DIMETHYL CARBONATE: GREEN SOLVENT AND AMBIDENT REAGENT

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Abstract- DMC is a versatile compound which represents an attractive eco-friendly alternative to both methyl halides (or dimethyl sulfate) and phosgene for methylation and carbonylation processes, respectively. DMC, produced nowadays by a clean process, possesses properties of no toxicity and biodegradability which makes it a true green reagent to be used in syntheses that prevent pollution at the source.
The reactivity of DMC is tunable: at T ≤ 90 °C, methoxycarbonylations take place, while at higher reaction temperatures, methylation reactions are observed with a variety of nucleophiles. Besides, DMC-mediated methylations are catalytic reactions which use safe solids (alkaline carbonates) avoiding the formation of undesirable inorganic salts as by-products. The high selectivity in methylation reactions is due to the ambident electrophilic character of DMC which reacts on its hard centre (the carbonyl group) with harder nucleophiles and on its soft one (the

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methyl group) with softer nucleophiles, according to the Hard-Soft Acid and Base (HSAB) theory.

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1. Introduction

Green chemistry was introduced with the aim to overcome health and environmental problems at the source by developing cleaner chemical processes for chemical industry through the design of innovative and environmentally benign chemical reactions. However this approach started to take hold only in the last two decades as a consequence of a combination of factors, including economic, regulatory, scientific, and even social factors. Each of these incentives has combined to make the 1990s the period during which green chemistry was introduced and has found implementation and commercialization on a wide industrial scale.

Green organic syntheses[1] must include, if not all, at least some of the following requirements: avoid waste,[2] be atom efficient,[3] avoid the use and production of toxic and dangerous chemicals, produce compounds that perform better or as well as the existing ones, and are biodegradable, avoid auxiliary substances (e.g. solvents) or use eco-compatible solvents (water or dense CO_2), reduce energy requirements, use renewable materials, and use catalysts rather than stoichiometric reagents.[4]

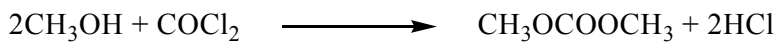
In particular it is important to find a replacement for toxic and dangerous reagents produced by eco-unfriendly processes and that are responsible for producing expensive-to-dispose-of inorganic salts. Methyl halides (CH_3X, X = I, Br, Cl), dimethylsulfate (DMS), and phosgene ($COCl_2$) are a representative examples of undesirable reagents used for methylation and carboxymethylation reactions. All these reagents are toxic and corrosive chemicals. Moreover the reaction requires a stoichiometric amount of a base as catalyst and produces a stoichiometric amount of inorganic salts that need to be disposed of.

Dimethylcarbonate (DMC) is an environmentally benign substitute for dimethyl sulphate and methyl halides since it is a well-known non-toxic reagent as compared to other carboxylating or alkylating agents (phosgene and methyl halides, respectively). Besides DMC does not produce inorganic salts. In fact, the leaving group, methyl carbonate, decomposes giving as by products only methanol and CO_2.

2. Properties of DMC

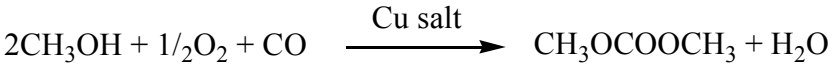
DMC is classified as a flammable liquid, smells like methanol and does not have irritating or mutagenic effects either by contact or inhalation. Therefore, it can be handled safely without the special precautions required for the poisonous and mutagenic methyl halides and DMS, and extremely toxic phosgene.

DMC has been produced for long time from phosgene and methanol. In this synthesis HCl was an unwanted side product (Scheme 1).



Scheme 1. Synthesis of DMC by phosgene

However since the middle eighties DMC is no longer produced from phosgene, but by oxidative carbonylation of methanol with oxygen through a process developed by Enichem (Italy)[5,6]:



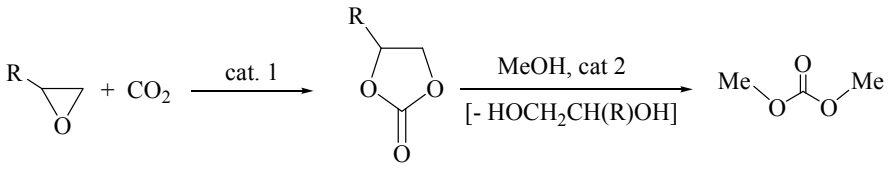
Scheme 2. Enichem synthesis of DMC

The most relevant features of this process are:

- low-cost and widely available raw materials with low toxicity;
- high production rates;
- non-toxic and easy disposable by-products (carbon dioxide and water)
- high quality product.

The new technology does not produce any by-products that are difficult to dispose of. The DMC obtained has also low toxicity and ecotoxicity (biodegradability >90% at 28 days OECD 301C; acute toxicity for fish; no effect at 1000 mg/l OECD 203).

