

## Synthetic and Mechanistic Aspects of Gas-Liquid Phase-transfer Catalysis: Carboxylate Esters

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The synthesis of esters from solid alkyl- and aryl-carboxylates and gaseous alkyl halides (RX), that is gas-liquid phase-transfer catalysis (g.l.p.t.c.) is promoted by the classical phase-transfer catalysts, quaternary phosphonium salts. The reaction is run under continuous-flow conditions in a column and the product is collected at the outlet. An investigation of the mechanism of the reaction shows the great importance of the liquid film of melted catalyst in promoting anion exchange between the underlying solid carboxylate salt and the gaseous alkyl halide which diffuses and reacts. This technique does not require the use of organic or aqueous solvents, leads to high conversion into esters for low carboxylate:RX molar ratios, and transforms large quantities of reagents with small volumes of solid bed.

PHASE-TRANSFER catalysis (p.t.c.), both liquid-liquid (l.l.p.t.c.) and solid-liquid (s.l.p.t.c.), has already demonstrated its versatility in producing easily available compounds, as well as those more difficult to prepare.<sup>1</sup> Classical phase-transfer catalysts include quaternary ammonium and phosphonium salts as well as crown ethers and cryptands. These bring the reactive anions into the organic phase in a poorly solvated form, which dramatically boosts reactivity.

New synthetic procedures for p.t.c. are currently being studied which allow the introduction of inorganic solid supports (silica gel, alumina, *etc.*) as promoters of solid solutions with the reagent anions in the presence or absence of organic solvents.<sup>2</sup> On the other hand, nucleophilic substitution reaction between two immiscible phases under continuous-flow conditions are also being studied in a reactor with a fixed bed consisting of a phase-transfer catalyst immobilized on polymeric matrices.<sup>3</sup>

We have recently shown that nucleophilic substitution reactions may occur between the gaseous phase of the organic substrate (alkyl halide) and the solid phase of the nucleophile salt, when the reaction is run in the presence of a phase-transfer catalyst. The observed reaction rate was high enough to allow the reaction to be run under continuous-flow conditions by placing the solid salt in a fixed column and allowing the alkyl halide to flow through. Synthesis in this manner has been described for alkyl halides<sup>4</sup> and phenolic ethers and thioethers.<sup>5</sup>

This paper reports the results obtained in the synthesis of esters using alkyl- and aryl-carboxylates as nucleophile sources.

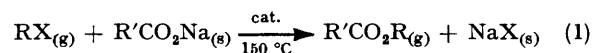
The synthesis of esters offers no great difficulties in the field of organic synthesis. Although there are numerous methods for preparing them, they all involve the use of organic or aqueous solvents. The present method was developed not only because it requires no solvents and so affords an already pure product in a decidedly short time, but also to show the technical and mechanistic differences to classical p.t.c.

In the case of l.l.p.t.c., a large excess of carboxylate is

required (2–10 times) because of the unfavourable partition coefficient between this and the product halide.<sup>6</sup> In s.l.p.t.c., on the other hand, the catalysts most often used are expensive (*e.g.* crown ethers and cryptands).

### RESULTS

As shown in equation (1), the esters were synthesized by introducing an alkyl halide into a column heated to 150 °C.

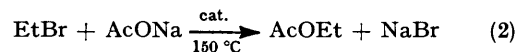


In each case, the alkyl halide was introduced into the column in the liquid phase at a rate of 40 ml/h using a peristaltic pump. The pressure conditions in the column were always such to guarantee that, at the operating temperature, both the alkyl halide and the product ester were gaseous (0.4–760 Torr).

Both the ester and the unchanged halide were condensed by cooling at the column outlet and collected. No by-products were observed using <sup>1</sup>H n.m.r. spectroscopy or g.l.c. The reactions were run in two different cylindrical columns (115 ml volume, 40 cm length and 230 ml volume, 50 cm length); the larger was used for the preparative syntheses reported in Tables 3 and 4 and in the Figure. In all the cases reported, the solid bed was prepared simply by dissolving the catalyst in methanol, adding the solid carboxylate, and completely removing the solvent.

