Conference paper

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Mustard carbonate analogues

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Abstract: Sulfur and nitrogen (half-)mustard carbonate analogues are a new class of compounds, easily synthesized by methoxycarbonylation reaction of the parent alcohols with dialkyl carbonates. In this work, their reactivity as novel, green electrophiles is reported. Reactions have been conducted in autoclave conditions at high temperature (180 °C), under pressure and in absence of any base, as well as, in neat at atmospheric pressure, lower temperature (150 °C) and in the presence of a catalytic amount of a base. Several nucleophiles have been investigated resulting, in some cases, in unexpected compounds, i.e., six-membered heterocycle piperidine. Reaction mechanism and kinetics have been studied confirming that these compounds retain the anchimeric effect of their mustard gas analogues, without being toxic. Noteworthy, a symmetrical nitrogen mustard carbonate has also been employed as reagent in the preparation of a new family of macrocycles i.e., azacrowns, before not easily accessible.

Keywords: alkylation; chlorine-free; dialkyl carbonates; Green Chemistry V; macrocycles; mustard compounds.

Introduction

Bis(2-chloroethyl) sulfide is a vesicant and blistering agent, famously known as mustard gas, that has been used in several chemical warfares, i.e., WWI and Iran-Iraq conflict [1–8].

Sulfur mustard is a colorless, odorless liquid when pure, however, at high concentrations, has a mustard oil smell, very similar to that of horseradish. Its nitrogen analogue, bis(2-chloroethyl)(ethyl)-amine, as well as their monochloro derivatives, 2-chloroethyl methyl sulfide and (2-chloroethyl)dimethylamine (Fig. 1), are also highly toxic and harmful to humans and the environment. Oxygen analogs, in which the central sulfur or nitrogen atom has been replaced by oxygen is known as oxygen mustard, bis-(2-chloroethyl) ether [9].

The toxicity of these compounds is strictly related to their high reactivity determined by the central sulfur or nitrogen atom and the terminal chloride group(s). In fact, mustard compounds readily eliminates a chloride ion by intramolecular nucleophilic substitution aided by the sulfur and nitrogen anchimeric effect, to form a highly reactive three-membered cyclic episulfonium/aziridinium ion (Fig. 1) [10]. This reaction mechanism is responsible for the mustards poisoning properties which induce the inflammation and the over-activation of poly(ADP-ribose) polymerase resulting in DNA permanent alkylation [1].

Nevertheless, mustards compounds are of great interest as electrophiles as demonstrated by their extensive use in inorganic [11–14] and organic synthesis [15–20], as well as, in the preparation of numerous pharmaceuticals intermediates. In fact, mustard compounds, being genotoxic and mutagenic, stop cell cycle progression and they are able, in some cases, to efficiently prevent the proliferation of cancer cells.

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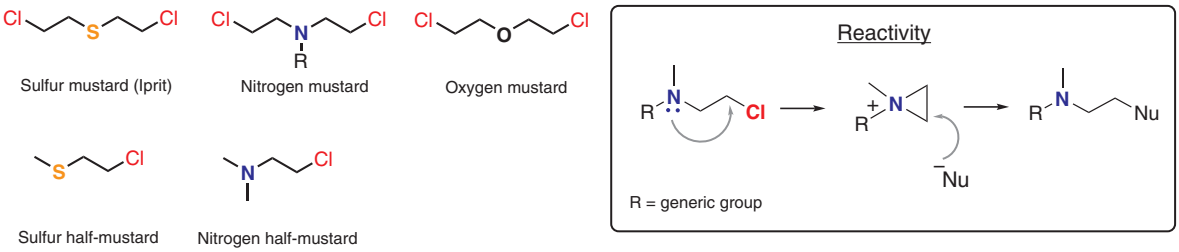


Fig. 1: Chemical structures and reactivity of nitrogen, sulfur and oxygen (half-) mustards.

As a result, both sulfur and nitrogen iprits and some opportunely synthetically designed derivates, i.e., "mustargen", cause dramatic tumor regression [21–27].

Over the years, our research group has demonstrated that the substitution of a chlorine atom with a carbonate moiety via dialkyl carbonate (DAC) chemistry resulted in new green synthetic pathways with various applications, i.e., synthesis of linear and cyclic carbamates, preparation of cyclic intermediates for the cosmetic industry and the selective mono-C-methylation of CH_2-acidic compounds such as arylacetonitriles, intermediates of anti-inflammatory drugs [28–34].

Compared to their halogen analogues, organic carbonates resulted green and harmless for the operators and the environment. Toxicological tests carried out on selected DACs did not show any acute dermal, oral or skin toxicity and their olfactory impact was insignificant.

In fact, short chain DACs such as dimethyl carbonate (DMC) are well known environmentally benign substitute for dimethyl sulfate and methyl halides in methylation reactions, and for phosgene in carboxymethylation reactions. In the presence of a nucleophile and a catalyst/base, DMC can act either as methylating agent ($B_{Al}2$ mechanism) or carboxymethylating agent ($B_{Ac}2$ mechanism) giving as by-products only methanol and eventually CO_2 [35–39].

In this prospect, recently the contradictory nature of mustard gas, i.e., highly toxic chemical weapons and extremely useful reagents and pharmaceuticals, has ignited our interest. The question we wanted to answer was: *would be feasible to synthesize mustard analogous carbonates that maintain the chemical behavior of the parent chlorine compounds as powerful electrophiles while losing their toxic properties?*

This article reports on our findings on new and so far unexplored carbonate mustard compounds: the synthesis, the chemical behavior in different reaction conditions, the kinetics study and their ongoing applications.

