

Green approaches to highly selective processes: Reactions of dimethyl carbonate over both zeolites and base catalysts*

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Abstract: Nowadays available by clean industrial processes, dimethyl carbonate (DMC) possesses properties of nontoxicity and biodegradability which make it a true *green* reagent/solvent to devise syntheses that prevent pollution at the source. In particular, the versatile reactivity of DMC allows both methylation and carboxymethylation protocols that can replace conventional and highly noxious reagents such as methyl halides (and dimethyl sulfate, DMS) and phosgene. In the field of DMC-mediated methylations, representative examples are the reactions of DMC with CH₂-active compounds and primary aromatic amines. In the presence of organic/inorganic bases or zeolites (faujasites) catalysts, these processes proceed with unprecedented selectivity (up to 99 %, at complete conversion) toward the corresponding mono-C- and mono-N-methyl derivatives, a result hitherto not possible with conventional alkylation reagents.

In the case of ambident amines (e.g., aminophenols, aminobenzyl alcohols, aminobenzoic acids, and aminobenzamides), the unique combination of DMC and zeolites allows not only a very high mono-N-methyl selectivity, but also a complete chemoselectivity toward the amino group. The other nucleophilic functionalities (OH, CO₂H, CH₂OH, CONH₂) are fully preserved from alkylation and/or transesterification reactions, usually observed over basic catalysts.

Keywords: dimethyl carbonate; methylation reaction; base catalysts; faujasite catalysts; organic synthesis.

INTRODUCTION

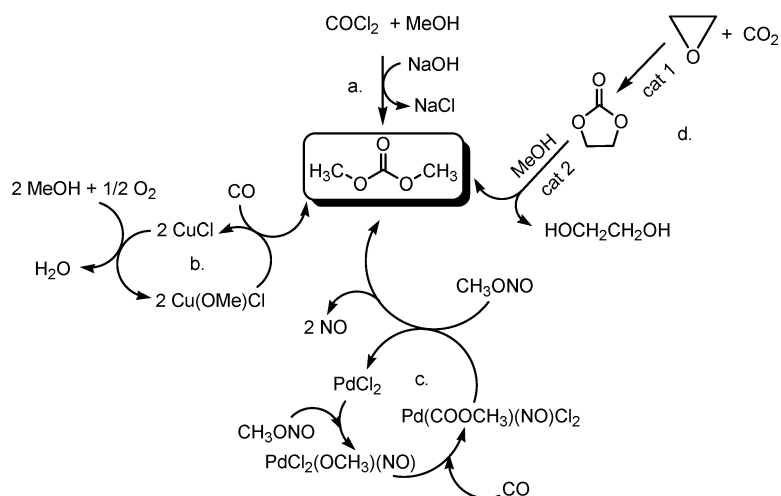
In the past two decades, the need for safer and more selective processes has fueled a growing interest for dimethyl carbonate (MeOCO₂Me, DMC), as a reagent/solvent for methylation and/or carboxymethylation protocols [1]. The green features of DMC can be readily recognized in several aspects which include not only its general reactivity and properties, but also its methods of synthesis as well.

Industrial preparation of DMC

Although the old phosgene route is still active in both SNPE and BASF plants (Scheme 1a) [2], this process is highly undesirable from both safety and environmental standpoints: the toxicity/corrosivity

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**Scheme 1**

of phosgene, the generation of contaminated salts, and careful waste-water treatments are major drawbacks.

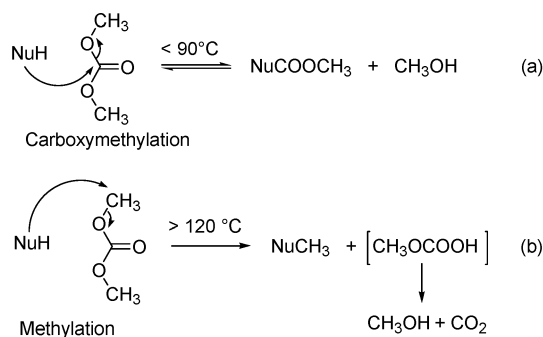
Today, modern units for the synthesis of DMC operate with clean technologies which are based on three different reactions (Schemes 1b–d).