The presence of a reagent bed supporting the inorganic solid proved to be unnecessary if the carboxylic acid or its salt had a melting point greater than 150 °C. However, if an inert, porous dispersing agent was added, the solid bed could be handled more easily before and after the reaction. Table 3 reports, as an example, the synthesis of octylbutyrate, conducted both in the absence and presence of silica gel. The results obtained show satisfactory yields in both cases, although higher absolute quantities of ester may be produced when the bed is not diluted.

The formation of ethyl acetate [equation (2)] was selected as a test reaction to optimize the reaction conditions and the stoichiometric ratios of reagents and to study the reaction



mechanism. The acetate ion is certainly 'harder' than other carboxylate anions, and so its reactivity results are particularly remarkable.

Tables 1 and 2 report the conversions into ethyl acetate with reaction (2) while varying the type of catalyst and its percentage. No conversion was observed in the absence of catalyst. Furthermore, the catalyst activity differed

TABLE 1

Ethyl acetate obtained from sodium acetate and ethyl bromide, as a function of the catalyst used under g.l.p.t.c. conditions <sup>a</sup>

Catalyst <sup>b</sup>	Melting point (°C)	Conversion <sup>c</sup> (%)
Bu <sub>4</sub> P <sup>+</sup> Br <sup>-</sup>	86–88	96
C <sub>16</sub> H <sub>33</sub> P <sup>+</sup> Bu <sub>3</sub> Br <sup>-</sup>	54	86
Bu <sub>3</sub> P <sup>+</sup> MeI <sup>-</sup>	135–136	59
C <sub>16</sub> H <sub>33</sub> P <sup>+</sup> Et <sub>3</sub> Br <sup>-</sup>	145–146	86
C <sub>16</sub> H <sub>33</sub> P <sup>+</sup> Me <sub>3</sub> Br <sup>-</sup>	202–204	0
Et <sub>3</sub> P <sup>+</sup> MeI <sup>-</sup>	323–325	0
18-Crown-6	37–39	32
Carbowax 6 000 <sup>d</sup>	55–62	4
Brij 35 <sup>e</sup>	39–41	3
NaLS <sup>f</sup>	205	0 (2) <sup>g</sup>
Silica gel <sup>h</sup>		20

<sup>a</sup> *T*, 150 °C; sodium acetate, 0.62 mol, 50.9 g; ethyl bromide, 0.42 mol, 45.8 g; flow rate, 40 ml/h. <sup>b</sup> 0.02 Mol. equiv. with respect to the sodium acetate. <sup>c</sup> By <sup>1</sup>H n.m.r. spectroscopy, established by integrating the quadruplets centred at (CCl<sub>4</sub>) 3.40 and 4.06 corresponding to CH<sub>2</sub>Br and CH<sub>2</sub>OAc, respectively. <sup>d</sup> Carbowax 6 000 [polyethylene glycol HO(C<sub>2</sub>H<sub>4</sub>O)<sub>*n*</sub>H, *n* 110–160]; Brij 35 [polyoxyethylene lauryl ether, C<sub>12</sub>H<sub>25</sub>(OCH<sub>2</sub>CH<sub>2</sub>)<sub>23</sub>OH]; NaLS (sodium laurylsulphate) all 10% by weight with respect to the sodium acetate. <sup>e</sup> *T*, 210 °C. <sup>f</sup> The bed was prepared by dissolving sodium acetate (0.42 mol, 34.4 g) in water, adding silica gel (34.4 g) and completely removing the water; ethyl bromide (0.28 mol, 30.5 g).

strikingly according to the type of the catalyst used: from cationic to anionic salt and from cyclic (crown ether) to acyclic polyether (Carbowax and Brij). A striking difference was, moreover, observed for phosphonium salts of melting points greater than and less than the operating temperature. Ammonium salts were not used due to their thermal instability. The thermally stable phosphonium salts were readily recovered in high yields at the end of the reaction.

