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Behaviour of iprit carbonate analogues in solventless reactions†

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Sulfur iprit carbonate analogues have been investigated in neat conditions at atmospheric pressure, in the presence and in the absence of a catalytic amount of base. Furthermore, their reaction mechanism has been discussed in detail. In these novel reaction conditions, sulfur mustard carbonate analogues, that previously showed poor or no reactivity, remarkably undergo efficient nucleophilic substitution with several substrates.

Introduction

Mustard gas, bis(2-chloroethyl) sulfide is a vesicant and blistering agent that has been used for almost 100 years in several chemical wars, *i.e.*, WWI and the Iran–Iraq conflict.[1] 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. The most deleterious molecular mechanisms in nitrogen and sulfur mustards poisoning are the inflammation and the over-activation of poly(ADP-ribose) polymerase resulting in DNA permanent alkylation.[1] Consequently numerous efforts have been made in order to detect, convert and/or degrade mustard gas into less poisonous products.[2]

The toxicity of sulfur and nitrogen iprits has been ascribed to the high reactivity of these molecules that readily eliminates a chloride ion by intramolecular nucleophilic substitution promoted by the sulfur or nitrogen anchimeric effect.[3] The resulting cyclic episulfonium/aziridinium ion intermediates undergo fast nucleophilic substitution (Fig. 1).[4] On the other hand, it is also noteworthy that mustard compounds, being genotoxic and mutagenic, stop cell cycle progression, thus, they are able, in some cases, to prevent efficiently the proliferation of cancer cells. As a result, both sulfur and nitrogen iprits and some opportunely synthetically designed derivates, *i.e.*, "mustargen", cause dramatic tumour regression.[5]

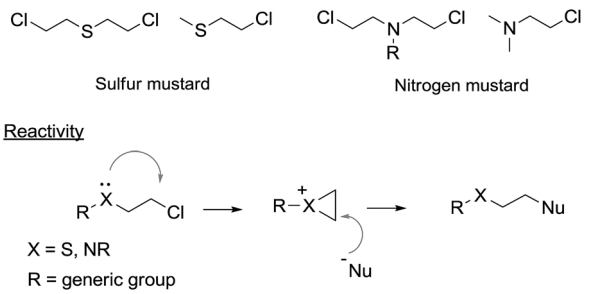

Fig. 1 Chemical structure and reactivity of sulfur and nitrogen mustards.

The contradictory nature of mustard molecules, *i.e.*, highly toxic chemical weapons and extremely useful reagents and pharmaceuticals, has contributed to the increasing interest in these compounds that, over the years, have been widely exploited in both inorganic[6] and organic chemistry.[7]

In previous works, we have extensively reported that substituting 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, selective mono-C-methylation of CH_2-acidic compounds such as arylacetonitriles, intermediates of anti-inflammatory drugs.[8]

Compared to their halogen analogues, organic carbonates resulted green and harmless for the operators and the environment. In particular, the toxicological tests carried out on selected DACs didn't show any acute dermal, oral or skin toxicity and their olfactory impact was insignificant.[8a,9] It is also noteworthy that, in many synthetic procedures, *i.e.*, synthesis of heterocycles, alkyl carbonates act as sacrificial molecules, as they are not incorporated in the final product (Fig. 2).[10d] This behaviour is comparable to the use of chlorine, halogen atoms or their suitable derivatives, as leaving groups (*i.e.*, tosyl chloride, mesyl chloride, *etc.*). However, in the case of dimethyl carbonate (DMC) the reaction products (CO_2 and methanol) are green and can be recycled, meanwhile when halogen chemistry is employed, waste salts, formed as by products, have to be disposed of resulting in a negative impact on the reaction green metrics.[11] Besides, as the chemical reactivity is concerned, halogen chemistry is more energetically intensive (*i.e.*, deriving

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† Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR spectra, GC-MS analysis, MS analysis and Hi-Res MS analysis of the new isolated pure products. See DOI: 10.1039/c4ra03254c

‡ The authors have contributed equally to this work.

