Solid–Liquid Phase-transfer Catalysis without Solvent: Selective Mono- and Di-alkylation of Benzyl Methyl Ketone

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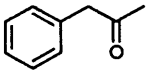
The alkylation of benzyl methyl ketone **1** has been performed by phase-transfer catalysis without solvent. Excellent yields of mono- **2** and di-alkyl derivatives **3** and **4** were obtained through general, selective and mild conditions.

Alkylation of ketones frequently requires the use of strong bases in inert solvents.[1,2] Phase-transfer catalysis (PTC) gives good results but some problems still remain, *viz.* non-effective control of the mono/dialkylation ratio and low yields.[3,4] These problems are solved by using complicated or toxic phase-transfer agents.[5]



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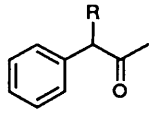
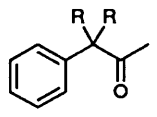
Several procedures have been described for the alkylation of benzyl methyl ketone (BMK) **1**. Methylation has been performed using methyl iodide, but this requires an equimolecular amount of phase-transfer agent.[6] Makosza[7] performed the monoalkylation by liquid–liquid PTC using alkyl, benzyl and allyl halides, and triethylbenzylammonium chloride with good results. Finally, excellent yields were obtained using complex and non-commercially available phase-transfer agents such as α-phosphoryl sulfoxides,[8] pyridine sulfoxides,[9] 1,3,5-triazine polyethers[10] or polymer-supported phosphonium salts.[11]

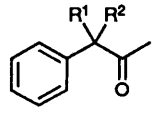
We have studied the alkylation of BMK by PTC in the absence of solvent. This method has several advantages: it affords high yields under very mild conditions, and selectivity is obtained in many substrates, in addition to easy work-up.[12] The selective preparation of monoalkyl and symmetrical and unsymmetrical dialkyl derivatives is now described.



2 a; R = Me
b; R = Et
c; R = Bu
d; R = C_8H_{17}
e; R = $C_{16}H_{33}$
f; R = CH_2Ph
g; R = $CH_2CH{=}CH_2$
h; R = $CH_2C{\equiv}CH$
i; R = Pr^i



3 a; R = Me
c; R = Bu
f; R = CH_2Ph
g; R = $CH_2CH{=}CH_2$
h; R = $CH_2C{\equiv}CH$



4 a; R^1 = $CH_2C{\equiv}CH$, R^2 = $CH_2CH{=}CH_2$
b; R^1 = $CH_2CH{=}CH_2$, R^2 = CH_2Ph
c; R^1 = Me, R^2 = CH_2Ph

Results

Monoalkylation of BMK.—Table 1 summarizes the results of the monoalkylation of BMK. Reactions were performed at room temperature with tetrabutylammonium bromide (TBAB) (10 mmol/mol), and alkyl halide:BMK:base (1:1:2) mole proportions. No solvent was used during the reactions.

Under these conditions, exclusive monoalkylation is achieved. However, 30% of the dialkylated product was obtained with allyl bromide (entry 9) and a similar result was expected with prop-2-ynyl bromide. Exclusive monoalkylation was obtained by using a 1:1 ketone:base mole ratio (entries 10 and 11). These results are explained by considering the high reactivity and the small steric size of these halides. These results were not observed with benzyl bromide, which has similar reactivity but probably higher steric hindrance.

Yield decreased to 80% with octyl bromide (entry 5). This could be explained by considering the lower reactivity of this halide and the existence of side reactions. Surprisingly, however, excellent yields were obtained when using potassium hydroxide with butyl and hexadecyl bromides (entries 3 and 7). As we previously described with less reactive halides,[12] the use of a stronger base, potassium *tert*-butoxide, gave excellent results with octyl bromide (entry 6).

Reaction with isopropyl bromide afforded a 10% yield of the *O*-alkylated product (entry 12), as expected from use of a secondary halide.[13] A similar result was obtained by Makosza[7] but with a lower yield.

Dialkylation of BMK.—Dialkylated BMKs have been previously prepared in good yields (60–80%) by dialkylation of BMK with an excess of alkyl halide or by alkylation of monoalkylated BMKs.[7]

We have prepared symmetrically disubstituted BMKs **3** by using both strategies. Table 2 shows the results obtained with an excess of alkylation agent. Considering the monoalkylation, the optimal ketone:alkyl halide:base mole proportions would be 1:2:3. For dialkylation these proportions have been modified only when complete transformation of the monoalkylated BMKs was not observed, or to minimize the effect of evaporation when using methyl iodide (entry 2).