The Figure shows the conversion into ethyl acetate as a function of the molar ratios of alkyl halide passed through the bed, using a phosphonium salt as catalyst. High and constant conversions were maintained up to 0.7 mol. equiv. of halide. The subsequent rapid decrease may be attributed to the fact that not all the carboxylate is physically accessible to the catalyst with equal facility. After the passage

TABLE 2

Influence of the percentage of Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup> as catalyst in the synthesis of ethyl acetate from sodium acetate and ethyl bromide under g.l.p.t.c. conditions <sup>a</sup>

Catalyst <sup>b</sup> (mol. equiv. × 10 <sup>2</sup> )	Conversion <sup>c</sup> (%)
0.0	0
0.5	43
1.0	76
2.0	96
5.0	96

<sup>a</sup> For reaction conditions see Table 1, footnote *a*. <sup>b</sup> With respect to the sodium acetate. <sup>c</sup> Established by <sup>1</sup>H n.m.r. spectroscopy; see Table 1, footnote *c*.

of 2.0 mol. equiv. of ethyl bromide, the residual sodium acetate in the column was only 3% (Table 4).

With ethyl bromide as the halide, the bromide and iodide tetrabutylphosphonium salts showed comparable activities.

In the latter case, the iodide ion, normally a p.t.c. poison, is removed from the column as ethyl iodide, so that Br<sup>-</sup> and AcO<sup>-</sup> are the only anions remaining in the bed. However, if ethyl iodide is the reagent halide with tetrabutylphosphonium iodide as catalyst, the conversion is always low.

In order to probe the extent of bromide–acetate exchange in the phosphonium salt, according to equation (3), and to



establish the presence or absence of eutectics amongst the four salts, thermal differential analysis was performed on a mixture (50% w/w) of Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup> and AcONa. These salts melt at 87 and 324 °C, respectively. Repetition of the

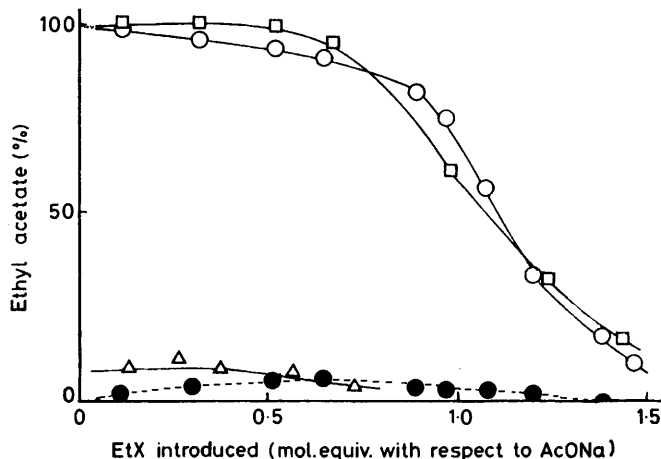


FIGURE Plot of the conversion of EtX into ethyl acetate as a function of the catalyst and of the alkylating agent: □, Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup>, EtBr; △, Bu<sub>4</sub>P<sup>+</sup>I<sup>-</sup>, EtI; ○, Bu<sub>4</sub>P<sup>+</sup>I<sup>-</sup>, EtBr. When the synthesis is carried out under the last of these conditions EtI was also produced, and its % in the collected products is shown by filled circles. For the reaction conditions see Table 1, footnote *a*.

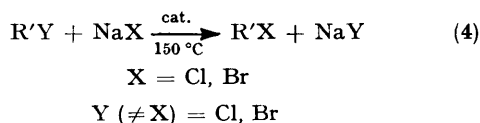
melting–solidification process several times gave no variation in the observed m.p. Moreover, no endothermic process was detected at temperatures below 87 °C and between 87 and 324 °C. Within the instrument's limits of detection, no eutectic points (that should have involved the presence of an acetate anion in the molten state) were observed. Equilibrium (3) is decidedly shifted to the left, as is observed in l.l.p.t.c. where [AcO<sup>-</sup>]/[Br<sup>-</sup>] = 0.05. In any case, the small concentration of Q<sup>+</sup>AcO<sup>-</sup>(l) necessarily present in the reagent bed has a reactivity which allows the reaction to be run under continuous-flow conditions.

