

Esters and Orthoesters as Alkylating Agents at High Temperature. Applications to Continuous-flow Processes

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At high temperature (180–200 °C) esters, orthoesters, carbonates and orthocarbonates have been found to alkylate acidic compounds *via* a B_{A1}2 mechanism. Phenol gives anisole with methyl acetate in the presence of potassium carbonate. Thiols and other CH-acidic compounds are also alkylated under such conditions.

The results obtained under batch conditions can be repeated under continuous-flow conditions, if the base which promotes the reaction can be used in catalytic amount. Continuous-flow alkylation of thiophenol by methyl acetate on a sodium acetate-type fixed bed, and other alkylations by orthoesters or orthocarbonates on a potassium carbonate catalytic bed, have been achieved.

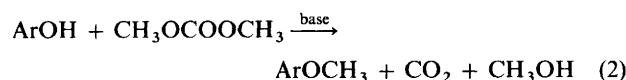
Change in temperature may lead to change in reaction mechanism. As the outcome of a reaction sensitive to changes in solvent polarity is likely to be changed at higher temperatures, such a reaction taking place in solution at higher temperatures is likely to resemble the corresponding gas-phase reaction.¹

A shift in reaction mechanism (from B_{Ac}2 to B_{A1}2) is reported to occur with esters. Because of solvation, nucleophilic attack on the carboxylic carbon of esters is favoured in solution, and a carboxylic derivative is obtained. In the gas phase, on the other hand, where solvation is absent, the nucleophile attacks the saturated carbon producing an S_N2 substitution *via* a B_{A1}2 mechanism.² Nucleophilic displacements on esters at ordinary temperatures are only observed in highly polar and aprotic solvents such as hexamethylphosphoric triamide (HMPT).³

We have previously reported that, at high temperature, under conditions of gas-liquid phase-transfer catalysis (GL-PTC) and of continuous-flow (CF),⁴ dialkyl carbonates react with nucleophiles to produce alkyl derivatives according to eqn. (1).⁵



In this way, phenols, thiophenols, aromatic amines, CH-acidic compounds (arylacetonitriles, malonate esters, lactones) gave the corresponding methyl derivatives when mixed with dimethyl carbonate (DMC) and passed over a catalytic bed composed of a phase-transfer (PT) catalyst and a weak base such as potassium carbonate. Eqn. (2) shows the reaction of phenols with DMC.



It has been observed that no transesterification occurs between DMC and phenol; methyl phenyl carbonate is only observed at shorter reaction time.⁶ The nucleophilic substitution which produces the ether predominates over the transesterification because the former is not an equilibrium reaction while the latter is.

With DMC it is possible to carry out the reactions by a truly catalytic process because the acidity of the reaction is removed as CO₂ [eqn. (2)]; the base is restored, and therefore it can be used in only a catalytic amount. In contrast, if dimethyl sulfate

were used in place of DMC, after methylation, the acid produced would destroy the base, and catalytic processes would not be possible (and nor therefore would CF processes); with 'classical' methylating compounds, batch conditions are, in fact, more appropriate.

In order to explore new alkylating agents which would be non-toxic and inexpensive, we report here the behaviour at high temperature of some orthocarbonates, carbonates, esters, orthoesters, acetals and ethers used as alkylating agents for phenol, thiophenol and phenylacetone.

Depending on the groups entering and leaving, each reaction requires different kinds and amounts of base, and therefore we carried out reactions, at first, under batch conditions which seemed to be appropriate to begin this study. Only successful syntheses in which the base behaved in a truly catalytic manner were then investigated under CF conditions.

Results

Methylation was the reaction chosen for all of the nucleophiles, although a number of benzylation and ethylation reactions were also carried out.

Methyl derivatives considered as potential alkylating agents were DMC and its orthoester tetramethyl orthocarbonate, methyl acetate, methyl formate and its orthoester trimethyl orthoformate, the dimethyl acetal of formaldehyde and *tert*-butyl methyl ether.

Autoclave reactions were performed under pressure. The reactor was charged with the substrate, the alkylating agent and the base which were then heated with stirring. Usually, the methyl derivative served as the solvent of the reaction. The reactions under CF conditions were carried out at atmospheric pressure and 180 °C by allowing the liquid mixture of the reagents to flow through the catalytic fixed-bed (see the Experimental section).

Batch reactions carried out in an autoclave are described first, and applications of the CF procedure are reported subsequently.