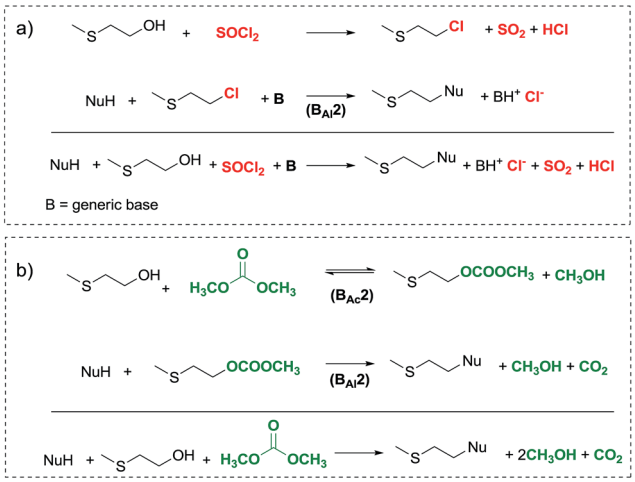


Fig. 2 Sacrificial molecules: a comparison between (a) chlorine and (b) DMC chemistries.

from Cl_2 production *via* electrolysis) and the resulting products are more reactive, meanwhile DMC chemistry requires higher temperatures to react.

An advantage of using DACs is that they can act as versatile solvent and/or as green reagents. In particular DMC, depending on the substrate and reaction conditions, can be a methoxycarbonylation agent ($B_{Ac}2$ mechanism) and/or a methylating agent ($B_{Al}2$ mechanism).[10] DMC is therefore an ambiphilic electrophile that has been shown to react in a surprisingly high selectivity with different monodentate and bidentate nucleophiles.[12]

In this prospect, we have recently reported the synthesis of novel sulfur half-mustard carbonate analogues (Fig. 3) *via* DMC chemistry. The replacement of a chlorine atom with a carbonate moiety resulted in molecules displaying a similar reactivity and kinetic behaviour of their chlorine homologues without showing any evident toxicological properties.[8,13,14]

The reaction mechanism involved in the selective alkylation of a nucleophile promoted by the anchimeric effect of the iprit carbonate analogues, includes both a $B_{Ac}2$ and a $B_{Al}2$ mechanism (Fig. 2). Thus, as in the case of chlorine chemistry, DMC acts a sacrificial molecule since it is not incorporated in the final product (Fig. 2).[10d]

Our previous investigation on the reactivity of new mustard carbonate analogues were conducted in the presence of a solvent, under pressure in an autoclave and without using any base. In these conditions, the reaction outcome was influenced by several factors, *i.e.*, temperature, nucleophile and concentration. Furthermore, since the reaction involves a positively charged intermediate (Fig. 1), it is also influenced by the solvent employed. In particular, acetonitrile resulted to be the best reaction media possibly due to its polarity which might stabilize the charged cyclic intermediate.

In this work we report on the reactivity of iprit carbonate analogues, through a deeper insight on their reaction mechanism. In particular, herein for the first time the reactivity of sulfur (half) mustard carbonate analogues has been investigated at atmospheric pressure and in neat conditions where, due to the enhanced viscosity of the reaction media and to the diminished mass diffusions of the reagents, several steps of the reaction mechanism are slowed down and thus observable. It is noteworthy that the absence of the solvent implements the greenness of the reaction although a small amount of base is required for nucleophiles that do not incorporate acidic protons. In these novel reaction conditions, the reactivity of sulfur (half-)mustard carbonate analogues with several nucleophiles resulted greatly enhanced.