Table 3 reports the syntheses of various esters using Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup> as catalyst (0.05 mol. equiv.). In the case of low boiling alkyl halides and for the reactions run at reduced pressure, the observed conversions are higher than the effective yields since part of the alkyl halide could not be collected by condensation at the outlet.

It should be noted that since more than one mole of carboxylate can be placed in the column, approximately 100 g of ester may, on average, be produced in each preparation.

In agreement with equation (1), as the ester is formed the carboxylate in the column is transformed into alkali halide. Since the catalyst does not degrade, subsequent nucleophilic reactions [equation (4)] can be run in the same column with no further manipulation. The results obtained are collected

in Table 4, in which the formation of trace amounts of a new ester, obtained from the small quantities of carboxylate



still in the column, is also reported. The conversions were much higher than those observed when the bed was prepared from commercially available alkali halide.

observed conversion is low and decidedly lower than that reported for potassium iodide under the same conditions.<sup>4b</sup> This is due to the different interactions between the iodide or the acetate and the polar inorganic support, and/or to the difference in nucleophilic reactivity of the two anions.

The polyethers Carbowax 6000 and Brij 35 have been observed to be excellent catalysts for soft anions like phenate, thiophenates, and mercaptides,<sup>5</sup> but give extremely low conversions in this case, since they do not

TABLE 3

Preparative syntheses of esters under g.l.p.t.c. conditions<sup>a</sup>

Expt. No.	Starting compounds	Products <sup>b</sup> (b.p. [°C/mmHg]; $n_D^{20}$ ; ref.)	Conversion <sup>c</sup> (%)	Yield <sup>d</sup> (%)	
1	AcONa	EtBr <sup>e</sup>	AcOEt (77/760; 1.3730; 9)	98	97 (95) <sup>f</sup>
2	AcONa	ClCH <sub>2</sub> CH <sub>2</sub> Cl	AcOCH <sub>2</sub> CH <sub>2</sub> OAc (90/18; 1.4161; 10)	67	58 (55) <sup>f</sup>
3	AcONa	PhCH <sub>2</sub> Cl	AcOCH <sub>2</sub> Ph (99—100/18; 1.5190; 11)	100	95 (94) <sup>f</sup>
4	AcONa	Me[CH <sub>2</sub> ] <sub>3</sub> Br	AcO[CH <sub>2</sub> ] <sub>3</sub> Me (168—170/760; 1.4098; 12)	86	84 (83) <sup>f</sup>
5	PrCO <sub>2</sub> Na	Me[CH <sub>2</sub> ] <sub>3</sub> Cl	PrCO <sub>2</sub> [CH <sub>2</sub> ] <sub>3</sub> Me (128—130/18; 1.4299; 13)	100	90 (87) <sup>f</sup>
6	PrCO <sub>2</sub> Na	Me[CH <sub>2</sub> ] <sub>2</sub> Cl <sup>g</sup>	PrCO <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> Me	61	61 (60) <sup>f</sup>
7	PrCO <sub>2</sub> Na	Me[CH <sub>2</sub> ] <sub>2</sub> Br	PrCO <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> Me	75	68 (65) <sup>f</sup>
8	BzONa	CH <sub>2</sub> =CHCH <sub>2</sub> Br	BzOCH <sub>2</sub> CH=CH <sub>2</sub> (119/16; 1.5193; 14)	100	90 (87) <sup>f</sup>
9	BzONa	BuBr	BzOBu (138/24; 1.4988; 15)	94	82 (80) <sup>f</sup>
10	2-ClC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> Na	EtBr	2-ClC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> Et (137/18; 1.5241; 16)	97	80 (78) <sup>f</sup>
11	4-ClC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	EtBr <sup>h</sup>	4-ClC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> Et (135—137/18; 1.5252; 17)	100	75 (71) <sup>f</sup>
12	2,4,6-Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub> CO <sub>2</sub> H	EtBr <sup>i</sup>	2,4,6-Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub> CO <sub>2</sub> Et (140—142/18; 1.5032; 18)	98	79 (73) <sup>f</sup>