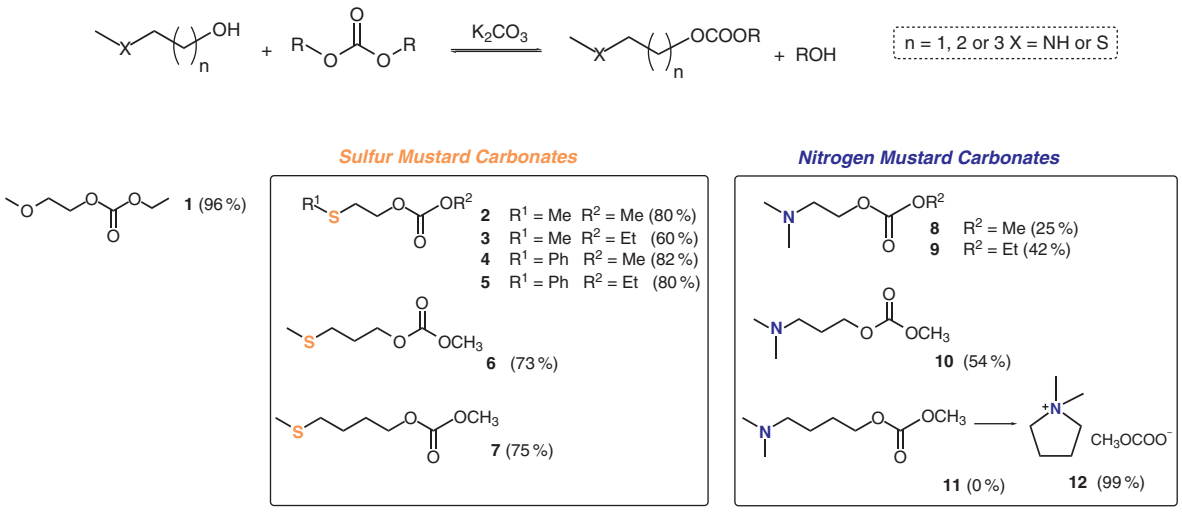
Results

Synthesis of mustard carbonates

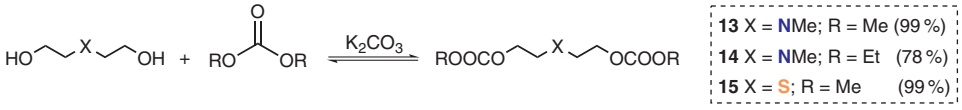
Sulfur half-mustard carbonates 2-(alkylthio)ethyl alkyl carbonates **2–5**, nitrogen half-mustard carbonates 2-(dimethylamino)ethyl alkyl carbonates **8–9** and 2-methoxyethyl ethyl carbonate **1** (Scheme 1) have all been synthesized in good yield by reacting the related commercially available alcohol with the selected DAC by $B_{Ac}2$ mechanism using potassium carbonate as a base (Scheme 1).

Sulfur and nitrogen half-mustard carbonates (methylthio)alkyl methyl carbonates **6–7** and (*N*,*N*-dimethylamino)propyl methyl carbonate **10** have also been synthesized by a similar synthetic approach (Scheme 1).

Interestingly, the reaction of 4-(*N*,*N*-dimethylamino)-1-butanol with DMC in the presence of a base did not lead to the carbonate **11**, but gave the quaternary ammonium salt **12** (Scheme 1) [40]. Most probably, the formation of the pyrrolidinium salt **12** occurs by a two step intermolecular cyclization reaction promoted by DMC. In the first step the methoxycarbonylation of the alcohol occurs via $B_{Ac}2$ mechanism, then a fast intramolecular alkylation leads to the 1,1-dimethyl pyrrolidinium salt **12** ($B_{Al}2$ mechanism).



Scheme 1: Synthesis of sulfur and nitrogen half-mustards carbonates **2–11**.



Scheme 2: Synthesis of sulfur and nitrogen mustard carbonates **13–15**.

Double-functionalized symmetrical mustard (iprit) carbonates were also prepared according to a similar synthetic procedure. Bis-*N*,*N*-[(2-alkylcarbonate)ethyl]methylamine **13–14** and bis-(2-methylcarbonate)ethyl sulphide **15** were easily synthesized in high yield (78–99 %) starting from the commercially available alcohols (Scheme 2).

Interestingly, as dialkyl carbonates, also the parents alcohols of mustard compounds are derived from easy accessible epoxides by reaction with the appropriate sulfur or nitrogen nucleophile [41, 42].

Although very simple, most of these (half-)mustard carbonates resulted unexpectedly novel, as an evidence of a chemistry not yet explored. It should be mentioned that, these compounds resulted stable, did not smell and did not show any vesicant properties or harm for the experiment operators.

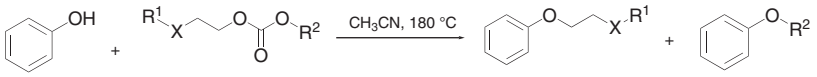
Chemical behavior of mustard carbonates

Reactions in autoclave

In a first set of experiments, sulfur and nitrogen half-mustard carbonate analogues were reacted with a simple nucleophile i.e., phenol. The reactions were conducted in autoclave at 180 °C using preferably acetonitrile as solvent and without any base (Scheme 3) [43].

Table 1 accounts on different aspects of the chemical behavior of mustard carbonates. The reactions of phenol with diethyl carbonate (DEC) and 2-methoxyethyl ethyl carbonate **1** were used as test reactions.

When phenol was reacted with DEC, used as reagent and solvent (entry 1, Table 1), it gave only ethoxybenzene **21** as product although the conversion of the starting material was modest (33 %). On the other hand, phenol did not react at all with 2-methoxyethyl ethyl carbonate **1** (entry 2, Table 1) in this reaction conditions. However, when the same reaction was carried out in the presence of K_2CO_3, ethoxybenzene **21** formed as the main product together with a small amount of (2-methoxyethoxy)benzene **16** (entry 3, Table 1). This result demonstrates that the bimolecular substitution ($B_{Al}2$ mechanism) is predominant in base-promoted DAC reactions. In the same way, the reaction of phenol with DEC in the presence of base resulted in the quantitative formation of ethoxybenzene after only 2 h (entry 1, Table 1 footnote c).



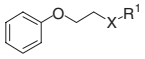
1 X=**O**; R^1=Me R^2=Et
2 X=**S**; R^1=R^2=Me
3 X=**S**; R^1=Me R^2=Et
4 X=**S**; R^1=Ph R^2=Me
5 X=**S**; R^1=Ph R^2=Et
8 X=**N**(CH_3); R^1=R^2=Me
9 X=**N**(CH_3); R^1=Me R^2=Et

16 X=**O**; R^1=Me
17 X=**S**; R^1=Me
18 X=**S**; R^1=Ph
19 X=**N**(CH_3); R^1=Me

20 R^2=Me
21 R^2=Et

Scheme 3: Reaction of phenol with oxygen, nitrogen and sulfur half-mustard carbonate analogues.

Table 1: Reaction of phenol with sulfur and nitrogen half-mustard carbonate analogues.[a]

#	Carbonate	Solvent	Time (h)	Conv.[b] (%)	Products Selectivity %	
						
1[c]	DEC	DEC	24	33	–	**21** (100)
2	**1**	CH_3CN	24	0	**16** (0)	**21** (0)
3[d]	**1**	CH_3CN	24	97	**16** (28)	**21** (72)
4	**2**	CH_3CN	24	100	**17** (100)	**20** (0)
5	**3**	CH_3CN	24	81	**17** (100)	**21** (0)
6[d]	**3**	CH_3CN	24	100	**17** (58)	**21** (41)
7	**4**	CH_3CN	24	36	**18** (45)	**20** (0)
8	**5**	CH_3CN	24	50	**18** (16)	**21** (0)
9	**8**	CH_3CN	5	100	**19** (100)	**20** (0)
10	**9**	CH_3CN	5	100	**19** (100)	**21** (0)

[a]Carbonate (1.0 eq. mol), phenol (3.0 eq. mol) in acetonitrile (100 ml) at 180 °C in autoclave.