- The oxycarbonylation of methanol catalyzed by copper salts (Scheme 1b), represents the first ever reported green and industrially viable alternative for the production of DMC in up to 12 000 t/y [3]. Key advantages of this process, patented by Enichem in the early 1980s [4], are the high safety improvement with respect to the phosgenation of MeOH, the high selectivity (and therefore, purity in the final product), and the sole formation of water as a by-product.
- The carbonylation of methyl nitrite over a Pd-catalyst (Scheme 1c), developed by UBE Industries in 1993 [5], is also a recognized eco-friendly method. In this case, methyl nitrite, which is one of the substrates for the formation of DMC, acts simultaneously as an efficient oxidant of the metallic catalyst. This expedient guarantees the catalytic cycle and further enhances the process safety since the direct introduction of O_2 (as in the Enichem route), is no longer necessary. UBE plants operate on a 3000 t/y capacity.
- The two-stage process of insertion of CO_2 into an epoxide, followed by a transesterification reaction with MeOH (Scheme 1d), is the most recent breakthrough in the production of DMC [6]. This strategy represents by far, the greener and more promising solution stemming from a naturally abundant and cheap building block such as carbon dioxide. The two reactions are presently carried out in separate units through established procedures [6,7]; though, many efforts are underway to set up a one-pot catalytic method [8].

Overall, thanks to the choice of raw materials, catalysts, conditions, etc., processes based on reactions i–iii actually prevent pollution at the source and impart the essential green attribute of nontoxicity to DMC [9].

General reactivity of DMC

In addition to its synthesis, the flexible reactivity of DMC is also a key feature to devise clean transformations without noxious reagents and wastes as well. DMC, in fact, possesses two electrophilic centers (the carbonyl and methyl carbon atoms), which, in the presence of a generic nucleophile (NuH), may undergo two distinct reactions (Schemes 2a,b) [10].

**Scheme 2**

In the first process (a), the nucleophile reacts through an addition/elimination mechanism, with the carbonyl group, and a carboxymethylated product (NuCO_2CH_3) is obtained. Under these conditions, DMC acts as a safe replacement of phosgene.

In the second one (b), instead, a $\text{S}_{\text{N}}2$ methylation reaction takes place via the attack of the nucleophile to the methyl carbon of DMC. In this case, DMC works as a substitute for harmful methyl halides and dimethyl sulfate (DMS).

Although a neat cut-off between pathways (a) and (b) is not always possible, two important factors may discriminate between methylation and carboxymethylation reactions: the temperature and the nature of the catalyst. In the presence of basic catalysis, the addition/elimination mechanism (a) is favored at low temperatures (up to the reflux of DMC, 90°C), while the methylation process predominates above 120°C . Solvation phenomena plausibly account for this change in reactivity [11]. In the presence of neutral or weak acidic catalysts (e.g., zeolites), DMC behaves primarily as a methylating agent (see below).

Finally, it should be noted that for both reactions of Scheme 2, the only co-products are MeOH, which is, in principle, recyclable to the synthesis of DMC, and CO_2 , which does not usually involve disposal problems. In contrast, methylation with methyl halides or DMS, and carbonylation with phosgene always generates stoichiometric amounts of inorganic salts.

Other general properties and advantages of DMC

Table 1 summarizes a comparison between general properties of DMC, conventional methylating agents (methyl iodide and DMS), and phosgene.

The toxicological profile of DMC shows that it is a nontoxic compound (it is classified as a flammable liquid), having no irritating or mutagenic effects either by contact or inhalation [9]. Therefore, it can be handled without the special precautions required for highly poisonous methyl halides and DMS, and the extremely toxic phosgene.

Reactions mediated by DMC also offer other relevant advantages from the synthetic/process standpoints: (i) they do not usually require additional solvents, since DMC may simultaneously act as a reagent and as a solvent for many organic substrates; (ii) they do not need waste-water treatment, nor do they consume stoichiometric bases thanks to their catalytic nature; and (iii) they can be easily controlled because of their slight, if any, exothermic progress.

In addition, the atom economy (AE) of DMC processes is often favorable with respect to usual alkylation or carboxylation reactions. As an example, if one compares the synthesis of anisole via the methylation of phenol with three different alkylating agents, such as MeI, DMS, and DMC, the calculated AEs are of 39.3, 41.5, and 57.8 %, respectively [12]. The true catalytic reaction of phenol with DMC proceeds with the highest AE.

Table 1 General properties of DMC, phosgene, DMS, and MeI.