<sup>a</sup> Catalyst, Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup>, 0.05 mol. equiv. with respect to the carboxylate; alkyl halide, 0.67 mol. equiv. with respect to the carboxylate; flow rate, 40 ml/h; T, 150 °C; the absolute quantities of carboxylate were a function of their porosity and density, ranging from 1.2 to 1.3 mol; 20 Torr. <sup>b</sup> The purified products were compared with authentic samples. <sup>c</sup> By n.m.r. spectroscopy, integrating the singlets, doublets, triplets, or quadruplets corresponding to CH<sub>2</sub>X and CH<sub>2</sub>OCO. <sup>d</sup> Established from the weight of the collected product on the basis of the conversion. <sup>e</sup> Atmospheric pressure; catalyst Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup>, see Experimental section. <sup>f</sup> Yield after distillation. <sup>g</sup> Bed mixed with silica gel, 1/1 by weight. <sup>h</sup> Bed prepared with potassium carbonate, as reported in the Experimental section; 0.4 Torr. <sup>i</sup> Bed prepared with potassium carbonate and silica gel, as reported in the Experimental section.

TABLE 4

Reactivity of alkali halides generated by g.l.p.t.c. and commercially available<sup>a</sup>

Reaction	Source of the alkaline halide	Conversion <sup>b</sup> (%)
BuBr $\xrightarrow[cat.]{NaCl}$ BuCl	AcONa + PhCH <sub>2</sub> Cl	42 <sup>c</sup>
BuBr $\xrightarrow[cat.]{NaCl}$ BuCl	AcONa + Cl(CH <sub>2</sub> ) <sub>2</sub> Cl	45 <sup>d</sup>
BuBr $\xrightarrow[cat.]{NaCl}$ BuCl	Commercial <sup>e</sup>	19
PhCH <sub>2</sub> Cl $\xrightarrow[cat.]{NaBr}$ PhCH <sub>2</sub> Br	AcONa + EtBr	72 <sup>f</sup>
PhCH <sub>2</sub> Cl $\xrightarrow[cat.]{NaBr}$ PhCH <sub>2</sub> Br	Commercial <sup>e</sup>	7

<sup>a</sup> For the reaction conditions see Table 1, footnote a; catalyst Bu<sub>4</sub>P<sup>+</sup>Br<sup>-</sup> 0.05 mol. equiv. with respect to the salt. <sup>b</sup> By <sup>1</sup>H n.m.r. spectroscopy. <sup>c</sup> Butyl acetate, 2%. <sup>d</sup> Butyl acetate, 0%. <sup>e</sup> The commercially available NaCl and NaBr were mechanically powdered and the fraction which passed through a sieve of 400 mesh (38 microns) was collected; the beds were prepared according to the typical procedure. <sup>f</sup> Benzyl acetate, 3%.

## DISCUSSION

*Efficiency of the various types of catalysts used in g.l.p.t.c.*

—As shown in Tables 1 and 2, the reaction does not proceed at all in the absence of catalyst.\* Even when the sodium acetate is dispersed on the silica gel, the

\* Because of the high conversions obtained in the presence of a catalyst, this test reaction was run several times, always giving 0% conversion into ethyl acetate.

sufficiently complex the cation of the hard acetate ion. Even the cyclic polyether 18-crown-6, with its much higher complexing power, does not give high conversions.

The phosphonium salts were shown to be much more active than 18-crown-6 and, of all the catalysts tested, were the best for g.l.p.t.c. This shows how capable they are of attacking the crystalline nucleophile and carrying it into the liquid phase to undergo reaction.

Contrary to l.l.p.t.c., the structure of the quaternary salt is not a determining factor in g.l.p.t.c. (such as the nature and length of the alkyl chain bonded to the heteroatom).<sup>7</sup> Indeed, even short alkyl chains like methyl and ethyl do not decrease the activity, since when no aqueous phase is present, no emulsions are formed and the catalyst does not distribute itself between the two phases.