Another industrial procedure developed and recently industrialized in China is the cleavage of cyclic carbonates (Scheme 3). Importantly, this synthesis doesn't use any chlorine.[7]



Scheme 3. Insertion of CO_2 to epoxides and cleavage of cyclic carbonates. Step 1. Catalyst: MgO, CaO. Step 2. Catalyst: zeolites exchanged with alkali and/or earth metal ions. R = H and CH_3

3. Reactivity of dimethylcarbonates according to the Hard-Soft Acid Base theory

DMC is a well-known non-toxic reagent showing three main green-chemistry features[8] as compared to other carboxylating or alkylating agents (phosgene and methyl halides, respectively):[9]

1. DMC does not produce inorganic salts in either acylation[10] (eq. 1) or alkylation[11] (eq.
2. 2) reactions:

$$Nu^- + CH_3OCOOCH_3 \rightleftharpoons NuCOOCH_3 + CH_3O^- \quad (1)$$

$$Nu^- + CH_3OCOOCH_3 \longrightarrow NuCH_3 + CH_3OCOO^- \quad (2)$$

$$CH_3OCOO^- \longrightarrow CH_3O^- + CO_2 \quad (3)$$

In fact, since the leaving group, methyl carbonate, decomposes (reaction 3), the base is restored and can be used in truly catalytic amounts. This feature allows utilization of continuous-flow (c-f) procedures (i.e. gas-liquid phase-transfer catalysis, GL PTC,[12] and continuously stirred tank reactor, CSTR[13]).

3. Since reaction 1 is an equilibrium and reaction 2 is not, the product of the process can be controlled, temperature being the key factor. In fact,

because methylation reactions involve higher Gibbs activation energies, low temperatures allow carboxymethylation, whereas high temperatures give methylation derivatives.[14] Moreover, also operating at 200-250 °C, decomposition and polymerization products or tars are not formed and usually clear reaction mixtures are obtained.

4. DMC has a very selective behaviour reacting with different nuclephiles (such as amines, CH_2 acidic compounds phenols etc.) acting as alkylating or carboxymethylating agent. This different reactivity of DMC with different nucleophiles may be rationalized by the Hard-Soft Acid and Base (HSAB) theory. Ralph Pearson introduced the Hard-Soft Acid-Basic (HSAB) theory in early 1963[15,16] as an attempt to unify inorganic and organic reactions. The principles of the HSAB theory were further developed by Mèndez,[17] and by Klopman.[18,19] According to the proposed theory hard nucleophiles preferably react with hard electrophiles and viceversa.[20] DMC, as electrophile, has three reactive centers that can interact with nucleophiles: the carbonyl, and two methyl groups (Figure 1). Such centers can be classified according to the HSBA principle: the carbonyl group is the harder electrophile, as a result of its polarized positive charge and sp^2 hybridization; the two methyl groups represent softer electrophiles, thanks to their sp^3 orbital and their saturated carbon atom.

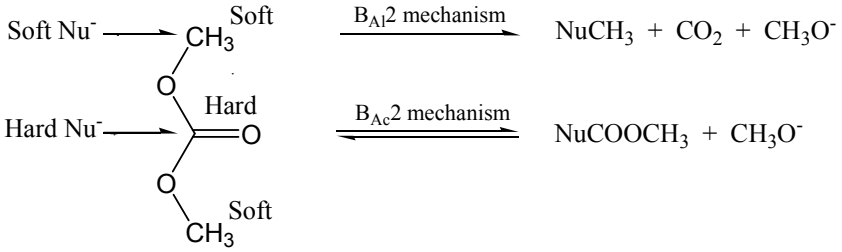


Figure 1. Hard and soft centres in the molecule of DMC

Many ambident nucleophiles are known, but few ambident electrophiles have been studied. Many investigations verified the compliance of reactivity of ambident nucleophiles and electrophiles with the HSAB theory. Among the ambident electrophiles we can mention esters and particularly propiolactones,[21a-d] α,*β*-unsaturated carbonyls,[22] 3-chloro-1,2-benzoisothiazol,[23] and tricholocarbonates.[24] Actually, also alkyl halides are

included among the ambident electrophiles, as they react with nucleophiles, yielding either products of substitution reactions (soft-soft reaction) or alkenes (hard-hard interaction).[25] At this regard, the reaction of 2-bromoethylarenes with different phenoxide anions is relevant: it yields different mixtures of ethers and alkenes, according to the nucleophilic nature of the anion species which can modulate the reaction outcome.[26] Here the reactivity of some soft/hard mono and bidentate nucleophiles with DMC is compared: nucleophiles at nitrogen, oxygen, and sulphur are considered. According to their nature, nucleophiles can discriminate between the carbon atoms of DMC. Some reactions have been already observed, while others are here reported for the first time.

3.1. REACTIVITY OF DIMETHYLCARBONATE WITH DIFFERENT NUCLEOPHILES

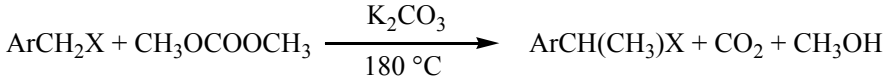
3.1.1. *Nuclephiles containing an acidic CH_2 moiety*

The reaction of CH_2 acidic compounds (such as arylacetonitriles, aryl acetates, aryloxyacetic esters, sulfones, sulfoxides, and lactones)[27] with DMC is highly selective, as it yields the sole monomethyl derivative. Regardless of the high temperature and the great excess of alkylating agent (DMC is also the solvent of the reactions), at complete conversion of the substrate selectivity for the monomethylated product is often >99%.Table 1 reports the selectivity in the monomethylation of some CH_2 acidic compounds.