[b]Calculated by GC-MS analysis using *p*-xylene as internal standard.

[c]When the reaction was performed in the presence of 1.0 mol. eq. of K_2CO_3 resulted in 100 % conversion into ethoxybenzene **19** after 2 h.

[d]The reaction was performed in the presence of 1.0 mol. eq. of K_2CO_3.

When phenol was reacted with the sulfur half-mustard carbonate analogues **2–3** methyl 2-phenoxyethyl sulfide **17** formed in quantitative yield (entries 4 and 5, Table 1). This result provides clear evidence that the anchimeric effect of the sulfur is crucial for the reaction to occur.

Furthermore, performing the same synthesis in the presence of a base, i.e., K_2CO_3, the sulfide **17** still formed as the main product, but ethoxybenzene **21** was also present in 41 % yield (entry 6, Table 1). This result confirms that i) the base activate the nucleophile toward the concurrent $B_{Al}2$ pathway; ii) in this reaction conditions the anchimeric effect does not need the presence of base which, on the contrary, resulted counterproductive.

The reaction between the sulfur half-mustard carbonate **3** and phenol was also conducted employing different solvents, i.e., cyclohexane, *N*,*N*-dimethyl formamide (DMF), dimethyl sulfoxide, tetrahydrofuran and toluene. Among them acetonitrile resulted the best reaction medium, although a complete study on the solvent effect has not yet been carried out.

2-(Phenylthio)ethyl alkyl carbonates **4** and **5** were also reacted with phenol (entries 7–8, Table 1) in autoclave conditions. In this cases, a low conversions of the starting carbonates and modest selectivity were observed (45 % and 16 %, respectively). These results might be ascribed to the lower sulfur nucleophilicity compared to the carbonates **2** and **3**.

Table 1 reports also the reactivity of the nitrogen half-mustard analogues 2-(dimethylamino)ethyl alkyl carbonates **8–9**. Both carbonates showed to react readily with phenol giving as sole product the

N,*N*-dimethyl-2-phenoxyethylamine **21** in quantitative yield (entries 9–10, Table 1). It is noteworthy that the reactions involving nitrogen half-mustard carbonates were much faster compared to the ones of sulfur mustard analogues. This is almost certainly ascribed to the easier formation of the aziridinium cation as the reaction intermediate compared to the episolfonium one.

Table 2 accounts on the reactivity of half-mustard carbonates **6–7**, **10** and symmetrical mustard carbonates **13–15** with phenol. Reaction were conducted in autoclave using acetonitrile as solvent and in the absence of any base [44].

Sulfur half-mustard 3-(methylthio)propyl methyl carbonate **6** did not react at all with phenol even after 24 h (entry 1, Table 2) under the investigated reaction conditions. On the contrary, 4-(methylthio)butyl methyl carbonate **7** showed to react with good yield (entry 2, Table 2).

3-(*N*,*N*-dimethylamino)propyl methyl carbonate **10** reacts readily with phenol under neutral condition resulting in the highly selective formation (94 %) of *N*,*N*-dimethyl-3-phenoxypropanamine **24** (entry 3, Table 2).

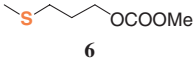
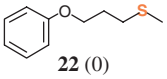
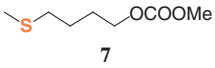
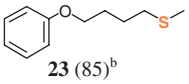
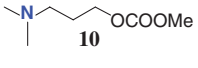
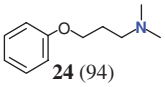
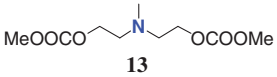
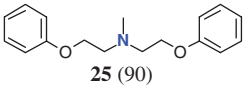
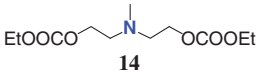
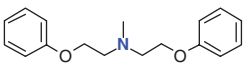
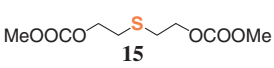
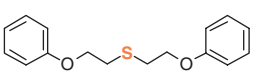
Reaction of bis-*N*,*N*-[2-alkylcarbonate)ethyl]methylamines **13–14** with phenol resulted in a double alkylation in quantitative conversion and high isolated yields (entries 4–5, Table 2).

Conversely, bis-(2-methylcarbonate)ethyl sulphide **15** did not react with any nucleophiles even at higher temperatures i.e., 200 °C. This result can be maybe ascribed to the steric hindrance of the reagent that was predominant on the anchimeric effect of the sulfur in this reaction conditions.

It should be mentioned that the alkylated products reported in Tables 1 and 2, **16–19** and **23–25**, respectively, have been isolated and fully characterized.

All the above reported alkylation reactions proceed most probably through a similar reaction mechanism, i.e., formation of a cyclic intermediate aided by the anchimeric effect of the nitrogen/sulfur atom (Fig. 2) followed by a nucleophilic attack. In particular reactions involving 2-(methylthio)ethyl methyl carbonate **2** and 2-(dimethylamino)ethyl methyl carbonate **8**, undergo via an episolfonium and aziridinium intermediate, respectively. Most probably due to the easier formation of the aziridinium cation intermediate, the reactions

Table 2: Reaction of phenol with sulfur and nitrogen (half-)mustard carbonate analogues.

#	Carbonate	Time (h)	Conv.[b] (%)	Products GC-MS %[b]
1[a]	 **6**	24	0	 **22** (0)
2[a]	 **7**	8	90	 **23** (85)[b]
3[a]	 **10**	6	80	 **24** (94)
4[c]	 **13**	5	100	 **25** (90)
5[c]	 **14**	6	100	 **25** (90)
6[c]	 **15**	24	0	 **26** (0)

[a]Reaction conditions: Nucleophile:carbonate 1:1 molar ratio in acetonitrile at 180 °C.

[b]GC-MS analysis showed also 13 % of anisole; d GC-MS analysis showed also 35 % of monomethylated product and several unidentified products.

[c]Reaction conditions: Nucleophile:carbonate 2:1 molar ratio in acetonitrile at 180 °C.