*The term g.l.p.t.c.*—On the other hand, there is a very sharp difference in activities between phosphonium salts with m.p.s greater than and less than the reaction temperature. This clearly demonstrates the importance of the liquid phase which surrounds the solid crystal of the nucleophile. This phase has a double function: (a) it is the medium in which the substitution reaction occurs † promoted by the diffusion of the gaseous alkyl halide) and by the presence of the carboxylate as the counterion

† Unpublished data from this laboratory on C- and O-alkylation ratios in malonic, acetoacetic, and acetylacetic syntheses carried out with this method clearly show that the reaction occurs in a polar, aprotic microenvironment.

in the phosphonium salt); and (b) it promotes anion exchange between the underlying unchanged salt and the halide obtained from the organic substrate.

It might be supposed that the only function of the catalyst is to supply a liquid phase to act as solvent for the nucleophile salt. However, sodium laurylsulphate (NaLS) showed no activity, and that of  $\text{Bu}_4\text{P}^+\text{Br}^-$  was decidedly greater than that of  $\text{Bu}_4\text{P}^+\text{I}^-$ . In particular, comparison of these latter two catalysts, which are probably of similar solubilizing ability, shows that the catalysis involves anion exchange between the two phases (solid and liquid), according to equation (3), in which  $[\text{Q}^+\text{AcO}^-]/[\text{Q}^+\text{Br}^-] > [\text{Q}^+\text{AcO}^-]/[\text{Q}^+\text{I}^-]$ . This is the same as the results obtained from l.l.p.t.c. and s.l.p.t.c.

Although macroscopically, according to equation (1), the reaction is seen as an exchange between a gaseous and a solid phase, at the mechanistic level it is promoted both by a diffusion exchange between the gaseous phases of the reagent and the product ester and the liquid phase, and by the regeneration of the catalyst in its active form by anion exchange between the liquid and solid phases. Referring to the function of the phase-transfer catalyst, one could name this process s.l.p.t.c., but this term may be misleading because it refers to a well-known catalysis process and, moreover, it would not take into account the way in which the reaction occurs.

The process of gas-liquid chromatography has similarities to this technique, and so we prefer to use the name g.l.p.t.c., thus describing the importance of the liquid phase and acknowledging that, for the reaction to proceed, exchange with the solid phase is equally important. On the other hand, this latter exchange is macroscopically quite significant since the catalyst (at 0.02 mol. equiv.), even in the absence of stirring, carries an amount of solid approximately 10 times its own weight. More exactly, as the reaction proceeds, the liquid film at the surface moves towards the inside of the carboxylate crystal.

The alkali halide reaction product remains behind. Deposited by the catalyst itself, it is in a physical form which is much more 'attackable' by the catalyst when it re-uses the previously deposited anion in a second reaction [equation (4)]. This accounts for the different conversions observed into  $\text{PhCH}_2\text{Br}$  and  $\text{BuCl}$  (Table 4) using beds prepared with commercial  $\text{NaBr}$  and  $\text{NaCl}$  and others containing these salts deposited by a previous reaction.\*

#### CONCLUSION

Although this technique offers several advantages, only some of its potential has been demonstrated to date. Its principal characteristics are: (a) no solvent is used; (b) the relatively high temperatures increase reaction rates enough for continuous-flow operation; (c) the reaction product can be collected at the outlet at the desired

\* This high reactivity may also result from a large number of crystalline defects and from the small size of the produced crystals. So far, the X-ray analyses have shown no differences between the commercial and g.l.p.t.c. produced  $\text{NaCl}$ ; the crystals of the produced salt showed, using a microscope, an average size of 5 microns.

degree of purity with no extractions and/or distillations required; (d) the catalyst can be recovered easily (see Experimental section); (e) large quantities of reagents can be transformed with respect to the effective volume occupied by the solid bed; (f) the salt deposited can be used in a subsequent reaction to give a high conversion, with no further handling; (g) since the entire system is isolated from the workplace, the handling of reagents, products, and solid bed is simpler; this is important when dangerous compounds are involved.