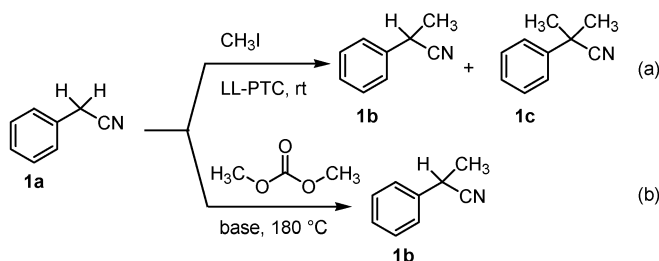
Properties	DMC	Phosgene	DMS/MeI
Oral acute toxicity (rats)	LD ₅₀ 13.8 g/kg		DMS: LD ₅₀ 440 mg/kg MeI: LD ₅₀ 76 mg/kg
Acute toxicity per contact (cavy)	LD ₅₀ > 2.5 g/kg		MeI: LD ₅₀ 110 mg/kg
Acute toxicity per inhalation (rats)	LC ₅₀ 140 mg/l; (4 h)	LC ₅₀ 16 mg/m ³ ; (75 min)	DMS: LC ₅₀ 1.5 mg/l (4 h)
Mutagenic properties	None		DMS: mutagenic
Irritating properties (rabbits, eyes, skin)	None	Corrosive	DMS: causes burns MeI: irritating to skin
Reagent hazard	No	Yes	Yes
Use of solvents	No	Yes/No	Yes
Waste-water treatment	No	Yes	Yes
NaOH consumption	No	Yes	Yes
By-products	MeOH, CO ₂	NaCl	NaI, NaSO ₄ Me
Thermodynamic	Not or slightly exothermic	Exothermic	Exothermic

METHYLATION REACTIONS WITH DMC: SELECTIVITY AND CHEMOSELECTIVITY

In this paper, emblematic examples of selective and chemoselective methylation processes are analyzed through the reactions of DMC with different nucleophiles belonging to the classes of methylene-active compounds and primary amines.

Mono-C-methylation of CH₂-active compounds: Synthesis and mechanistic investigations

Good models for methylene-active compounds are arylacetonitriles (**1**). In the presence of several organic and inorganic bases, compounds **1** can be alkylated in the α -position with conventional techniques involving alkyl halides [13]. However, when reactive electrophiles are used, a low selectivity is observed due to the formation of mixtures of mono- and bis-C-alkylation products [14]. For instance, under the best ever reported conditions (i.e., liquid–liquid phase-transfer catalysis), the overall mono-C-methyl selectivity of the reaction of phenylacetonitrile (**1a**) with MeI, is slightly over 70 %, at a 94 % conversion (Scheme 3a) [15].

**Scheme 3**

The small difference in acidity between the two methylene protons of **1a** makes them react almost simultaneously, and because of very close boiling points, products **1b** and **1c** cannot be separated in a high purity/yield. The resulting procedure is therefore useless.

This scenario completely changes when DMC is used in place of methyl iodide (Scheme 3b). In the presence of a weak base (e.g., K_2CO_3), despite the quite high temperature required for the reaction (180 °C), the mono-*C*-methylation of **1a** with DMC proceeds with a selectivity >99 %, at quantitative conversion [16]. DMC totally inhibits the multiple substitution. This result is quite general: it can be extended not only to different arylacetoneitriles, but also to several CH_2 -active compounds (WCH_2Z) such as arylacetatesters (**2**), aroxyacetic acid derivatives (**3**), and sulfones bearing α -methylene groups (**4**) [16,17].

Table 2 reports some examples which refer to reactions carried out at temperatures of 180–220 °C in the presence of K_2CO_3 as a catalyst.

Table 2 Selective mono-*C*-methylation of CH_2 -active substrates (WCH_2Z) with DMC.

Entry	WCH_2Z		T (°C)	Product, $WCH(CH_3)Z$ (%, Selectivity)	Isolated yield (%)
	W	Z			
1	1d : <i>o</i> -MeOC ₆ H ₄	CN	180	>99	85
2	1e : <i>p</i> -ClC ₆ H ₄	CN	180	>99	89
3	1f : <i>p</i> -FC ₆ H ₄	CN	180	>99	81
4	2a : C ₆ H ₅	CO ₂ CH ₃	200	92	80
5	2b : (6-CH ₃ O)naphthyl	CO ₂ CH ₃	220	99	90
6	3a : C ₆ H ₅ O	CO ₂ H	200	96	81
7	3b : C ₆ H ₅ O	CO ₂ CH ₃	190	94	80
8	4a : C ₆ H ₅	SO ₂ Ph	180	92	81
9	4b : C ₆ H ₅	SO ₂ CH ₃	180	96	85

In a typical procedure, a solution of the substrate WCH_2Z in DMC (10^{-1} – 10^{-2} M), reacts in a stainless steel, electrically heated autoclave under an autogenous pressure of 6–15 bars. In all cases, regardless of the nature and the position of aryl substituents of compounds **1–4**, a high mono-*C*-methylation selectivity of 92–99 % is achieved. Very often, products [$WCH(CH_3)Z$] can be isolated in good-to-excellent yields (80–90 %), by a simple filtration of the catalyst and removal of DMC under vacuum, without any further purification. A noteworthy application of this method is for the synthesis of precursors for nonsteroidal anti-inflammatory drugs (NSAIDs) belonging to the class of hydratropic acids. Well-known cases are those of ibuprofen, ketoprofen, and naproxen, whose preparation can be scaled up to batches of 250 kg, with overall yields >95 % [18].

