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Green Organic Syntheses: Organic Carbonates As Methylating Agents

PIETRO TUNDO, ALVISE PEROSA
Dipartimento di Scienze Ambientali, Università Ca' Foscari, Dorsoduro 2137 – 30123, Venezia, Italy

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ABSTRACT: Dimethylcarbonate (DMC) is a valuable methylating reagent that can replace methyl halides and dimethylsulfate in the methylation of a variety of nucleophiles. It couples tunable reactivity and unprecedented selectivity towards mono-*C*- and mono-*N*-methylation. In addition, it is a prototype example of a *green reagent*, because it is nontoxic, is made by a clean process, is biodegradable, and reacts in the presence of a catalytic amount of base, thereby avoiding the formation of undesirable inorganic salts as by-products. Depending on the reaction conditions, DMC can be reacted under plug-flow, CSTR, or batch conditions. Other remarkable reactions are those where DMC behaves as an oxidant. The reactivity of other carbonates is reported as well. © 2002 The Japan Chemical Journal Forum and John Wiley & Sons, Inc. Chem Rec 2: 13–23, 2002

Key words: methylation; dimethylcarbonate; green chemistry; phase-transfer catalysis

Introduction

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

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

In particular, an underdeveloped area of chemistry is in the replacement of reagents that are toxic, dangerous, produced by eco-unfriendly processes, not selective, and that produce inorganic salts that are expensive to dispose of—in short, not green. Typical examples of undesirable reagents used for methylation and carboxymethylation are methyl halides (CH_3X), dimethylsulfate (DMS), and phosgene ($COCl_2$). Examples of the methylation of phenol by CH_3X and DMS to give anisole, and of carboxymethylation of an alcohol by $COCl_2$ are shown in Scheme 1. These toxic and waste producing reagents have a valuable green alternative in dimethylcarbonate (DMC).

Since 1980, with the development of gas liquid phase transfer catalysis (GL-PTC),[5] our group has had a long-standing interest in the use of DMC as an environmentally friendly substitute for DMS and CH_3X in methylation reactions, and for phosgene in carboxymethylation reactions (Scheme 2).

Among the specific synthetic and environmental advantages of DMC, and of alkyl carbonates in general, is that they are esters of carbonic acid, that is, derivatives of CO_2, an envi-

Correspondence to: P. Tundo, e-mail: tundop@unive.it

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$$PhOH + (CH_3)_2SO_4 + NaOH \longrightarrow PhOCH_3 + NaCH_3SO_4 + H_2O$$

$$PhOH + CH_3I + NaOH \longrightarrow PhOCH_3 + NaI + H_2O$$

$$2ROH + COCl_2 + 2NaOH \longrightarrow ROCOOR + 2NaCl + 2H_2O$$

Scheme 1. Methylation and carboxymethylation using DMS, CH_3I, and $COCl_2$.

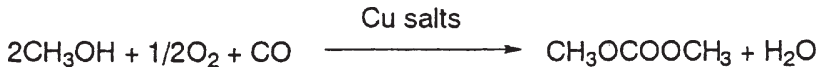
$$PhOH + CH_3OCOOCH_3 \xrightarrow{\text{cat. base}} PhOCH_3 + CO_2 + CH_3OH$$

$$ROH + CH_3OCOOCH_3 \xrightarrow{\text{cat. base}} ROCOOCH_3 + CH_3OH$$

Scheme 2. Methylation and carboxymethylation using DMC.

Pietro R. Tundo graduated from the University of Bologna (chemistry, 1969). He was a Professor at the University of Torino (Assistant: 1972–1983; Associated: 1983–1986) and at the University of Messina (1986–1989). Since 1989, he has been a Full Professor of organic chemistry at Ca' Foscari University of Venice. He was a Research Associate, Senior Research Associate at the University of College Station (Texas: 1979–1981), Potsdam (New York: 1989–1990), and Syracuse (New York: 1991–1992). He is the founder and President of the Interuniversity Consortium "Chemistry for the Environment" (INCA: 1993). He is chairman of the IUPAC Interdivisional Sub-Committe on Green Chemistry and a member of the OECD Issue Team for the Sustainable Chemistry Program. He is the author of about 150 scientific papers and 25 patents on synthetic and mechanistic organic chemistry. He is the sole author of the book Continuous Flow Methods in Organic Synthesis. ■

Dr. Perosa received his Laurea degree in 1992 from Ca' Foscari University in Venice, Italy, with a thesis on homogeneous catalysis. As a Fulbright scholar at Case Western Reserve University, Cleveland, Ohio, he obtained a PhD in organometallic chemistry in 1996. His current interests are in research on dimethylcarbonate as a green reagent, on the catalytic multiphase reduction of haloaromatics, and on the development of fullerene based devices. He is also active in the development of green chemistry research and education. ■



Scheme 3. Enichem synthesis of DMC.

ronmentally acceptable compound, which does not cause emissions of volatile organic compounds (VOCs) in the atmosphere.

