Alkylation Reactions of Ethyl Malonate, Ethyl Acetoacetate, and Acetylacetone by Gas–Liquid Phase-Transfer Catalysis (G.L.–P.T.C.)

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Malonyl, acetoacetyl, and acetylacetonyl alkylation reactions have been carried out in the gaseous state under gas–liquid phase-transfer catalysis (g.l.–p.t.c.) conditions using potassium carbonate or sodium hydrogencarbonate as the base. No alkali metal was used to generate the reactive anion. No solvents are used in the process, and the reaction mixture requires no stirring. The phase-transfer catalysts which promote the reaction: phosphonium salts, crown ethers, and poly(ethylene glycol) are also the medium in which the reaction occurs; they direct *C*- or *O*-alkylation, as a function of the methylene compound and the alkylating agent used. The malonic ester alkylation using poly(ethylene glycol) gives rise to improved selectivity for *C*-monoalkylation compared with the other catalysts.

Alkylation of active methylene compounds—diethyl malonate and ethyl acetoacetate in particular—is a widely used synthetic procedure the products of which have diverse uses. According to the vast literature on the subject the reactive anion is generated with a strong base, in general sodium alkoxide.[1] Recently, however it has been reported that when dimethylformamide is used as the solvent, even bases such as potassium carbonate can produce the diethyl malonate anion and so promote the subsequent nucleophilic substitution reaction with an alkyl halide.[2]

Also recently reported are methods which use quaternary onium salts and crown ethers as catalysts to promote anion activation. Brändström has described the alkylation in chlorinated solvents of acetoacetic esters and acetylacetone with various electrophiles, when the corresponding anions have quaternary ammonium counter ions.[3] Makosza has described the alkylation of diethyl malonate, ethyl acetoacetate, and ethyl 2-cyanopropionate with some alkyl halides.[4]

We have reported a synthetic method, gas–liquid phase-transfer catalysis (g.l.–p.t.c.), which allows organic synthesis to be carried out in the absence of solvent and without stirring.[5] The gaseous reagents are passed over a solid bed of reactant bearing a phase transfer catalyst. In g.l.–p.t.c., in addition to classical phase transfer catalysts, poly(ethylene glycol) (PEG, also known as Carbowax) is also effective. This low-cost, non-toxic material owes its activity to the fact that it complexes alkali metal cations in a similar way to crown ethers. However, it is less reactive than the latter under liquid–liquid phase-transfer catalysis (l.l–p.t.c.) conditions.[6,‡]

As previously reported, under g.l.–p.t.c. conditions, the reactive anion may even be generated *in situ*, by reaction of the corresponding conjugate acid with a base.[7] Described below is the application of g.l.–p.t.c. to the malonic, acetoacetic, and acetylacetonic alkylations, using an alkaline carbonate or hydrogen carbonate as the base with a phase transfer catalyst adsorbed on it.

Results and Discussion

Equations (1), (2), and (3) show the alkylation of diethyl malonate, ethyl acetoacetate and acetylacetone, respectively, under g.l.-p.t.c. conditions.

In all cases the reaction was run at 170 °C and 20 Torr: under these conditions both the reagents and products are gaseous during the synthesis. In fact, g.l.–p.t.c. requires the compounds to be gaseous since a liquid phase would lower the reaction rate and wash the catalyst away from the solid bed.

$$\mathrm{EtO_2CCH_2CO_2Et + BuX \xrightarrow[cat.]{base} \underset{\textit{C}\text{-alk.}}{(EtO_2C)_2CHBu} + \underset{\textit{C,C}\text{-dialk.}}{(EtO_2C)_2CBu_2}} \tag{1}$$

$$\mathrm{EtO_2CCH_2COMe + BuX \xrightarrow[cat.]{base} \underset{\textit{C}\text{-alk.}}{EtO_2CCHBuCOMe} + \underset{\textit{O}\text{-alk.}}{EtO_2CCH{=}C(OBu)Me} + \underset{\textit{C,C}\text{-dialk.}}{EtO_2CCBu_2COMe} + \underset{\textit{C,O}\text{-dialk.}}{EtO_2CC(Bu){=}C(OBu)Me}} \tag{2}$$

$$\mathrm{MeCOCH_2COMe + BuX \xrightarrow[cat.]{base} \underset{\textit{C}\text{-alk.}}{(MeCO)_2CHBu} + \underset{\textit{O}\text{-alk.}}{MeCOCH{=}C(OBu)Me} + \underset{\textit{C,C}\text{-dialk.}}{(MeCO)_2CBu_2} + \underset{\textit{C,O}\text{-dialk.}}{MeCOCBu{=}C(OBu)Me}} \tag{3}$$