The low reactivity of butyl bromide, together with the low accessibility of the monoalkyl derivative due to steric hindrance, does not permit complete transformation into the dialkylated product (entry 3) even when the temperature was increased (entry 4).

Dialkylations were performed in two steps but without isolation of the intermediate monoalkyl derivative (Table 3). A large amount of base is needed because water produced in the first deprotonation solvates the hydroxide ion hence reducing

Table 1 Preparation of monosubstituted BMKs **2**

Entry	Product	R	X	Proportions[a]	Base	**2**:**3**	**2** (%)[b]	Lit. (%)
1	**2a**	Me	I	1:1:2	KOH	100:0	95	96[9]
2	**2b**	Et	I	1:1:2	KOH	100:0	94	97[9]
3	**2c**	Bu	Br	1:1:2	KOH	100:0	92	93[17]
4	**2c**	Bu	Br	1:1:1	Bu^{t}OK	100:0	*c*	
5	**2d**	C_8H_{17}	Br	1:1:2	KOH	100:0	80	
6	**2d**	C_8H_{17}	Br	1:1:1	Bu^{t}OK	100:0	98	
7	**2e**	$C_{16}H_{33}$	Br	1:1:2	KOH	100:0	92	
8	**2f**	$PhCH_2$	Br	1:1:2	KOH	100:0	96	77[7]
9	**2g**	CH_2=$CHCH_2$	Br	1:1:2	KOH	70:30	*c*	
10	**2g**	CH_2=$CHCH_2$	Br	1:1:1	KOH	100:0	90	85[7]
11	**2h**	C≡CCH_2H	Br	1:1:1	KOH	100:0	90	70[16]
12	**2i**	Pr^i	Br	1:1:2	KOH	100:0	87[d]	43[7]

[a] Ketone:halide:base mole proportions. [b] Isolated product. [c] Not isolated. [d] 10% of *O*-alkylation product was also obtained.

Table 2 Preparation of symmetrically disubstituted BMKs

Entry	Product	RX	Proportions[a]	*t*/h	**2**:**3**	**3** (%)
1	**3a**	MeI	1:4:3	24	50:50	*b*
2	**3a**	MeI	1:3:4	24	0:100	82
3	**3c**	BuBr	1:2:3	24	37:63	60
4[c]	**3c**	BuBr	1:2.5:3	24	48:52	*b*
5	**3f**	$PhCH_2Br$	1:2:3	5.5	0:100	80
6	**3g**	CH_2=$CHCH_2Br$	1:2:3	2.5	7:93	*b*
7	**3g**	CH_2=$CHCH_2Br$	1:2.5:3	2.5	31:69	*b*
8	**3g**	CH_2=$CHCH_2Br$	1:2.5:3	24	0:100	86
9	**3h**	CH≡CH_2Br	1:2.5:3	3	0:100	88

[a] Ketone:halide:base mole proportions. [b] Not isolated. [c] Temperature 60 °C.

Table 3 Preparation of symmetrically disubstituted BMKs **3** in two steps

Entry	Product	RX	Proportions[a]	Ratio[b]	*t*/h	**2**:**3**	**3** (%)
1	**3a**	MeI	1:1.1:2	1.5:1	24	25:75	*c*
2	**3a**	MeI	1:1.1:2	1.5:2	24	18:82	*c*
3	**3a**	MeI	1:1.1:1	1.1:4	24	0:100	73
4	**3f**	$PhCH_2Br$	1:1:2	1:1	72	0:100	54
5	**3f**	$PhCH_2Br$	1:1:2	1.5:1	24	0:100	80
6	**3g**	CH_2=$CHCH_2Br$	1:1:1	1:1	7.5	50:50	*c*
7	**3g**	CH_2=$CHCH_2Br$	1:1:2	1:1	7.5	7:93	70
8	**3h**	HC≡CCH_2Br	1:1:1	1:1	7.5	48:52	*c*
9	**3h**	HC≡CCH_2Br	1:1:1	1:2	24	0:100	64

[a] First addition, ketone:halide:base mole proportions. [b] Second addition, halide:base mole ratio. [c] Not isolated.