#### EXPERIMENTAL

$^1\text{H}$  N.m.r. spectra were recorded on a Hitachi-Perkin Elmer R-24B 60 MHz spectrometer using tetramethylsilane as the internal standard. A Varian series 1440 gas chromatograph and a Masterflex model No. 7013 peristaltic pump were used. Differential thermal analyses were run on a Du Pont 990 thermal analyser. All organic and inorganic reagents were ACS grade and were used with no further purification. The silica gel used was Merck (Art. No. 7734) Kieselgel 60 (70-230 mesh, pore diameter 60 Å, specific surface area 500 m<sup>2</sup>/g). The catalysts were supplied by C. Erba (sodium laurylsulphate), Fluka (Brij 35 and 18-crown-6), and Merck (Carbowax 6000).

*Synthesis of Quaternary Phosphonium Salts.*—All these catalysts were prepared from the corresponding phosphine by reaction with the appropriate alkyl halide.

Tributylhexadecylphosphonium bromide was prepared according to Starks,<sup>8</sup> m.p. 54 °C.

Tetrabutylphosphonium-bromide and -iodide were prepared as previously described.<sup>4b</sup>

Triethyl- and tributyl-phosphine were available commercially.

Trimethylphosphine was prepared in diethyl ether solution by direct distillation of the reaction mixture comprising the Grignard, prepared from methyl iodide with an excess of magnesium in diethyl ether, and phosphorus tribromide.

Hexadecyltrimethylphosphonium bromide was prepared by adding an estimated excess of 1-bromohexadecane to the reaction mixture just described and leaving the mixture to stand at room temperature for 30 days. The white solid was filtered off, washed, and crystallized from methylene dichloride-diethyl ether, to give m.p. 197-200 °C;  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ )  $J$  13.9 Hz,  $\text{P}^+\text{-Me}$  (Found: Br, 21.0. Calc. for  $\text{C}_{15}\text{H}_{42}\text{BrP}$ : Br, 20.95%).

Triethylhexadecylphosphonium bromide was prepared by the reaction of triethylphosphine (11.8 g, 0.10 mol) with 1-bromohexadecane (45.8 g, 0.15 mol) at 60 °C for 48 h. It was crystallized from methylene dichloride-diethyl ether with a yield of 38.1 g (90%), m.p. 145-146 °C;  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ )  $J$  13.5 Hz,  $\text{P}^+\text{-CH}_2\text{Me}$  (Found: Br, 19.0. Calc. for  $\text{C}_{22}\text{H}_{48}\text{BrP}$ : Br, 18.87%).

Tributylmethylphosphonium iodide was prepared by adding methyl iodide (28.2 g, 0.20 mol) to tributylphosphine (20.2 g, 0.10 mol) which was being stirred and cooled in an ice-bath. After 5 h at room temperature the solid mass was crystallized from methylene dichloride-diethyl ether, yield 29.2 g (85%), m.p. 135-136 °C;  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ )  $J$  13.5 Hz,  $\text{P}^+\text{-Me}$  (Found: I, 36.8. Calc. for  $\text{C}_{13}\text{H}_{30}\text{IP}$ : I, 36.86%).

Triethylmethylphosphonium iodide was prepared by adding methyl iodide (28.2 g, 0.20 mol) to triethylphosphine (11.8 g, 0.10 mol) which was being stirred and cooled in an

ice-bath. After 5 h at room temperature the solid mass was crystallized from methylene dichloride-diethyl ether, yield 23.2 g (89%), m.p. 323–325 °C;  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ )  $J$  13.2 Hz,  $\text{P}^+-\text{Me}$ ;  $J$  13.1 Hz,  $\text{P}^+-\text{CH}_2\text{Me}$ ; and  $J$  18.4 Hz,  $\text{P}^+-\text{CH}_2\text{Me}$  (Found: I, 48.5. Calc. for  $\text{C}_7\text{H}_{18}\text{IP}$ : I, 48.79%).

**Preparation of the Catalytic Beds.**—The catalyst was dissolved in methanol, the carboxylate added, and the suspension evaporated to remove the solvent. The solid mass obtained was dried at 130 °C for 15 h.

When carboxylic acid was used instead of its sodium salt, it was added to the methanol solution of the catalyst together with potassium carbonate (2.0 mol. equiv. with respect to the acid). The suspension was then treated as described above.