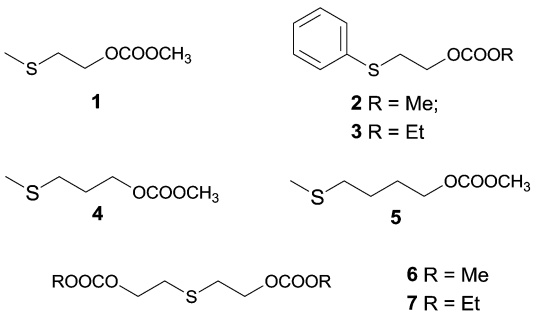


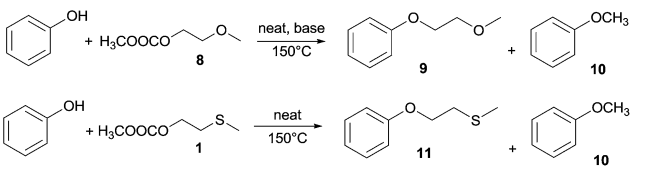
Fig. 3 Sulfur mustard carbonate analogues.

Results and discussion

In a typical reaction, the selected nucleophile (1.0 eq. mol.), the mustard carbonate analogue (2.0 eq. mol.) and eventually a catalytic amount of base (0.2 eq. mol.) are placed in a test tube and heated in solventless conditions at 150 °C at atmospheric pressure.

In order to confirm the presence of the anchimeric effect also under solventless reaction conditions, the reactivity of 2-(methoxy)ethyl methyl carbonate **8** and of 2-(methylthio)ethyl methyl carbonate **1** with phenol was firstly compared (Scheme 1; entries 1–4, Table 1).

Table 1 (entry 1) shows that the reaction of phenol with 2-(methoxy)ethyl methyl carbonate **8** in neat and in the absence of a base resulted only in unconverted starting materials; no methylation or alkylation of the phenol occurred. This result demonstrates that carbonate **8** 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 **9** (entry 2, Table 1). In fact, the phenolate anion, formed in the presence of K_2CO_3, can then attack either the methyl or the 2-(methoxy)-ethyl moiety of the carbonate **8**.



Scheme 1 Reaction of phenol with 2-(methylthio)ethyl methyl carbonate **1** and with 2-(methoxy)ethyl methyl carbonate **8**.

Table 1 Reaction of phenol with carbonates **8** and **1** with different bases/catalysts in neat[a]

#	Base/catalyst	Carb.	Conv. (%)	Selectivity (% GC-MS) $PhO(CH_2)_2XCH_3$	Selectivity (% GC-MS) $PhOCH_3$
1	None	**8**	0	0	0
2	K_2CO_3	**8**	100	19	81
3	None	**1**	56[b]	86	6
4	K_2CO_3	**1**	100[b]	90	0
5	*t*-BuOK	**1**	100[b]	79	7
6	NaOMe	**1**	80[b]	87	2
7	DBU[c]	**1**	75	92	6
8	Al_2O_3	**1**	66[b]	85	3
9	KW2000[d]	**1**	64[b]	86	4
10	$Zn(Ac)_2$	**1**	83	97	0
11	$Sn(OBu)_2$	**1**	61[b]	87	1

[a] Reaction conditions: phenol/carbonate/base 1.0/2.0/0.2 eq. mol., neat at 150 °C for 5 hours. [b] Some unidentified products were present in the reaction mixture. [c] 1,5-Diazabiciclo[5.4.0]undec-5-ene. [d] Hydrotalcite KW2000 was used in 0.2 weight%.

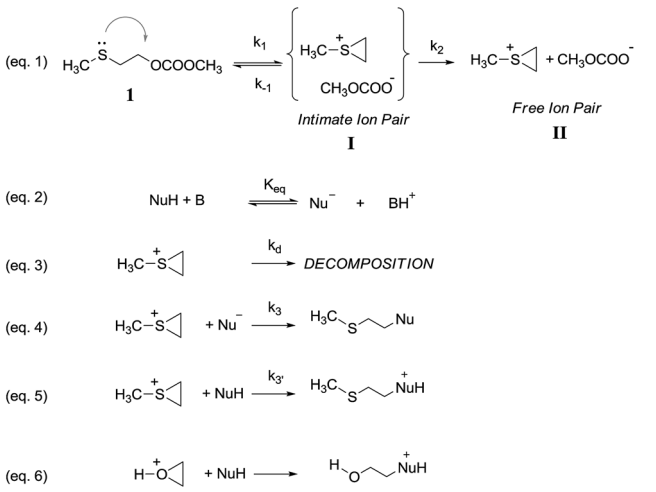


Fig. 4 Possible reaction mechanism for the base-promoted alkylation reaction of 2-(methoxy)ethyl methyl carbonate **8**.