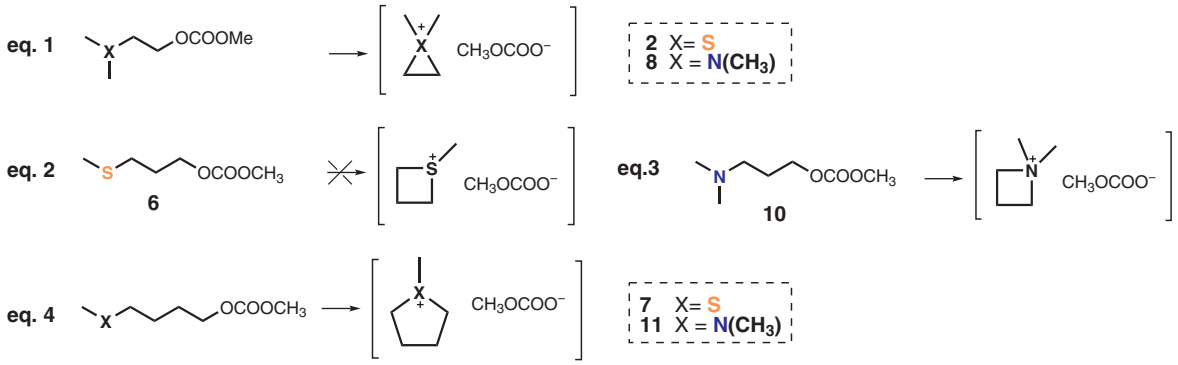


Fig. 2: Reaction mechanism of sulfur and nitrogen half-mustard carbonates.

involving nitrogen half-mustard carbonates were much faster compared to the ones of sulfur mustard analogues (Table 1).

Similarly reactions conducted on 3-(methylthio)propyl methyl carbonate **6** and 3-(N,N-dimethylamino) propyl methyl carbonate **10** undergo via a 1,1-dimethylazetidinium and 1-methylthietanium four members intermediate (eqs. 2 and 3, Fig. 2).

Results collected (Table 2) seem to suggest that the 1-methylthietanium, only scarcely reported in the literature [45], is a less stable intermediate compared to 1,1-dimethylazetidinium [46]. Most probably the anchimeric effect of the sulfur mustard carbonate **6** is not strong enough to stabilize the strained four members cyclic intermediate. On the other hand, both mustard carbonates **7** and **11** resulted very reactive. As expected, five-members cyclic intermediates are less sterically strained, thus sulfur and nitrogen anchimeric effect are strong enough to promote the alkylation reaction. However, 4-(*N*,*N*-dimethylamino)butyl methyl carbonate **11**, once formed, undergoes fast intramolecular cyclization leading to the very stable quaternary ammonium salt **12** isolated as pure in quantitative yield.

In order to investigate the reaction mechanism, kinetics study were carry out both on sulfur and nitrogen half-mustard compounds [43]. Figure 3 depicts, as an example, the reaction kinetics of 2-(dimethylamino)ethyl ethyl carbonate **9** with phenol (1:1 molar ratio) in acetonitrile according to the reaction conditions reported in entry 10, Table 1. Plotting the experimental values of ln (C_0/C) and 1/C against the first- and second-order rate equations, respectively, it is evident that the reaction fits first-order kinetics (Fig. 3) and corroborates the reaction mechanism reported in Fig. 2.

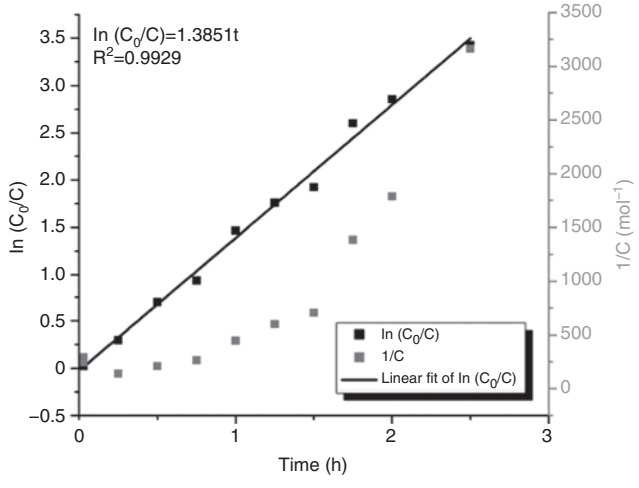


Fig. 3: A comparison between first (black) and second (grey) order kinetics plotting of the reaction of carbonate **9** with phenol (1:1 molar ratio in autoclave 180 °C) where C is the concentration of the carbonate **9** (mol/l); *p*-xylene was used as internal reference [43].

Reactions with different nucleophiles

Novel mustard carbonates react readily with a wide range of nucleophiles, i.e., C–H and O–H acidic compounds, carboxylic acids, amines and inorganic anions, and give the related product in the absence of any base.

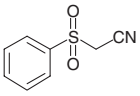
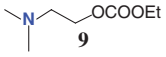
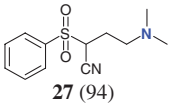
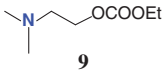
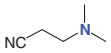
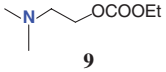
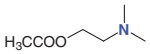
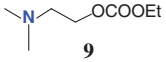
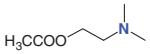
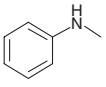
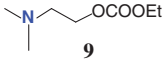
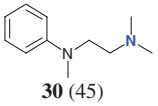
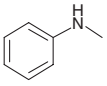
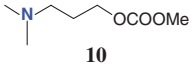
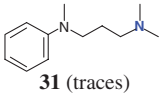
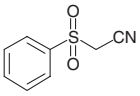
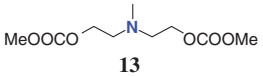
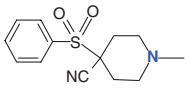
In particular Table 3 reports the reaction of nitrogen half-mustard carbonate **9–10** and of symmetrical mustard carbonate **13** with several nucleophiles.

2-(Dimethylamino)ethyl ethyl carbonate **9** was reacted at 180 °C in autoclave in acetonitrile and under neutral conditions with an organic compounds with CH_2-acidic i.e., (phenylsulfonyl)acetonitrile (entry 1, Table 3); a salt i.e., potassium cyanide and potassium acetate (entries 2 and 4, Table 3); a carboxylic acid i.e., acetic acid (entry 3, Table 3); and an amine i.e., *N*-methylaniline (entry 5, Table 3). In all cases the reactions, monitored till complete disappearance of the starting carbonate **9**, showed the formation of the expected substituted compounds **27–31** as the main reaction products together with small amounts of several by-products that were not isolated.

3-(*N*,*N*-dimethylamino)propyl methyl carbonate **10** reacted readily with phenol (entry 3, Table 2), however, when *N*-methylaniline, a weaker nucleophile, was employed, only a modest conversion and poor selectivity towards the wanted product **31** was observed (entry 6, Table 3).

Finally, it is noteworthy that the reaction of phenylsulphonyl acetonitrile with mustard carbonate **13** underwent an intermolecular cyclization leading to the formation of a substituted piperidine **32** in high yield.

Table 3: Reaction of phenol with sulfur and nitrogen (half-)mustard carbonate analogues.