Tetramethyl Orthocarbonate and DMC.—In order to evaluate the reactivity of tetramethyl orthocarbonate and DMC, their reactions with thiophenol and phenol were carried out. Thiophenol (2.0 g, 0.018 mol), tetramethyl orthocarbonate (7.41 g, 0.054 mol), K₂CO₃ (5.02 g, 0.036 mol) and THF (20 cm³) were reacted in an autoclave at 195 °C; 100% conversion of

Table 1 Conversion of phenol into anisole by methyl acetate [eqn. (2)]. Influence of the base.^a

Reaction time/h	Reagent molar ratio (Phenol:methylacetate:K ₂ CO ₃)	Conversion ^b (%)
3	1:20:0.75	5 ^c
3	1:20:1	23 ^c
8	1:20:1	40 ^c
3	1:20:1.5	28 ^c
8.15	1:20:1.5	60 ^c
3	1:20:2	46 ^c
8.50	1:20:2	95 ^c
8.65	1:20:2	100 ^d

^a All reactions were carried out in an autoclave at 195 °C. ^b By GC following the decrease of initial phenol. ^c Starting from 2 g of phenol. ^d Starting from 6 g of phenol; when reaction was complete, the base was filtered and washed with 20 cm³ of diethyl ether. Distillation of the remaining liquid mixture gave 4.8 g of anisole (70% yield).

Table 2 Reactions of methyl acetate carried out in autoclave at 195 °C. Substrate, methyl acetate and base 1:20:2 molar ratio, respectively.

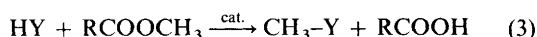
Substrate	Base	Reaction time/h	Conversion ^a (%)	Products
PhOH	AcONa	8.5	8	PhOAc
PhSH	AcONa	8.5	26	PhSCH ₃
PhSH	K ₂ CO ₃	6.25	100	PhSCH ₃
PhOH	K ₂ CO ₃	7.00 (8.65)	69 (100)	PhOCH ₃
PhCH ₂ CN	K ₂ CO ₃	8.0	5	PhCH(CH ₃)CN

^a Conversion was determined by GC following the decrease of initial substrate. No other products were observed. Also, dimethylmalonate was used as alkylating agent in the conditions reported above, using K₂CO₃ as base. After 3.65 h, thiophenol gave only thioanisole; conversion was 91%. The reaction of thiophenol with ethyl acetate afforded ethyl phenyl sulfide: under the conditions of entry 3, complete conversion was observed after 6.08 h (45% after 2.5 h).

thiophenol into thioanisole was observed after 3.75 h. Under the same conditions, the reaction of phenol with tetramethyl orthocarbonate gave only 17% anisole after 3.75 h. The reaction with DMC was faster, and 100% conversion into anisole was observed after only 2.75 h.

The reactions of DMC in an autoclave were not extensively investigated because, as previously reported, they are already known to give satisfactory results in the CF process.⁶

Esters.—When used as alkylating agents, esters react according to eqn. (3), where a methyl derivative is shown. Since the



leaving group is a carboxylic acid it consumes the base which, therefore, cannot be used in catalytic amounts, but must be used in at least stoichiometric quantity.

This is clearly shown in Table 1 where reaction (3) was performed in the presence of different molar ratios of potassium carbonate: the reaction goes to completion only when the base is present in excess.

The reaction of methyl acetate with other nucleophiles is reported in Table 2. It is shown that potassium carbonate gives the methyl derivatives, while the less basic sodium acetate produces the methyl derivative only in the case of thiophenol. Phenol yields the transesterification derivative under such

conditions. However, K₂CO₃ is a strong enough base to produce the anion of the phenylacetone nitrile.⁷

It would be possible in this case to carry out methylation reactions under CF conditions only with thiols that are able to undergo the reaction in the presence of acetate base acting as a catalyst (see Table 5 below).

Dimethyl malonate also effectively undergoes methylation reactions; as reported in the footnotes of Table 2, the results parallel those obtained with methyl acetate.

Benzyl esters behave in a similar manner, giving benzylated derivatives under such conditions.

Benzylation reactions were carried out in an autoclave at 195 °C using a substrate:benzyl acetate:base molar ratio of 1:3:2, respectively. Using 2.0 g of thiophenol (or phenol) the solvent was 20 cm³ of THF. Accordingly, benzyl phenyl sulfide was obtained from thiophenol at a high rate, and with potassium carbonate as a base, 100% conversion was observed after 150 min. In contrast the reaction of phenol under the same conditions provided, after 280 min, 40% conversion into benzyl phenyl ether.