This article reports on a survey of the chemistry of organic carbonates as methylating agents, with particular emphasis on DMC, under a variety of conditions. The substrates on which the reaction can occur are phenols, aromatic amines, sulfones, thiols, and methylene-active compounds, the latter being in some cases precursors in the synthesis of anti-inflammatory drugs.

The discussion will cover the following points:

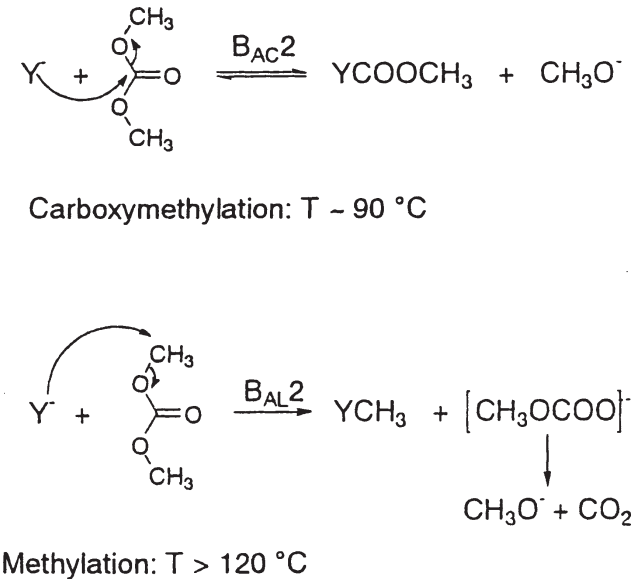
1. Unique features of DMC.
2. Reaction conditions.
3. Mechanism.
4. DMC as a green oxidant.
5. Other organic carbonates.

Unique Features of DMC

DMC has a number of properties that make it a truly green reagent, particularly if compared to CH_3X and DMS, both commonly used as alkylating agents, or to phosgene, which is used as a carboxymethylating reagent (Scheme 1).

1. First of all, DMC is biodegradable and nontoxic,[6,7] and it does not have irritating or mutagenic effects either by contact or inhalation.[8] Therefore, it can be handled safely without special precautions, unlike CH_3X, DMS, and phosgene, which are irritating, poisonous, and mutagenic.
2. Also, DMC is not produced from phosgene, but by catalytic oxidative carbonylation of methanol with oxygen, a process developed by Enichem (Italy)[9,10] and UBE.[11] This process for the production of DMC avoids the use of highly dangerous phosgene, which eventually contaminates the product. In addition, it is free from the formation of inorganic salts, which eventually need to be disposed of (Scheme 3).
3. DMC exhibits a versatile and tunable chemical reactivity: depending on the experimental conditions, it can give either carboxymethylation or methylation of a nucleophile (Scheme 4).[12]

At the reflux temperature (T = 90°C), DMC acts as a carboxymethylating agent (in place of phosgene) by a $B_{AC}2$ (bimolecular, base catalyzed, acyl cleavage, nucleophilic substitution) mechanism where the nucleophile attacks the carbo-



Scheme 4. Nucleophilic substitution on DMC by $B_{AC}2$ and $B_{AL}2$ mechanisms.

nyl carbon of DMC, giving the transesterification product. At higher temperatures (usually $T \geq 160$°C) where DMC acts as a methylating agent a $B_{AL}2$ (bimolecular, base catalyzed, alkyl cleavage, nucleophilic substitution) mechanism predominates, where the nucleophile attacks the methyl group of DMC. Of the two, only the methylation reaction is irreversible because the CH_3OCOO^- anion that is formed decomposes to methoxide and CO_2.

Because both methylation and methoxycarbonylation generate CH_3O^-, both reactions can be conducted in the presence of catalytic amounts of base. This avoids the formation of unwanted inorganic salts as by-products and the related disposal problems. In principle, the methanol produced can be recycled for the production of DMC.[13] In contrast, methylation with RX or DMS and carbonylation with phosgene all generate stoichiometric amounts of inorganic salts.

Reaction Conditions

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

In an autoclave, DMC is maintained liquid by autogenous pressure. In the gas phase, a flow reactor is necessary, DMC and the reagent are in the vapor phase, and they must be brought into

contact with the catalyst. This apparent limitation of the operative conditions, has, however, spurred the development of new applications and alternative reaction engineering, namely, GL-PTC and continuously fed stirred tank reactor (CSTR).