Table 4 Preparation of unsymmetrically disubstituted BMKs **4**

Entry	Product	RX	R^2X	Ratio[a]	**4** (%)	Lit. (%)
1	**4a**	CH_2=$CHCH_2Br$	HC≡CCH_2Br	1.2:1.5	84	
2	**4b**	$PhCH_2Br$	CH_2=$CHCH_2Br$	1.2:1.5	88	73[7]
3	**4c**	MeI	$PhCH_2Br$	1.2:2	82	60[7]

[a] Second addition, halide:base mole ratio.

its reactivity. The optimal conditions for monoalkylation were used in the first step. Under these conditions similar results were obtained but with longer reaction times and larger amounts of base.

The preparation of unsymmetrically disubstituted BMKs **4** was performed in two steps but in 'one pot,' by successive addition again of the alkylation agents without isolation of the intermediate monoalkylated BMK (Table 4).

The optical conditions for monoalkylation were used in the first alkylation step but the reaction time was extended to 24 h to assure the complete transformation of BMK. Unsymmetrically disubstituted BMKs have been obtained in good yield and selectively.

Conclusions.—PTC in the absence of solvent affords excellent yields of monoalkylated BMKs. The method is applicable to any alkyl halide from C-1 to C-16 and also to secondary alkyl, benzyl, allyl and prop-2-ynyl halides.

Symmetrically and unsymmetrically disubstituted BMKs are prepared in good yield; only the dibutylated BMK **3c** is not exclusively formed.

Reactions are performed under very mild conditions, at room temperature, and require the use of simple bases and phase-transfer agents, while results are at least comparable with those obtained under more sophisticated conditions.

As we previously reported,[14] this method, based in an interfacial mechanism, permits the use of iodides using catalytic

amounts of quaternary ammonium salts while classical phase-transfer methods require equimolecular amounts of phase-transfer agent.[6]

Experimental

M.p.s were determined in a Gallenkamp capillary apparatus and are uncorrected. Microanalyses were performed at the Centro Nacional de Química Orgánica, C.S.I.C., Madrid, Spain. IR spectra were recorded with a Philips PU 9500 spectrophotometer. ^{1}H NMR spectra ($CDCl_3$) were recorded in a Bruker AW-80 (80 MHz) with $SiMe_4$ as internal standard. *J*-Values are given in Hz. Analytical TLC was performed on DC-Alufolien silica gel 60 F_{254} (Merck). Preparative TLC (PLC) was performed on 20 × 20 cm plates of 2 mm thickness silica gel 60 F_{254} (Merck). Silica gel 60 (70–230 mesh) (Merck) was used in column chromatography.

Monoalkyl BMKs **2a**–i (*Table 1*).—In a round-bottom flask were stirred BMK **1** (25 mmol), finely ground potassium hydroxide or potassium *tert*-butoxide, and TBAB at room temperature for 1 h [similar results were obtained using an ultrasonic bath (50 Hz, 150 W) for 20 min]. The appropriate alkyl halide was added and the mixture was stirred for the required time (Table 1). Extraction with diethyl ether (2 × 50 cm^3), removal of the solvent and distillation afforded the pure products.

3-*Phenylbutan*-2-*one* **2a**. B.p. 108–110 °C/21 mbar* (lit.,[15] 106–110 °C/22 mbar); ν_{max}(liquid)/cm^{-1} 1712 (C=O); δ_H 1.35 (3 H, d, *J* 7, CH*Me*), 2.01 (3 H, s, COMe), 3.71 (1 H, q, C*H*Me) and 7.2–8.0 (5 H, m, Ph).

3-*Phenylpentan*-2-*one* **2b**. B.p. 116–118 °C/25 mbar (lit.,[15] 116–123 °C/23 mbar); ν_{max}(liquid)/cm^{-1} 1710 (C=O); δ_H 0.81 (3 H, t, *J* 7, CH_2*Me*), 1.4–2.4 (2 H, m, CH_2Me), 2.01 (3 H, s, COMe), 3.50 (1 H, t, C*H*CH_2) and 7.2–8.0 (5 H, m, Ph).

3-*Phenylheptan*-2-*one* **2c**. B.p. 142–144 °C/25 mbar (lit.,[15] 131–135 °C/16 mbar); ν_{max}(liquid)/cm^{-1} 1710 (C=O); δ_H 0.7–2.3 (9 H, m, Bu), 2.03 (3 H, s, COMe), 3.58 (1 H, t, *J* 7, C*H*CH_2) and 7.2–7.6 (5 H, m, Ph).