A similar chemoselectivity for the $B_{Al}2$ mechanism between methyl and primary carbons was already observed studying the reactivity of several unsymmetrical DACs. Most probably the observed products selectivity can be ascribed to the phenoxide attacking preferably the less sterically hindered alkyl moiety.[15] Thus, we can confidently exclude any anchimeric effect on oxygen compounds **8**, either in the presence and in the absence of a base.

On the contrary, when 2-(methylthio)ethyl methyl carbonate **1** was reacted with phenol, despite the moderate conversion, the alkylated product **11** formed in good selectivity already without the base (entry 3, Table 1). Importantly from a mechanistic point of view, the reaction mixture showed also the presence of some unidentified products that weren't detected in the experiments carried out in autoclave and in the presence of a solvent.[13] This result might be explained according to the reaction mechanism reported in Fig. 4. The reaction intermediate, *i.e.*, the episolfonium ion, is trapped in a molecular cage in an intimate ion pair[16] (**I**) where diffusion phenomena limit and influence the reaction rate. The trapped cyclic intermediate **I**, is in equilibrium with the starting carbonate **1** according to constant k_{-1} (eqn (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; eqn (3), Fig. 4).[17]

The moderate conversion of the nucleophile observed (entry 3, Table 1) 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. Thus, to enhance the nucleophilicity of the phenol, its reaction with the carbonate **1** was investigated in the presence of several bases, *i.e.*, alkali carbonate (entry 4), strong bases (entries 5–6), tertiary amine (entry 7), basic alumina, hydrotalcite (entries 8–9) and metallic homogenous catalysts (entries 10–11).[18]

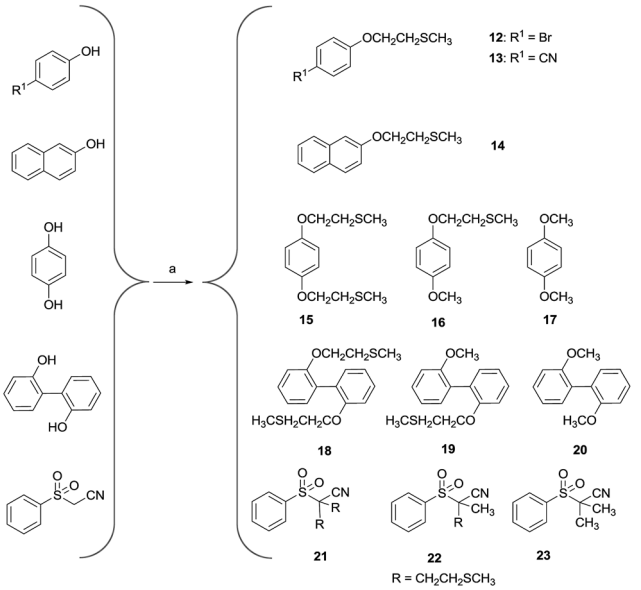
Results showed that methyl (2-phenoxyethyl) sulfide **11** was the major product formed in all the experiments conducted under solvent free conditions in the presence of a base (entries 4–8, Table 1). Furthermore, the reaction proceeded with quantitative conversion of phenol. In some cases, small amount 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).[19] On the other hand when Lewis acids catalysts (entries 9–11, Table 1) were used, the reaction outcome was similar to that without any base (entry 3, Table 1).

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 **11** (eqn (4), Fig. 4).

In terms of reaction mechanism, the role of the base can be illustrated by the eqn (2)–(5) in the Fig. 4. In fact, most probably, the selected nucleophile, once deprotonated by the base (eqn (2), Fig. 4), can react with the episolfonium intermediate (eqn (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 (eqn (5), Fig. 4). This latest reaction pathway is similar to the one involved in the acid-catalysed nucleophilic substitution of epoxides (eqn (6), Fig. 4).

