A Quick and Efficient Route to 2-Substituted Cyclopentanones and Cyclohexanones

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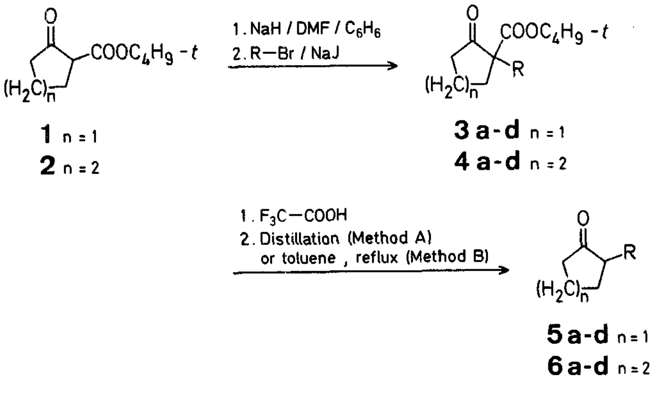
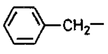
We recently required an efficient route to a variety of 2-substituted cyclopentanones and cyclohexanones; e.g. **5d** and **6d**.

Alkylation of the cycloalkanone enamines[1] gave disappointing yields and although the corresponding 2-methoxycarbonylcycloalkanones[2] underwent alkylation in high yields, problems were encountered with the acid- and base-catalysed demethoxycarbonylations. This problem is often encountered when the alkylated β-keto ester has a quaternary α-carbon atom[3] and, in such cases, the use of O-alkyl ester cleavage conditions often gives improved yields[4,5]. In our hands, however, the yields of **5d** and **6d** were still low using a variety of O-alkyl cleavage conditions and in addition the reactions were extremely slow.

To circumvent these problems we decided to employ 2-*t*-butoxycarbonylcycloalkanones in the alkylation reaction; treatment of the product with acid would be expected[6] to produce the corresponding β-keto acid which should readily decarboxylate. This protocol is well established in acyclic systems[6] but, to our knowledge, has not been applied to the preparation of 2-alkylated cyclopentanones and cyclohexanones. Fortunately, the preparation of 2-*t*-butoxycarbonylcyclohexanone (**2**) has been described in the literature[7] (although its alkylation reactions were not investigated) and we have found that the same procedure can be used for the cyclopentanone analogue **1**.



3-6	a	b	c
R	$H_2C{=}CH{-}CH_2{-}$	$H_3C{-}CH_2{-}C{\equiv}C{-}CH_2{-}$	
	d		
R	$H_3COOC{-}(CH_2)_3{-}C{\equiv}C{-}CH_2{-}$		

The *t*-butyl esters **1** and **2** were successfully alkylated under standard conditions with a variety of bromoalkanes and the products **3** and **4** were treated directly with trifluoroacetic acid to produce the corresponding carboxylic acids. Two procedures were used for decarboxylation. The volatile products were simply distilled using a Kugelrohr apparatus and the decarboxylated ketones **5** or **6** collected (Method A). Higher boiling ketones were decarboxylated in boiling toluene (Method B). The ketones **5** and **6** produced in this way could usually be used without further purification although trace amounts of coloured impurities were sometimes present and these were removed by straight-forward column chromatography.

A variety of compounds were produced by these procedures (Table) including the original targets **5d** and **6d**. Where comparisons are possible, this procedure is more efficient than the corresponding transformation using methyl/ethyl esters[8].

2-*t*-Butoxycarbonylcyclopentanone (1):

Sodium hydride (60% in oil, 40 g, 1 mol) is washed with several portions of dry petroleum ether under nitrogen in the normal way to remove the oil. Dry benzene (400 ml) is added and the suspension is stirred under nitrogen and di-*t*-butyl adipate (5 g, 0.02 mol) and *t*-butanol (2 ml) are added in one portion. The mixture is then boiled under reflux with vigorous stirring for 30 min. A second portion of di-*t*-butyl adipate (120 g, 0.465 mol) in dry benzene (200 ml) is then added drop-

Table. 2-Substituted Cyclopentanones **5** and Cyclohexanones **6** prepared

Product	Yield [%][a]	b.p. [°C]/torr	Molecular formula[b] or Lit. b.p. [°C]/torr
5a	88[c]	77-80°/15[d]	78-85°/20[9]
5b	92[c]	100-105°/12	100°/9[10]
5c	91[c]	100-110°/0.2[e]	153-154°/19[11]
5d	93[f]	oil	$C_{13}H_{18}O_3$ (222.3)
6a	80[c]	85°/15	87°/16[8a]
6b	85[c] (80)[g]	116-122°/8[h]	not reported in Ref.[12]
6c	91[c] (83)[g]	150°/0.6[i]	119-121°/0.01[13]
6d	90[c] (83)[g]	oil[j]	$C_{14}H_{20}O_3$ (236.3)

[a] Overall yields for 1→5 and 2→6, respectively.

[b] Satisfactory microanalyses obtained: C ±0.10, H ±0.13.

[c] Dealkoxycarbonylation by Kugelrohr distillation, further purification not necessary unless otherwise stated.

[d] Semicarbazone m.p.: 179-181°C (Ref.[9], m.p. 178-180°C).

