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New developments in dimethyl carbonate chemistry*

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Abstract: Dimethylcarbonate (DMC) is a valuable methylating reagent which can replace methyl halides and dimethylsulfate in the methylation of a variety of nucleophiles. It couples tunable reactivity and unprecedented selectivity toward mono-*C*- and mono-*N*-methylation in the reactions of acidic CH_2 and primary aromatic amines, respectively. In addition, it is a prototype example of a *green reagent*, since it is nontoxic, made by a clean process, and biodegradable, and it reacts in the presence of a catalytic amount of base thereby avoiding the formation of undesirable inorganic salts as by-products. Other remarkable reactions are those where DMC behaves as an oxidant: cyclic ketones are transformed into α,ω-dimethyl esters with a reaction of atom efficiency of 1.0.

INTRODUCTION

Environmental concern and legislation, coupled with the prospect of a competitive advantage, are pushing the chemical industry to develop cleaner chemical processes. Green chemistry [1], by the design of environmentally compatible chemical reactions, offers the tools to approach pollution and sustainability concerns at the source.

In order to be eco-friendly, or *green*, organic syntheses must meet, if not all, at least some of the following requirements: avoid waste [2], be atom efficient [3], avoid use and production of toxic and dangerous chemicals, produce compounds which perform better or equal to existing ones and are biodegradable, avoid auxiliary substances (e.g., solvents), reduce energy requirements, use renewable materials, use catalysts rather than stoichiometric reagents [4].

In particular, an underdeveloped area of chemistry is in the replacement of reagents which are toxic, dangerous, produced by eco-unfriendly processes, not selective, and which produce expensive-to-dispose-of inorganic salts, in short: not green. Emblematic examples of undesirable reagents used for methylation and carboxymethylation are methyl halides (CH_3X), dimethylsulfate (DMS), and phosgene ($COCl_2$).

In the mid-1980s, Enichem Synthesis patented a production technology for the preparation of dimethyl carbonate, based on the reaction of oxicarbonylation of methanol [5]:

$$2\ MeOH + CO + \tfrac{1}{2}\ O_2 \xrightarrow{Cu\ salts} MeOCO_2Me + H_2O$$

With respect to the older industrial route (the phosgenation of methanol), this new process offered two basic advantages from the operational and environmental standpoints: it was much safer (no corrosive reagents were used, and water was the only co-product), and it allowed obtaining DMC in a high purity as a nontoxic compound. These features were readily recognized, and since the birth of the

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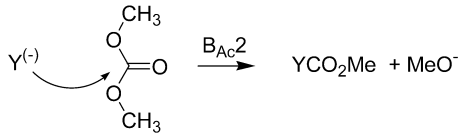
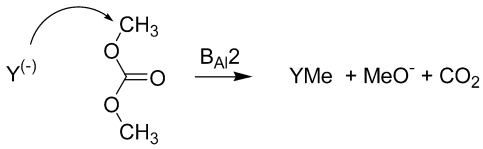
Enichem procedure, an intense research activity was addressed worldwide to innovative applications of DMC and its higher homologs, as reagents and nonpolluting solvents in synthetic organic chemistry. In fact, among the specific synthetic and environmental advantages of DMC, and in, general, of alkyl carbonates, is that they are esters of carbonic acid, i.e., derivatives of CO_2, an environmentally acceptable compound that does not cause emissions in the atmosphere.

The molecule of dimethyl carbonate possesses two active centers (alkyl and carbonyl carbons), whose reactivity can be tuned with the temperature. In particular, two distinct pathways can be recognized in the reaction of DMC with a generic anionic nucleophile (Y^-):

i) at T = 90 °C (reflux of DMC), DMC behaves as an ester, and a methoxycarbonylation reaction takes place through a $B_{Ac}2$ mechanism:



ii) at a higher temperature (T ≥ 120 °C), a methylation reaction occurs via a $B_{Al}2$ mechanism:



Of the two, only the methylation reaction is irreversible because the CH_3OCOO^- anion that is formed decomposes to methoxide and CO_2.