#	Nucleophile	Carbonate	Time (h)	Products GC-MS %[b]
1[a]		 **9**	7	 **27** (94)
2[a]	KCN	 **9**	4	 **28** (50)
3[a]	CH_3COOH	 **9**	4	 **29** (60)
4[a]	CH_3COOK	 **9**	3	 **29** (70)
5[a]		 **9**	5	 **30** (45)
6[b]		 **10**	5	 **31** (traces)
7[c]		 **13**	7	 **32** (100)

[a]Nucleophile/carbonate 3/1 molar ratio in acetonitrile at 180 °C in autoclave. The conversion of the carbonate **9**, calculated by GC-MS analysis using *p*-xylene as internal standard, was always quantitative. Isolated yield for compounds **15**–**17** resulted modest as purification of these compounds by column chromatography resulted sometime difficult possibly due to their polarity.

[b]Reaction conditions: Nucleophile:carbonate 2:1 molar ratio in acetonitrile at 180 °C. Conversion was 45 %.

[c]Reaction conditions: Nucleophile:carbonate 1:1 molar ratio in acetonitrile at 180 °C. Isolated yield of **33** was 60 %.

The substituted piperidine was isolated as pure in 60 % yield by column chromatography. This reaction is a remarkable example of a intermolecular cyclisation proceeding through a double alkylation reaction.

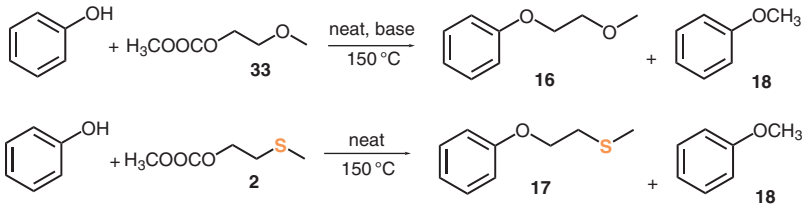
Reactions in neat

The reactivity of selected mustard carbonate analogues have also been investigated in neat conditions at atmospheric pressure and in the presence of a catalytic amount of base [47]. In particular this study was focused on sulfur mustard carbonates that resulted less reactive than nitrogen in autoclave conditions.

In order to confirm the presence of the anchimeric effect also under solventless reaction conditions, the reactivity of 2-(methoxy)ethyl methyl carbonate **34** and of 2-(methylthio)ethyl methyl carbonate **2** with phenol was firstly compared (Scheme 4; entries 1–4, Table 1).

Table 4 (entry 1) shows that the reaction of phenol with 2-(methoxy)ethyl methyl carbonate **33** in neat and in the absence of a base resulted only in unconverted starting materials. This result confirms that carbonate **33** has no anchimeric effect. On the other hand, when the reaction was carried out with K_2CO_3 as a base, the nucleophilicity of phenol resulted enhanced leading mostly to the formation of anisole and a small amount of the alkylated product (2-methoxyethoxy)benzene **16** (entry 2, Table 1). The phenolate anion, formed in the presence of K_2CO_3, can evidently attack either the methyl or the 2-(methoxy)ethyl moiety of the carbonate **33**. Most probably the products selectivity observed can be ascribed to the phenoxide attacking preferably the less sterically hindered alkyl moiety [48].

On the contrary, when 2-(methylthio)ethyl methyl carbonate **2** was reacted with phenol, despite the moderate conversion, the alkylated product **17** formed in good selectivity already without the base (entry 3, Table 4). The moderate conversion of the nucleophile observed can be also ascribed to the scarce mass diffusivity of the neat reaction conditions and/or to the absence of an acidic proton in the substrate.



Scheme 4: Reaction of phenol with 2-(methylthio)ethyl methyl carbonate **2** and with 2-(methoxy)ethyl methyl carbonate **33**.

Table 4: Reaction of phenol with carbonates **33** and **2** with different bases/catalysts in neat.[a]

#	Base/catalyst	Carbonate	Conversion (%)	Selectivity (% GC-MS)	
				$PhO(CH_2)_2XCH_3$	$PhOCH_3$
1	None	**33**	0	**16** (0)	0
2	K_2CO_3	**33**	100	**16** (19)	81
3	None	**2**	56[b]	**17** (86)	6
4	K_2CO_3	**2**	100[b]	**17** (90)	0
5	*t*-BuOK	**2**	100[b]	**17** (79)	7
6	DBU[c]	**2**	75	**17** (92)	6
7	Al_2O_3	**2**	66[b]	**17** (85)	3
8	$Sn(OBu)_2$	**2**	61[b]	**17** (87)	1

[a]Reaction conditions: phenol/carbonate/base 1.0/2.0/0.2 eq. mol., neat at 150 °C for 5 h.

[b]Some unidentified products were present in the reaction mixture.

[c]1,5-Diazabiciclo[5.4.0]undec-5-ene.

To enhance the nucleophilicity of the phenol, its reaction with the carbonate **2** was investigated in the presence of several bases, i.e., alkali carbonate (entry 4), strong bases (entry 5), tertiary amine (entry 6), basic alumina (entries 7) and metallic homogenous catalysts (entries 8).

Results showed that methyl (2-phenoxyethyl) sulfide **17** was the major product formed in all the experiments conducted under solvent free conditions in the presence of a base. Furthermore, the reaction proceeded with quantitative conversion of phenol. In some cases, small amount of anisole were detected.

In particular, the best performance, in terms of conversion and selectivity (100 % and 90 %, respectively), was achieved employing K_2CO_3 as base (entry 4, Table 1). On the other hand when Lewis acid catalyst (entries 8, Table 4) was used, the reaction outcome was similar to that without any base (entry 3, Table 4).

These data confirm that the episolfonium ion is the key intermediate of the reaction. In fact, when Lewis acids were employed they did not affect positively the reaction as the acidic sites do not have any influence on the positively charged intermediate. Conversely, the presence of the base promotes the formation of the phenoxide leading to the selective formation of the alkylated product **33**.

From a mechanistic point of view, the absence of the solvent might affect the reaction outcome (Fig. 4). Compared to the autoclave conditions were acetonitrile was used solvent, in this case the reaction intermediate, i.e., the episolfonium ion, is trapped in a molecular cage in an intimate ion pair [49–51] (**I**) where diffusion phenomena limit and influence the reaction rate. The trapped cyclic intermediate **I**, is in equilibrium with the starting carbonate **2** according to constant k_{-1} (eq. 1). Once the episulfonium intermediate is freed from the solvent cage (**II** according to k_2 constant) it can then either react with the nucleophile or, in the absence of CH_3OCOO^- anion and nucleophiles, decompose into other products (according to a k_d; eq. 3, Fig. 4).