Table 1. Monomethylation of several CH_2 acidic compounds (from ref. 27a)

Entry	Substrate	T (°C)	Product	Conversion	Selectivity[a]
1	$PhCH_2SO_2Me$	200	$PhCH(Me)SO_2Me$	98	100
2	$PhOCH_2COOH$	200	PhOCH(Me)COOMe	100	96
3	$PhCH_2CN$ (GL-PTC)	180	PhCH(Me)CN	98	99
4	$PhCH_2CN$ (batch)	180	PhCH(Me)CN	100	99.5

[a] Selectivity is defined as monomethylated products/(monomethylated product + dimethylated product) x 100



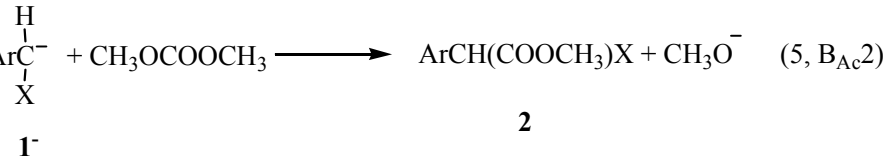
Scheme 4. Monoalchilation of nitriles, esters and sulfones, X= CN, $COOCH_3$, SO_2R, SO_2Ar

Scheme 4, for example, refers to monoalkylation of nitriles, esters, and sulfones. This reaction has an industrial relevance, since ArCH-(CH_3)COOH are well know anti-inflammatory agents.[27a]

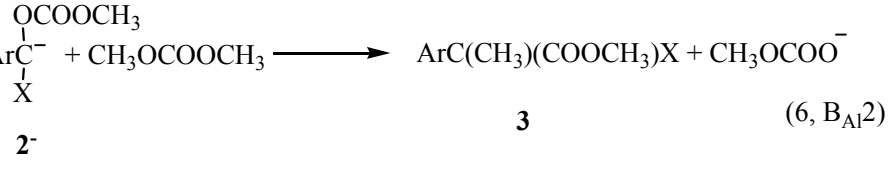
The reasons for the selectivity in monomethylation of these compounds are not immediately evident. Isolation of intermediates and a detailed kinetic study showed that the reaction mechanism does not imply a simple nucleophilic substitution (eq 4).[14,27a]

(4)

In fact, monomethylation derives from an unusual reaction pathway that involves the reactivity of anion **1**$^-$ and anion **2**$^-$, according to two consecutive nucleophilic displacements: the first one follows a $B_{Ac}2$ mechanism, while the second occurs through a $B_{Al}2$ mechanism (eqs 5 and 6, respectively):



(5, $B_{Ac}2$)

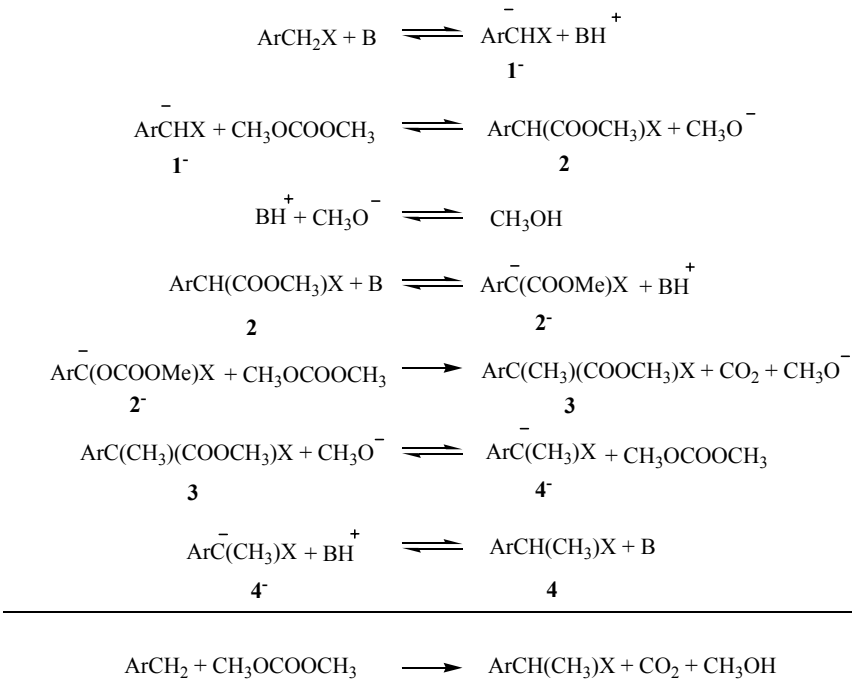


(6, $B_{Al}2$)

Accordingly, **4** is produced through a series of consecutive pathways, all of them being very selective.

Scheme 5 accounts for such a behaviour: the reaction proceeds through the carboxymethylation specie **2**, which afterward reacts with the methyl of DMC.

In summary, while anion $ArCH^-X$ does not give $ArC(CH_3)_2X$, also anion $ArC^-(COOCH_3)X$ does not allow the formation of $ArC(COOCH_3)_2X$.