These reactions are also efficiently catalyzed by a number of inorganic or organic bases (i.e., alkaline carbonates, metal alkoxides, phosphazenes, DBU, DMAP, etc.) whose nature may affect the methylation rate, but they show no appreciable effects on the final selectivity [16,19]. Other conditions described in this methylation procedure also deserve a general comment. In order to exploit the methylating capability of DMC, a relatively high reaction temperature is necessary, and accordingly, reactors (autoclaves) for pressures up to 15 bars have to be used. This experimental set-up may appear not to fit the criteria of safety and of energy demand expected for a green process. However, especially in the industrial practice, such conditions are not at all prohibitive, and advantages must be seen on a global balance based on the greenness of the reagent(s)/solvent, the truly catalytic use of a base, the total absence of wastes, and other favorable process metrics (AE, mass index, etc.).

Why is mono-*C*-methylation selectivity so high? The most interesting and best-studied experiments to shed light on the reaction mechanism are based on the occurrence of two intermediates (**I₁** and **I₂**) whose structures are reported in Fig. 1.

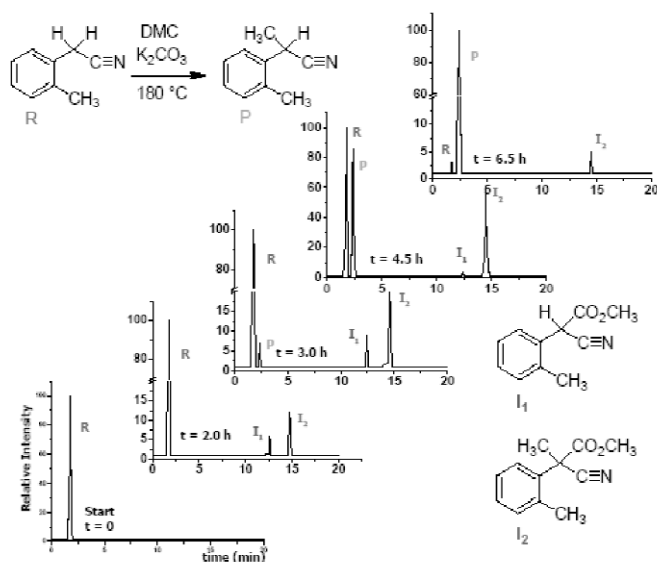
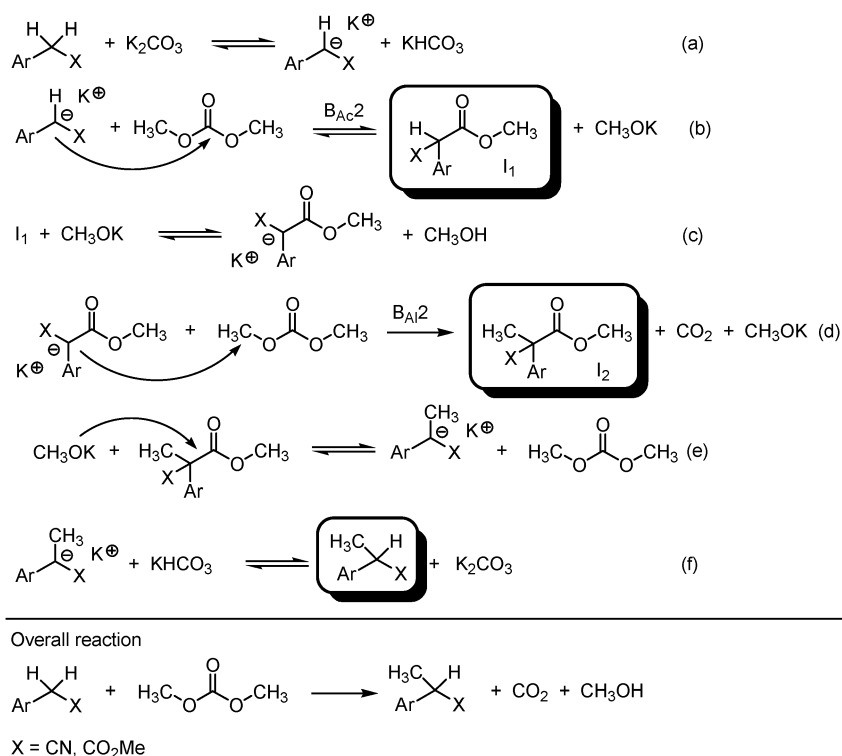