When the reaction is conducted in the presence of a base, the selected nucleophile is deprotonated (eq. 2, Fig. 4) and can react with the episolfonium intermediate (eq. 4, Fig. 4). However, it must be mentioned that the episolfonium intermediate can also react, in the absence of the base, with a neutral nucleophile (if the acidic compound dissociates in some extent according to K_{eq}) resulting in the formation of the protonated alkylated product (eq. 5, Fig. 4). This latest reaction pathway is similar to the one involved in the acid-catalyzed nucleophilic substitution of epoxides (eq. 6, Fig. 4).

In order to validate, the role of the base in the proposed reaction mechanism (Fig. 4), several nucleophiles having different acidity, i.e., aromatic alcohols, aromatic diols and compounds incorporating acidic $-CH_2$, were tested in this reaction condition. Among them *p*-cyanophenol was particularly reactive due to the

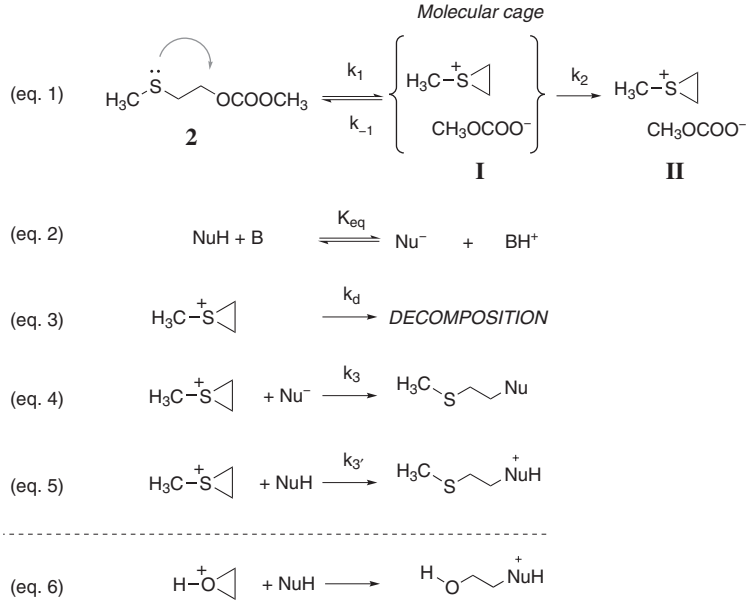


Fig. 4: Possible reaction mechanism for the base-promoted alkylation reaction of 2-(methylthio)ethyl methyl carbonate **2**.

presence of the electro withdrawing cyano moiety. In fact, when the reaction was carried out in the absence of a base, this substrate was converted in high yield into the alkylated derivative **35** (entry 1, Table 5).

In this case, the reaction mechanism mirrors the one reported in eq. 5, Fig. 4, i.e., the presence of a base is not necessary. This substrate was also reacted in solventless conditions with several (half-mustard) carbonate analogues (Scheme 5).

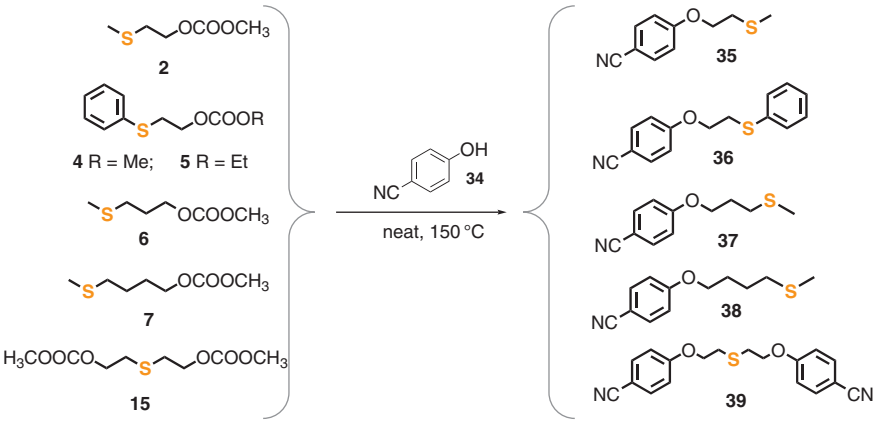
In the previously discussed batch reaction conditions in autoclave, sulfur mustard carbonates showed quite limited or no reactivity towards nucleophiles with the exception of 4-(methylthio)butyl methyl carbonate **7**. In this case study, methyl 2-(phenylthio)ethyl carbonate **4** and ethyl 2-(phenylthio)ethyl carbonate **5** reacted readily with *p*-cyanophenol in neat at 150 °C forming the alkylated product **36** in quantitative yield. 3-(Methylthio)propyl methyl carbonate **6** can also be converted into the alkylated product **37** with a good selectivity (45 %). In this case the formation of the methylated product was also detected in relevant amount (55 %). This result can be ascribed to the formation of the 1-methylthietanium, a 4-membered cyclic intermediate, which is known to be less stable than the 3- or 5-memebered intermediates. On the other hand, 4-(methylthio)butyl methyl carbonate **7** showed to react readily with the nucleophile forming the alkylated product **38** in good yield (66 %).

The reaction of *p*-cyanophenol with double-functionalized symmetrical mustard carbonate **15** was also investigated. In this case, the bisalkylated product **39** was not detectable by GC-MS and the reaction was followed by thin layer chromatography. Therefore, the reported yields (54 %) refer only to the isolated pure compound **39**.

Table 5: Reaction of *p*-cyanophenol with different sulfur mustard carbonate analogues in neat.[a]

#	Carbonate	Time (h)	Conv. (%)	Selectivity (% GC-MS)	
				Alkylated product	PhOAlk
1	**2**	5	100	**35** 95	**20** 5
2	**4**	24	93	**36** 98	**20** 2
3	**5**	24	88	**36** 100	**21** 0
4	**6**	21	100	**37** 59	**20** 40
5[b]	**7**	7	87	**38** 64	**20** 31
6[c]	**15**	21	–[d]	**39** 54[e]	**20** 0

[a]Reaction conditions: *p*-cyanophenol/carbonate 1.0/2.0 eq. mol., neat at 150 °C.
[b]Reaction conditions: *p*-cyanophenol/carbonate 1.0/1.0 eq. mol.
[c]Reaction conditions: *p*-cyanophenol/carbonate 2.0/1.0 eq. mol.
[d]The products are not visible on GC-MS analysis.
[e]Isolated yield.



Scheme 5: Reaction of *p*-cyanophenol with different sulfur mustard carbonate analogues in neat.

