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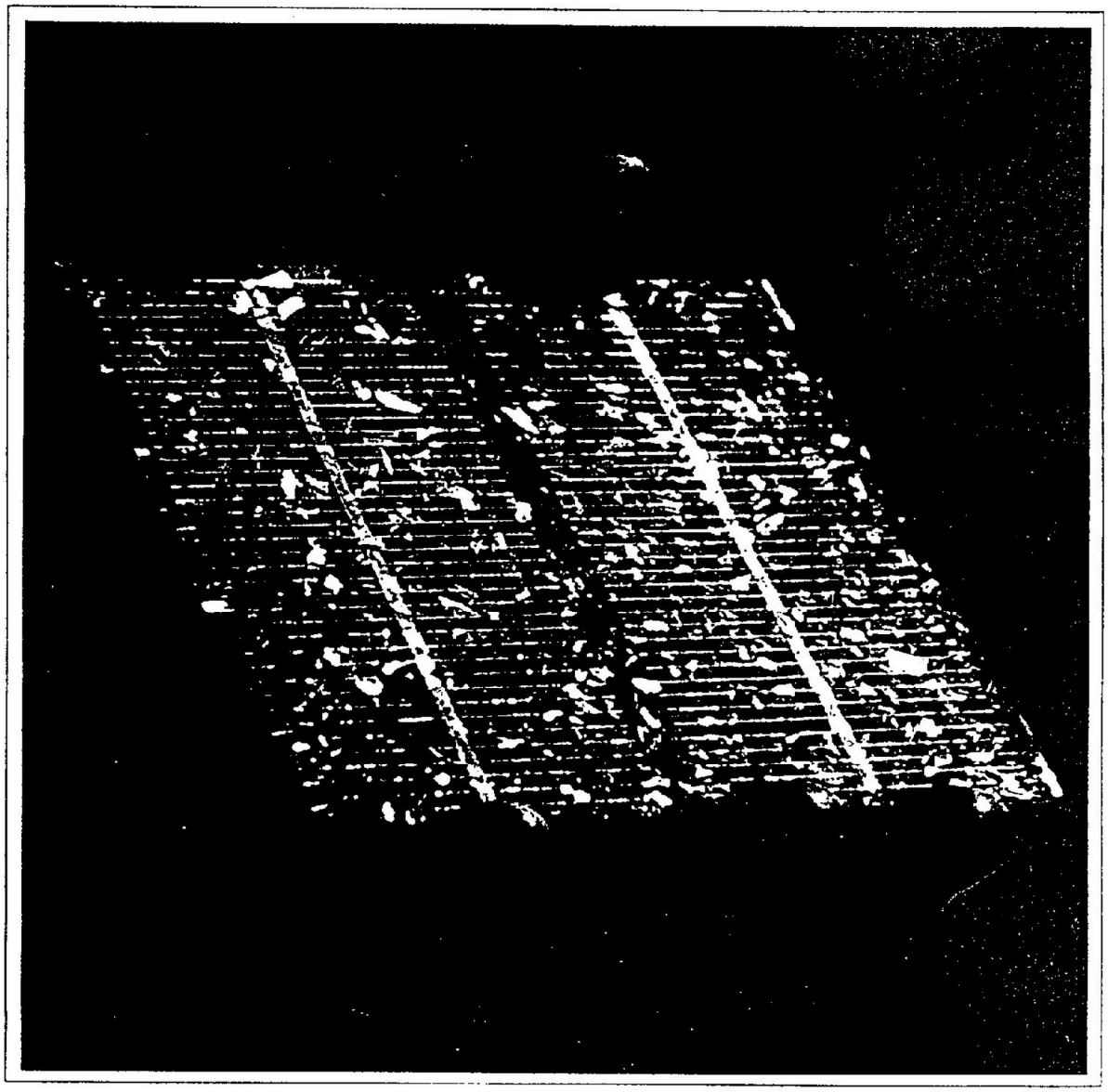

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Monomethylation of activated esters and thiophenol with different alkylating agents under gas-liquid phase-transfer catalysis (GL-PTC) conditions

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Operating under GL-PTC conditions, the reactions of lactones and activated esters with dimethylcarbonate and of thiophenol with methyl and ethyl esters are here reported; the former produce selectively mono-methylated derivatives, the latter give the correspondingethers. There reactions are carried out under continuous-flow conditions using a catalytic bed constitued by supported PEGs (in the case of lactones and activated esters) or a classical onium salt (in the case of thiophenol) and a base as co-catalyst.

Transfer of reagents and/or products from one phase to another phase occurs in different situations and is related with reactions performed with supported reagents or catalyst.

In typical phase-transfer supported reactions carried out under continuous-flow conditions, a gaseous mixture of reagents flows through a catalytic bed where, at operating conditions, the catalyst constitutes a liquid film dispersed over a supporting solid [1].