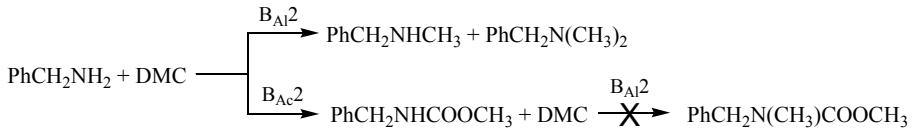
Scheme 5. Reaction pathway for the monomethylation of CH_2 acidic compounds with DMC

We can assert that anions $\mathbf{1}^-$ and $\mathbf{2}^-$ give different compounds since they have different soft/hard character. Their difference in hardness provides a reason for the discrimination observed between the two electrophilic centers of DMC. The hard nucleophile $\mathbf{1}^-$ attacks only the carbonyl of DMC (eq 5), while the anion of the product $\mathbf{2}^-$ is a softer nucleophile thus it selectively produces the methyl derivative (eq 6). The change in hardness/softness of the anion, due to the presence of the carboxymethyl group, is enough to significantly alter the reactivity of the DMC molecule. The combination of

the dual electrophilic character of DMC with its reaction products allows two consecutive steps to occur in a selective way both in the reaction sequence and yield: first the hard-hard reaction occurs and produces only a soft anion; then a soft-soft nucleophilic displacement leads to the final product. Since hard-soft and soft-hard interactions are inhibited, neither double methylation nor double carboxymethylation take place.

3.1.2. *Nitrogen nucleophiles*

In the absence of a base, aliphatic amines such as benzylamine react with DMC to give both alkylation and carboxymethylation products, without any selectivity (entry 1, Table 2 and Scheme 6); both $B_{Ac}2$ and $B_{Al}2$ mechanisms are followed, demonstrating an intermediate character of amine nitrogen towards DMC, in terms of hardness and softness.



Scheme 6. Reaction of benzylamine with DMC in the absence of a base.

Strong bases, such as potassium *tert*-butylate or sodium methoxide, catalyse the reaction of carboxymethylation of aliphatic and aromatic amines at 90 °C.

In fact, it is well-known that bases significantly accelerate aminolysis and transamination reactions. Bunnett[28] suggested that the direct participation of a base was the reason for the enhanced reactivity of nitrogen nucleophiles with the carbonyl. In accordance with other authors,[29] naked RNH^- is excluded from the mechanism; it looks like the role of the base is that of removing H^+ from protonated nitrogen during or after the attack, increasing in any case the negative charge on nitrogen atom. Whatever the exact mechanism may be, the presence of a base enhances the hardness of the nucleophile. So, the reactivity with harder electrophiles (the carbonyl in this case) is raised and aminolysis reactions are highly favoured. DMC represents a valid model molecule; its reactivity can explain the competition between the harder RNH^- (more or less naked) and the softer RNH_2, through the HSAB theory. The behaviour of amines in the presence and in the absence of a base reported in Table 2 confirms that since the

hardness of the nucleophile is increased while operating in the presence of a base, the $B_{Ac}2$ rate is dramatically accelerated and carboxymethyl derivatives are selectively obtained. Once formed, the urethanes need the presence of a base to further react with DMC. In these conditions, their RN^-COOCH_3 anions, softer nucleophiles than RNH^-, undergo solely $B_{Al}2$ reactions. This was proved by the fact that no $RN(COOCH_3)_2$ products, deriving from a $B_{Ac}2$ reaction mechanism, were never observed.

With aliphatic amines high yields of carbamates occur quantitatively in few minutes (entries 2 and 7, Table 2). Then, if the reaction is protracted, the already formed carbamates react again with DMC to give the corresponding *N*-methyl derivative (entries 3 and 8, Table 2). Scheme 7 outlines this behaviour.

Table 2. Reaction of amines with DMC in the presence and absence of bases[a] (from ref. 30b)

Entry	Amine	Base	Time	MNM[b]	DNM[b]	CARB[b]	NMC[b]
1	Benzylamine	-	360	12	6	4	-
2	Benzylamine	$(CH_3)_3COK$	1	-	-	100	-
3	Benzylamine	$(CH_3)_3COK$	30	-	-	32	68
4	Aniline	-	360	-	-	-	-
5	Aniline	$(CH_3)_3COK$	1	-	-	100	-
6	Aniline	$(CH_3)_3COK$	180	-	-	60	40
7	1-decylamine	$(CH_3)_3COK$	1	-	-	100	-
8	1-decylamine	$(CH_3)_3COK$	60	-	-	56	44

[a] DMC reflux temperature, 90 °C, molar ratio amine/DMC/base 1.0/40/1.2; MNM = mono-N-methylation; DNM = di N-methylation; CARB = Carbamate; NMC = N-methyl carbamate.

[b] values reported as percentage.

$$PhCH_2NH_2 + DMC \underset{}{\overset{base}{\rightleftharpoons}} PhCH_2NHCOOCH_3 + CH_3OH$$

$$PhCH_2NHCOOCH_3 + DMC \xrightarrow{base} PhCH_2N(CH_3)COOCH_3 + CO_2 + CH_3OH$$

Scheme 7. Reaction of benzylamine with DMC in the presence of a base.