Through a horizontal glass column of volume *ca.* 120 ml containing 50—60 g of solid potassium carbonate (or sodium hydrogencarbonate) previously charged with the catalyst (Carbowax 6000, tetrabutylphosphonium bromide, 18-crown-6, or dibenzo-18-crown-6) was passed a mixture of the active methylene compound and the electrophilic alkylating agent, BuX (generally 1-bromobutane) at a constant liquid flow of 80 ml h^{-1} using a metering pump. The reaction products were collected by condensation at the column outlet.

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[‡] However when PEG is chemically bound to an insoluble support and cannot move into the aqueous phase, it still shows good activity in promoting phase-transfer catalysed reaction[6]

Ethyl Malonate Alkylation.—Table 1 gives the results obtained for Equation (1) on varying the base and the catalyst, using 1-bromobutane as the alkyl halide. Table 2 gives the results using Carbowax as the catalyst and butyl compounds with different leaving groups. In all Tables the conversions refer to the active methylene compound used, while the yields refer to the distribution of alkylated products obtained.

The molar ratio of the reagents (2.5:1.5:1.0, base:alkylating agent:methylene compound) allows higher conversions to be achieved if the products collected are passed through a second time. In fact, when the reaction mixture (containing unchanged 1-bromobutane) is passed over the same bed used for entry 4 in Table 1, under the same conditions, an increase in the *C*-alkylation product is observed (from 22.7 to 38.5%) although there are no traces of any *C,C*-dialkylation.

Ethyl Acetoacetate Alkylation.—Table 3 gives the data obtained using 1-bromobutane as the electrophile in Equation (2), as a function both of the base and the catalyst. Table 4 gives the results with various leaving groups. In this case the carbanion is stabilized by the presence of the carbonyl group. The ease of generating it leads to higher conversions than those achieved in the malonate alkylation. Furthermore, relatively high percentages of *O*-alkylation are observed. The Figure

Table 1. Alkylation of diethyl malonate with 1-bromobutane, as a function of the base and of the catalyst, under g.l.–p.t.c. conditions[a]

Entry	Catalytic bed[b]	Conversion (%)	Product composition (%) *C*	*C,C*
1	K_2CO_3	2.6	100	
2	$NaHCO_3$	9.6	100	
3	K_2CO_3 + Carbowax 6000 (5%)	25.0	100	
4	$NaHCO_3$ + Carbowax 6000 (5%)	22.7	100	
5	K_2CO_3 + $Bu_4P^+Br^-$ (5%)	74.8	69.5	30.5
6	K_2CO_3 + 18-crown-6 (5%)	58.9	83.2	16.8
7	K_2CO_3 + dibenzo-18-crown-6	81.1	86.3	13.7

[a] Alkyl halide:methylene compound:base = 1.5:1.0:2.5 (mol:mol); T = 170 °C; P = 20 Torr; liquid flow, 80 ml h^{-1}. [b] The catalyst proportion is by % weight in the case of Carbowax, and by mol% in the other cases.

Table 2. Alkylation of diethyl malonate with various electrophiles, under g.l.–p.t.c. conditions[a]

Entry	Electrophile	Conversion (%)	Product composition (%) *C*	*C,C*
1	BuCl	1.4	100	
2	BuBr	25.0	100	
3	BuI	43.5	98	2
4	BuOMs	40.0	90	10

[a] Catalytic bed, K_2CO_3 + Carbowax 6000 (5% by weight); alkyl halide:methylene active compound:base = 1.5:1.0:2.5, mol:mol; T = 170 °C; P = 20 Torr; liquid flow, 80 ml h^{-1}.

