Gas-Liquid Phase-Transfer Catalysis

Reaction of Dialkyl Carbonates

by Maurizio Selva and Pietro Tundo

Owing to the great extent of reactions involving anions, GL-PTC may open the way to new catalytic processes and provide connections between primary chemistry and secondary or fine chemistry where selectivity is a very important question and versatility is needed.

Among the reactions carried out under gas-liquid phase-transfer catalysis (GL-PTC) conditions, those of dimethyl carbonate (DMC) are of relevance [1], since DMC can be considered an environmentally safe reagent: while its traditional synthesis involved phosgene, now, it is also produced by oxidative carbonylation of methanol. The current industrial production has been set up by EniChem [2].
DMC can be used as a carboxylating agent ($B_{Ac}2$ mechanism, Figure 1a), and as a methylating agent ($B_{Al}2$ mechanism, Figure 1b) in place of phosgene dimethylsulfate (or methylchloride), respectively.
In particular, methylation reactions occur at high temperatures when the nucleophilic anions attack the methyl group (instead of the acyl carbon) of the organic carbonate. The leaving group (methoxycarbonate anion, CH_3OCOO^-) is not stable: it rapidly decomposes into methanol and CO_2 so that the base can be used in catalytic amounts (i.e. methoxide anion is regenerated). This fact produces remarkable effects for the reactions to be carried out under continuous-flow (c.-f.) conditions. In fact, both carboxylation with phosgene and methylation with dimethylsulfate reactions generate stoichiometric quantities of inorganic salts as byproducts because a base must be used as a reagent; instead, in the corresponding processes of DMC, no salts are produced and methanol can be recycled in the DMC production plant. The comparison between GL-PTC processes and batch ones utilizing DMC are reported in Table 1.
The carboxymethylation reaction is an equilibrium type reaction while the methylation reaction is not. Moreover, methylation occurs at high temperatures; so, as one desires, either carboxymethyl or methyl derivatives can be obtained. Some reactions of DMC carried out under GL-PTC are reported below.

Phenols and thiols

Under GL-PTC conditions, both phenols and thiols are readily methylated by DMC to give the corresponding

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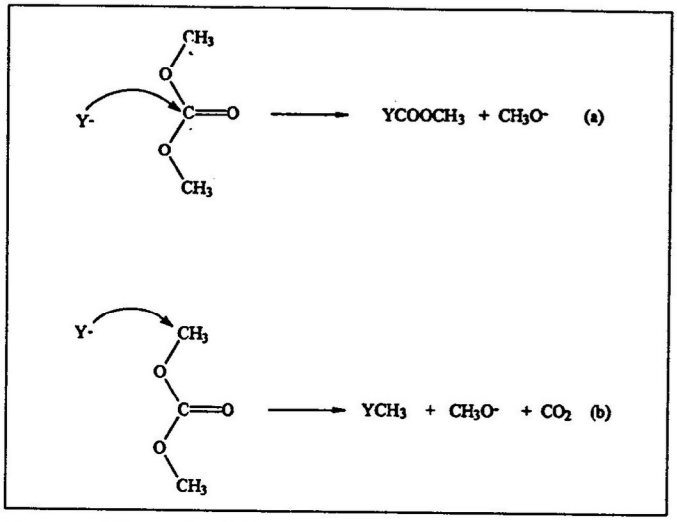


Figure 1 - The nucleophile Y- attacks the acyl carbon of DMC: a) transesterification reaction occurs via $B_{Ac}2$ mechanism; b) methylation reaction occurs via $B_{Al}2$ mechanism

anisoles and methyl thiothers (Eqs. 1 and 2, respectively) [3]. No C-alkylated compounds have been observed.

$$ArOH + CH_3OCOOCH_3 \xrightarrow[K_2CO_3]{PEGs} ArOCH_3 + CH_3OH + CO_2 \quad (1)$$

$$RSH + CH_3OCOOCH_3 \xrightarrow[K_2CO_3]{PEGs} RSCH_3 + CH_3OH + CO_2 \quad (2)$$