Due to the lower nucleophilicity aromatic amines are less reactive, as in the absence of a base they do not react at the reflux temperature of DMC at 90 °C (aniline, entry 4, Table 2). For example aniline was reacted in the absence of a base at 200 °C in an autoclave using DMC as solvent; after 24 h the conversion was 61% without selectivity: 15% monomethylation

product, 37% dimethylated product, and 9% carbamate were observed.[30] Aromatic amines in the presence of a base follow the behaviour of aliphatic ones reported in Scheme 7 even if the formation of *N*-methyl carbamate requires longer reaction time (entry 6, Table 2).

When weaker bases like potassium carbonate are used as catalysts, the reactions have to be carried out at high temperatures in an autoclave in order to achieve high conversion of the starting material. Table 3 shows results obtained with aromatic and aliphatic amines. Aliphatic amines, that are harder nucleophiles, give mainly the corresponding carbamates and methylcarbamates after 22 h, while aromatic amines react slower, and their softness is responsible for the formation of mono and dimethylated products.

Table 3. Reaction of amines with DMC in the presence of K_2CO_3 after 22h (from ref. 30 c)

Entry	Amine	MNM[b]	DNM[b]	CARB[b]	NMC[b]
1	Aniline	6.2	2.6	8.3	41.0
2	*p*-Chloroaniline	6.3	2.1	5.7	47.5
3	*p*-Anisidine	1.3	13.4	1.8	83.0
4	*n*-Octylamine	-	1.2	53.7	45.0
5	Phenethylamine	-	-	77.0	23.0

Conditions: T=180 °C, molar ratio amine/DMC/base 1.0/40/3; MNM = mono-N-methylation; DNM = di N-methylation; CARB = Carbamate; NMC = N-methyl carbamate,[b] values reported as percentage.

In contrast, with K_2CO_3 as catalyst and under GL-PTC conditions at high temperature, monomethylation of aromatic amines occur selectively (Table 4).[5] It is well known that the role of P-T agent is to complex the alkaline metal cation thus enhancing the strength of the "naked anion".

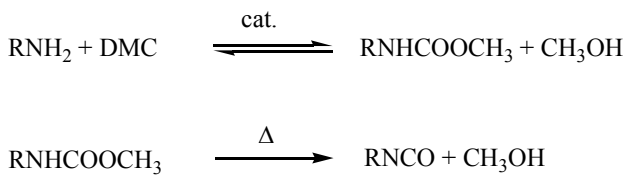
Table 4. Reaction of aromatic amines with DMC under GL-PTC conditions[a] (from ref. 30d)

		Composition at the equilibrium of the reaction mixture				
Entry	**Amine**	**Amine[b]**	**MNM[b]**	**DNM[b]**	**CARB[b]**	**NMC[b]**
1	Aniline[c]	54.3	40.8	1.6	-	3.3
2	*o*-toluidine[d]	27.7	47.0	0.3	-	25.0
3	o-Chloroaniline[d]	14.6	62.7	-	-	22.7
4	p-Chloroaniline[c]	10.1	70.0	-	-	19.9

[a] Column V=151 ml. filled with 95 g of K_2CO_3 coated with 5 wt% of PEG 6000, T=180°C , Flow=24 ml/h; [b] values reported as percentage; [c] molar ratio amine/DMC 1/4; [d] molar ratio amine/DMC 1/10;.

The reaction between DMC and amines to carbamates is of strong interest for the industrial field, mainly as they represent the first step of a

non-phosgene route to the production of isocyanates, in fact isocyanates can be produced by thermal decomposition of carbamates, as reported in the general Scheme 8.



Scheme 8. Reactions of an amine to isocyanate.

In addition to the production of isocyanate without phosgene, carbamates themselves are relevant industrial products because they can be applied mainly in pharmaceutical and in crop protection sectors.

Strong efforts have been done by industrial companies in order to discover new processes and find suitable catalysts for the carboxymethylation of amines, in particular aromatic, with dialkylcarbonates. There are a lot of patents that report findings related to this topic, hereafter some of them are gathered.

In 1981 Bayer patented a process for the production of N,O-disubstituted carbamates (urethanes) by reacting primary aromatic amines with dialkylcarbonates in the presence of neutral or basic inorganic or organic compounds of lead, titanium, zinc or zirconium as catalysts.[31] Table 5 summarises some of the most interesting examples reported.

Table 5. Process for the synthesis of N,O–disubstituted urethanes (from ref. 31).

Example	Amine	Dialkyl carbonate	Catalyst	T (°C)	Time (h)	Yield to urethane (%)
1	Aniline	DEC[a]	Ti tetra butylate	130÷140	6÷7	96
2	Aniline	DBC[b]	Zr tetra propylate	190	5÷6	89
3	Aniline	DEC[a]	Pb acetate	135÷136	6	96
5	Aniline	DEC[a]	Zn stearate	132÷135	9	97

[a] Diethylcarbonate; [b]Dibutylcarbonate;

In the same year also DOW reported a process for preparing carbamates from an organic carbonate and an aromatic amine in the presence of catalytic quantities of compounds of Zn, Sn or Co salts of monovalent organic compounds having a pKa value of less than 2.8 and other compounds having more than one carbonyl group per molecule and oxides, sulfides and carbonates at a temperature of at least 200 °C.[32-33] A wide screening of catalysts was reported in the examples, all carried out in autoclaves. The best results for the carboxymethylation of aniline with DMC, in terms of carbamate selectivity, were achieved with zinc (naphtenate, pivalate, benzoate, acrylate, oxyacetate, acetate, propionate, carbonate) and tin catalysts (dibutyl tin dilaurate, dibutyltin oxide polymer, dibutyltin maleate).