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 under continuous flow (CF) conditions or in batch.

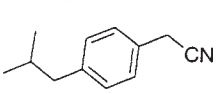
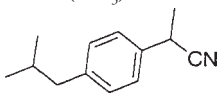
Continuous Flow

Under GL-PTC conditions, a gaseous stream of reagent and DMC flows over a catalytic bed (usually a porous inorganic support coated with a base that activates the nucleophile) coated with a phase transfer (PT) agent. Phosphonium salts,[14] crown ethers,[15] and poly(ethylene 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.[16,17]

The continuous flow methylation reaction with DMC takes place by GL-PTC[5,18] in a plug-flow reactor made by a bed of K_2CO_3 coated with PEG 6000 (0.5–5% mol. eq.), heated to 160–180°C. A mixture of DMC and substrate are fed into the reactor and the methylated product is condensed and collected at the other end. Quantitative conversion and 100% mono-methyl selectivity are obtained from substrates such as the ones shown in Table 1.[4,19–24]

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

Table 1. Reactions of DMC with different nucleophiles under GL-PTC conditions.

Reagent	Product	Yield
ArOH	$ArOCH_3$	100%
ArSH	$ArSCH_3$	100%
$ArNH_2$	$ArNHCH_3$	100%
ROH	$ROCOOCH_3 + (RO)_2CO$	100%
$PhCH_2CN$	$PhCH(CH_3)CN$	100%
		
	(Ibuprofen® precursor)	100%

Conditions: GL-PTC, plug-flow reactor, catalyst: K_2CO_3 coated with 0.5–5 mol % of PEG 6000, T = 160–180°C.

An example reaction is the methylation of phenol under GL-PTC conditions (Fig. 2). In a typical experimental procedure, a 2:1 mixture of DMC and phenol flows over a catalytic bed made of 95 g of K_2CO_3 coated with 5 wt % PEG 6000 at 180°C, with a flow rate (liquid) of 24 mL/min. Pure anisole is recovered.[19,20]

Pyrocathecol and hydroquinone can also be selectively mono- or di-alkylated under CF conditions in a pilot plant scale.[12]

An alternative CF methodology was developed as well, by using a CSTR (Fig. 3).[25] In a CSTR, the gas phase remains in contact with the catalytic phase for a long enough time to react. At atmospheric pressure and at T = 160–200°C, phenol is transformed quantitatively into anisole under gradientless con-

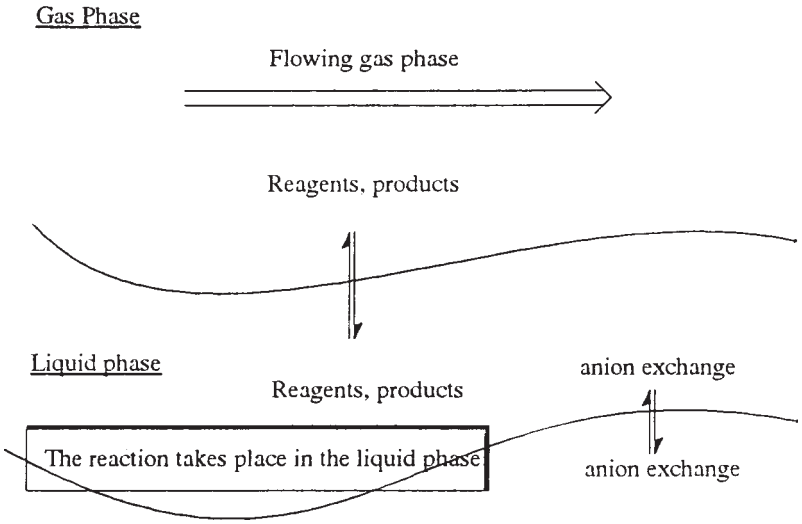


Fig. 1. General mechanism of gas liquid phase transfer catalysis (GL-PTC).

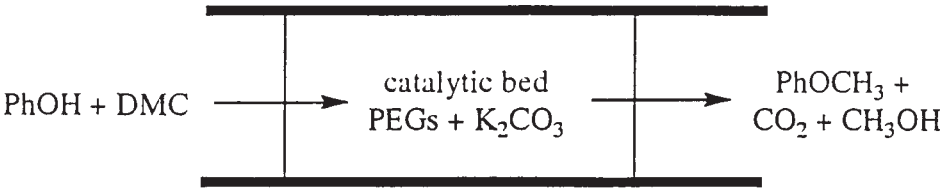


Fig. 2. CF methylation of phenol in a plug-flow reactor under GL-PTC conditions.