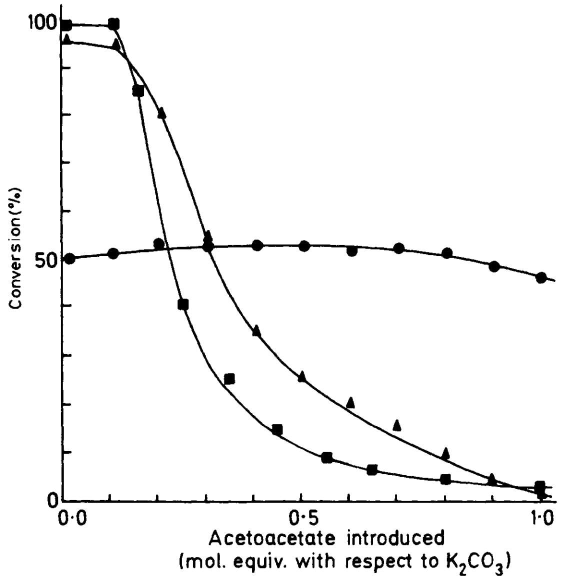

Figure. Alkylation of ethyl acetoacetate with 1-bromobutane, as a function of the number of moles of ester introduced into the column containing K_2CO_3 coated with: 5 mol% 18-Crown-6 (■), 5 mol% $Bu_4P^+Br^-$ (▲), and 5% (by weight) Carbowax 6000 (●), according to equation (2). Ethyl acetoacetate: 1-bromobutane = 1.0:1.5, mol:mol; T = 170 °C; P = 20 Torr

Table 4. Alkylation of ethyl acetoacetate with various electrophiles, under g.l.–p.t.c. conditions[a]

Entry	Electrophile	Conversion (%)	Alkylation product composition *C*	*O*	*C,C*	*C,O*
1	BuCl	7.6	60	31	9	
2	BuBr	52.0	73	25	2	
3	BuI	67.5	72	19	7	2
4	BuOMs	37.6	58	39	2	1

[a] See Table 2, footnote *a*.

Table 3. Alkylation of ethyl acetoacetate with 1-bromobutane, as a function of the base and of the catalyst, under g.l.–p.t.c. conditions[a]

Entry	Catalytic bed[b]	Conversion (%)	Product composition (%) *C*	*O*	*C,C*	*C,O*
1	K_2CO_3	3.0	100			
2	$NaHCO_3$	9.8	100			
3	K_2CO_3 + Carbowax 6000 (5%)	52.0	72.5	25.2	2.3	
4	$NaHCO_3$ + Carbowax 6000 (5%)	16.5	89.7	10.3		
5	K_2CO_3 + $Bu_4P^+Br^-$ (5%)	86.1	17.9	30.2	34.4	17.5
6	K_2CO_3 + 18-crown-6 (5%)	88.6	37.5	29.4	22.0	11.1
7	K_2CO_3 + dibenzo-18-crown-6 (5%)	97.1	40.1	32.1	18.2	9.6

[a] See Table 1, footnote *a*. [b] See Table 1, footnote *b*.

Table 5. Alkylation of acetylacetone with 1-bromobutane, as a function of the base and of the catalyst, under g.l.–p.t.c. conditions[a]

			Alkylation product composition (%)			
Entry	Catalytic bed[b]	Conversion (%)	*C*	*O*	*C,C*	*C,O*
1	K_2CO_3	19.8	58.4	41.6		
2	$NaHCO_3$	19.8	68.4	31.6		
3	K_2CO_3 + Carbowax 6000 (5%)	35.0	54.5	45.5		
4	$K_2CO_3 + Bu_4P^+Br^-$	82.4	16.1	39.0	16.6	28.3
5	K_2CO_3 + 18-crown-6 (5%)	95.5	19.1	47.8	11.0	22.1
6	K_2CO_3 + dibenzo-18-crown-6 (5%)	97.6	32.0	39.3	11.6	17.1

[a] See Table 1, footnote *a*. [b] See Table 1, footnote *b*.

shows the progress of the alkylation of ethyl acetoacetate as a function of three different catalysts. A mixture of the ester and 1-bromobutane was introduced continuously into the column and various samples of the reaction mixture were successively collected and analysed.