Azacrowns from mustard carbonate analogues

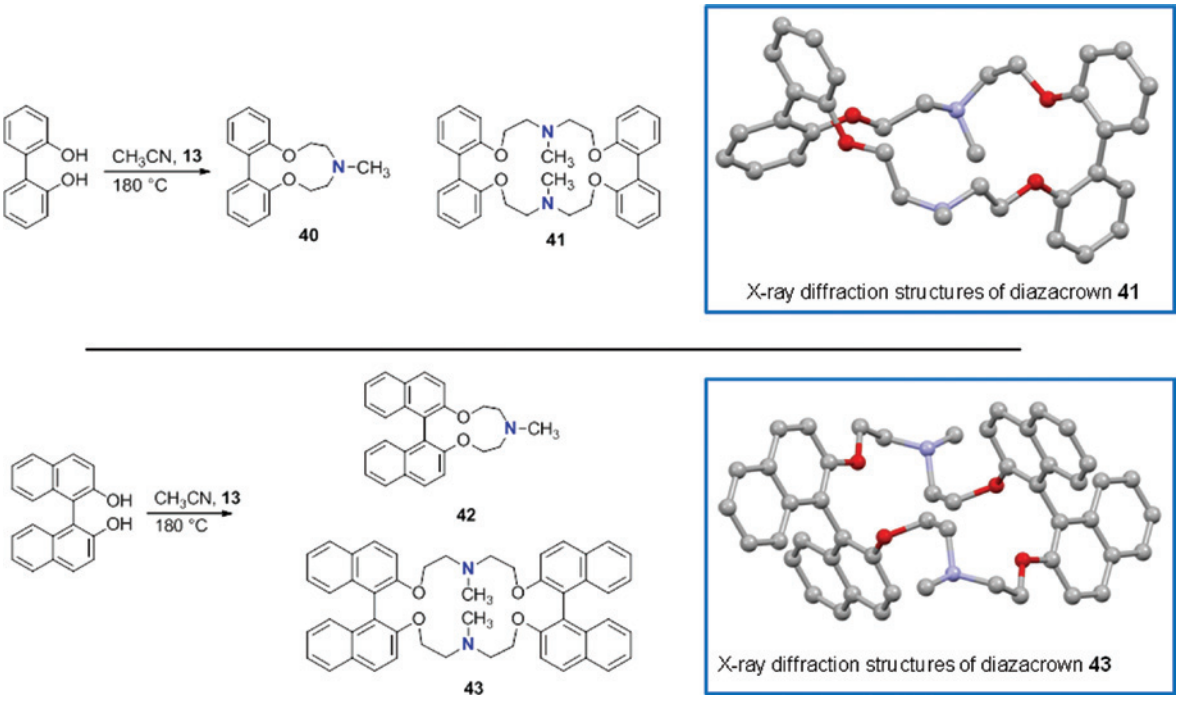
Polycondensation reaction of the nitrogen mustard carbonate **13** analogue with aromatic diols under dilution conditions resulted in a series of azacrowns previously not easily accessible [52].

In particular, reaction of symmetrical nitrogen mustard carbonate **13** with biphenyl-2,2′-diol in the presence of potassium nitrate as template at 180 °C in an autoclave, led to a new family of macrocycles (Scheme 6).

Azacrown **40** and diazacrown **41** have been isolated straightforwardly from the reaction mixture by column chromatography in 17 % and 23 % yield, respectively. Diazacrown **41** has also been characterized by single crystal X-ray diffraction analysis. In each molecule the two biphenyl units share the same axial chirality, whereas molecules of both (*R*,*R*) and (*S*,*S*) configuration occur in the unit cell of the centrosymmetric structure. This arrangement, homo-chiral within each molecule, has been reported for the X-ray diffraction structure of the related, biphenyl based, bis(biphenyl) 22-crown-6 ether macrocycle [53].

A similar polycondensation reaction was carried using racemic 1,1′-bis-2-naphthol as substrates (Scheme 6). The smallest macrocycle **42** was isolated in 19 % yield by column chromatography and crystallized. According to an X-ray diffraction analysis, this compound is the racemate of the azacrown **42** [52]. Two additional compounds were chromatographically isolated from the reaction mixture, one crystalline (5 % yield) and the other as an oil (17 % yield). Both of them, on the basis of Hi-Res MS and NMR data, are compatible with the chemical formula of the diazacrown **43**. The lower-yield compound has been successfully crystallized and its X-ray diffraction structure is shown in Scheme 6 (bottom). One half molecule composes the asymmetry unit, the second half being generated through an inversion center. Therefore, the two 1,1′-bi-2-naphthyl units are of opposite axial chirality and the crystallized molecule is the meso isomer of 5. As a consequence, the other isolated compound must be the mixture of the (*R*,*R*) and (*S*,*S*) isomers of **43**.

This approach to azacrowns is not restricted to bisphenyl diols, but can also be used for the one-pot synthesis of dibenzo 18-, 20- and 22-diazacrown-6. These compounds, hitherto not accessible, can now be easily synthesized by reaction of nitrogen mustard carbonate **13** with catechol, resorcinol or hydroquinone, thus affording diazacrowns **44–46** (Scheme 7) in the absence of any base. Cyclic dimers **44**, **45** and **46** were



Scheme 6: Synthesis of azacrowns **40–43** from nitrogen mustard carbonate **13**.