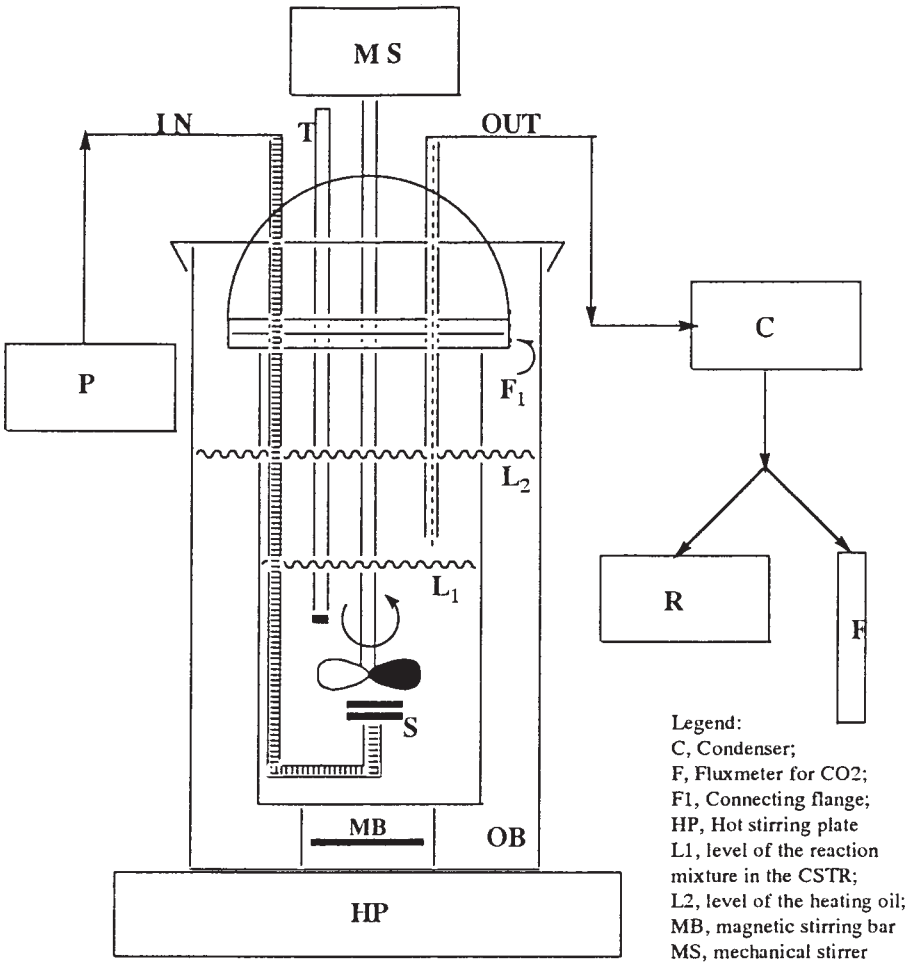


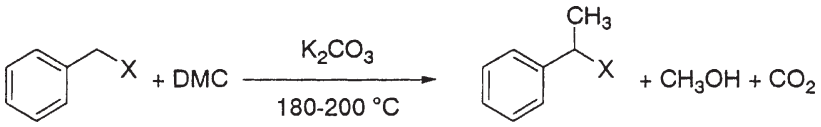
Fig. 3. CSTR reactor.

ditions with a space velocity of 9×10^{-2} h^{-1}, using a 1.05:1 mixture of DMC and phenol as feed. The reaction can run without interruption for 2 weeks.

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 performed on a number of different substrates and, under such conditions, the reaction mechanism can be investigated, because sampling of the reaction mixture is possible. For compounds susceptible to multiple methylation, the reaction mechanism is of special interest because, as will be seen, methylation with DMC totally inhibits multiple substitution in both *N*- and *C*-alkylation, for primary aromatic amines and for CH_2-active compounds, respectively.



Scheme 5. Mono-*C*-methylation of arylacetonitriles.

The most interesting and studied reaction, particularly in view of its selectivity, is the mono-*C*-methylation of arylacetonitriles (Scheme 5). These can be effectively mono-*C*-methylated with selectivity greater than 99% at complete conversions.[26] The same reaction under PTC conditions using CH_3I yielded a mono-dimethylated ratio, which never exceeded 2.4.[27] This reaction is interesting in view of the synthesis of anti-inflammatory drugs. Table 2 shows some results.

Primary aromatic amines react with DMC under the same conditions (batch or GL-PTC, K_2CO_3, PEGs) and selectively yield the mono-*N*-methylated product.[12,21] 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 6).[28]

Similarly, in the presence of weak inorganic bases (K_2CO_3), the reactions of DMC with sulfones bearing α-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 7).[29]

In summary, all the nucleophiles indicated up to now are efficiently methylated (and mono-methylated where 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).[30] 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 8).

