Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.76; H, 8.13.

6-Bicyclo[3.2.1]octanone 7. Lithium (20 mg, 3 mmol) was dissolved in 40 mL of liquid ammonia at −40 °C under nitrogen, and a solution of 100 mg (0.4 mmol) of ketone **2** (**6**) in 5 mL of dry tetrahydrofuran was added over a 5-min period to the stirring mixture. The stirring was continued for 10 min. Enough ammonium chloride was added to discharge the color of the mixture and the ammonia was allowed to evaporate. Sulfuric acid solution, 25 mL of 2%, was added and the mixture extracted with chloroform. The extract was washed with water, dried, and evaporated. Chromatography of the residue and elution with 50:1 hexane–ethyl acetate gave 90 mg (90%) of liquid ketone **7**: ^{1}H NMR δ 0.99 (s, 3, Me), 2.10 (s, 2, benzyl H), 2.72 (s, 2, $COCH_2$), 7.0–7.4 (m, 5, Ar H).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.06; H, 8.98.

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Registry No. *syn*-**1**, 99885-24-2; *anti*-**1**, 99885-25-3; **2**, 62701-58-0; **3**, 62733-87-3; **4a**, 33235-14-2; *syn*-**5a**, 99885-18-4; *anti*-**5a**, 99885-19-5; *syn*-**5b**, 99885-20-8; *anti*-**5b**, 99885-21-9; *syn*-**5b** (acid chloride), 99885-22-0; *anti*-**5b** (acid chloride), 99885-23-1; *syn*-**5c**, 99885-27-5; *anti*-**5c**, 99885-28-6; **7**, 99885-26-4; 3-methyl-2-cyclohexenone, 1193-18-6; benzyltriphenylphosphonium chloride, 1100-88-5.

Solid–Liquid Phase-Transfer Catalysis without Solvent: Mild and Efficient Conditions for Saponifications and Preparations of Hindered Esters

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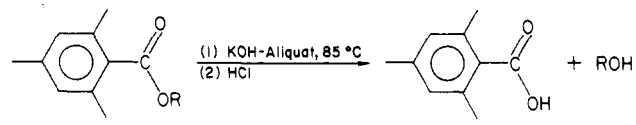
Recently, we reported that, when used in the absence of organic solvent, the "solid KOH–Aliquat 336 (2%) system" was an efficient basic agent which allowed generating in situ (for subsequent alkylations) oxyanions from acids[1] and aliphatic[2] or aromatic alcohols[3,4] and which also promoted β-elimination from secondary halides.[5]

In this work, we attempted to test the efficacy of this basic system for the difficult problem of hindered ester hydrolysis (saponifications). To this purpose, the hydrolysis of mesitoic esters constitutes a classical test to evaluate the ability of a basic system to act as a strong nucleophile toward an ester carbonyl group. This study is of prime interest for a great need still exists for efficient and mild methods, since current procedures suffer from many disadvantages connected to poor yields or cost and toxicity of solvents and catalysts (crown ethers, cryptates, ...).

In the course of the present study, we have extended some previous experiments on carboxylate alkylations[1] to the improvement of hindered ester synthesis also in need of efficient and mild methods[6,7] since a number of useful and reliable methods are not suitable in this case.

Table I. Saponification of Mesitoic Esters 1a and 1d



(10 mmol)

1a, R = CH_3
d, R = n-C_8H_{17}

ester	mol equiv of KOH	time, h	isolated yield, %
1a	2	5	70
	5	2	80
	5	5	93
1d	5[a]	24	80
	5	2	53
	5	5	87[b]

[a] 60 °C. [b] An isolated yield of 83% in n-octanol was obtained.

Results and Discussion

Saponification of Mesitoic Esters. It was shown using oxygen-18 labeled experiments that, even in the absence of organic solvent, the mechanism consists of a nucleophilic attack by hydroxide ion on the carbonyl carbon of mesitoic esters.[11]

Thus, in our hands, methyl and octyl mesitoate (**1a** and **1d**) saponifications have been performed without organic solvent in the presence of powdered KOH (as a commercial base containing about 15% water) and 2% Aliquat 336[8] which mainly consists of methyltrioctylammonium chloride. These are assumed to be solid–liquid phase-transfer catalysis (PTC) conditions where neat esters constitute the organic liquid phase. The main results are listed in Table I.