Other suitable catalysts for the carboxymethylation of aromatic amines are zinc or copper carbamates. In 1997 it was patented a process[34] for the preparation of carbamates from an aromatic amine and DMC in the presence of N,N-substituted carbamate complexes of zinc and copper. Table 6 summarises results reported in some of the patent examples, high selectivity was reported with aniline, while with MDA a considerable amount of N-methyl derivatives was found.

Table 6. Process for the synthesis of aromatic urethanes (from ref. 34).

Ex.	Amine	Catalyst	T (°C)	Time (h)	Conversion (%)	Selectivity to urethane (%)
1	Aniline	Zn diethyl-carbamate[b]	170	2	≥99	99
4	Aniline	Zn diethyl-carbamate[c]	130	11	96	98
5	MDA[a]	Zn diethyl-carbamate[c]	160	3	99	63
7	Aniline	Cu diisopropyl-carbamate[d]	170	12	98	95

[a] 4,4'-methylenedianiline; [b]amount 1.0% per mole of amine; [c]amount 1.5% per mole of amine; [d]amount 6.6% per mole of amine.

Another process for the synthesis of aromatic urethanes was obtained by reacting an organic carbonate, in particular DMC, with an aromatic diamine or polyamine in the presence of a Lewis acid catalyst[35]; the yield and selectivity is increased by a partial removal of the alcohol co-produced

during the reaction. In Table 7 conditions and data found in some of the examples, carried out with Zn acetate dihydrate as catalyst, are reported. Diurethanes of 4,4' MDA, 80/20 2,4/2,6 TDA and polymeric MDA (a mixture of MDA and MDA oligomers) are key intermediates as they can give by cracking the corresponding isocyanates MDI, TDI and polymeric MDI that are fundamental raw materials for the production of a wide range of polyurethanes.

Table 7. Process for the synthesis of aromatic urethanes (from ref. 35).

Ex.	Amine	$ZnAc.2H_2O$ (w% on amine)	T (°C)	Time (hours)	Conversion (%)	Selectivity to diurethanes (%)
1	MDA[a]	4.0	140	1.5	≥99	97
2	TDA[b]	5.4	170	2.0	≥99	93
3	Polymeric MDA[e]	4.0	140	1.5	≥99	96

[a] 4,4'-methylenedianiline; [b]80/20 2,4/2,6 toluenediamine; [c] mixture of methylenedianiline and methylenedianiline oligomers.

Full processes for the preparation of aromatic isocyanates by DMC were also patented. In particular recently it was published a patent which claims an integrated process for the production of aromatic isocyanates without phosgene.[36] In the examples the various phases of the process are reported, starting form the reaction of the amine (TDA) with DMC to carbamate with zinc acetate dihydrate as catalyst, following a passivation treatment of the urethane catalytic residues and then pyrolysis of urethane in gas phase.

3.1.3. *Oxygen nucleophiles*

Alcohols give only transesterification products with DMC (Scheme 8), either under GL-PTC at 180 °C or under batch conditions. [37]

$$ROH + DMC \underset{}{\overset{PEG,\ K_2CO_3}{\rightleftharpoons}} ROCOOCH_3 + CH_3OH$$

Scheme 9. Reaction of alcohol with DMC.

Also, operating at 200 °C the reaction occurs at the carbonyl atom only. In fact, when 1-octanol was used in reactions with DMC in the presence of

K_2CO_3,[38] no methyl ether was observed, but methyl octyl carbonate and dioctyl carbonate were the only products formed. Methylation of alcohols was reported to occur also operating in the presence of tertiary amines[39] N,N'-dimethylamino-pyridine, 1,4-diazobicyclo[2,2,2]octane). In this case, however, the catalyst modifies the hard-soft character of the two centers, thus allowing the nucleophilic displacement by the alcoxide to occur.

p-Substituted phenols were used in reactions with DMC at its reflux temperature in the presence of K_2CO_3. Under such conditions the softer phenoxide anions could discriminate between the two centers of DMC and their substituent controlled the reaction outcome.

Table 8. Reaction of phenols with DMC in the presence of K_2CO_3[a] (from Ref. 30b)

Entry	ArOH	% Conversion	% ArOMe	% ArOCOOMe
1	p-Methoxyphenol	7.0	23	77
2	p-Cresol	36.3	39	61
3	Phenol	27.7	72	28
4	p-Chlorophenol	62.0	98	2
5	p-Cyanophenol[b]	100	100	-

[a] DMC reflux temperature, 90 °C; molar ratio phenol/DMC/K_2CO_3 1.0/40/1.2. Conversions after 53h.

[b] 82% Conversion in the methylated derivate after 30h.