Thus, working on a 1000 g catalytic bed composed of 5% PEG 6000 and 95% K_2CO_3 at 180 °C, 1.0 mole of phenol is transformed in about one hour into anisole using a 2.0 M excess of DMC (Figure 2) [3]. In particular, the reaction of phenol with DMC was also performed in a pilot plant reactor: operating at 220 °C, anisole was continuously produced for three weeks without stopping, over a catalytic bed supported on γ-alumina [4].
Thiophenol is more reactive than phenol: a solution of thiophenol, DMC and cyclohexane (1:1:4, v:v:v; DMC/thiophenol, 1:2 under ratio) was sent at a flow rate (liquid) of 3.3 ml/min. on 95 g of potassium carbonate coated with 5 wt% of PEG 6000 at 180 °C. Total conversion into thioanisole was observed.

Alcohols

Instead of methyl ethers, hard alkoxide anions RO^- act as bases and give transesterification products on DMC (Eq. 3 and 4), according to a $B_{Ac}2$ mechanism:

$$ROH + DMC \rightleftharpoons ROCOOCH_3 + CH_3OH \quad (3)$$

$$ROH + ROCOOCH_3 \rightleftharpoons ROCOOR + CH_3OH \quad (4)$$

Transesterification reactions on DMC is used for the production of higher homologues of carbonic acid esters without phosgene as a starting material [3]. Using the GL-PTC technique, a continuous-flow process can be easily set-up.

Primary aromatic amines

Using c.-f. methods, the mono-alkylation of anilines in the gas phase can be carried out industrially with methanol (ethylene and dialkyl ethers are also used). High temperatures (up to 400 ∞C), high pressures or long contact time are needed [5]. The result is a mixture of monomethyl, dimethyl and unreacted anilines. Under the conditions of reactions 1 and 2, aromatic amines produce selectively only mono-N-methylanilines [6]; Eq. 5 describes the overall process.

$$ArNH_2 + CH_3OCOOCH_3 \xrightarrow[K_2CO_3]{PEGs} ArNHCH_3 + CH_3OH + CO_2 \quad (5)$$

The reaction does not occur in the absence of PEGs; besides, in the absence of K_2CO_3 the reaction produces only the urethane $ArNHCOCH_3$. Therefore, it is the base that promotes the subsequent alkylation reaction.
In the case of anilines, at 91% conversion and using a DMC/aniline molar ratio of 10, less than 1% of N,N'-dimethylaniline is produced. The uncommon selectivity was justified in terms of two independent and selective reaction pathways. As usually occurs in solution, aniline reacts with DMC giving *only* the urethane $PhNHCOOCH_3$. This compound exchanges its acidic hydrogen with activated CO_3^{2-}, thus yielding the corresponding anion $PhN(-)COOCH_3$. This, in turn, *selectively* gives the N-monoalkylated product $PhN(CH_3)COOCH_3$ through a $B_{Al}2$ mechanism. A final alcoholysis affords $PhNHCH_3$. Thus, the observed selectivity can be explained both by the inability of $PhN(CH_3)COOCH_3$ to produce anions (and so to be further alkylated) and by the fact that $PhNH_2$ and $PhNHCH_3$ are not deprotonated by reaction with activated carbonate (no PhNH(-) and $PhN(-)CH_3$ formation occurs and consequently, no S_N2 displacement on DMC may take place).

Aryl acetonitriles and methyl arylacetates

When performed with GL-PTC, the reactions of DMC with methylene-active compounds such as arylacetonitriles and methyl aryl acetates produce monomethylated derivatives, with a selectivity not previously observed. In fact, monomethylation reactions of methylene-active compounds are not a one step industrial process because of the relevant quantity