Orthoesters.—Thiophenol, phenol and phenylacetone nitrile were treated with methyl orthoformate in the presence of potassium carbonate and potassium *tert*-butoxide as bases.

The results reported in Table 3 show that K₂CO₃ is an effective base only for the powerful nucleophile thiophenol. The reaction of phenol with methyl orthoformate under such conditions produces only the transesterification product after a considerably longer time.

In the presence of potassium *tert*-butoxide the anions produced give the corresponding methyl derivatives with either phenol or phenylacetone nitrile. With the latter, the reaction rate is higher, but methylation is not selective because the dimethyl derivative is also produced in higher amounts at complete conversion of the substrate.

Acetals and Ethers.—Several attempts were made to use acetals and ethers as effective alkylating agents. Thiophenol, phenol or phenylacetone nitrile was treated with dimethoxy-methane, and *tert*-butyl methyl ether using K₂CO₃ and potassium *tert*-butoxide as bases. After 8 h, conversion into the methyl derivative was observed only in the case of thiophenol, and that being negligible (2%).

Benzyl Methyl Carbonate.—In order to compare the activity of benzyl and methyl as alkylating groups, the mixed carbonate was prepared and reacted with phenol and thiophenol in 3:1 molar ratio, using THF as the solvent and K₂CO₃ as the base. As shown in Table 4, the alkylating ability of methyl and benzyl groups in benzyl methyl carbonate are about the same.

Continuous-flow Processes.—Batch reactions of thiols with esters, orthoesters and orthocarbonates, and of phenol with orthoesters and orthocarbonates were also carried out under CF conditions because the base is not consumed during such processes. They are reported in Table 5. It is shown that methyl esters effectively alkylate thiophenol to produce thioanisole and that phenol is only *O*-alkylated with tetramethyl orthocarbonate and methyl orthoformate. Increasing the flow rate decreases the conversion, as residence time in the reactor is reduced. Polyethylene glycols (PEG) were used as PT agent with K₂CO₃ as the catalyst, but sodium acetate required the more efficient phosphonium salt Bu₄P⁺Br⁻ as the PT agent.

Discussion

From the analysis of the products obtained under either batch or CF conditions it is suggested that, operating at high

Table 3 Reactions of methyl orthoformate carried out in autoclave at 195 °C. Substrate, methyl orthoformate and base 1:20:2 molar ratio, respectively.

Substrate	Base	Reaction time/h	Conversion ^a (%)	Products
PhSH	K ₂ CO ₃	3	100	PhSCH ₃
PhOH	K ₂ CO ₃	9	65	PhOCH(OCH ₃) ₂
PhCH ₂ CN	K ₂ CO ₃	8	0	—
PhOH	Bu ^t OK	7.25	40	PhOCH ₃
PhCH ₂ CN	Bu ^t OK	4	100	PhC(CH ₃) ₂ CN (90%) PhCH(CH ₃)CN (4%)

^a By GC following the decrease of initial substrate.**Table 4** Reactions of benzyl methyl carbonate carried out in autoclave at 195 °C. Substrate, benzyl methyl carbonate and K₂CO₃ 1:3:2 molar ratio, respectively.^a

Substrate	Reaction time/h	Conversion (%) ^b	Products ^c
PhSH	1.5	85	PhSCH ₃ (43%) PhCH ₂ SPh (42%)
PhSH	2.25	100	PhSCH ₃ (52%) PhCH ₂ SPh (48%)
PhOH	1.5	51	PhOCH ₃ (19.5%) PhCH ₂ OPh (29.5%)
PhOH	3.85	95	PhOCH ₃ (42%) PhCH ₂ OPh (58%)

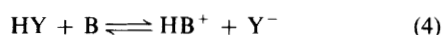
^a Starting from 2.0 g of substrate, 20 cm³ of THF was used as solvent.^b By GC, following the decrease of initial substrate. ^c Benzyl and methyl alcohols were formed as by-products during the reactions; both alcohols gave transesterification reactions with benzyl methyl carbonate, producing dibenzyl and dimethyl carbonate.

temperature, nucleophilic substitution might proceed *via* a B_{Al}2 mechanism, probably because high temperature increases the nucleophilicity of anions by reducing their hydration shell.

It is notable that, operating under batch conditions, no PT catalyst is necessary, possibly because the base utilized is sufficiently soluble in the reaction mixture to promote the reaction.