Initially, the carbanion [$ArCH^{(-)}X$] undergoes a methoxycarbonylation reaction by an attack on the acyl carbon of DMC ($B_{Ac}2$ mechanism). The resulting intermediate [$ArCH(CO_2Me)X$, (3)] reacts through its anion [$ArC^{(-)}(CO_2Me)X$, (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 [$ArCH(CH_3)X$].

The kinetic analysis conducted on the mechanism of Scheme 8[31] allows some general considerations.

The rate-determining step of the overall transformation is the methoxycarbonylation reaction. The similarity of k_{-2} and k_6 reveals that both the starting reagent 2a and its methyl derivative 1a undergo demethoxycarbonylation reactions at comparable rates while the methylation step of the intermediate 4a is the fastest reaction.

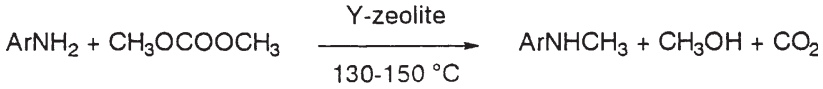
Overall, the comparison of the kinetic behavior of the investigated steps reveals that the nonequilibrium methylation reaction is crucial in driving the overall process to completion. In fact, the higher rate of step 5 allows both the rapid consumption of 3a and the accumulation of 4a, which serves as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

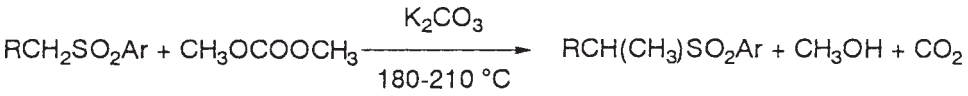
Table 2. Mono-*C*-methylation of arylacetonitriles.

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

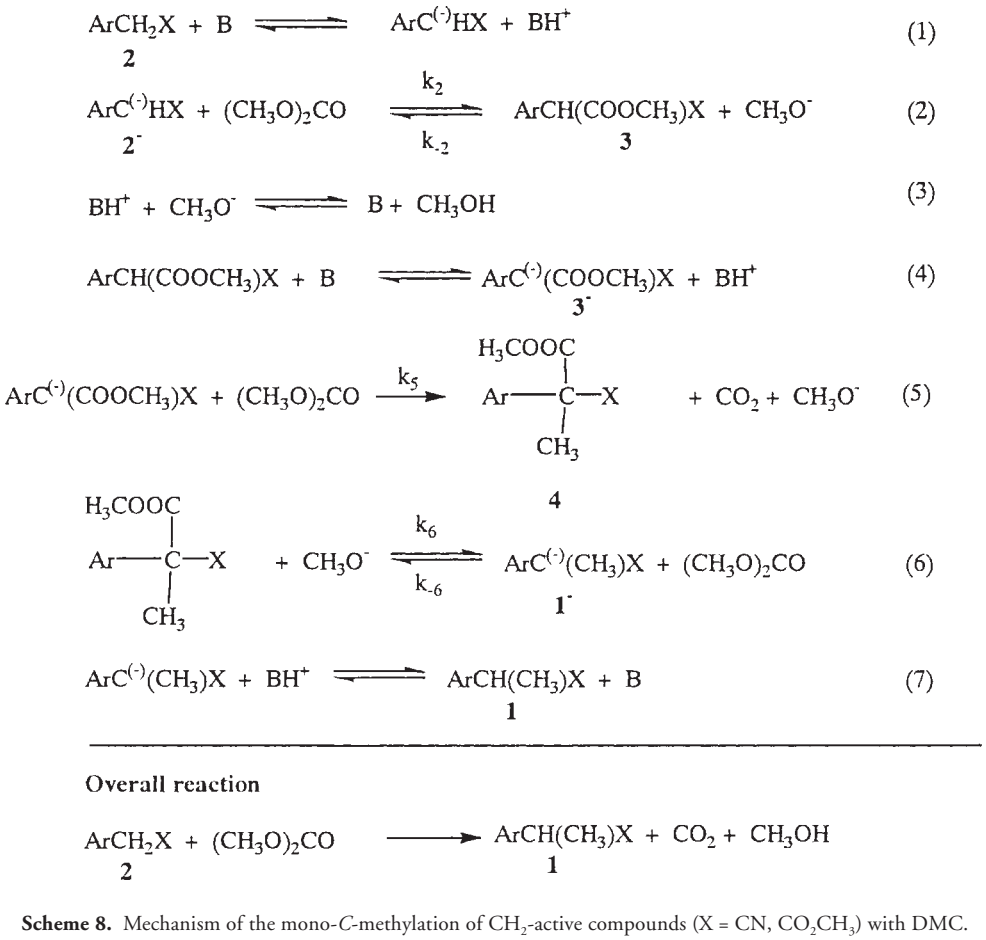
Conditions: Autoclave, substrate: DMC:K_2CO_3 = 1:18:2 molar ratio, T = 180–220°C.