Acetylacetonic Alkylation.—Table 5 gives the results for the acetylacetone alkylation [Equation (3)], as a function of the base and the catalyst. When the product mixture collected is passed over the bed a second time (entry 3, Table 5), and then a third time, the conversion increases (from 35.0 to 58.3 and 66.8% respectively), although the product distribution is practically the same. Passing a fresh mixture of the reagents over the bed used in entry 4 of Table 5, under the same conditions affords a 52.4% conversion, with 26.6% *C*-alkylation, 43.0% *O*-alkylation, 15.0% *C,C*-dialkylation, and 15.4% *C,O*-dialkylation products.

It is well known that alkylation of ambident nucleophiles may be directed towards the 'soft' centre by using very polar and protic solvents, or to the 'hard' centre by using aprotic solvents.[8] The selectivity in these cases depends to a great extent on the reactive anion: in the case of the ethyl malonate, ethyl acetoacetate, and acetylacetone reactions, the carbon alkylation products (soft centre) are present when all solvents are used, while in the case of ethyl acetoacetate, and even more for acetylacetone a shift towards oxygen alkylation is observed as the aprotic nature of the solvent is increased.

It can be shown that dialkylation is a function of the strength of the base used; the *C*-monoalkylation product can produce a further anion, which leads in turn to *C,C*-dialkylation or *C,O*-dialkylation.

The leaving group of the electrophile is also important in this regard: all other conditions being equal, increased *C*-alkylation with respect to *O*-alkylation is observed, in the order I > Br > Cl > OMs.[9]

All of these effects are present under g.l.–p.t.c. conditions as well, and help in understanding the mechanism of catalysis. In particular, in agreement with the literature, the leaving group affects the *C,C*:*C,O* ratio of the product distribution (Tables 2 and 4).

Effect of the Base.—The use of potassium carbonate or sodium hydrogencarbonate alone, in the presence of the reagents in the gas phase, leads to little or no conversion. In order to proceed, the reaction requires the presence of an organic liquid phase to absorb the reagents from the gas phase: the reaction will not occur in the gas phase or at the gas–solid interface. The liquid phase is provided by the catalyst in its molten state.

For the reaction to occur, Equations (4) and (5) must be satisfied.

$$HA + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A^- + BH^+ \qquad (4)$$

HA = active methylene compound, B = base

$$A^- + RX \xrightarrow{k_2} AR + X^- \qquad (5)$$

RX = alkyl halide

It is not necessary under g.l.–p.t.c. conditions that Equation 4 should be markedly shifted toward the formation of the reactive anion, as is usually required in classical syntheses. However, the reaction rate is affected: when $k_{-1} \gg k_2$ (as is readily predictable, since both k_1 and k_{-1} involve acid–base proton shifts and are very fast) Equation (6) applies:[10] The assertion

$$k_{obs} = \frac{k_{-1}}{k_1} k_2 = K_{eq} k_2 \qquad (6)$$

that the reaction rates of the reported syntheses under g.l.–p.t.c. conditions follow Equation (6) is based on the following evidence. (*a*) The rate follows the same trend as the pK_a values of the active methylene compounds,[11,*] being lowest for ethyl malonate; (*b*) the rate depends on the strength of the base used (it is lower for hydrogencarbonate than for carbonate); (*c*) the rate follows the same order as classical nucleophilic substitution of alkyl halides: RI > RBr > RCl (Tables 2 and 4).

The conversion also increases with the time that the reaction mixture remains on the catalytic bed, as shown by passing the reaction mixture a second and then a third time through the same bed. The conversion increases, but the distribution of the products does not change: this fact shows that, under conditions of anion-activation by PEG, the carbonate cannot generate the anion of the monoalkylated compound.