Table 8 reports the results and clearly shows that phenoxides undergo nucleophilic substitution on either the methyl or the carbonyl group (Scheme 9). The substituent on the aromatic ring clearly influences the reactivity: softer phenoxide anions give S_N2 displacement only, while harder ones allow both $B_{Ac}2$ and $B_{Al}2$ reactions.

$$ArOH + DMC \xrightarrow{K_2CO_3} ArOCH_3 + CO_2 + CH_3OH$$

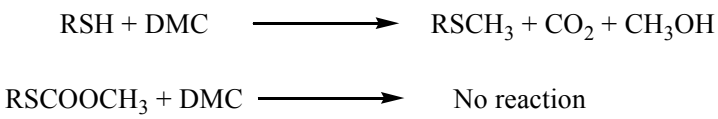
$$ArOH + DMC \underset{}{\overset{K_2CO_3}{\rightleftharpoons}} ArOCOOCH_3 + CH_3OH$$

Scheme 10. Reaction of phenols with DMC.

3.1.4. *Sulfur nucleophiles*

Aliphatic and aromatic thiols were reacted with DMC under comparable conditions: the results reported in Table 9 show that they produce only the methylated derivatives (Scheme 10): both 1-octanthioland thiophenol (entry 2 and 3, Table 9) attack the methyl group.

Since the sulfur nucleophiles are very reactive, thiophenol was able to react in the absence of a base as well (entry 1), giving thioanisole. To rule completely out $RSCOOCH_3$ as a possible intermediate in the reaction, *n*-$C_8H_{17}SCOOCH_3$ was refluxed with DMC in the absence of potassium carbonate (Scheme 9): no reaction was observed after 24 h, showing that $RSCOOCH_3$ is not an intermediate in methylation reactions with thiolates.



Scheme 11. Reaction of thiols with DMC.

Table 9. Reactivity of thiols and alcohols with DMC in the presence and absence of K_2CO_3[a] (from ref. 40).

Entry	Thiol	Base	Time (h)	% RSMe (ROMe)	% RSCOOMe (ROCOOMe)
1	Thiophenol	-	1	27	-
2	Thiophenol	K_2CO_3	4	100	-
3	1-Octanthiol	K_2CO_3	24	34	-
4	1-Octanol	K_2CO_3	7	-	65

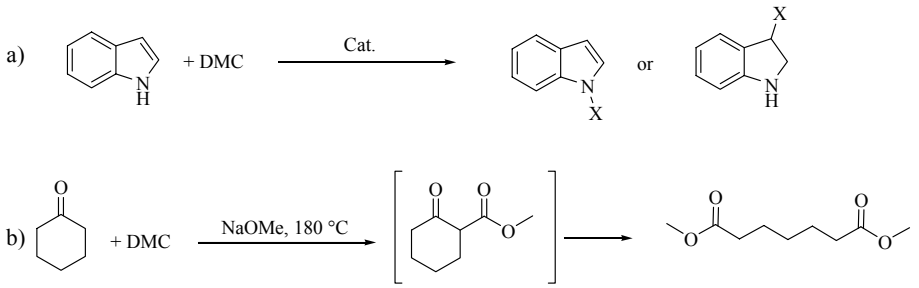
[b] DMC reflux temperature, 90 °C; molar ratio thiol/DMC/K_2CO_3 1.0/40/1.2

It is well established that sulfur and oxygen anions behave in an opposite way with electrophilic centres during nucleophilic substitutions.[40] The comparison of the reactivity of 1-octanthiol and 1-octanol with DMC (entries 3 and 4, Table 9) outlines the difference in chemoselectivity of RS^- and RO^- anions, due to their diverse hardness. Under all of the investigated conditions, alkoxides show a $B_{Ac}2$ reaction mechanism, differently from thiolates, which react via a $B_{Al}2$ type.

3.2. REACTIVITY OF DIMETHYLCARBONATE WITH AMBIDENT NUCLEOPHILES

Ambident nucleophiles are considered to be bidentate molecules whose nucleophilic centres have direct chemical interaction with each other, such as a ketone with its enol-carbanion tautomers.

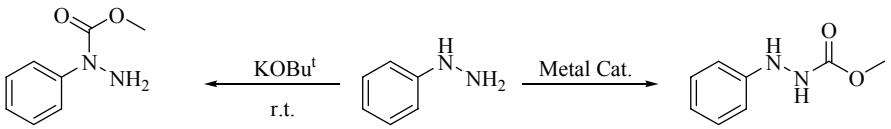
In the literature there are reactions of DMC with what would be considered ambident nucleophiles. For instance, indole is an ambident nucleophile. Using various organic chemistry procedures, reactions can either occur at the nitrogen or the conjugated arene carbon.[41] In the field of DMC chemistry, Shieh and co-workers were able to selectively methylate the nitrogen using DABCO as a catalyst in contrast to other systems that effected carboxymethylation at the same nucleophilic centre.[42] Also cyclic ketones have been successfully reacted with DMC to produce acyclic diesters via carboxymethylation at the alpha carbon. [43] In these examples, however, the ambidenticity of these systems toward DMC has not been shown (Scheme 12). Only activation of one of the two centres has occurred.