The reaction rate depends on many factors: the base, the alkylating compounds and the nucleophile. These aspects will be discussed below.

Influence of the Base.—The base present in the reaction mixture influences the rate because equilibrium (4) determines the amount of anion present in the reaction medium.



Influence of the base is clearly shown in Table 1. If acetate is used, equilibrium (4) is shifted sufficiently to the right for alkylation to occur in the case of thiols, but not in the case of phenols. Increasing the basicity increases the number of compounds able to be alkylated, as shown in Table 3 where phenylacetonitrile is satisfactorily alkylated only in the presence of *tert*-butoxide anion.

Influence of the Leaving Group.—DMC was previously reported to be a satisfactory methylating agent with respect to many nucleophiles.⁵ In methylation with DMC the utilization of the weak base potassium carbonate was possible because the leaving group 'methoxy carbonic acid' readily decomposes into methanol and CO₂. The same behaviour does not occur with esters, and therefore a stoichiometric amount of base is needed to promote the reaction.

In order to compare the electrophilic character of the alkylating agents considered here, it is necessary to correlate the

reaction rates of comparable derivatives. From the results in Tables 2, 3 and 4, it is possible to observe that carbonates react faster with nucleophiles than orthocarbonates, and that orthoesters are better electrophiles than esters.

Another correlation is that orthocarbonates react faster than orthoesters. Acetals and ethers do not react under such conditions. Such trends might be explained by the effect of the leaving group: the less basic the leaving group, the higher the electrophilic character of the compound. However, further studies are necessary in order to clarify some unexpected results.

Influence of the Nucleophile.—It is well known that thiols are powerful nucleophiles; under our conditions they were also able to operate in acidic media. In contrast, phenol undergoes alkylation only in the presence of strong bases. Interestingly, the carbanion of phenylacetonitrile (Table 3) reacts faster than the phenoxide anion if the base is strong enough to allow the formation of anions during the reaction.

Continuous-flow Process vs. Batch Process.—The main difference between CF and batch processes is that under batch conditions the reaction environment is modified during the reaction, whereas under CF conditions it does not change. More exactly, in each section of the plug-flow reactor, the reaction environment of the immobilized bed does not change over time. The reactions under CF conditions were carried out according to GL-PTC conditions, whose general aspects are included in the more comprehensive catalysis called supported liquid-phase catalysis.⁸

As shown in Table 5, the reaction rates of thiophenol and phenol with trimethyl orthoformate were comparable to those already reported for phenol with DMC under GL-PTC conditions.⁵

The transfer of batch processes to CF conditions was also shown to be possible in alkylation reactions. In this way less expensive compounds such as methyl esters may be considered for use in alkylations of phenol, thiophenols and some CH-acidic derivatives.

Conclusions

That the conditions reported here have not been investigated before may be because, operating at high temperature, low-boiling compounds develop high pressures. Moreover, many chemists believe that high temperatures decompose many organic compounds while, in fact, the simple ones considered here are stable at high temperature, allowing clean reactions free from by-products. The latter have to be avoided in order to transfer batch processes into CF ones, as they lead to tars which may occlude the reactor thus increasing operational costs. These results may enlarge applications of CF processes.

However, other studies are necessary, such as those concerning the solubility of the base in the reaction mixture at the reported temperature. Such results may explain some aspects which are not yet clarified, regarding the reactivity of the electrophiles discussed.

Table 5 Reactions carried out under continuous-flow conditions, at 180 °C and atmospheric pressure

Substrate	Alkylating agent	Catalytic bed ^b	Alk./Sub. (mol: mol) ^b	Flow rate/ cm ³ h ⁻¹	Conversion ^c (%)	Products
PhSH	AcOMe	10% AcONa + 10% Bu ₄ P ⁺ Br ⁻	8.0	10.0	33	PhSCH ₃
PhSH	AcOMe	5% AcONa + 5% Bu ₄ P ⁺ Br ⁻	10.0	4.5	100	PhSCH ₃
PhSH	HCOOMe	5% HCOONa + 5% Bu ₄ P ⁺ Br ⁻	10.0	5.5	72	PhSCH ₃
PhSH	EtCOOMe	5% AcONa + 5% Bu ₄ P ⁺ Br ⁻	10.0	4.5	36	PhSCH ₃
OctSH	CH ₂ (COOMe) ₂	5% AcONa + 5% Bu ₄ P ⁺ Br ⁻	10.0	5.5	100	OctSCH ₃
PhSH	HC(OCH ₃) ₃	5% K ₂ CO ₃ + 5% PEG 6000	10.0	5.5	100	PhSCH ₃
PhOH	C(OCH ₃) ₄ ^d	5% K ₂ CO ₃ + 5% PEG 6000	1.0	10.0	54	PhOCH ₃
PhOH	HC(OCH ₃) ₃	5% K ₂ CO ₃ + 5% PEG 6000	4.0	10.0	42.5	PhOCH ₃ (1.7%) PhOCH(OCH ₃) ₂ (40.8%)