Our attempts at saponification of hindered esters **1a** and **1d** are very fruitful, and very good yields of acids are obtained (93% and 87%, respectively). The best results are reached when the saponifications are performed at 85 °C for 5 h using 5 mol equiv of powdered KOH + 2% Aliquat 336 (third and sixth entries).

In order to appreciate the efficiency of our basic system, we have collected in Table II the best results described until now. It is clear from this table that the "solid KOH–Aliquat" system is very attractive: (1) From a reactivity point of view, it is one of the most efficient for obtaining good yields under rather mild conditions. These conditions constitute a large improvement when compared to the literature methods which need stoichiometric amounts of crown ethers or cryptands in toluene[9,10] or the prior and rather difficult preparations of reagents such as "anhydrous KOH"[11] or PEG grafted to a cross-linked polystyrene.[12] However, it appears that the KOH/Me_2SO

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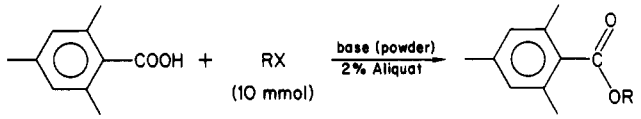
Table II. Comparative Efficiencies of Various Basic Systems for Saponification of Methyl Mesitoate (1a)

basic system (activated KOH)	solvent	temp, °C	time, h	isolated yield, %	ref
KOH + dicyclohexyl 18-crown-6	toluene	74	31	58	9
KOH + cryptand [2.2.2] (1 equiv)	toluene	25	12	70	10
	Me_2SO	25	0.1	*a*	10
anhydrous KOH (from KO-*t*-Bu + H_2O)	Et_2O	20	72	72	11
aq NaOH + Aliquat (classical liq–liq PTC)	light petroleum	20	1	9	12
KOH + alumina (dispersion)	toluene	20	45	60	13
aq KOH + PEG grafted to cross-linked polystyrene (10%) triphase catalysis	none	70	72	81	14
KOH + Aliquat (2%)	none	85	5	93	this work

[a] Yield is not indicated; half-time reaction is about 1 min using a saturated solution of KOH in Me_2SO (10^{-3} M) and 1 equiv of [2.2.2].

Table III. Ester Formation from Mesitoic Acid and Different RX in the Presence of Base and Aliquat 336



1a, R = CH_3
b, R = C_2H_5
c, R = C_4H_9
d, R = C_8H_{17}
e, R = $C_{16}H_{33}$

no.	RX	base	temp, °C	time, h	yield, % GLC	yield, % isolated
7	CH_3I	KOH	20	1	100	98
8	C_2H_5Br	KOH	60	1	100[a]	98
9	$(C_2H_5)_2SO_4$	KOH	60	1	69	
10	*n*-C_4H_9Br	KOH	60	2	82	
11		KOH	85	2	98	88
12	*n*-$C_8H_{17}Br$	KOH	60	5	90	
13		KOH	85	2	100	94
14		KOH	85	5	72	
15		$KHCO_3$	85	2	55	
16		K_2CO_3	85	2	100	88
17	*n*-$C_{16}H_{33}Br$	KOH	85	8	84	
18		K_2CO_3	85	8	100	88

[a] Without Aliquat: 3%.

(10^{-3} M) + 2.2.2 (1 equiv) is superior.[10] (2) From workup simplifications and economic points of view, it is obvious that the present system is the best by far when compared to the others. It does not need any prior preparation of reactants or extraction and washing steps due to solvent use, and it avoids the utilization of expensive or toxic solvents or reagents.

Preparation of Mesitoic Esters. As a generalization to our previous work[1] concerning simple aromatic esters, a number of typical mesitoic esters were prepared in the absence of organic solvent under solid–liquid PTC conditions. The reactions were performed with stoichiometric amounts of mesitoic acid (2,4,6-trimethylbenzoic acid) and an alkylating agent in the presence of an excess (2.5 equiv/mol) of a powdered base (KOH or for comparison purposes $KHCO_3$ or K_2CO_3) and 2% mol Aliquat 336. The main results are given in Table III.