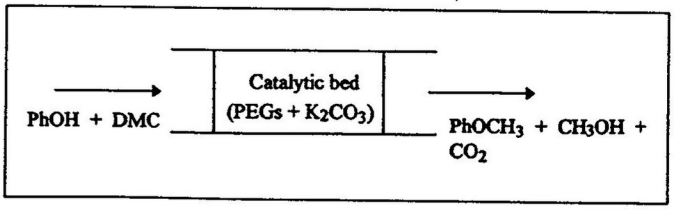


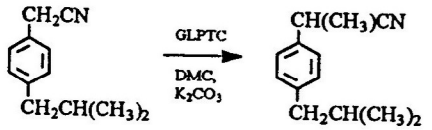
Figure 2 - The reaction of phenol and dimethyl carbonate under GL-PTC conditions

of dimethyl derivatives obtained with the usual alkylating agents, either under classical [7] and PTC conditions [8-9]. The mono-methylation reactions of arylacetonitriles and arylacetoesters are noteworthy because they may produce 2-arylpropionic acid (anti-inflammatory drugs) by a methylation process starting from readily available intermediates.
Actually, using DMC, either under GL-PTC [10] or batch conditions [11], it is possible to synthesize 2-arylpropionic acid derivatives with >99% purity in monomethyl derivatives, with complete conversion and using a 10-30 molar excess of DMC (Eq. 6, Table 2).

$$ArCH_2X + DMC \longrightarrow ArCH(CH_3)X + CH_3OH + CO_2 \quad (6)$$

$$X = CN, COOCH_3$$

For instance, a large excess of DMC, up to 30 molar equivalents, has been employed in reaction 7, for the production of Ibuprofen, the well known anti-inflammatory agent.



(7)

Working at atmospheric pressure, double methylation was less than 0.4% at 95% conversion. 2-(4-isobutylphenyl)propanonitrile is hydrolyzed and Ibuprofen is obtained [10a].
Generally, under the same conditions, the methylation of phenylacetic esters to give the corresponding 2-phenylpropionic esters proceeds slower than with nitriles (Eq. 6), the selectivity being equally high [11].

$$ArCH_2X + B \rightleftharpoons ArC(-)HX + BH^+$$

$$ArC(-)HX + DMC \rightleftharpoons ArCH(COOCH_3)X + CH_3O^-$$

$$BH^+ + CH_3O^- \rightleftharpoons B + CH_3OH$$

$$ArCH(COOCH_3)X + B \rightleftharpoons ArC(-)(COOCH_3)X + BH^+$$

$$ArC(-)(COOCH_3)X + DMC \longrightarrow Ar-\underset{CH_3}{\overset{COOCH_3}{\overset{|}{\underset{|}{C}}}}-X + CO_2 + CH_3O^-$$

$$Ar-\underset{CH_3}{\overset{COOCH_3}{\overset{|}{\underset{|}{C}}}}-X + CH_3O^- \rightleftharpoons ArC(-)(CH_3)X + DMC$$

$$ArC(-)(CH_3)X + BH^+ \rightleftharpoons ArCH(CH_3)X + B$$

Total Reaction

$$ArCH_2X + DMC \longrightarrow ArCH(CH_3)X + CH_3OH + CO_2$$

$$X = CN, COOCH_3$$

Scheme 1

Table 1 - Reactions of dimethylcarbonate with different nucleophiles under batch and c.-f. conditions (GL-PTC)

Reagent	Product	
	Batch	GL-PTC
ArOH	$ArOCOOCH_3$	$ArOCH_3$
ArSH	$ArSCH_3$	$ArSCH_3$
$ArNH_2$	$ArNHCOOCH_3$	$ArNHCH_3$
ROH	$ROCOOCH_3$+$(RO)_2CO$	$ROCOOCH_3$ + $(RO)_2CO$
$ArCH_2CN$	$ArCH(COOCH_3)CN$	$ArCH(CH_3)CN$

Table 2 - Mono-methylation of arylacetonitriles and methyl arylacetates by DMC

X	Ar	Conv. (%)	Selectivity in mono-methylation	Intermediate for
CN	4-isobutylphenyl	99	99	Ibuprofen
CN	3-carboxymethylphenyl	100	>99	Ketoprofen
$COOCH_3$	2-(6-methoxynaphthyl)	100	>99	Naproxen