Many examples regarding this configuration are present in very important industrial processes like cracking of hydrocarbons by phosphoric acid supported on kieselgur [2], oxidation of SO_2 to SO_3 [3] promoted by vanadia oxides, production of 1,2-dichloroethane by oxychlorination of ethylene with oxygen and HCl with Deacon catalyst [4], hydroformylation of propene in gas phase with Wilkinson catalyst present in molten triphenylphosphine [5].

All these types of catalysis are referred as "Supported liquid-phase catalysis" (SL-PC) [6].

Phase-transfer processes occurring in SL-PC are shown in Fig. 1.

The figure shows a simple reaction (eq. 1)

$$A + B \rightarrow C \qquad (1)$$

between two compounds A and B: compound A reacts

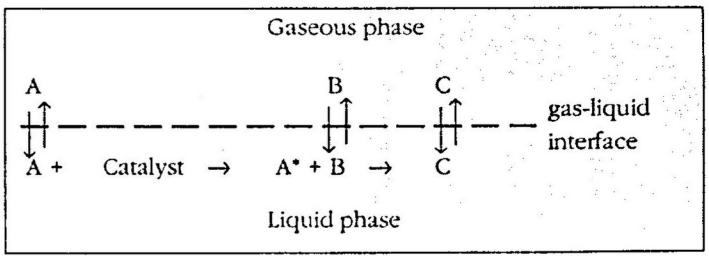
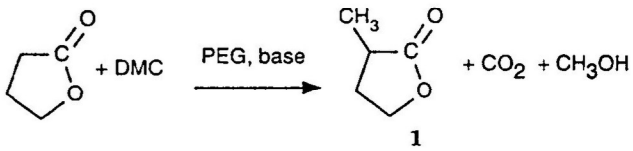


Fig. 1 - Phase transfer at gas-liquid interface in supported liquid-phase catalysis

with the catalyst to form an intermediate A* which, in turn, reacts with B giving the product C; once generated in the liquid phase, C diffuses into the gaseous one.
More recently, a new SL-PC process has been introduced, namely the gas-liquid phase-transfer catalysis (GL-PTC) [7]: a classical phase-transfer catalyst (also polyethylene glycols, PEGs, can be used), is distributed on a solid support which may contain a co-catalyst, as, for example, a base. According to Fig. 1, the liquid phase of the catalyst absorbs the reagents from the gas phase and then promotes the reaction; the products then diffuse into the gas phase and leave the reactor. Many examples of such reactions were reported: they include transesterification reaction, transhalogenation in hydrocarbons, formation of esters, ethers, etc... [8].
Foremost reactions performed in GL-PTC conditions are those concerning the utilization of alkyl carbonates and dimethylcarbonate (DMC) in particular; the latter is a versatile and environmentally safe substitute of the toxic dimethylsulfate (DMS) [9]. Reactions of DMC already reported in GL-PTC conditions are those including the reactions of DMC with several nucleophiles [10]; they obey to the general equation:

$$HY + (CH_3O)_2CO \rightarrow Y\text{-}CH_3 + CO_2 + CH_3OH \quad (2)$$

where HY is an acidic compound that in the presence of a base gives the anion Y^-.
According to eq. 2, phenols give the corresponding methylethers, mercaptans give tioethers, anilines *mono*-N-methylanilines and arylacetonitriles give selectively the *mono*-C-methyl derivative; the latter opens the way for a new synthesis of pure 2-arylpropionitriles [10].
In any case, when double methylation may occurs, alkylation by DMC under GL-PTC conditions allows always high selectivity in *mono*-methylation [11].
An interesting feature for the reactions of DMC under GL-PTC conditions lies in the fact that they can be performed over an actual catalytic bed whereas reactions by means of DMS or other methyl halydes require the utilization of a base in a stoichiometric amount in GL-PTC the acidity involving the reactions of DMC is removed as CO_2, well-compatible with basic co-catalysts of carbonate type.
We report here preliminary results on the alkylation with DMC of cyclic esters and activated esters which occur with high selectivity according to the equation (3) and (4), respectively [12].



1 (3)

$$PhCH_2COOCH_3 + DMC \rightarrow PhCH(CH_3)COOCH_3 + {+}CO_2 + CH_3OH \quad (4)$$

Alkylation of γ-butyrolactone does not occur easily; this explains the fact that *mono*-methylated compound **1** is costly; its synthesis is achieved by utilizing crown ethers as catalysts in the presence of strong bases; otherwise, more complicated reaction schemes have to be followed [13].
Operating under GL-PTC conditions, the less expensive alkylating DMC and the weak base K_2CO_3 are able to produce the *mono*-methylderivate *1* with high selectivity, starting from the inexpensive lactone. Some data are reported in Tab. 1.
Interestingly, under the conditions reported in Tab. 1, alkylations of six or seven-membered rings lactones (5-valerolactone, 6-caprolactone) does not produce comparable results: in both cases, selectivity in *mono*-methylation is about 10%.
With the aim of exploring new and non-toxic alkylating

Tab. 1 - Methylation of γ-butyrolactone and methyl-phenylacetate by DMC under GL-PTC conditions. T=180 °C, atmospheric pressure. Catalytic bed: polyethylene glycol 6000 (5 wt%) and K_2CO_3 (5 wt %) supported on corundum.