In the case of 2,4,6-trimethylbenzoic acid, silica gel was also added to the suspension (2 : 1 by weight, with respect to the acid). The addition of a supporting solid was necessary for acids or acid salts of m.p. less than the reaction temperature.

**Ester Synthesis.**—(a) *Typical procedure.* For the sake of brevity, the synthesis of ethyl acetate is described. A column (230 ml) filled with sodium acetate which contained  $\text{Bu}_4\text{P}^+\text{I}^-$  (0.05 mol. equiv.) was run through with ethyl bromide until the original salt was exhausted (see also the Figure, open circles). A substitution reaction was run subsequently on the column. The other reactions differ from this in the equivalents of catalyst used and in that they were run under reduced pressure (Table 3). For the more volatile halides, under conditions of reduced pressure, not all of the unchanged halide was collected by condensation, so that spontaneous purification sometimes occurred during collection of the product ester.

In detail, for ethyl acetate, the column was filled with 130 g of bed composed of sodium acetate (105.1 g, 1.28 mol) and tetrabutylphosphonium iodide (24.9 g, 64 mmol). The liquid ethyl bromide was introduced into the column using a peristaltic pump at a rate of 40 ml/h. Samples of the condensed reaction mixture were collected at the column outlet and analysed by  $^1\text{H}$  n.m.r. spectroscopy. The degree of conversion was established by integrating the quadruplets corresponding to  $\text{CH}_2\text{OCO}$  and  $\text{CH}_2\text{Br}$  (Figure). No by-products were observed by either n.m.r. spectroscopy or g.l.c.

After 64 ml of ethyl bromide (0.85 mol) had passed through the column, the ester was collected separately to give the result reported in Table 3.

Ethyl bromide (128 ml, 1.7 mol) was added at the same flow rate to remove acetate ion from the bed. Reduced pressure was subsequently applied to the system to remove the last traces of ethyl halide. Benzyl chloride (98 ml, 0.85 mol) was then allowed to pass through the column at a pressure of 20 Torr and a velocity of 40 ml/h. The condensed product showed 72% conversion into benzyl bromide, established by integrating the singlets centred at  $\delta$  ( $\text{CCl}_4$ ) 4.45 and 4.35, which correspond to benzyl chloride and benzyl bromide, respectively.

The solid bed was then removed from the column and shaken for 5 min in methylene dichloride. After filtration and washing of the solid bed with fresh methylene dichloride, the organic solution was treated with an excess of aqueous KI. The organic layer was dried, the solvent was almost completely removed and diethyl ether was added. Crystalline tetrabutylphosphonium iodide precipitated, m.p. 98–99 °C, yield 22.5 g (90%, with respect to the amount previously placed on the column).

The inorganic salts were then dissolved in water (2 l) and this solution was analysed potentiometrically ( $\text{Ag}/\text{Ag}^+$  electrode) which showed 0.67 mol of  $\text{Cl}^-$  and 0.66 mol of  $\text{Br}^-$  present. These results are consistent with the conversions observed in the previous reactions.

(b) *Ethyl 4-Chlorobenzoate.* Ethyl bromide (7.5 ml, 0.1 mol) was passed at a rate of 40 ml/h through a solid bed prepared from 4-chlorobenzoic acid (24.6 g, 0.16 mol), potassium carbonate (32.6 g, 0.23 mol), and tetrabutylphosphonium bromide (2.7 g, 7.9 mmol) while the system was held at 0.4 Torr.

The condensed ester (13.8 g, 75% with respect to the alkyl halide) contained no ethyl bromide.

(c) *Ethyl 2,4,6-Trimethylbenzoate.* Ethyl bromide (5.5 ml, 75 mmol) was passed at a rate of 40 ml/h through a solid bed prepared from 2,4,6-trimethylbenzoic acid (9.4 g, 57 mmol), potassium carbonate (11.8 g, 85 mmol), tetrabutylphosphonium bromide (0.97 g, 2.8 mmol), and silica gel while the system was held at 20 Torr. The condensed (8.5 g) showed only traces of ethyl bromide. The condensate was further distilled to give 8.0 g of ester (73% with respect to the acid).

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