literature procedure[7] from 3-(4-methoxyphenyl)propionic acid, m.p. 109.5—110.5 °C (lit.,[7] m.p. 109—111 °C).

1-*Iodopent*-2-*yne*. Prepared by standard procedure from commercially available (Lancaster Synthesis) pent-2-yn-1-ol.

1-*Bromo-oct*-2-*yne*. Prepared by standard procedure from commercially available (Lancaster Synthesis) oct-2-yn-1-ol.

General Procedure for the Birch Reduction and Alkylation of 6-Methoxyindanone followed by Ozonolysis and Oxidation.

Methyl 3-(3-*Oxo*-2-*pent*-2-*ynylcyclopent*-1-*enyl*)*propionate* (**4d**).—A solution of 6-methoxyindan-1-one (**1**) (1.30 g, 8.0 mmol) in dry THF (8 ml) and dry t-butyl alcohol (1.7 ml, 17.7 mmol) was slowly added to a solution of potassium (0.87 g, 22.3 mmol) in liquid ammonia (40 ml) under nitrogen at −78 °C. The mixture was stirred for 0.5 h after which a solution of lithium bromide (1.80 g, 21.2 mmol) in THF (8 ml) was introduced, and the resulting mixture stirred for an additional 0.5 h. 1-Iodopent-2-yne (1.70 g, 8.9 mmol) and aqueous THF (50%; 7 ml) were then simultaneously added rapidly, and the ammonia subsequently removed under reduced pressure. The residue was diluted with water (50 ml) and the mixture extracted with ether (3 × 30 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford a yellow-orange oil. The crude product (**2d**) (2.0 g) was dissolved in dry methanol (30 ml) and the solution cooled to −78 °C. Ozone was then bubbled through it until t.l.c. analysis indicated the absence of starting material. The mixture was then allowed to warm up to −30 °C, and zinc metal powder (0.92 g, 14.1 mmol) was added followed by the dropwise addition of aqueous acetic acid (50%; 3.6 ml). After warming up to room temperature the mixture was filtered, and the filtrate evaporated under reduced pressure. Water (20 ml) and chloroform (20 ml) were added to the residue, and the aqueous layer washed with chloroform (2 × 20 ml). The combined organic extracts were sequentially washed with saturated aqueous sodium hydrogen carbonate (30 ml), water (30 ml), and brine (30 ml) and then dried and evaporated. The crude oily aldehyde (**3d**) was dissolved in acetone (20 ml) and the solution cooled to 0 °C and treated with Jones reagent. After 15 min excess of oxidant was quenched with methanol. The green mixture was filtered through a short pad of silica, washed well with ethyl acetate, and the filtrate concentrated. Purification by flash chromatography, eluting with light petroleum–ether gave the *title compound* (**4d**) (0.54 g, 29%) as a pale yellow oil, b.p. 102 °C/0.006 mmHg (Found: C, 71.5; H, 7.8. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%); $\nu_{max.}$(film) 1 735, 1 695, and 1 645 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 3.71 (3 H, s, CO_2Me), 3.12—3.07 (2 H, m, C≡CCH_2), 2.90 (2 H, br t, *J* 7.5 Hz, 3-CH_2), 2.63 (2 H, br t, *J* 7.5 Hz, 2-CH_2), 2.56—2.51 (2 H, m, CH_2CH_2CO), 2.43—2.38 (2 H, m, CH_2CH_2CO), 2.14 (2 H, qt, *J* 7.5 and 2 Hz, CH_3CH_2), and 1.08 (3 H, t, *J* 7.5 Hz, CH_3CH_2); *m*/*z* 234 (M^+, 81%), 219 (16), 203 (9), 175 (38), and 161 (100).

When 1-bromopent-2-yne was used in place of the iodide, the overall yield of the title compound (**4d**) was reduced to 23%.

Methyl 3-(2-*Methyl*-3-*oxocyclopent*-1-*enyl*)*propionate* (**4a**).—The general procedure was adopted with 6-methoxyindan-1-one (**1**) (1.50 g, 9.3 mmol) and iodomethane to afford the *title compound* (**4a**) (0.19 g, 11%) as a pale yellow oil, b.p. 65—75 °C/0.1 mmHg (Found: M^+, 182.0947. $C_{10}H_{14}O_3$ requires *M*, 182.0943); $\nu_{max.}$(film) 1 740, 1 695, and 1 650 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 3.69 (3 H, s, CO_2Me), 2.75 (2 H, br t, *J* 7.4 Hz, 3-CH_2), 2.55 (2 H, br t, *J* 7.4 Hz, 2-CH_2), 2.53—2.47 (2 H, m, CH_2CH_2CO), 2.40—2.35 (2 H, m, CH_2CH_2CO), and 1.72 (3 H, s, CH_3); *m*/*z* 182 (M^+, 100%), 167 (4), 151 (13), 123 (62), and 122 (43).

Methyl 3-(2-*Ethyl*-3-*oxocyclopent*-1-*enyl*)*propionate* (**4b**).—The general procedure was followed using 6-methoxyindan-1-one (**1**) (1.50 g, 9.3 mmol) and iodoethane to yield the *title compound* (**4b**) (0.16 g, 9%) as a pale yellow oil (Found: M^+, 196.1104. $C_{11}H_{16}O_3$ requires *M*, 196.1100); $\nu_{max.}$(film) 1 740, 1 695, and 1 645 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 3.67 (3 H, s, CO_2Me), 2.74 (2 H, br t, *J* 7.5 Hz, 3-CH_2), 2.52 (2 H, br t, *J* 7.5 Hz, 2-CH_2), 2.46—2.42 (2 H, m, CH_2CH_2CO), 2.36—2.32 (2 H, m, CH_2CH_2CO), 2.17 (2 H, q, *J* 7.5 Hz, CH_3CH_2), and 0.95 (3 H, t, *J* 7.5 Hz, CH_3CH_2); *m*/*z* 196 (M^+, 45%), 181 (5), 165 (11), and 137 (100).

