Synthesis of 2-Alkylcyclohexanones Using Solvent-free Conditions and Microwave Technology

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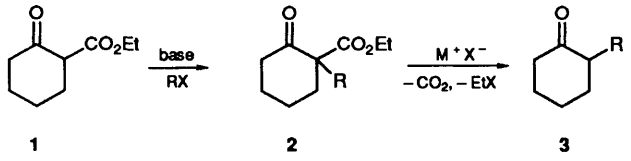
An expeditious solvent-free route to 2-alkylcyclohexanones from 2-ethoxycarbonylcyclohexanone is described *via* a solid–liquid phase transfer catalysed alkylation using Bu^{t}OK as base and Aliquat® 336 as catalyst and a LiBr–H_2O–NBu_4Br induced dealkoxycarbonylation under microwave activation in a focused open-vessel Maxidigest system. Yields were ⩾75% over two steps.

2-Alkylcyclohexanones are useful intermediates or synthons[1] which can be prepared by direct mono-alkylation of cyclohexanone. Unfortunately, mono-alkylation of ketones is difficult to perform and troublesome di- and poly-condensations are observed.[2,3] Therefore, multi-step syntheses have to be considered. Among these methods, the Stork enamine reaction is an interesting alternative to the ketone alkylation but it is not very efficient for ordinary primary and secondary halides.[4,5] Consequently, we consider here a two step process starting from ethyl 2-oxocyclohexanecarboxylate **1**, consisting of an alkylation then deethoxycarbonylation (Krapcho reaction) sequence (Scheme 1).



1 **2** **3**

a R = Et
b R = Bu
c R = C_6H_{13}

Scheme 1

Alkylation of Ester **1** (*Table* 1).—Alkylation using solid–liquid phase transfer catalysis (PTC) in the absence of solvent was considered. This method has been shown to be amongst the most efficient, providing good to excellent yields under very mild conditions.[6]

The conditions employed here are the use of Bu^{t}OK as a base, Aliquat® 336 in catalytic amount (6 mol%) as a transfer agent and RBr in equivalent amounts as the electrophile (R = Et, Bu, C_6H_{13}). For the sake of comparison with more classical conditions, we have tested the same base in dimethyl sulfoxide (DMSO), a dipolar aprotic solvent generally advocated for this type of reaction.[7] Comparison of the two methods clearly shows the superiority of the PTC without solvent conditions. Not only are the yields higher but also cost, safety, ease of work-up are very favourable with this method. Also, compared to classical PTC methods using NaOH in $CHCl_3$–H_2O[8,9] or in PhMe–H_2O,[10] these conditions are milder, cheaper and even more efficient.

Deethoxycarbonylation of **2** (*Table* 2).—This reaction was considered according to three methodologies: (i) Krapcho reaction using $CaCl_2$ (5 equiv.) in DMSO in the presence of water (2 mol equiv.);[11] (ii) subsequent hydrolysis and decarboxylation using H_3O^+ at high temperature;[12] (iii) a PTC without solvent method (2 equiv. LiBr, 2 equiv. H_2O, 10 mol% NBu_4Br) coupled with microwave irradiation[13] in a single mode focused digestion system.[14] It appears that the only efficient and general method is the PTC–microwave one, as excellent yields (>87%) of isolated pure products are obtained within 20 min of irradiation in the absence of solvent.

Table 1 Alkylation of **1** under PTC without solvent or in DMSO[a]

	Bu^{t}OK–Aliquat®		Bu^{t}OK–DMSO	
R	*t*/min	Yield **2** (%)[b]	*t*/h	Yield **2** (%)[b]
Et	20	96[c]	3	75
Bu	30	93	3	68
C_6H_{13}	30[d]	83	3	65

[a] Reactions at room temp. unless otherwise stated. [b] Isolated yield after flash chromatography or distillation. [c] Using ethyl bromide (1.5 equiv.). [d] T = 80 °C.

This result is a new illustration of the potential of microwave use in organic synthesis. However, in order to check the possibility of a non thermal specific effect of microwaves when compared to conventional heating, we have performed the dealkoxycarbonylation of **2a** as a typical case at the same temperature in a oil bath (Table 3). Clearly, the excellent results obtained under microwave activation are not only due to thermal effects as the yields are quasi-quantitative after 15 min whereas, at the same temperature, classical heating is non-operative. The total conversion needs 3 h and the yields (60%) are limited by degradation products. Consequently, compared with conventional heating, there are two main advantages: a large reduction in time with simpler experimental conditions, and prevention of the degradation of the product at high temperature.

Experimental

Alkylation of Ethyl 2-Oxocyclohexanecarboxylate **1**.—To a mixture of the ester **1** (5 g, 25 mmol) and 6% of Aliquat® 336 (715 mg, 1.5 mmol) was added Bu^{t}OK (3.3 g, 25 mmol, 1 equiv.) under magnetic stirring over 15 min; alkyl bromide (25 mmol, 1 equiv.) was then added slowly. The flask was left under the experimental conditions (time and temperature) indicated in

Table 2 Dealkoxycarbonylation of esters **1** and **2**[a]

	Krapcho conditions	Yield (%)	Hydrolysis[c] saponification	$LiBr–H_2O–NBu_4Br$ Microwave	Yield (%)	T/°C[d]
1	$DMSO–H_2O$, 3 h, 155 °C	87[b]		8 min, 30 W	96	138
2a	$CaCl_2–H_2O$, DMSO, 150 °C	20	42	15 min, 30 W	94	160
2b			42	20 min, 45 W	89	167
2c			40	20 min, 90 W	87	186

[a] Yields based on isolated **3**. [b] From ref. 15. [c] H_3O^+, 120 °C, 2 h. [d] Final temp.

Table 3 Dealkoxycarbonylation of **2a**[a]

	Microwave[b]		Oil bath	
t/min	**2a** (%)	**3a** (%)	**2a** (%)	**3a** (%)
15	0	94	100	0
60			64	22
180			0	60

[a] $LiBr–H_2O–NBu_4Br$ (2:2:1 equiv.), no solvent, 160 °C. [b] Focused system.

Table 1. Finally, the mixture was diluted with ethyl acetate (50 cm^3) and filtered on Florisil (10 g). The crude products were analysed by GC with an internal standard and distilled under reduced pressure and characterised by MS and ^1H NMR [δ 1.9 (t or q, J, α-CH_2 6.5 Hz)]. B.p.s: **2a** 76–78 °C/0.2 mmHg; **2b** 96–98 °C/0.5 mmHg; **2c** 110–112 °C/1.0 mmHg.

2-Alkylcyclohexanones.—A mixture of lithium bromide (1.73 g, 20 mmol), tetrabutylammonium bromide (323 mg, 1 mmol), water (360 mm^3, 20 mmol) and ethyl 1-alkyl-2-oxocyclohexanecarboxylate **2** (10 mmol) was placed in a Pyrex tube. The tube was then introduced into a Maxidigest MX 350 Prolabo microwave reactor fitted with a rotational system. Microwave irradiation was carried out for a suitable power and time (see Table 2). An approximate final temperature was measured by introducing a digital thermometer at the end of irradiation. The mixture was cooled to ambient temperature. After elution with ethyl acetate (50 cm^3) and subsequent filtration on Florisil, organic products were analysed by GC and finally purified by chromatography on silica gel (pentane–ethyl acetate, 95:5) and were characterised by MS, ^1H NMR (loss of CO_2Et) and comparison with authentic samples.

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