3-*Phenylundecan*-2-*one* **2d**. B.p. 110–112 °C/0.15 mbar; ν_{max}(liquid)/cm^{-1} 1710 (C=O); δ_H 0.6–1.7 (17 H, m, C_8H_{17}), 2.00 (3 H, s, COMe), 3.58 (1 H, t, *J* 7, C*H*CH_2) and 6.9–8.0 (5 H, m, Ph); *m/z* M^+, ($C_{17}H_{26}O$) 246.4 (Found: C, 82.65; H, 10.85. $C_{17}H_{26}O$ requires C, 82.87; H, 10.63%).

3-*Phenylnonadecan*-2-*one* **2e**. M.p. 34.5–35 °C; b.p. 156–158 °C/0.03 mbar; ν_{max}(liquid)/cm^{-1} 1702 (C=O); δ_H 0.6–2.1 (33 H, m, $C_{16}H_{33}$), 1.99 (3 H, s, COMe), 3.52 (1 H, t, *J* 7, C*H*CH_2) and 7.0–8.1 (5 H, m, Ph); M^+, ($C_{25}H_{42}O$) 358.6 (Found: C, 83.5; H, 11.8. $C_{25}H_{42}O$ requires C, 83.73; H, 11.80%).

3,4-*Diphenylbutan*-2-*one* **2f**. B.p. 184–186 °C/25 mbar (lit.,[15] 119–122 °C/1 mbar); ν_{max}(liquid)/cm^{-1} 1710 (C=O); δ_H 1.91 (3 H, s, COMe), 2.7–3.1 (1 H, dd, *J* 7.2 and 13.8, CHC*H*), 3.2–3.6 (1 H, dd, *J* 7.2 and 13.8, CHCH*H*), 3.86 (1 H, t, *J* 7.2, C*H*CH_2) and 6.7–7.7 (10 H, m, Ph).

3-*Phenylhex*-5-*en*-2-*one* **2g**. The isolation was performed by PLC, using light petroleum (50–70 °C)–ethyl acetate (95:5); b.p. 128–130 °C/26 mbar (lit.,[15] 119–121/15 mbar); ν_{max}(liquid)/cm^{-1} 1638 (C=C) and 1714 (C=O); δ_H 2.02 (3 H, s, COMe), 2.00–3.01 (2 H, m, CHCH_2CH=), 3.67 (1 H, t, *J* 7, C*H*CH_2), 4.80–5.14 (2 H, m, CH=CH_2), 5.47–5.91 (1 H, m, C*H*=CH_2) and 7.23 (5 H, m, Ph).

3-*Phenylhex*-5-*yn*-2-*one* **2h**. B.p. 74–76 °C/0.15 mbar (lit.,[16] 112–113 °C/2 mbar); ν_{max}(liquid)/cm^{-1} 1720 (C=O), 2120 (C≡C) and 3290 (≡CH); δ_H 1.85 (1 H, t, *J* 2.4, C≡CH), 2.02 (3 H, s, COMe), 2.24–3.10 (2 H, m, CHCH_2), 3.85 (1 H, t, *J* 7, C*H*CH_2) and 7.25 (5 H, m, Ph).

4-*Methyl*-3-*phenylpentan*-2-*one* **2i**. Separation from the *O*-alkylated product was performed by column chromatography using light petroleum (50–70 °C)–ethyl acetate (99:1). The product had b.p. 114–116 °C/15 mbar (lit.,[7] 89–90 °C/6 mbar); ν_{max}(liquid)/cm^{-1} 1708 (C=O); δ_H 0.64 and 0.96 [6 H, 2 d, *J* 6.3, CHMe_2], 2.04 (3 H, s, COMe), 2.08–2.62 [1 H, m, C*H*Me_2]; 3.28 (1 H, d, *J* 10.4, CHCO) and 7.25 (5 H, m, Ph).

Dialkylated BMKs **3**.—*Method A* (*Table 2*). In a round-bottom flask were placed BMK **1** (10 mmol), TBAB and potassium hydroxide and the flask was placed in an ultrasonic bath for 20 min. The mixture was cooled to 0 °C, the appropriate halide was added, and the reaction mixture was stirred at room temperature for the required time (see Table 2). The reaction mixture was extracted with diethyl ether (2 × 25 cm^3) and the solvent was removed under reduced pressure. PLC [light petroleum (50–70 °C)–ethyl acetate (99:1)] afforded the pure products.

Method B (*Table 3*). The first step was performed as in method A. After 24 h, a second addition of base and alkyl halide was performed and the mixture was stirred for the required time. Isolation was performed as in method A.