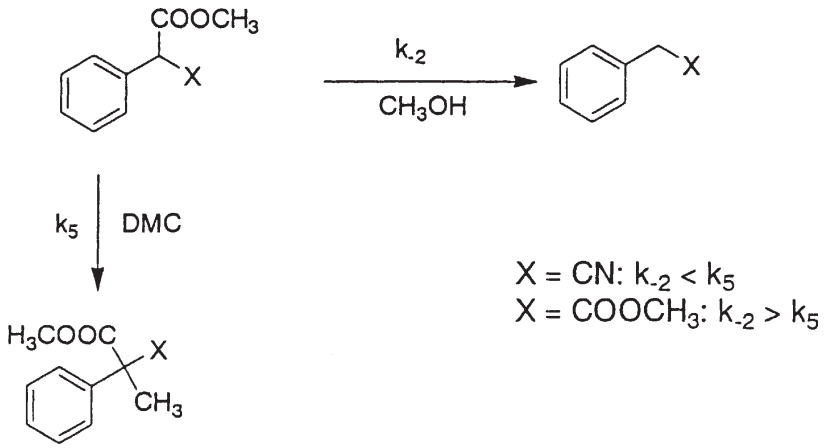
Scheme 6. Mono-*N*-methylation of aromatic amines.



Scheme 7. Mono-*C*-methylation of alkylarylsulfones.



Scheme 8. Mechanism of the mono-*C*-methylation of CH_2-active compounds (X = CN, CO_2CH_3) with DMC.



Scheme 9. Demethoxycarbonylation (k_2) versus methylation (k_5) for CH_2-active compounds.

Finally, it should be noted that esters and nitriles in the demethoxycarbonylating step behave in a manner opposite to those in the methylating step. For nitriles, the methylation rate predominates over methoxycarbonylation; for esters, demethoxycarbonylation predominates (Scheme 9).

DMC As a Green Oxidant

DMC can also be considered as an organic oxidant. In fact, nucleophilic reagents that undergo carboxymethylation end up in an oxidation state higher than their precursors (Scheme 10).

We have reported some examples of this behavior applied to synthetic organic chemistry.

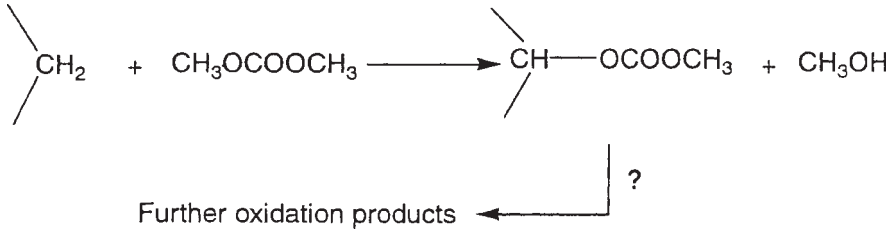
Oximes

Oximes react with DMC to yield *N*-methyl oxazolinones.[32] This reaction is quite general for oximes, including cyclic ones, provided an α-methylene is present (Scheme 11).

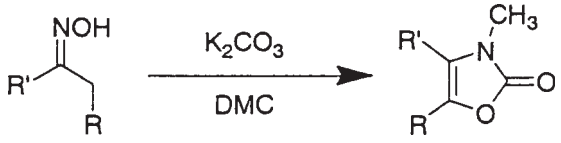
The reactions were conducted in a steel autoclave at 180–190°C, and yields were up to 48%. The mechanism is like a [3,3]-sigmatropic rearrangement where DMC expresses its dual carboxymethylating/methylating reactivity (Scheme 12).