Since both methylation and methoxycarbonylation generate CH_3O^-, both reactions can be carried out in the presence of catalytic amounts of base. This avoids the formation unwanted inorganic salts as by-products and the related disposal problems. In principle, the methanol produced can be recycled for the production of DMC. On the contrary, methylation with RX or DMS, and carbonylation with phosgene, all generate stoichiometric amounts of inorganic salts.

This dual reactivity makes dimethyl carbonate a versatile intermediate for the replacement of dangerous chemicals such as phosgene for carbonylation processes and dimethylsulfate (DMS) or methyl chloride for methylation reactions. Table 1 reports major environmental benefits of DMC-based procedures [6].

In particular, the present contribution deals with the reaction of dimethyl carbonate carried out at high temperatures (140–220 °C), and it will describe the main features of methylation processes as well as some special applications of DMC and higher dialkyl carbonates (dibenzyl carbonate).

Table 1 Comparison between DMC- and phosgene- or dimethylsulfate-based reactions.

Phosgene or DMS	DMC
Dangerous reagent	Harmless reagent
Use of solvent	No solvent
Waste water treatment	No waste water
NaOH consumption	The base is catalytic
By-products: NaCl, Na_2SO_4	By-products: MeOH, CO_2
Exothermic	Slightly or not exothermic

REACTION CONDITIONS

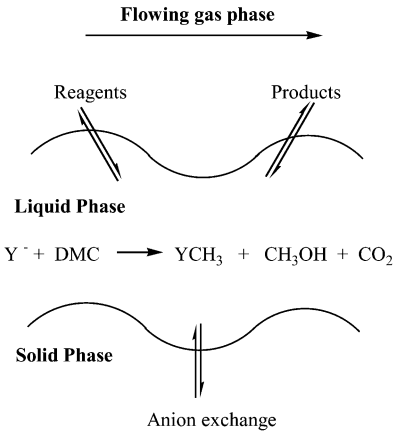
Since the DMC methylation reactions take place at a relatively high temperature (T > 160 °C) they must be carried out either in batch in an autoclave, or in the gas phase.

In the autoclave, DMC is maintained liquid by the autogenous pressure. In the gas phase, a flow reactor is necessary, DMC and the reagent are in the vapor phase and must be brought in contact with the catalyst. This apparent limitation of the operative conditions has, however, spurred the development of new applications and alternative reaction engineering, namely: gas–liquid phase-transfer catalysis (GL-PTC) [7], and continuously fed stirred tank reactor (CSTR) [8].

Accordingly, under different conditions DMC is used as a methylating reagent for a variety of substrates: phenols, thiols, thiophenols, aromatic amines, arylacetonitriles, arylacetoesters, aroxyacetonitriles, aroxyacetoesters, alkylarylsulfones, benzylarylsulfones, and lactones, either in continuous-flow (CF) conditions or in batch.

Continuous-flow methylations

The light terms of the class of dialkyl carbonates, particularly DMC and diethylcarbonate (DEC), are suitable to carry out reactions under GL-PTC conditions [7]. The GL-PTC technique, introduced by Tundo in the early 1980s, [7a] is briefly illustrated in Scheme 1 for the case of DMC-mediated processes.



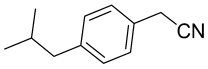
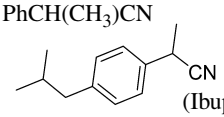
Scheme 1 Under GL-PTC conditions, the reaction takes place in the liquid film of PEG covering the solid particles of the base.

A mixture of reagents (DMC and a substrate YH) is vaporized (T = 180–210 °C) into a plug-flow cylindrical reactor whose enlarged section is depicted in Scheme 1. The reactor is filled with a bed composed of a catalytic base (usually K_2CO_3) which generates the reactant nucleophile Y^-, and a Phase-Transfer (PT) which acts as an anion activator. Both the base and PT-agent can be supported on inert solids (pumice, alumina). Under the reaction conditions, the PT catalyst melts, forming a liquid film (onto the solid particles), which adsorbs the reactants (Y^- and DMC) and desorbs gaseous products. These latter are collected by condensation at the outlet of the reactor.

Molten phosphonium salts [8] and polyethylene glycols (PEGs) can be used as PT agents. PEGs in particular, although less efficient than other PT agents, are desirable because they are thermally stable, nontoxic, and inexpensive [9].