^a All reactions were carried out using 45 g of catalytic bed; % wt of base and PT catalysts are indicated. ^b Alkylating agent and substrate molar ratio. The low boiling alkylating agent was used as gaseous carrier. ^c Conversions were determined by GC at steady state conditions (reached after 7.5 h), following the decrease of initial substrate. ^d Cyclohexane (11.5 cm³, g⁻¹ of phenol) was used as gaseous carrier.

Experimental

All the compound used were of ACS grade and were used without further purification. Corundum spheres were supplied by Industrie Bitossi, Vinci (Firenze). NMR spectra were recorded using a Varian EM 390 spectrometer (90 MHz). A Varian GC3300 was used for GC analysis.

Autoclave.—The stainless-steel autoclave had an inner volume of 250 cm³ and was equipped with a purging valve through which, at room temperature, air was removed before the reaction by purging with a N₂ stream.

A thermocouple and a needle valve were fixed on the autoclave head. The former dipped into the reaction mixture and the latter was connected to a 1/8 inch stainless-steel suction pipe which, in turn, was immersed in the reaction mixture. In this way it was possible to extract samples during the course of the reactions.

Continuous-flow Apparatus.—Reactors were cylindrical glass columns packed with catalytic beds thermostatted at the reaction temperature by a continuous circulation of oil. The liquid reaction mixture was introduced at the inlet of the reactor by a syringe pump.

Execution of the Batch Reactions.—All reactions were carried out by loading into the autoclave the mixture of alkylating agent, nucleophile and base in the molar ratio 1:20:2 (except for the case of benzylation reactions and reactions with tetramethyl orthocarbonate where molar ratios were 1:3:2 and THF was used as solvent). The autoclave was heated in an electrical oven to the desired operating temperature (195 °C; heating rate = 5 °C min⁻¹), while the reaction mixture was kept under magnetic stirring. Pressure increased up to 20–25 bar at 195 °C according to the alkylating compound. Samples extracted during the reactions were analysed by GC.

Preparation of the Catalytic Beds.—Two types of catalytic beds were prepared.

(a) *Entries 1–5, Table 5.* Bu₄P⁺Br⁻ and the base (sodium acetate or formate) were dissolved in the required amount of deionized water. A suitable quantity of corundum spheres were then added to the above solution in order to obtain the required % wt. of phosphonium salt and base. The water was removed under reduced pressure and the solid was dried at 130 °C overnight.

(b) *Entries 6–8, Table 5.* Polyethylene glycol (PEG 6000) (10 g) and K₂CO₃ (10 g) were dissolved in the required amount of deionized water. Corundum spheres (2.5 mm in diameter, 180 g) were added to the above solution and water was then removed under reduced pressure. The coated spheres were put in an oven at 130 °C for 12 h.

Execution of the CF Reactions.—The reactions were carried out at atmospheric pressure. The reactor was packed with the coated corundum spheres and thermostatted at the reaction temperature (180 °C). The liquid mixture of reagents introduced at the inlet of the reactor became gaseous in the catalytic bed where the PT catalyst constituted a liquid film over a solid inert support. The products were recovered by simple condensation and analysed by GC.

Benzyl Methyl Carbonate.—A mixture of benzyl alcohol (54 g, 0.50 mol), dimethyl carbonate (210 cm³, 2.50 mol) and K₂CO₃ (104 g, 0.75 mol) was heated under reflux on an oil bath at 100 °C with magnetic stirring. Reaction was followed by GC. When 70% conversion was reached, methanol was removed by distillation. Heating was maintained for an additional 2 h (the final conversion was 96%). K₂CO₃ was filtered off and the excess of DMC was removed. The product was distilled (b.p. = 125–127 °C/20 mmHg). Obtained 66 g, yield 80%. δ_{H} (90 MHz, CDCl₃, Me₄Si) 3.78 (3 H, s, Me), 5.20 (2 H, s, -CH₂Ph) and 7.25–7.55 (5 H, m, Ph).

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