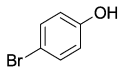
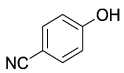
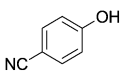
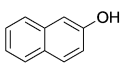
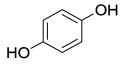
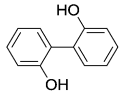
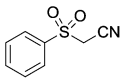
In order to validate, the role of the base in the proposed reaction mechanism (Fig. 4), several nucleophiles having different acidity, *i.e.* aromatic alcohols, aromatic diols and compounds incorporating acidic $-CH_2$, were tested in this reaction condition (Scheme 2, Table 2).

In particular, the reaction of *p*-bromo and *p*-cyanophenol with iprit carbonate **1** resulted in the quantitative conversion



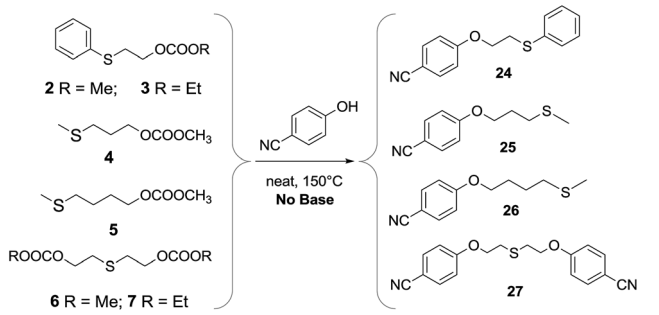
Scheme 2 Reaction of different nucleophiles with mustard analogue carbonate **1**; a = carbonate **1** (1.0 eq. mol) K_2CO_3 (0.2 eq. mol), neat at 150 °C for 5 hours.

Table 2 Reaction of 2-(methylthio)ethyl methyl 1 carbonate with different nucleophiles in neat[a]

			Selectivity (% GC-MS)	
#	Substrate	Conv. (%)	$PhO(CH_2)_2XCH_3$	$PhOCH_3$
1		100[b]	**12** 57	43
2		100	**13** 58	41
3[c]		100	**13** 95	5
4		100[d]	**14** 55	17
5[e]		92[d,f]	**15** 63, **16** 15	**17** 1
6[e]		100[b]	**18** 62, **19** 28	**20** 8
7[e]		100	**21** 31, **22** 43	**23** 25

[a] Reaction conditions: nucleophile/carbonate/K_2CO_3 1.0/2.0/0.2 eq. mol., neat at 150 °C for 5 hours. [b] After 2 hours. [c] Reaction without any base. [d] Some unidentified product were present in the reaction mixture. [e] Molar ratio nucleophile/carbonate/K_2CO_3 1.0/4.0/0.4. [f] After 3 hours.

and discrete selectivity towards the alkylated products **12**, **13** (57% and 60% respectively). Among these two nucleophiles *p*-cyanophenol has an enhanced acidity due to the presence of the



Scheme 3 Reaction of *p*-cyanophenol with different sulfur mustard carbonate analogues **2–7** in neat.

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 **13**.

In this case, the reaction mechanism mirrors the one reported in eqn (5), Fig. 4, *i.e.*, the presence of a base is not necessary. Reacting β-naphtol with iprit carbonate **1** resulted in the complete conversion of the substrate and moderate yield (entry 4, Table 2) due to some unidentified product formed, possibly due to the decomposition of the carbonate iprit.

The reactivity of aromatic diols hydroquinone and biphenyl-2,2′-diol was also investigated. In this case, both compounds showed a quantitative conversion and a good selectivity towards the bis alkylated products **15** and **18** (65 and 62% respectively). Only small amount of other alkylated derivatives were detected (**16** and **17**, **19** and **20**).