3-*Methyl*-3-*phenylbutan*-2-*one* **3a**. B.p. 125–127 °C/20 mbar (lit.,[7] 100 °C/15 mbar); ν_{max}(liquid)/cm^{-1} 1711 (C=O); δ_H 1.45 (6 H, s, Me_2), 1.90 (3 H, s, COMe) and 7.0–7.6 (5 H, m, Ph).

3-*Benzyl*-3,4-*diphenylbutan*-2-*one* **3f**. M.p. 80–82 °C (from MeOH) (lit.,[7] 82–84 °C); ν_{max}(KBr)/cm^{-1} 1708 (C=O); δ_H 2.00 (3 H, s, COMe), 3.30 (4 H, s, CH_2Ph) and 6.6–7.6 (15 H, m, Ph).

3-*Allyl*-3-*phenylhex*-5-*en*-2-*one* **3g**. B.p. 118–120 °C/1 mbar (lit.,[7] 138–141 °C/8 mbar); ν_{max}(liquid)/cm^{-1} 1639 (C=C) and 1708 (C=O); δ_H 1.90 (3 H, s, COMe), 2.70 [d, 4 H, *J* 6.6, (CH_2CH=)$_2$], 4.85–5.75 [m, 6 H, (CH=CH_2)$_2$] and 7.0–7.6 (5 H, m, Ph).

3-*Phenyl*-3-(*prop*-2-*ynyl*)*hex*-5-*yn*-2-*one* **3h**. B.p. 143–145 °C/0.1 mbar; ν_{max}(liquid)/cm^{-1} 1708 (C=O), 2120 (C≡C) and 3296 (≡CH); δ_H 1.90 (2 H, t, *J* 2.8, ≡CH), 1.95 (3 H, s, COMe), 3.02 (4 H, d, *J* 2.8, CH_2C≡) and 7.0–7.6 (5 H, m, Ph); M^+, ($C_{15}H_{14}O$) 210.27 (Found: C, 85.7; H, 6.65. $C_{15}H_{14}O$ requires C, 85.68; H, 6.71%).

Unsymmetrically Dialkylated BMKs **4** (*Table 4*).—In a round-bottom flask were mixed BMK **1** (10 mmol), TBAB and the appropriate base, and the flask was placed in an ultrasonic bath for 20 min, then the appropriate halide was added and the mixture was stirred at room temperature for 24 h. The second halide, base and TBAB were added at this time and, after 20 min in an ultrasonic bath, the mixture was stirred at room temperature for 24 h. Isolation was performed as in method A.

2-*Phenyl*-3-(*prop*-2-*ynyl*)*hex*-5-*en*-2-*one* **4a**. B.p. 118–120 °C/0.15 mbar; ν_{max}(liquid)/cm^{-1} 1640 (C=C), 1708 (C=O), 2118 (C≡C) and 3292 (≡CH); δ_H 1.85–2.00 (4 H, m, ≡CH and Me), 2.72–3.12 (4 H, m, 2 × CH_2), 4.92–5.65 (3 H, m, CH=CH_2) and 7.0–7.5 (5 H, m, Ph); M^+ ($C_{15}H_{16}O$), 212.29 (Found: C, 84.7; H, 7.5. $C_{15}H_{16}O$ requires C, 84.86; H, 7.59%).

3-*Benzyl*-3-*phenylhex*-5-*en*-2-*one* **4b**. M.p. 63–65 °C (from MeOH) (lit.,[7] 64–66 °C); ν_{max}(KBr)/cm^{-1} 1639 (C=C) and 1707 (C=O); δ_H 1.97 (3 H, s, COMe), 2.67 (2 H, d, *J* 7, CH_2CH=), 3.40 (2 H, s, CH_2Ph), 4.95–5.80 (3 H, m, CH=CH_2) and 6.5–7.7 (10 H, m, Ph).

3-*Methyl*-3,4-*diphenylbutan*-2-*one* **4c**. B.p. 156–158 °C/1 mbar (lit.,[7] 112 °C/0.1 mbar); ν_{max}(liquid)/cm^{-1} 1709 (C=O); δ_H 1.38 (3 H, s, Me), 1.95 (3 H, s, COMe), 3.18 (2 H, s, CH_2) and 6.6–7.2 (10 H, m, Ph).

* 1 mbar = 10^2 Pa, ≈0.75 mmHg.

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