From the results of Table III, all the mesitoic esters **1a–e** can be prepared in high yields (isolated yields ≥ 88%) under mild conditions, with a very easy workup and without the presence of added organic solvent during the reactions (i.e., economical conditions). There is great potential for such a solvent-free solid–liquid PTC technique in organic synthesis. For comparison purposes, Table IV shows the best usual preparations of short chains mesitoic esters **1a–c**.

The present procedure noticeably improves and simplifies the synthesis of mesitoic esters. The previous procedures generally dealt with alkylation reactions (cf. Table IV) or transesterifications performed with diethyl (trichloromethyl)phosphonate,[24] 2-chloro-3,5-dinitropyridine,[25] or *S*-2-pyridyl thioates in the presence of $CuBr_2$ in acetonitrile.[7]

The essential role of catalytic amounts of tetraalkylammonium salt (Aliquat 336) was again emphasized since only 3% of **1b** is obtained in its absence vs. 98% in its

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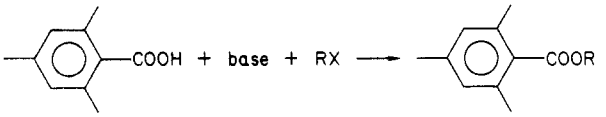
Table IV. Some Recent Preparations of Mesitoic Esters



system base–solvent	RX	time, h	temp, °C	yield,[a] %	ref
	Compound **1a**				
KOH–Aliquat 2%	CH_3I	1	20	(98)	this work
KOH–HMPA/EtOH (1:1)	CH_3I	0.5	25	96	15
NaOH–HMPA	CH_3I (4 equiv)	0.2	25	99	16
DBU[b]–CH_3CN	CH_3I	1	25	(96)	17
K_2CO_3–acetone	$(CH_3)_2SO_4$	1	56	95	18
CH_2Cl_2	Me_3O^+, BF_4^-	24	25	(90)	19
	Compound **1b**				
KOH–Aliquat 2%	C_2H_5Br	1	60	(98)	this work
NaOH–HMPA	C_2H_5I (4 equiv)	0.2		96	20
K_2CO_3–acetone	C_2H_5I	16	56	100	21
Resin AG1-8X–CH_3OH	C_2H_5I	20	65	(94)	21
K_2CO_3–silica gel $Bu_4P^+Br^-$ (gas–liquid PTC)	C_2H_5Br	2 (20 torr)	170	(73)	22
CH_2Cl_2	Et_3O^+,BF_4^-	24	25	(90)	19
DBU[b]–benzene	C_2H_5I	2	25	80	23
	Compound **1c**				
KOH–Aliquat 2%	C_4H_9Br	2	85	(88)	this work
Resin AG1-8X–CH_3OH	C_4H_9Br	25	65	8	21
Resin AG1-8X (Na salt)–toluene/water	C_4H_9Br	24	75	53	21
grafted resin on polystyrene–toluene/water	C_4H_9Br	92	75	93	21

[a] Isolated yields are in parentheses. [b] DBu = 1,5 diazabicyclo[5.4.0]undec-5-ene.

presence during alkylation by ethyl bromide: this fact is confirmation for a solid–liquid PTC process.

With regard to the choice of the base, the use of KOH leads to satisfactory results. However, with rather poor electrophilic reagents (e.g., *n*-$C_{16}H_{33}Br$), the utilization of powdered K_2CO_3 seems to give better results. Quantitative yields are thus obtained (cf. runs 17 and 18). This observation is certainly due to a partial saponification of the product esters **1d** and **1e** by KOH–Aliquat at 85 °C (compare runs 13 and 14).

The results constitute a new illustration in organic synthesis of the potential of reactions performed under solid–liquid PTC conditions in the absence of solvent. They emphasize the exceptional basicity and nucleophilicity toward carbonyl esters group of the [solid KOH + 2% Aliquat 336] system.

Experimental Section

Since the reactions performed were all similar in many respects, only typical reactions are described as specific examples.