Scheme 12. Reaction of DMC with a) Indole and b) ketones. X = CH_3 or $COOCH_3$

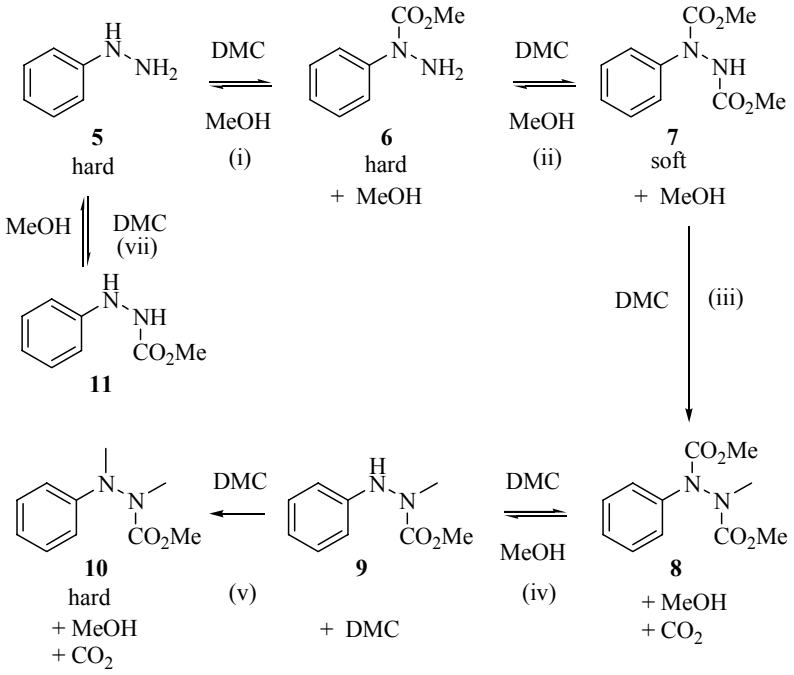
Lately some investigations have been conducted regarding the reaction of the ambident nucleophile phenylhydrazine with DMC.[44] Phenylhydrazine contains two non-equivalent nitrogen nucleophilic centres. **N-1** is relatively more acidic due to the electron withdrawing effect of the phenyl ring substituent while **N-2** possesses reactivity similar to that of an aliphatic amine.

Both of these centres were selectively carboxymethylated (hard reaction, Scheme 13). Classical metal catalysts such as $Pb(OAc)_2$ or $Sn[O_2CCH(Et)Bu]_2$ effected **N-2** activation under refluxing conditions (Table 10, entries 4-6) whilst potassium *t*-butoxide at room temperature activated **N-1** (Table 10, entry 1). It was reasoned that the reaction with a strong base was due to the deprotonation of **N-1** creating an anion with hard nucleophilicity.[45]



Scheme 13. Selective carboxymethylation of phenylhydrazine.

Under more forcing conditions using base, cascading reactions involving carboxymethylation, methylation and methanolysis were observed (Scheme 14). The importance of the connectivity of the nitrogens to each other was shown. Firstly, a second carboxymethylation occurred at **N-2**, due to the added electron withdrawing carboxyl moiety at **N-1**, presumably lowering the pka of **N-2**. Consequentially, **N-2** underwent methylation. Possessing a carboxyl moiety, electronic stabilisation of **N-2** makes it a soft nucleophilic centre.



Scheme 14. Overall reaction of phenylhydrazine and DMC under basic conditions.

Table 10. Reaction of phenylhydrazine with DMC (from ref. 44).

Entry	Product	Base/ Catalyst	Equiv. Base	Conditions	Time	Yield (%)
1	**6**	$(CH_3)_3COK$	1	Rt	25 min	85 [a]
2	**8**	$(CH_3)_3COK$	1	Reflux, (removal of MeOH)	3 h 10 min	95 [a]
3	**9**	NaOMe	4	Reflux 3 eq NaOMe, then 1 eq of NaOMe and MeOH reflux	5 h 40 min 3 h 30 min	79 [a]
4	**11**	$Pb(OAc)_2$	1	Reflux	18 h	76 [a]
5	**11**	$Pb(OAc)_2$	0.2	Reflux	20 h	70 [a]
6	**11**	$Sn[O_2CCH(Et)Bu]_2$	0.2	Reflux	25 h 45 min	58 [a]

[a] isolated product;
[b] crude product 80% of **11** and 20% of **6**;

Methanol produced in the reaction also became a factor, as it reacted with the fully substituted hydrazine compound **9**. Methanolysis tended to occur mainly at **N-1**. This allowed for selective production of either **8** or **9** by adding or removing methanol respectively, facilitating or circumventing the methanolysis process (Table 10, entries 2 and 3).

Once **9** was produced, **N-1** was available to nucleophilically attack DMC once more. Notably, both methylation and carboxymethylation occurred thereafter, signifying that **N-1** of **9** possesses both soft and hard character. This was presumably attributable to both electron donating and withdrawing substitutents attached to the two nitrogens, once again adding to the importance of the nitrogen connectivity of this ambident nucleophile, phenyldrazine.

4. Conclusions

DMC is a green solvent and reagent since it incorporates several fundamental aspects of green chemistry: it is synthesised by a green process using CO_2 as building block, it reacts selectively with a great variety of compounds as methylating or carboxymethylating reagent, it requires only catalytic amount of base and it produces no waste (high atom economy). Several industrial processes already involve DMC as reagent (or solvent) and many other are under investigation at the moment. In fact studies on DMC chemistry has demonstrated that it is possible to control the selectivity of the methylation and/or carboxymethylation reaction both on simple (amines, alcohols, thiols, etc.) and more complex nucleophiles (hydrazines, sugars, amino acids etc.).This opens new pathways for innovative green processes leading to a more eco-sustainable future.

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