Fig. 1

In particular, Fig. 1 illustrates the model example of the methylation of *o*-tolylacetonitrile with DMC carried out at $180\text{ }^\circ\text{C}$, in the presence of K_2CO_3 as the catalyst. Five different mass chromatograms taken at different times (0, 2, 3, 4.5, and 6.5 h), describe the progress of the reaction. Besides the reagent and the product (R and P, respectively), a carboxymethyl- and a (methyl)carboxymethyl-derivative (I_1 and I_2) of *o*-tolylacetonitrile are observed. The concentrations of I_1 and I_2 grow up to a maximum (10 and 60 % for I_1 and I_2 , respectively), and then rapidly fall to zero at the end of the reaction, when 2-(*o*-tolyl)propionitrile (P) is recovered at a very high purity [16]. This behavior is quite general for compounds **1–4** of Table 2: analogous intermediates are always detected, although their relative amounts are strongly affected by the nature of the initial substrate.

This good evidence, along with a detailed kinetic investigation of reactions of compounds $PhCH(CO_2Me)CN$ and $PhC(CH_3)(CO_2Me)CN$ (independently synthesized) with DMC [20], supports the reaction mechanism outlined in Scheme 4 for the case of arylaceto-nitriles and -esters.

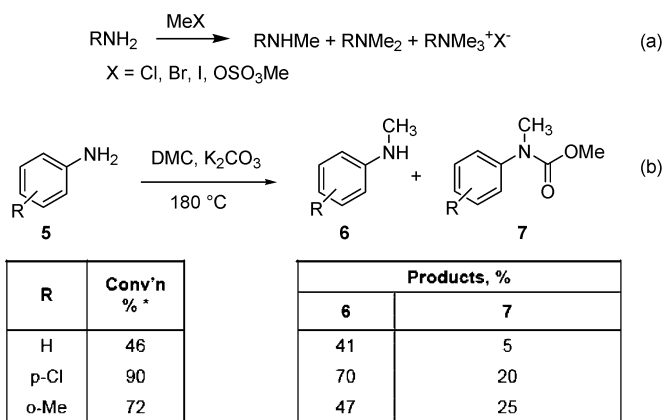
The two nucleophilic anions generated by reactions (a) and (c) allow the formation of intermediates I_1 and I_2 , respectively. In these processes, DMC exhibits a dual reactivity: it behaves subsequently as a methoxycarbonylating and as a methylating agent through $B_{Ac}2$ and $B_{Al}2$ mechanisms [eqs. (b) and (d)]. Steric reasons on the crowded anionic center of I_1^- or the lack of solvation at temperatures $\geq 180\text{ }^\circ\text{C}$ (or both), may favor the methylation reaction of step d), with respect to a $B_{Ac}2$ one [11]. Finally, I_2 is subjected to a demethoxycarbonylation reaction to the final product [$ArCH(CH_3)X$]. At this stage, the reasons why direct S_N2 displacements of both $ArCH^{(-)}X$ and $ArC(CH_3)^{(-)}X$ anions on DMC are apparently not allowed (if so, bis-*C*-methylation of $ArCH_2X$ substrates would be observed), still remain an open question of the mechanistic proposal.



Scheme 4

Mono-N-methylation of primary aromatic amines: Selectivity, chemoselectivity, and mechanistic investigation

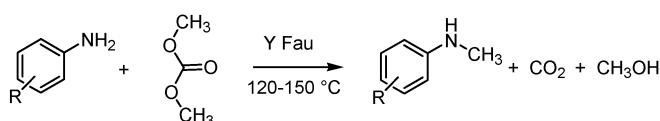
The selectivity issue considered for CH₂-active compounds is even more important for the alkylation of primary amines. In this case, conventional alkylation procedures are not usually feasible for the preparation of secondary amines: especially for methylation reactions, only mixtures of tertiary amines and quaternary ammonium salts are obtained (Scheme 5a) [21].



* Conv'n: Conversion of anilines 5

Scheme 5

The reaction outcome is improved if DMC is used in place of methyl halides or DMS. For example, under the same conditions described for arylacetonitriles (180 °C, K_2CO_3), different anilines (**5**) react with DMC to yield the corresponding mono-*N*-methyl anilines (**6**: $ArNHMe$, Scheme 5b) [22]. Yet, the overall selectivity is not satisfactory because sizable amounts of methyl carbamates (**7**: $ArNHCO_2Me$, 5–25 %) form through a competitive $B_{Ac}2$ process. An elegant and very efficient synthetic solution comes from different catalysts such as alkali metal-exchanged Y and X faujasites, a particular class of zeolites. [23]. In the presence of these solids in fact, a number a primary aromatic amines even deactivated by both steric or electronic effects, undergo mono-*N*-methylation reaction with an unprecedented high selectivity (93–98 %) at conversion up to 95 % [24]. Some results are reported in Scheme 6.