Preparation of *n*-Octyl Mesitoate. To a mixture of 0.5 mmol of Aliquat 336 (240 mg) and 25 mmol of finely ground KOH, which contained 15% w/w water (1.61 g) was added 11 mmol of mesitoic acid (1.804 g) in a Pyrex flask. After shaking 5 min, 10 mmol of *n*-octyl bromide (1.93 g) was added, and the mixture was shaken for 5 min at room temperature. The reaction mixture was left, without any shaking or stirring, in an oil bath at 85 °C for 2 h. The organic products were removed with 50 mL of diethyl ether and the mixture was filtered through 5 g of Florisil (to retain mineral salt and Aliquat 336). The esters were analyzed by GLC with an internal standard (butyl phthalate in this case). The product was isolated after solvent evaporation and, eventually, subjected to Florisil (or silica gel) column chromatography with pentane as an eluant to give *n*-octyl mesitoate (2.416 g, 88%). The purity of the ester was checked by GLC, IR, NMR, and analysis.

Saponification of Methyl Mesitoate. Methyl mesitoate (1.78 g, 10 mmol) was added to a Pyrex flask containing a mixture of 1 mmol of Aliquat 336 (480 mg) and 50 mmol of finely ground KOH (3.22 g), which contained 15% w/w water. After 5 min of agitation at room temperature, the flask was left, in an oil bath at 85 °C for 5 h, without any shaking or stirring. Starting ester and Aliquat were extracted into 50 mL of diethyl ether. The product mesitoic acid was obtained after addition of 50 mL of water and acidification with diluted HCl. The precipitate was then removed and dried (1.525 g, 93%). It was characterized by its melting point (153–154 °C)[11] and IR and ^1H NMR spectra.

Spectral Data of Esters. ^1H NMR spectra were recorded with a Perkin-Elmer R 32 spectrometer and chemical shifts are expressed as δ relative to tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 1310.

Methyl mesitoate (1a):[19] NMR ($CDCl_3$) 2.30 (s, 9 H), 3.90 (s, 3 H), 6.90 (s, 2 H); IR (film) 1725 cm^{-1}.

Ethyl mesitoate (1b):[19,23] NMR ($CDCl_3$) 1.35 (t, 3 H), 2.30 (s, 9 H), 4.35 (9, 2 H), 6.90 (s, 2 H); IR (film) 1725 cm^{-1}.

***n*-Butyl mesitoate (1c):**[21] NMR ($CDCl_3$) 0.8–1.9 (m, 7 H), 2.30 (s, 9 H), 4.35 (t, 2 H), 6.90 (s, 2 H); IR (film) 1725 cm^{-1}.

***n*-Octyl mesitoate (1d):** NMR ($CDCl_3$) 0.8–1.9 (m, 15 H), 2.30 (s, 9 H), 4.35 (t, 2 H), 6.90 (s, 2 H); IR (film) 1725 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.26; H, 10.14. Found: C, 77.90; H, 10.19.

***n*-Cetyl mesitoate (1e):** mp 37–38 °C; NMR ($CDCl_3$) 1.0–1.4 (m, 31 H), 2.30 (s, 9 H), 4.35 (t, 2 H), 6.90 (s, 2 H); IR (film) 1725 cm^{-1}. Anal. Calcd for $C_{26}H_{44}O_2$: C, 80.41; H, 11.34. Found: C, 80.54; H, 11.30.

GLC of Esters. Products were analyzed with an internal standard on a 15% SE30 column, length = 1 m, carrier gas N_2, p = 1.2 kg (oven temperature, t): **1a**, 120 °C, 2.82 min; **1b**, 120 °C, 4.12 min; **1c**, 140 °C, 5.52 min; **1d**, 200 °C, 3.46 min; **1e**, 270 °C, 4.81 min.

Registry No. a, 2282-84-0; b, 1754-55-8; c, 70116-77-7; d, 99921-94-5; e, 99921-95-6; MeI, 74-88-4; EtBr, 74-96-4; Et_2SO_4, 64-67-5; BuBr, 109-65-9; *n*-$C_8H_{17}Br$, 111-83-1; *n*-$C_{16}H_{33}Br$, 112-82-3; $(C_8H_{17})_3NMe^+Cl^-$, 5137-55-3; mesitoic acid, 480-63-7.

Calixarenes. 18. Synthesis Procedures for *p*-*tert*-Butylcalix[4]arene

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Calixarenes, which are stoma-containing macrocyclic compounds with shapes ranging from baskets to wheels,[1] were first synthesized by Zinke and Ziegler[2] in 1941 by the

(1) For reviews of the calixarenes, see: Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161; *Top. Curr. Chem.* **1984**, *123*, 1.

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