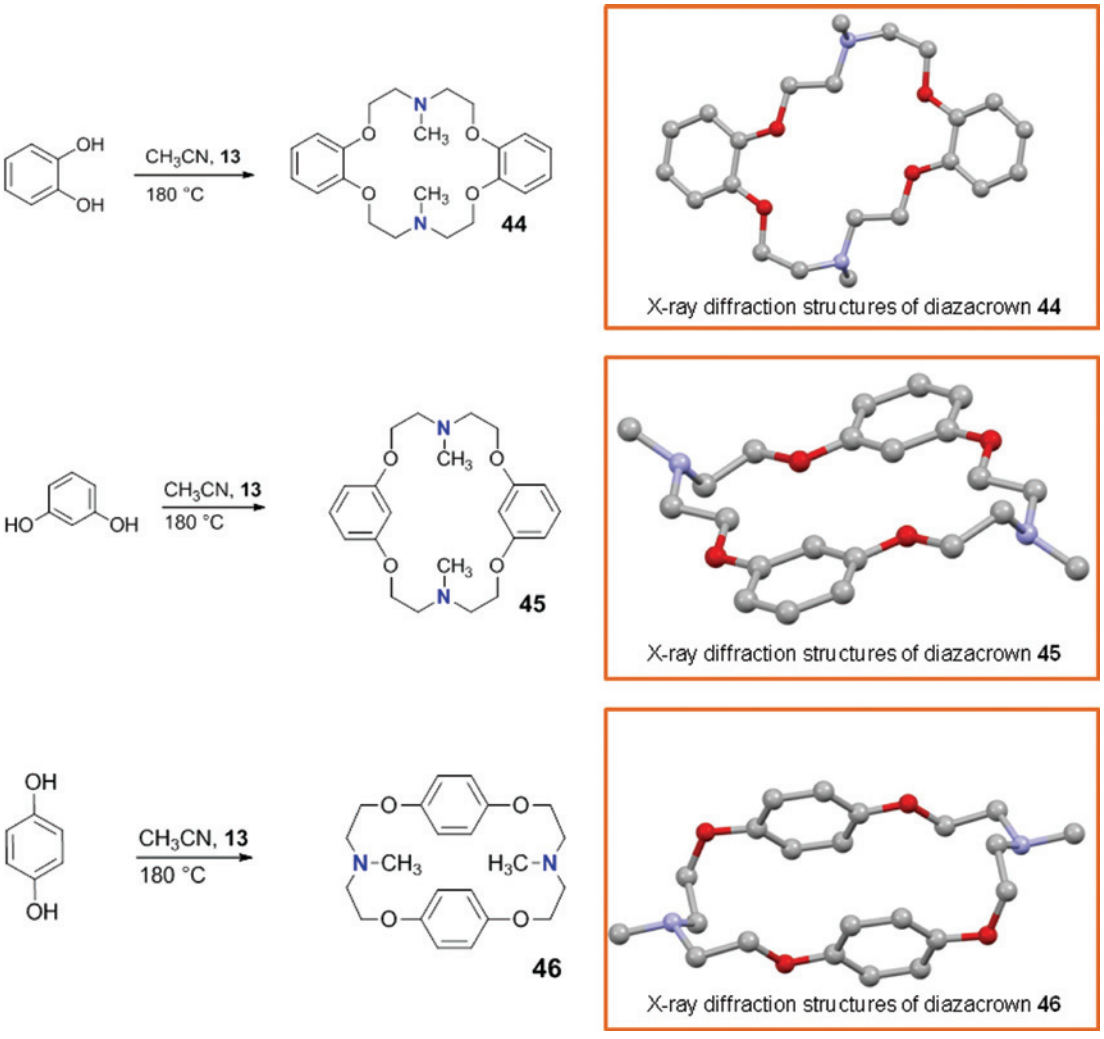
isolated in pure form by column chromatography in 18 %, 12 % and 12 % yield, respectively, and characterized in detail, including single crystal X-ray diffraction analysis (Scheme 7).

Geometrical considerations suggest that among the synthesized dibenzo-macrocycles, diazacrown **44** is the most promising candidate for complexation of a metal ion such as silver cation.

Conclusions

The replacement of a chlorine by a carbonate moiety in half-nitrogen and -sulfur mustard compounds gave new, unexplored and safe compounds that showed good reactivity. The reactions involving the half-mustard carbonate analogues and a nucleophile proceed through an intramolecular S_N2 mechanism promoted by the sulfur and nitrogen anchimeric effect which is the rate-determining step; the subsequent nucleophilic attack, being faster, does not influence the reaction rate. The reactivity of mustard carbonates have been investigated both in autoclave and in neat conditions.

When the reaction was conducted at high temperature and under pressure in an autoclave, the presence of a base was not required since, when used, it promotes unwanted by-products. Nitrogen mustard carbonates resulted more reactive in these conditions than sulfur ones.



Scheme 7: Synthesis of diazacrowns **44–46**.

Under neutral conditions, nitrogen mustard carbonates are capable to react readily with several nucleophiles including CH_2-acidic compounds i.e., (phenylsulfonyl)acetonitrile; a salt i.e., potassium cyanide and potassium acetate; a carboxylic acid i.e., acetic acid and an amine i.e., *N*-methylaniline.

Interestingly, when phenyl sulphonyl acetonitrile was reacted with the nitrogen symmetrical mustard carbonate **12** it resulted in the formation of a piperdine by intermolecular cyclization via a double $B_{Al}2$ mechanism.

The reaction kinetics have been also investigated for the reaction of phenol and simple half-mustard carbonates **9** with phenol. Plotting the experimental values against the first- and second-order rate equations, the reaction resulted to fit a first-order kinetics as the one of its parent mustard compounds.

The reactivity of mustard carbonates was then investigated in solventless reaction conditions. Sulfur iprit carbonates were employed in neat, at atmospheric pressure and at lower temperature (150 °C), in the presence of a base and in its absence. Several bases and catalysts have been investigated; K_2CO_3 resulted the most efficient.

The results collected demonstrated clearly that also in solventless reaction the sulfur (half-) mustard carbonate analogues exhibited its anchimeric effect via formation of episolfonium intermediate. However, due to the scarce mass diffusivity of the neat reaction conditions and in the absence of an acidic proton in the nucleophile, the use of a base is necessary. This was useful to explain the importance of the intimate and the free ion pair in the reaction mechanism.

In the case of nucleophiles incorporating acidic proton, such as *p*-cyanophenol, the use of the base can be avoided without affecting the conversion or the selectivity of the alkylation reaction. It is also noteworthy that in these novel reaction conditions, some sulfur mustard carbonates, that previously showed little or no reactivity with nucleophiles, undergo efficient nucleophilic substitution with several substrates.

If we compare the reactivity as electrophile of a simple half-mustard compound such as 2-chloro-*N*,*N*-dimethylethanamine with its carbonate analogues, it is evident that the nitrogen iprit necessitates milder reaction conditions, i.e., lower reaction temperature (0–90 °C) and in general a short reaction time (1–10 h) [54–57]. However, in most of the reactions they require the presence of a base. Furthermore, the use 2-chloro-*N*,*N*-dimethylethanamine requires particular precautions of the operators due to its high toxicity.

The carbonate mustard analogue, on the other hands, is efficient as electrophile at higher temperature (150–180 °C), but it does not require auxiliary base and most importantly it can easily handle without any special safety measure.

Furthermore when a symmetrical nitrogen mustard carbonate analogue **13** was reacted with several aromatic diols afforded new families of azacrown compounds. Spectroscopic data, high resolution mass analysis and in several cases X-ray investigation confirmed the proposed structures. These macrocycles have not been previously reported as the nitrogen mustard moiety was accessible only using the toxic mustard gas. The reactions have been conducted in autoclave and in the absence of base as the cyclization proceeds due to the anchimeric effect of the mustard carbonate compound. This synthesis is a poignant example of green chemistry applied to supramolecular chemistry. Application of this synthetic procedure to more complex supramolecular structures is under investigation.

It must point out that, due to their recent discovery, these compounds are still not fully exploited and their applications in organic, inorganic, supramolecular and polymeric chemistry is currently under investigation. Furthermore, an accurate determination of the mustard carbonate analogous toxicological properties is still to be conducted in details.

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