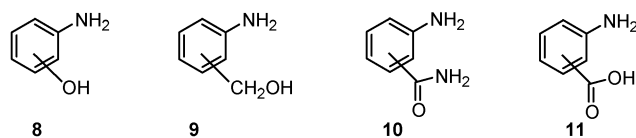
R	Catalyst	T (°C)	t (min)	Mono- <i>N</i> -methyl Selectivity (%)	$ArNHMe$ (Yield, %)
H	NaY	130	195	98	84
	K_2CO_3	180	220	87 ^a	13
<i>p</i> -NO ₂	KY	150	600	93	79
<i>p</i> -CN	KY	150	270	98	83
<i>o</i> -CO ₂ Me	NaY	150	330	96	84
2,6(Me) ₂	NaY	150	300	94	76

^a $PhN(Me)CO_2Me$ (34 %) is observed

Scheme 6

In a typical procedure, a solution of $ArNH_2$ in DMC (10^{-1} – 10^{-2} M; $Ar = Ph, p-O_2NC_6H_5, p-NCC_6H_5, o-MeO_2CC_6H_5, 2,6-(Me)_2C_6H_3$) reacts in an autoclave at 130–150 °C, with commercial MY or MX ($M = Na, K$, from Aldrich: Art. 334448 and 283592, respectively) catalysts, to produce $ArNHMe$ in good isolated yields (76–84 %).

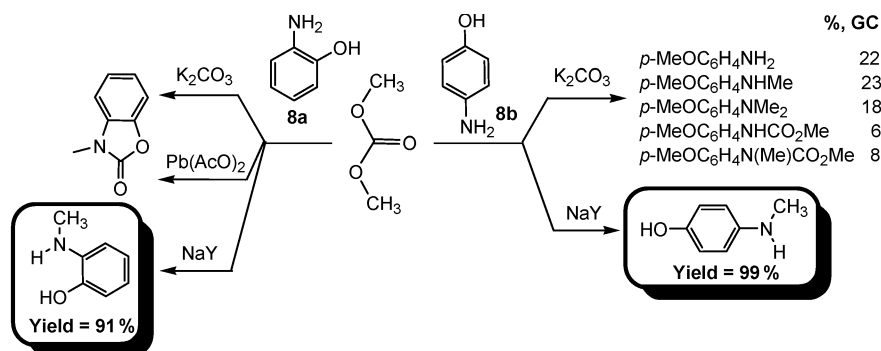
This result finds an even more notable application in the reaction of DMC with ambident primary amines such as anilines bearing functional groups susceptible to undergo themselves methylations or carboxymethylations with DMC. Examples of these substrates are aminophenols (**8**), aminobenzyl-alcohols (**9**), aminobenzamides (**10**), and aminobenzoic acids (**11**), etc. (Scheme 7).



Scheme 7

It should first be noted that under basic catalysis, DMC readily reacts with: (i) phenols to produce anisoles ($PhOMe$) [10]; (ii) benzyl alcohols and carboxylic acids to yield transesterification and esterification products ($ArCH_2OCO_2Me$ and RCO_2Me , respectively) [18a,25]; and (iii) carboxamides to give *N*-methylamides ($RCONHMe$) [26].

The behavior is completely changed by the use of faujasites. Scheme 8 clearly exemplifies the situation of aminophenols (**8**).

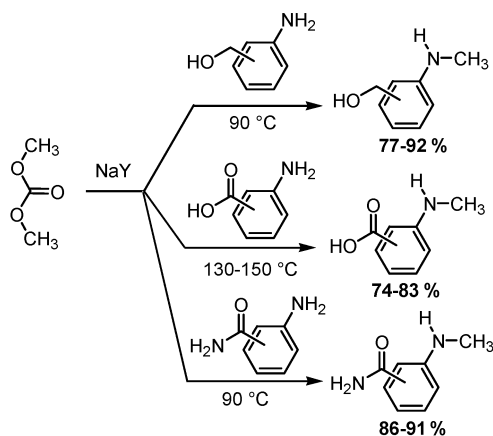


Scheme 8

In the presence of K_2CO_3 as a catalyst, the reaction of *p*-aminophenol with DMC produces a plethora of compounds which form through several competitive O- and N-methylation, and carboxymethylation processes (Scheme 8, top right). By contrast, a very high chemoselectivity is attained when NaY is used: the exclusive methylation at the N-atom is observed and, in particular, only the mono-*N*-methyl derivative is isolated in a substantially quantitative yield (99 %, bottom right) [27].