Methyl 3-(2-*Allyl*-3-*oxocyclopent*-1-*enyl*)*propionate* (**4c**).—The general procedure was followed using 6-methoxyindan-1-one (**1**) (1.27 g, 7.8 mmol) and allyl iodide to afford the *title compound* (**4c**) (0.49 g, 30%) as a pale yellow oil, b.p. 86—90 °C/0.2 mmHg (Found: C, 69.2; H, 7.8. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%); $\nu_{max.}$(film) 1 740, 1 700, and 1 645 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 5.77 (1 H, ddt, *J* 10, 10, and 6.5 Hz, =C*H*CH_2), 5.30—4.93 (2 H, m, H_2C=), 3.68 (3 H, s, CO_2Me), 2.95 (2 H, d, *J* 6.5 Hz, =CHCH_2), 2.75 (2 H, t, *J* 7 Hz, 3-CH_2), 2.58—2.48 (4 H, m, 2-CH_2 and CH_2CH_2CO), and 2.42—2.37 (2 H, m, CH_2CH_2CO); *m*/*z* 208 (M^+, 100%), 177 (15), 149 (71), and 135 (39).

Methyl 3-(2-*Oct*-2-*ynyl*-3-*oxocyclopent*-1-*enyl*)*propionate* (**4e**).—The general method was followed using 6-methoxyindan-1-one (**1**) (1.50 g, 9.3 mmol) and 1-bromo-oct-2-yne to afford the *title compound* (**4e**) (0.64 g, 25%) as a pale yellow oil, b.p. 140 °C/0.15 mmHg (Found: C, 73.9; H, 9.0. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.8%); $\nu_{max.}$(film) 1 740, 1 705, and 1 645 cm^{-1}; δ_H(250

MHz; $CDCl_3$) 3.70 (3 H, s, CO_2Me), 3.19 (2 H, m, $C{\equiv}CCH_2$), 2.92 (2 H, br t, *J* 8 Hz, 3-CH_2), 2.62 (2 H, br t, *J* 8 Hz, 2-CH_2), 2.56—2.51 (2 H, m, CH_2CH_2CO), 2.44—2.37 (2 H, m, CH_2CH_2CO), 2.09 (2 H, tt, *J* 7 and 2.5 Hz, $CH_2C{\equiv}C$), 1.48—1.25 (6 H, m, $CH_2CH_2CH_2$), and 0.88 (3 H, t, *J* 7.5 Hz, CH_3CH_2); *m/z* 276 (M^+, 10%), 261 (4), 247 (10), 220 (100), 189 (20), and 159 (57).

Methyl 3-(2-*Benzyl*-3-*oxocyclopent*-1-*enyl*)*propionate* (**4f**).—The general method was followed using 6-methoxyindan-1-one (**1**) (1.50 g, 9.3 mmol) and benzyl bromide to give the *title compound* (**4f**) (1.06 g, 44%) as a pale yellow oil, b.p. 125 °C/0.05 mmHg (Found: C, 74.5; H, 7.2. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%); $\nu_{max.}$(film) 3 060, 3 030, 1 740, 1 700, 1 640, 1 600, 1 580, and 1 495 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.30—7.10 (5 H, m, Ph), 3.67 (3 H, s, CO_2Me), 3.54 (2 H, s, $PhCH_2$), 2.78 (2 H, br t, *J* 7.5 Hz, 3-CH_2), and 2.54—2.38 (6 H, m, 2-CH_2 and CH_2CH_2CO); *m/z* 258 (M^+, 86%), 227 (11), 199 (50), 185 (18), and 91 (100).

Methyl 3-(2-*Ethoxycarbonylmethyl*-3-*oxocyclopent*-1-*enyl*)-*propionate* (**4g**).—The general conditions for the Birch reduction of 6-methoxyindan-1-one (**1**) (1.5 g, 9.3 mmol) were followed, except that after the addition of a solution of lithium bromide in THF the mixture was quenched by the simultaneous addition of ethyl bromoacetate (1.7 g, 10.2 mmol) in THF (3 ml) and solid ammonium chloride (2 g). After evaporation of ammonia under reduced pressure, pH 7 buffer (100 ml) was introduced, and the aqueous layer extracted with ether (3 × 50 ml) in the normal way. Ozonolysis and subsequent oxidation and decarboxylation gave the *title compound* (**4g**) (0.49 g, 21%) as a pale yellow oil, b.p. 115—120 °C/0.2 mmHg (Found: C, 61.3; H, 7.4. $C_{13}H_{18}O_5$ requires C, 61.4; H, 7.1%); $\nu_{max.}$(film) 1 740, 1 705, and 1 650 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 4.12 (2 H, q, *J* 7 Hz, OCH_2CH_3), 3.67 (3 H, s, CO_2Me), 3.25 (2 H, s, EtO_2CCH_2), 2.80—2.72 (2 H, m, $MeO_2CCH_2CH_2$), 2.62—2.54 (4 H, m, MeO_2CCH_2 and CH_2CH_2CO), 2.45—2.40 (2 H, m, CH_2CH_2-CO), and 1.25 (3 H, t, *J* 7 Hz, OCH_2CH_3); *m/z* 254 (M^+, 52%), 223 (28), 209 (49), 208 (60), 195 (34), and 180 (100).

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