Quantitative conversion and 100% mono-methyl selectivity are obtained from substrates such as the ones shown in Table 2 [7,10].

Table 2 Reactions of DMC with different nucleophiles under GL-PTC conditions.

Reagent	Product
ArOH	$ArOCH_3$
ArSH	$ArSCH_3$
$ArNH_2$	$ArNHCH_3$
ROH	$ROCOOCH_3 + (RO)_2CO$
$PhCH_2CN$	$PhCH(CH_3)CN$
	 (Ibuprofen® precursor)

The role of the PEG is to complex the alkaline metal cation, thereby increasing the basicity of the carbonate, which generates the reactive nucleophilic anion from the substrate. A general mechanistic scheme for the GL-PTC is shown in Scheme 1, which shows the immobilized PT liquid phase wherein the reaction takes place, with continuous transfer of the products and reactants between the gas and liquid phases.

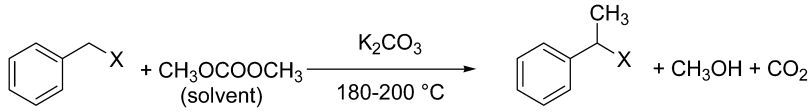
Batch methylation reactions

Batch methylation reactions with DMC must necessarily be run in sealed autoclaves given its boiling point (90 °C) and the reaction temperature (>160 °C).

Batch methylations with DMC can be carried out on a number of different substrates, and under such conditions the reaction mechanism can be easier investigated, since sampling of the reaction mixture is possible.

The most interesting and studied reaction, particularly in view of its selectivity, is the mono-*C*-methylation of arylacetonitriles (Scheme 2). These can be effectively mono-*C*-methlyated with selectivity greater than 99% at complete conversions [11]. This reaction is interesting in view of the synthesis of anti-inflammatory drugs. Table 3 shows some results.

Primary aromatic amines react with DMC under the same conditions (batch or GL-PTC, K_2CO_3, PEGs) and yield selectively the mono-*N*-methylated product [7,10].



Conversion > 90%, Mono-*C*-methylation selectivity > 99%

Scheme 2 Mono-*C*-methylation of arylacetic derivatives.

Table 3 Mono-*C*-methylation of $ArCH_2X$.

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

In the presence of suitable zeolites, and at atmospheric pressure, the same amines yield the corresponding mono-*N*-methyl derivatives [$ArNH(CH_3)$] with selectivities >90%, at conversions up to 95% (Scheme 3) [12].

$$ArNH_2 + CH_3OCOOCH_3 \xrightarrow[130\text{-}150\ ^\circ C]{\text{Y-zeolite}} ArNHCH_3 + CH_3OH + CO_2$$

Scheme 3 Mono-*N*-methylation of aromatic amines.

Likewise, in the presence of weak inorganic bases (K_2CO_3), the reactions of DMC with sulfones bearing-methylenic groups (RCH_2SO_2R'; R = Alkyl, Aryl; R' = Aryl) afford the respective mono-*C*-methylated compounds [$RCH(CH_3)SO_2R'$] with >99% selectivity, at complete conversions (Scheme 4) [13].

$$RCH_2SO_2Ar + CH_3OCOOCH_3 \xrightarrow[180\text{-}210\ ^\circ C]{K_2CO_3} RCH(CH_3)SO_2Ar + CH_3OH + CO_2$$

Scheme 4 Mono-*C*-methylation of alkylarylsulfones.

In summary, all the nucleophiles indicated until now are efficiently methylated (and mono-methylated were applicable) with DMC, both under CF and batch conditions.