Likewise, when *o*-aminophenol and DMC react over a base (K_2CO_3) or even an acidic [$Pb(AcO)_2$] catalyst, simultaneous methylation and carboxymethylation reactions take place at the N- and O-terms of the substrate, and a *N*-methylbenzoxazolone is obtained (Scheme 8, top left). The NaY-catalyzed process affords solely *o*-(*N*-methyl)aminophenol in a 91 % yield (bottom left) [27].

Faujasite catalysts (e.g., NaY) turn out to be effective for the methylations of all compounds **8–11** above described (*ortho*- and *para*-isomers), with DMC. In these cases, the reaction not only shows a very high mono-*N*-methyl selectivity (up to 99 %), but it proceeds with a complete chemoselectivity toward the amino group, the other functionalities (OH, CO₂H, CONH₂) being fully preserved from alkylation and/or transesterification reactions (Scheme 9) [27,29].



Scheme 9

After a mild thermal treatment (70 °C at 10 mm, overnight), the faujasite can be reactivated and recycled, virtually indefinitely, without any loss of activity and/or selectivity.

To discuss this fine control on both mono-*N*-methyl and chemoselectivities, the knowledge of adsorption phenomena of reagents over the catalyst becomes mandatory. Model cases of aniline and DMC are suitable to this scope. According to Czjiek et al. [30], diffraction techniques prove that aniline dif-

fuses into the supercages of solid faujasites, and it is able to interact via both H-bonds between amine protons and basic oxygen atoms of the zeolite framework, and the formation of a π complex between the aryl ring and a Lewis-acid cation (e.g., a sodium cation in a NaY zeolite). On the other hand, IR experiments also show that the molecule of DMC undergoes a strong perturbation when adsorbed over X and Y faujasites [31]. Figure 2 details the comparison between IR spectra of DMC as such (blue curve), and of DMC dosed in subsequent pulses over a NaY surface (black curve).

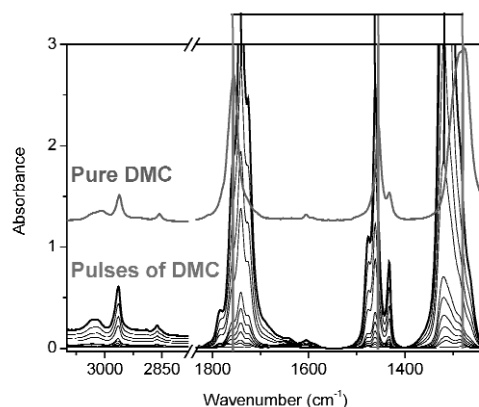
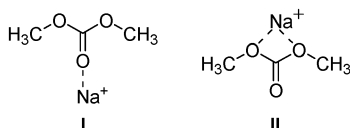


Fig. 2

The black curves indicate that many new vibrational components appear both in the region of 1450 and 1760 cm^{-1} , proving that the carbonyl stretching modes as well as the $\delta(\text{CH}_3)$ modes of methyl groups of DMC are remarkably modified upon the adsorption on the faujasite [32]. This evidence, along with B3-LYP calculations on several Na^+ /DMC model adducts [31], lead to the conclusion that DMC is hosted by the zeolite supercages where acid–base complexes are formed between basic oxygen atoms of the carbonate moiety and the Lewis acidic sites (metal cations) of the catalyst. Scheme 10 reports the case for a NaY faujasite.

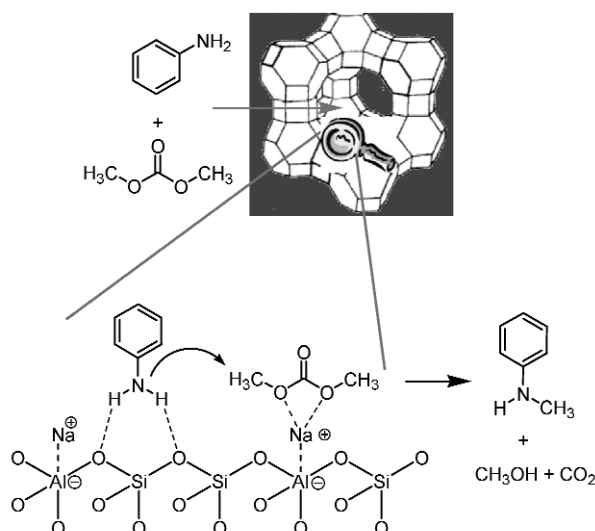


Scheme 10

The formation of complexes I and II implies a lengthening of O-CH₃ bonds of DMC: in other words, DMC undergoes an electrophilic activation within the pores of the solid.