[e] Semicarbazone m.p.: 195-196°C (Ref.[11], m.p. 198-200°C).

[f] Decarboxylation in refluxing toluene, crude product purified by column chromatography on silica gel eluting with 1:9 ether/petroleum ether.

[g] Yield after column chromatography on silica eluting with ether/petroleum ether mixtures, to remove coloured impurities.

[h] Identical with a sample prepared according to Ref.[12].

[i] Semicarbazone m.p.: 166-168°C (Ref.[13], m.p. 168-169°C).

[j] I.R. (film): ν = 1740, 1710 cm⁻¹.
^{1}H-N.M.R. (CDCl$_3$): $\delta = 1.2-2.2$ (m, 17H); 3.69 ppm (s, 3H, OCH$_3$) ppm.

wise to the boiling mixture over 45 min and the mixture is boiled under reflux with vigorous stirring for a further 4.5 h. The resulting thick suspension is then cooled to 0°C and sufficient 10% aqueous acetic acid is added to obtain a neutral (litmus) solution. The mixture is then poured into water (750 ml), extracted with diethyl ether (2 x 500 ml), the combined extracts washed with saturated aqueous sodium hydrogen carbonate solution (250 ml) and water (250 ml), dried with magnesium sulfate, and the solvent removed in vacuo. Distillation under reduced pressure gives **1** as a colourless liquid; yield: 65.3 g (73%); b.p. 80-85°C/2 torr; R_f: 0.25 [silica, ether/hexane (1:2)].

$C_{10}H_{16}O_3$	calc.	C 65.22	H 8.89
(184.2)	found	65.02	8.68

I.R. (film): $\nu = 1755$, 1720 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): $\delta = 1.44$ (s, 9H, t-C$_4$H$_9$); 2.18 (m, 6H); 2.92 ppm (t, 1H, $J = 6.7$ Hz).

2-*t*-Butoxycarbonylcyclohexanone (**2**) can be prepared by the same procedure[7].

2-Allylcyclohexanone (6a); Typical Procedure using Dealkoxycarbonylation Method A:

Sodium hydride (50% in oil, 0.72 g, 0.015 mol) is washed with several portions of dry petroleum ether under nitrogen in the normal way to remove the oil. Dry benzene (50 ml) and dimethylformamide (50 ml) are then added followed by a solution of 2-*t*-butoxycarbonylcyclohexanone (**2**; 3 g, 0.015 mol) in dimethylformamide (5 ml). The mixture is then stirred under nitrogen until evolution of hydrogen ceases (~30 min) and then sodium iodide (0.23 g, 1.53 mmol) and allyl bromide (1.8 g, 0.015 mol) are added. After 1 h, T.L.C. analysis indicates that all starting material has been consumed and water (50 ml) is added. Extraction with diethyl ether (2 x 100 ml), drying with magnesium sulfate, and removal of the solvent in vacuo gives the crude alkylated product **4a** to which trifluoroacetic acid (15 ml) is added. The reaction is stirred until T.L.C. analysis indicates complete disappearance of starting material (~30 min) and then water (50 ml) is added. Extraction with diethyl ether (2 x 50 ml), drying with magnesium sulfate, and removal of the solvent in vacuo gives the crude β-keto acid. Kugelrohr distillation of this crude product (50°C/0.8 torr) gives pure **6a**; yield: 1.60 g (77%); b.p. 85°C/15 torr (Ref.[8a], b.p. 87°C/16 torr).

2-(6-Methoxycarbonylhex-2-yn-1-yl)-cyclopentanone (5d); Typical Procedure using Decarboxylation Method B:

As described for the preparation of **6a**, a slurry of sodium hydride (3 mmol) in benzene/dimethylformamide (1:1, 10 ml) is prepared under nitrogen. 2-*t*-Butoxycarbonylcyclopentanone (**1**; 0.374 g, 2.03 mmol) in benzene/dimethylformamide (1:1, 5 ml) is added with stirring. After the hydrogen evolution has ceased, methyl 7-bromohept-5-ynoate (0.481 g, 2.20 mmol) and sodium iodide (0.1 g, 0.67 mmol) dissolved in benzene/dimethylformamide (1:1, 5 ml) are added and stirring is continued for 2 h at 20°C. Work-up as described above yields a crude product which is stirred in trifluoroacetic acid (5 ml) for 3 h. The crude β-keto acid is isolated as described before and dissolved in toluene/methanol (10:1, 20 ml). After adding a small amount of solid sodium hydrogen carbonate (~0.5 g) to neutralise any remaining trifluoroacetic acid, the mixture is boiled under reflux for 4 h, cooled, washed with water, dried with magnesium sulfate, and the solvent removed in vacuo. The residue is chromatographed on silica (Merck 7734, 10 g), elution with ether/petroleum ether (1:9) gives **5d** as a colourless oil; yield: 0.39 g (93%); R$_f$: 0.6 [silica, ether/hexane (1:1) as eluent].

$C_{13}H_{18}O_3$	calc.	C 70.27	H 8.11
(222.3)	found	70.23	8.24

M.S.: $m/e = 222$ (M$^+$).

I.R. (film): $\nu = 1735$, 2960 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): $\delta = 1.54$-2.30 (m, 18H); 3.60 ppm (s, 3H, OCH$_3$).

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