MECHANISM

Experimental evidence of DMC-mediated alkylation of CH_2-active compounds with DMC supports the hypothesis that the reaction does not proceed through a S_N2 displacement of the $ArCH^{(-)}X$ nucleophile (X = CN, CO_2Me) on DMC ($B_{Al}2$ mechanism) [14]. Rather, the selectivity arises from consecutive reactions involving two intermediate species observed during the reaction: $ArCH(CO_2Me)X$ (**3**) and $ArC(CH_3)(CO_2Me)X$ (**4**) (Scheme 5).

$$ArCH_2X + B \rightleftharpoons ArC^{(-)}HX + BH^+ \quad (1)$$
(**2**)

$$ArC^{(-)}HX + (CH_3O)_2CO \rightleftharpoons ArCH(COOCH_3)X + CH_3O^- \quad (2)$$
(**2**$^-$) (**3**)

$$BH^+ + CH_3O^- \rightleftharpoons B + CH_3OH \quad (3)$$

$$ArCH(COOCH_3)X + B \rightleftharpoons ArC^{(-)}(COOCH_3)X + BH^+ \quad (4)$$
(**3**$^-$)

$$ArC^{(-)}(COOCH_3)X + (CH_3O)_2CO \longrightarrow Ar{-}\underset{\displaystyle CH_3}{\overset{\displaystyle H_3COOC}{\overset{|}{\underset{|}{C}}}}{-}X + CO_2 + CH_3O^- \quad (5)$$
(**4**)

$$Ar{-}\underset{\displaystyle CH_3}{\overset{\displaystyle H_3COOC}{\overset{|}{\underset{|}{C}}}}{-}X + CH_3O^- \rightleftharpoons ArC^{(-)}(CH_3)X + (CH_3O)_2CO \quad (6)$$
(**1**$^-$)

$$ArC^{(-)}(CH_3)X + BH^+ \rightleftharpoons ArCH(CH_3)X + B \quad (7)$$
(**1**)

Overall reaction

$$ArCH_2X + (CH_3O)_2CO \longrightarrow ArCH(CH_3)X + CO_2 + CH_3OH$$
(**2**) (**1**)

Scheme 5 Mechanism of the mono-*C*-methylation of CH_2-active compounds (X = CN, CO_2CH_3) with DMC.

Initially, the carbanion [$ArCH^{(-)}X$] undergoes a methoxycarbonylation reaction by an attack to the acyl carbon of DMC ($B_{Ac}2$ mechanism); the resulting intermediate [$ArCH(CO_2Me)X$, (**3**)] reacts through its anion [$ArC^{(-)}(CO_2Me)X$, ($\mathbf{3}^{-}$)] with the alkyl carbon of DMC to yield the corresponding methyl derivative [$ArC(CH_3)(CO_2Me)X$, (**4**); $B_{Al}2$ mechanism]. Finally, compound **4** is subjected to a demethoxycarbonylation reaction to the final product [$ArCH(CH_3)X$].

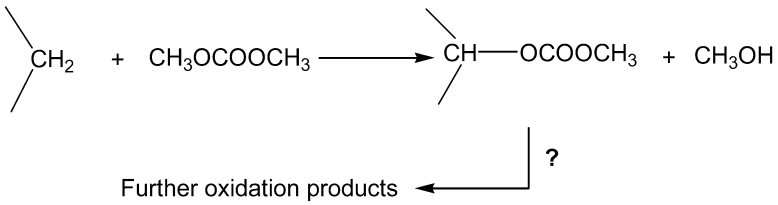
On the whole, the comparison of the kinetic behavior of the investigated steps reveals that the non-equilibrium methylation reaction is crucial to drive the overall process to completion. In fact, the higher rate of step 5 allows both the rapid consumption of **3** and the accumulation of **4**, which serves as a reactant for step 6; in other words, both equilibria 2 and 6 are controlled by the irreversible reaction 5.

The mechanism evinces the crucial action of the methoxycarbonyl group, which by increasing the acidity of **3** acts as a promoter, significantly accelerating step 5. The reasons for this promoting effect, and the related $B_{AC}2/B_{AL}2$ selectivity are still not completely understood.

Finally, it should be noted that esters (X = COO CH_3) and nitriles (X = CN) behave in an opposite manner in the demethoxycarbonylating vs. methylating step: for nitriles, the methylation rate predominates over methoxycarbonylation; for esters, demethoxycarbonylation takes place preferentially.

DMC AS GREEN OXIDANT

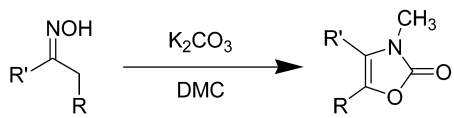
DMC can also be considered as an organic oxidant (Scheme 6). In fact, nucleophilic reagents which undergo carboxymethylation end up in a higher oxidation state than their precursors.