Based on these considerations, the mono-*N*-methyl selectivity observed in the reaction of anilines and DMC can be discussed through the following mechanism (Scheme 11).

A pictorial description is offered for the model case of aniline. Once the amine and DMC diffuse into the supercages of NaY, they may approach each other only according to the steric requisites of their adsorption patterns. Scheme 11 also gives an enlarged view of possible surface interactions which can be affected by both the geometric features (shape selectivity) and amphoteric properties of the catalyst [33]. The reaction proceeds via a $\text{S}_{\text{N}}2$ displacement of aniline on DMC. With respect to aniline, the product, mono-*N*-methyl aniline (PhNHMe), plausibly forms different H-bonds ($\text{N-H}\cdots\text{O}$ -zeolite) with the solid cage. In particular, the NHMe group may force the molecule farther from the catalytic surface in a fashion less suitable to meet DMC and react with it. This behavior can account for the mono-*N*-




Scheme 11

methyl selectivity observed, which is peculiar to the use of DMC. In fact, the bis-*N*-methylation of primary aromatic amines occurs easily with conventional methylating agents (i.e., DMS), also in the presence of alkali metal-exchanged faujasites as catalysts [34].

The mechanism of Scheme 11 is possibly validated for amines **8–11**: the molecular size estimation of these substrates indicates that they are all expected to be hosted by the catalytic supercavity of NaY [29]. On the contrary, if this “in-cage adsorption” is hindered by bulky substituents, a remarkable drop of selectivity is observed: for example, in the case of 3,5-di-*tert*-butylaniline, a modest selectivity of 82 % is attained even at a low conversion of 9 % [35].

Finally, the reaction chemoselectivity can be discussed according to the principle of hard and soft acids and bases, which affirms that, in a S_N2 -type reaction involving a soft electrophilic center (i.e., the methyl carbon of DMC), an ambident nucleophile becomes more likely to attack with its less electronegative atom [36]. This statement fits the investigated reaction where the methylation takes place exclusively at the aminic N-atom of anilines **8–11**. On condition, however, that reactant amines are “solvated” by their adsorption within the zeolite cage: Scheme 11 clearly show that a high chemoselectivity is not otherwise possible with catalysts different from faujasites. The nature of the substrate also plays a role. For example, at 135 °C, the reaction of aminothiophenols with DMC yields a mixture of *N*- and *S*-methyl derivatives even when NaY zeolite is the catalyst (Table 3) [29].

Table 3 The reaction of aminothiophenols (*ortho* and *para*) with DMC carried out at 135 °C, in the presence of a NaY catalyst.

Substrate 	Conv. (%)	<i>t</i> (h)	Products, % (by GC)			
			HSC ₆ H ₄ NHMe	MeSC ₆ H ₄ NH ₂	MeSC ₆ H ₄ NHMe	MeSC ₆ H ₄ NMe ₂
<i>ortho</i>	74	8	19	23	27	5
<i>para</i>	78	4	53	9	6	6

In this case, the higher polarizability of the thiol group (with respect to OH) does not allow discrimination between the *N*- and *S*-nucleophilic terms of reagents.

CONCLUSIONS

In combination with either base or zeolite catalysts, the use of DMC provides powerful methods for straightforward syntheses of mono-*C*- and mono-*N*-methyl derivatives of CH₂-active compounds and anilines, respectively. Reactions proceed with selectivity up to 90–99 %, hitherto not achievable with conventional reagents and techniques. General cornerstones of the DMC-based procedures are safety and simplicity, and their intrinsic eco-friendly character as nontoxic methylating agent/solvent and catalysts are used, and no wastes are generated. A further added value from both synthetic and environmental standpoints is the high chemoselectivity (observed for amines), which avoids derivatization (protection/deprotection) sequences.

As far as the reaction mechanisms, the selectivity of base-catalyzed mono-*C*-methylation reactions is explained through a B_{Ac}²/B_{Al}² sequence, while mono-*N*-methylation processes likely proceed via nucleophilic displacements (S_N2-type) assisted by the steric/acido-base requites of the supercavities of faujasite catalysts. In this latter case, the chemoselectivity observed for ambident amines is primarily driven by the nature of the adsorption of reagents over the zeolite, as well as by the different polarizability of nucleophilic terms (NH₂ and OH, CO₂H, CH₂OH, CONH₂ groups) of compounds **8–11**.

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