Substrate	Catalytic bed (g)	DMC/Substrate (mol:mol)	Flow rate (liquid) (ml/h)	% Conversion
1) γ-butyrolactone	60	10	20	12
2) γ-butyrolactone	65	4	20	18
3) γ-butyrolactone	100	4	8	23
4) γ-butyrolactone	300	10	6	61
5) $PhCH_2COOCH_3$	45	10	7	14
6) $PhCH_2COOCH_3$	100	10	8	57

Note: Preliminary results on methylation of γ-butyrolactone were obtained in batch conditions, by heating at 210 °C, in an autoclave, a mixture of γ-butyrolactone, DMC and K_2CO_3 (molar ratio = 1 : 5 : 1). After 6 hours, conversion was 100% and selectivity in *mono*-methylation was 93%. Yield on distillate product (K_p 0.65=94-97 °C) was 70%.

Tab. 2 - Alkylation of thiophenol by esters under GL-PTC conditions according to equation 5. T=180 °C and atmospheric pressure.

Alkylating agent	Catalytic bed[a]	(g)	Ester/Substrate (mol:mol)	Flow rate (ml/h)	% Conversion to thioanisole
1) Methyl acetate	10% $AcONa/Bu_4P^+$	(45)	8.0	10	33
2) Methyl acetate	5% $AcONa/Bu_4P^+$	(65)	10.0	4.5	100
3) Methyl formate	5% $HCOONa/Bu_4P^+$	(45)	10.0	5.5	72
4) Ethyl acetate	5% $AcONa/Bu_4P^+$	(45)	10.0	4.5	36

a) weight percentage of phosphonium salt on acetate or formate salts.

agents to be used under continuous-flow conditions we were interested in the use of methylesters of formic and acetic acid. In this connection, reactions would occur according to the equation 5.

$$HY + CH_3OCOCH_3 \rightarrow YCH_3 + CH_3COOH \qquad (5)$$

Acetic acid is the co-product and therefore the catalyst contains acetate (or formate) anion as the source of basicity. Moreover, because the reaction 5 is not an equilibrium reaction it can be satisfactorily shifted to the right provided that in the equilibrium 6 the reactive anion is present in a slight amount but enough.

$$CH_3COO^- + HY \rightleftarrows CH_3COOH + Y^- \qquad (6)$$

We observed that only mercaptans give raise to reaction 5. Some data are reported in Tab. 2. Reaction 5 with phenols as reagents was not successfull maybe because of the related unfavourable equilibrium 6.
GL-PTC can usefully open the way to new reactions: high temperatures and massive phase-transfer in the absence of solvents may increase anions nucleophilicity and develop)different reaction pathways, thus allowing the use of non toxic alkylating agents under continuous-flow conditions.

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Experimental section

Preparation of the catalytic bed (Tab.1)
PEG 6000 (10 g) and K_2CO_3 (10 g) were dissolved in the required amount of deionized water. To this solution 180 g of corundum spheres (2.5 mm in diameter) were added and water was removed under vacuum. The coated spheres were put in an oven at 130 °C for 12 hours.

Preparation of the catalytic bed (Tab. 2)
PEG 6000 (10 g) and the base (sodium acetate or formate, 10 g) were dissolved in the required amount of deionized water.
To this solution 1 g of $Bu_4P^+ Br^-$ and a suitable amount of corundum spheres (2.5 mm in diameter) were added to give a 5 wt% support either in catalyst and base. The water was removed under vacuum and the solid was drying at 130 °C overnight.

Continuous-flow reactions
The reactions were carried out at atmospheric pressure. A column was packed with the coated corundum spheres and was thermostated at the reaction temperature (180 °C) with a continuous oil circulation. The liquid reagent mixture was continuously passed into the reactor with a syringe pump. The liquid mixture became gaseous in the reactor entrance. The products were recovered by simply condensation and analyzed by gas chromatography.

A typical reaction: selective α-methylation of γ-butyrolactone
A liquid mixture of γ-butyrolactone and dimethylcarbonate (1:10 mol/mol) with a liquid flow rate of 6 ml/h was passed continuously through 300 g of catalytic bed loaded in a glass column (50 cm in lenght and 3 cm in diameter). The reaction was continued for 40 hours. The collected effluent contained 60.8% of γ-methyl -butyrolactone, the remainder being starting material not converted.

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