Scheme 6 DMC as green oxidant.

Some examples of this behavior, applied to synthetic organic chemistry have been reported by us.

Oximes react with DMC to yield *N*-methyl oxazolinones [15]. The reaction is quite general for oximes, including cyclic ones, provided an α-methylene is present (Scheme 7).

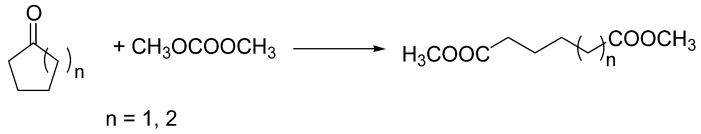


Scheme 7 *N*-methyl oxazolinones from oximes.

The reactions were carried out in a steel autoclave at 180–190 °C, and yields were up to 48%. The mechanism is likely a [3,3]-sigmatropic rearrangement where DMC expresses its dual carboxymethylating/methylating reactivity.

Ketones

A potentially valuable green industrial application of DMC as an oxidant regards its use in the synthesis of α,ω-diesters from cyclic aliphatic ketones [16]. In particular, cyclopentanone and cyclohexanone react with DMC (or DEC) and a base (K_2CO_3) to yield adipic and pimelic methyl (or ethyl) esters, respectively (Scheme 8). This reaction has 100% atom economy, [3] meaning that all the atoms of the reagents end up in the product.



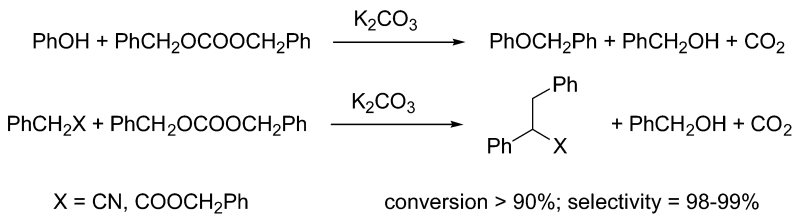
Scheme 8 α,ω-Diesters from cyclic aliphatic ketones.

Such diesters are of interest for the production of polyesters and polyamides [17]. The proposed mechanism involves a retro-Claisen condensation. This application, along with being intrinsically green, is also industrially remarkable. In fact, it may replace the inorganic waste and N_2O-producing oxidation of cyclohexanone by nitric acid (for the synthesis of adipic acid), and allow the industrially clean production of C_6 and C_7 α,ω-diesters, which are the building blocks for nylon 6,6 and 7,7, respectively.

OTHER ORGANIC CARBONATES

Having dealt until now exclusively with DMC, the question arises of what happens with other carbonates. Naturally $B_{AL}2$ reactivity decreases rapidly as the alkyl group of the alkly carbonate grows bigger. The only exception being dibenzylcarbonate, whose benzylation activity is comparable to the methylating strength of DMC.

Dibenzylcarbonate (DBzlC) can be used to benzylate phenylacetonitrile, benzyl phenylacetate and phenol, in refluxing DMF, and with K_2CO_3 catalyst (Scheme 9) [18]. DBzlC seems to be particularly attractive as a selective benzylating agent because simple reaction conditions can be used, and the high selectivity observed (at almost complete conversion) makes work-up and separation of the mono-*C*-alkyl product very easy.



Scheme 9 Benzylation of phenol and CH_2-active compounds with DBzlC.

The mechanism is analogous to the one sketched out for DMC (Scheme 6), and involves consecutive carboxybenzylation/benzylation steps.

CONCLUSIONS

DMC is a truly eco-friendly methylating reagent. In the vast majority of the cases here described, the final reaction mixture is clear and yields no tars or other by-products. DMC paves the way to the devel-

opment of other new green alkylating agents as well. In fact, trimethyl orthoformate has recently been shown to function as an alkylating agent for arylacetonitriles into 2-arylpropionitriles [19]. Analogously, there are some examples of methyl esters of carboxylic acids, such as benzoates [20] and acetates, used as methylating agents.

In conclusion, the powerful methylating ability of dimethylcarbonate is just the initial stepping stone toward the development of new environmentally acceptable and industrially useful alkylating agents.

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