Effect of the Catalyst.—In the reactions reported, the effectiveness of the catalyst, based on the conversion achieved, varies in the order: phosphonium salt ~ crown ether > PEG. This order is consistent with previous reports of both classical p.t.c.[12] and in g.l.–p.t.c.[13] However, the cases reported here show less discrimination in the activity of the different catalysts compared with those of esters synthesised using g.l.–p.t.c., for which PEG shows practically no catalytic activity.[13] The high catalytic activity observed here for PEG seems to be related to the softness of the large organic anion involved and to the stabilizing nature of the PEG phase. Even though the present case involves an extra anion (the base), it may be reasonably supposed that on going from hard anions (carboxylates, halides) to soft anions (phenoxides, malonates), discrimination in activity by the catalyst between the various anions tends to disappear.

Under g.l.–p.t.c. conditions, the catalyst regenerates and promotes the reaction by carrying out a double anion transfer between the liquid and the solid phase. The activated base continuously moves from the solid to the liquid phase (the molten catalyst), where it reacts with the active methylene

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* The pK_a values of ethyl malonate, ethyl acetoacetate, and acetylacetone are 13, 11, and 9, respectively.

compound, while the X^- anion progressively produces the solid alkaline halide.[14]

As shown in Tables 1, 3, and 5, the nature of the catalyst affects the ratios *C*:*O* alkylation and mono:dialkylation. This behaviour comes from the fact that under g.l.–p.t.c. conditions the catalyst, dispersed as a liquid film on the surface of the base, is also the medium in which the reaction occurs. PEG, in particular, directs the reaction mainly toward the *C*-monoalkylation product, owing to its polar nature, and to its slight anion activation of the base, which is consequently not able to generate the anion of the *C*-monoalkylated compound.

In its liquid state, the crown ether provides an aprotic, less polar medium, and therefore favours both *O*-alkylation and the *C*,*C*-dialkylated product. This effect is accentuated with tetrabutylphosphonium salts, [8b,d] as shown by the higher percentages of *C*,*C*-and *C*,*O*-dialkylation.

The catalyst used is therefore important both in generating and stabilizing the reactive anion, and in directing the reaction toward *C*- or *O*-alkylation in the case of ambident anions. These effects are not observed in l.l.–p.t.c. and s.l.–p.t.c., since under these conditions the catalyst forms only a small part of the reaction medium.

Experimental

Reagents were obtained commercially and used without further purification. Butyl methanesulphonate was prepared according to the literature.[15] G.l.c. analyses were performed on a Varian Vista 6000 instrument equipped with a CDS 111L integrator. A Superior Electric Type 3552RC pump was used to deliver the reagents in the liquid state to the double-jacket column (40 cm long, 2 cm in diameter) thermostatted with a Lauda NS-HT ultrathermostat.

Preparation of the Catalytic Bed.—The catalyst (0.5 mol) [$Bu_4P^+Br^-$ (17.0 g), 18-crown-6 (13.2 g), dibenzo-18-crown-6 (18.0 g), Carbowax 6000 (6.9 g; corresponding to 5% by weight)] was dissolved in CH_2Cl_2. To the solution was added K_2CO_3 or $NaHCO_3$ (0.95 mol), previously dried in an oven at 120 °C for 2 h. The resulting suspension was evaporated under reduced pressure, and the residue oven-dried at 120 °C for 3 h.

Alkylation of Ethyl Malonate, Ethyl Acetoacetate, and Acetylacetone under G.l.–P.t.c. Conditions.—The column was filled with the catalytic bed (50—60 g, depending on the density of the solid mass) and thermostatted at 170 °C under reduced pressure (20 Torr). A 1.5:1.0 molar ratio mixture of the alkyl halide and the compound to be alkylated was introduced into the column using the pump at liquid flow rate of 80 ml h^{-1}, in a quantity which varied as a function of the quantity of the base in the column, so that the molar ratio between the base and active methylene compound was 2.5. The mixture vapourised at the column inlet, and the gaseous products were collected by condensation at the outlet. The product mixture was analysed qualitatively and quantitatively by gas chromatography (Varaport column containing 5% SE-30; 100—240 °C; 20 °C min^{-1}) by comparison with authentic samples or with known reaction mixtures from classical syntheses.[16]

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