Imines

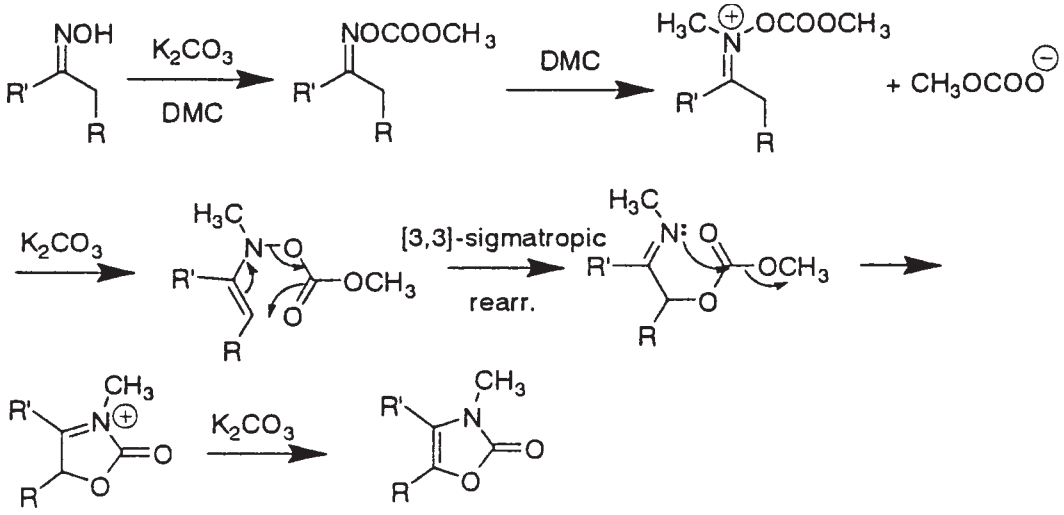
The reaction of allylimines under the same conditions provides further evidence for the mechanism of Scheme 12. In



Scheme 10. DMC as a green oxidant.



Scheme 11. *N*-methyl oxazolinones from oximes.



Scheme 12. Mechanism for the synthesis of *N*-methyl oxazolinones from oximes.

fact, *N*-cyclohexylideneallylimine undergoes *N*-methylation by DMC followed by an aza-Claisen rearrangement (Scheme 13).[28]

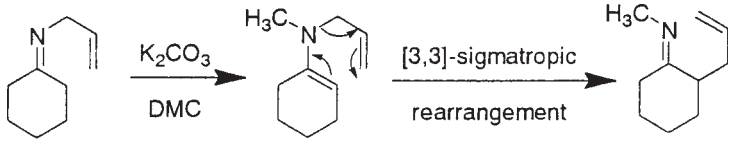
Ketones

A potentially valuable green industrial application of DMC as an oxidant is its use in the synthesis of α,ω-diesters from cyclic aliphatic ketones.[33] 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 14). This reaction has 100% atom economy,[3] meaning that all of the atoms of the reagents end up in the product. Such diesters are of interest for the production of polyesters and polyamides.[34] The proposed mechanism involves a retro-Claisen condensation.

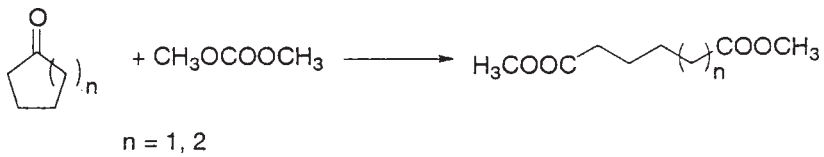
This application, along with being intrinsically green, is also industrially remarkable. In fact, it may replace the inorganic waste- and N_2O-producing oxidation of cyclohexanone by nitric acid (for the synthesis of adipic acid), and enable the industrially clean production of C_6 and C_7 α,ω-diesters, which are the building blocks for nylon 6,6 and 7,7, respectively.

Other Organic Carbonates

Up to now, having discussed DMC exclusively, the question arises as to what happens with other carbonates. Naturally, $B_{AL}2$ reactivity decreases rapidly as the alkyl group of the alkyl carbonate grows larger (see Table 3 for comparison). The only exception to this decrease is dibenzylcarbonate (DBzlC), which has a benzylation activity that is comparable to the methylating strength of DMC. Mixed alkyl methyl carbonates ROCOOCH$_3$ have a double advantage: they exclusively me-



Scheme 13. Reaction of *N*-cyclohexylideneallylimine with DMC.



Scheme 14. α,ω-Diesters from cyclic aliphatic ketones.

Table 3. Reactions of phenol with different alkyl methyl carbonates.[a]

Entry	R =	Time (h)[b]	Products (%) PhOCH$_3$	PhOR
1	Et	15	90	10
2	n-Pr	17	95	5
3	i-Pr	40	73	2
4	n-Bu	15	97	3
5	$CH_3O(CH_2)_2O(CH_2)_2$	20	>99	–
6	Bn	5	84	16
7	Allyl	21	83	17

[a] T = 120°C, pheno (3.3 mmol):K_2CO_3:3 = 1:1.5:5. DMF (30mL).
[b] Time for complete conversion of the substrate.

thylate (as long as R > *n*-C_3) and sometimes have a high enough boiling point to do so at atmospheric pressure.