The mechanism of these reactions has been investigated carrying out the methylation of arylacetonitriles and methyl arylacetates by DMC under batchwise conditions [12]. Typically, reactions were run in a stainless-steel autoclave at 180-220 °C using a mixture of the substrate, DMC and K_2CO_3 in a 1:20:2 molar ratio, respectively.
The proposed mechanism for these reactions is reported in Scheme 1.
DMC has a double reactivity (see Figure 1):

i) it is a methoxycarbonylating agent (reaction with the ArCH-CN anion) according to a $B_{Ac}2$ mechanism;
ii) it is a methylating agent (on the $ArC(-)(COOCH_3)CN$ anion) according to a $B_{Al}2$ mechanism. Both reaction pathways are highly selective, since the S_N2-type methylation of the ArCH(-)CN is very slow.

This mechanism is also evidenced by the fact that the selectivity is strongly depressed in the presence of iodomethane: in fact, if CH_3I is added (0.05 eq with respect to the reacting nitrile) to the reacting mixture, the selectivity in the mono-methylderivative falls down from 99.5% to 80%.
Paradoxically, those factors which are expected to reduce selectivity (high temperature and an excess of the alkylating agent) instead promote it:

i) high temperatures allow a reaction pathway ($B_{Al}2$ mechanism) not otherwise attainable;
ii) DMC is also a good solvent for these reactions: it provides a suitable low-polar and aprotic environment which orients the reactivity of ArCH(-)X toward methoxycarbonylation and $ArC(-)(CO_2Me)X$ toward methylation, by using alkaline carbonates as bases.

The results attest that DMC can effectively replace the toxic dimethyl sulfate as a new and safe methylating agent when the reactions are carried out under GL-PTC conditions [13]. According to the mechanism of Scheme 1, also the methylation of aroxyacetonitriles and methyl aroxyacetates with DMC proceeds with a selectivity up to 99% in the mono-methyl derivatives: 2-aroxy propionitriles and methyl 2-aroxypropionates are the corresponding products (Eq. 8) [14].
Operating at high temperature (180-220 °C), other

$$ArOCH_2X + DMC \xrightarrow{base} ArOCH(CH_3)X + CH_3OH + CO_2 \qquad (8)$$

$$X = CN, COOCH_3$$

dialkylcarbonates allow both O- and C-alkylation in high yields of phenols and methylene-active compounds, respectively. For instance, the reaction of phenols with dibenzylcarbonate (DBzlC) affords benzyl aryl ethers, while arylacetonitriles and benzyl arylacetates are selectively mono-C-benzylated by DBzlC to the corresponding 2-aryl-3-phenyl propionitriles and benzyl 2-aryl-3-phenylpropionates (Eq. 9) [15].

$$ArCH_2X + PhCH_2OCOOCH_2Ph \xrightarrow{base} ArCH(CH_2Ph)X + PhCH_2OH + CO_2 \qquad (9)$$

$$X = CN, COOCH_2Ph$$

Also in this case, the selectivity in the mono-alkylated products was >99%; the reaction goes through the formation of carboxybenzylated and benzyl carboxybenzylated intermediates, according to the mechanism shown in Scheme 1.

Conclusions

Provided that the organic compounds are thermally stable, higher temperatures not only increase reaction rate but may also open the way to unexplored reactions and new syntheses.
GL-PTC offers new possibilities both by extending the PTC applications and by allowing effective c.-f. processes. Under GL-PTC conditions, some of the reported reactions occur as foreseen but some others are quite unusual and have surprising selectivity as the reactions of dialkyl carbonates which actually become catalytic and can be carried out indefinitely under c.-f. conditions. In addition, GL-PTC is profitable both for laboratory preparations and for industrial applications. In fact, owing to the great extent of reactions involving anions, GL-PTC may open the way to new catalytic processes and provide connections between primary chemistry (where c.-f. methods are widely used) and secondary or fine chemistry where selectivity is a very important question and versatility is needed. ◆

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