DBzlC

DBzlC can be used to benzylate phenylacetonitrile, benzyl phenylacetate, and phenol, in refluxing DMF with a K_2CO_3 catalyst (Scheme 15).[35] 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) facilitates work-up and separation of the mono-*C*-alkyl product. The mechanism is analogous to the one sketched out for DMC (Scheme 8), and involves consecutive carboxybenzylation/benzylation steps.

Mixed Organic Carbonates

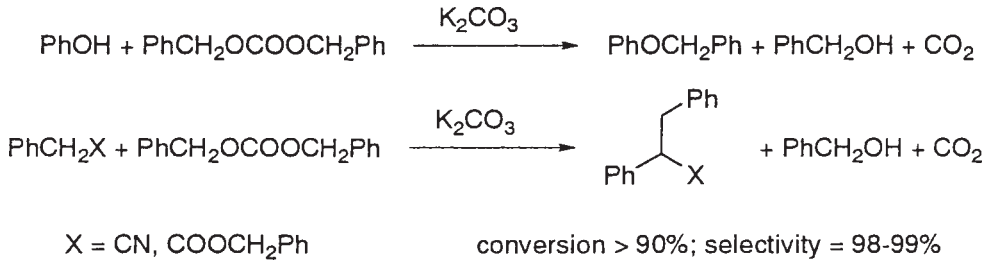
A major operative drawback of DMC methylations is the reaction temperature (≥160°C), which is well over the boiling point of DMC (90°C). As discussed earlier, pressurized vessels are necessary under batch conditions, while under CF conditions substrates must have a relatively high vapor pressure in order to be fed into suitable plug-flow reactors. This problem was overcome by using asymmetric alkyl methyl carbonates ($ROCOOCH_3$) as methylating agents.[36] The concept behind this use was that a heavy enough R group would raise the boiling point of the carbonate and allow reactions at ambient pressure while the steric bulk of the R moiety would favor methylation with respect to the competitive formation of the alkyl aryl ethers (ArOR).

Our results show that good chemoselectivity (>99%) in the *O*-methylation of phenols is obtained at atmospheric pressure with $ROCOOCH_3$ compounds, provided that R has at least three carbon atoms (Scheme 16, Table 3).

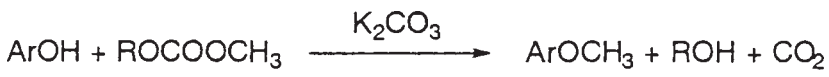
Different phenols can be methylated at atmospheric pressure using carbonate $CH_3O(CH_2)_2O(CH_2)_2OCOOCH_3$ at 140°C in the presence of triglyme and K_2CO_3. Table 4 shows the results.

In all cases, the reaction proceeds with a very high methyl chemoselectivity (95–99%) and good yields in isolated products (80–86%). In a similar manner, amines can be methylated with $CH_3O(CH_2)_2O(CH_2)_2OCOOCH_3$ in the presence of NaY faujasite.[37]

By combining zeolite reactivity and the asymmetric carbonate, primary aromatic amines (*p*-$XC_6H_4NH_2$, X = H, Cl, NO_2) can be mono-*N*-alkylated in a single step with asymmetrical dialkyl carbonate $CH_3O(CH_2)_2O(CH_2)_2OCOOCH_3$, in the presence of a commercially available NaY faujasite. No solvents are required. Mono-*N*-alkyl anilines are obtained with a very high selectivity (90–97%) in good to excellent yields (68–94%) on a preparative scale. The reaction probably takes place within the polar zeolite cavities and through the combined effects of the dual acid-base properties of the catalyst.



Scheme 15. Benzylation of phenol and CH_2-active compounds with DBzlC.



Scheme 16. Methylation of phenols with mixed organic carbonates ($ROCOOCH_3$).

Table 4. *O*-Methylation of different phenols by methyl 2-(2-methoxyethoxy)ethyl carbonate.[a]

Entry	Ar	Conv. (%)	Yield (%) [b]	Purity (%)
2	Ph	100	81	>99
3	*p*-MePh	100	79	>99
5	2-Naphthyl	100	83	>99

[a] T = 140°C, substrate::K_2CO_3:3e = 1:1.1:5. Triglyme (50mL).
[b]Isolated yields of O-methylated derivatives.

Conclusions

DMC is a truly eco-friendly methylating reagent. In the vast majority of cases described here, the final reaction mixture is clear, and yields no tars or other by-products. DMC paves the way to the development of other new green alkylating agents as well. For example, trimethyl orthoformate has recently been shown to function as an alkylating agent for arylacetonitriles into 2-arylpropionitriles.[38] Analogously, there are some examples of methyl esters of carboxylic acids, such as benzoates[39] and acetates, being used as methylating agents.

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

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