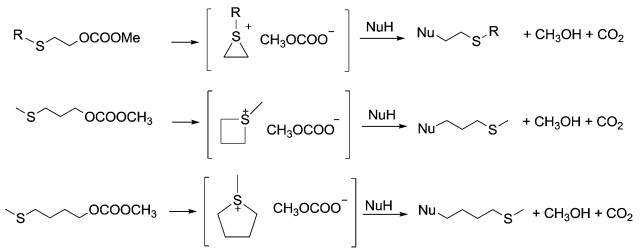
On the other hand, when (phenylsulfonyl)acetonitrile, that incorporates an acidic $-CH_2$ moiety, was reacted with half-mustard carbonate **1** the selectivity towards bisalkylated product **21** was lower than in the other cases studied. Methyl alkyl derivative **22** was the main products (43%) and the bismethyl compound **23** was also present in modest amount (25%).[20]

In order to confirm the reaction mechanism proposed in Fig. 4 and to further explore the applications of iprit carbonates in solventless conditions, several (half-mustard) carbonate analogues *i.e.*, **2–7**, were also reacted in the absence of a base with *p*-cyanophenol (Scheme 3, Table 3).

Table 3 Reaction of *p*-cyanophenol with different sulfur mustard carbonate analogues in neat[a]

				Selectivity (% GC-MS)	
#	Carb.	Time (h)	Conv. (%)	$PhO(CH_2)_2XCH_3$	$PhOCH_3$
1	**2**	24	93	**24** 98	2
2	**3**	24	88	**24** 100	0
3	**4**	21	100	**25** 59	40
4[b]	**5**	7	87	**26** 64	31
5[c]	**6**	21	—[e]	**27** 54[d]	0
6[c]	**7**	24	—[e]	**27** 50[d]	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] Isolated yield. [e] The products are not visible on GC-MS analysis.



Scheme 4 Reaction mechanism of a generic nucleophile with different sulfur mustard carbonate analogues.

These iprit carbonates differ from the previously studied half-mustard carbonate analogue **1** as they include an aromatic ring in the molecule **2**, **3**; incorporate a propyl (**4**) or butyl (**5**) moiety in the backbone; or they present a symmetrical structure **6**, **7**. As a result the reaction intermediates vary according to the mustard carbonate used. Thus either a 3-, 4- or 5-membered cyclic intermediate will be first formed and will be subsequently attacked by the selected nucleophile (Scheme 4).

In the previously studied batch reaction conditions in autoclave, sulfur mustard carbonates **2–7** showed very limited or no reactivity towards nucleophiles with the exception of 4-(methylthio)butyl methyl carbonate **5**.[8]

In this case study, *p*-cyanophenol was selected as nucleophile. In fact, due to the high acidity of its hydroxyl unit, the use of the base can be avoided (Table 3).

Both methyl 2-(phenylthio)ethyl carbonate **2** and ethyl 2-(phenylthio)ethyl carbonate **3** reacted readily with *p*-cyanophenol in neat at 150 °C forming the alkylated product **24** in quantitative yield. 3-(Methylthio)propyl methyl carbonate **4** can also be converted into the alkylated product **25** 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-memebered cyclic intermediate, which is known to be less stable than the 3- or 5-memebered intermediates.[21] On the other hand, 4-(methylthio)butyl methyl carbonate **5** showed to react readily with the nucleophile forming the alkylated product **26** in good yield (66%).

The reaction of *p*-cyanophenol with double-functionalized symmetrical mustard carbonate **6** and **7** was also investigated. In this case, the bisalkylated product **27** wasn't detectable by GC-MS and the reaction was followed by thin layer chromatography. Therefore, the reported yields (54 and 50% respectively) refer only to the isolated pure compound **27**.[22] It is noteworthy that the reaction mechanism proposed in Fig. 4 (eqn (5)) perfectly fits also these latest data.

Conclusions

Herein for the first time the reactivity of mustard carbonates in solventless reaction conditions with several nucleophiles are reported. In our previous work, sulfur (half-)mustard carbonate analogues, have been investigated in batch conditions employing an autoclave, high temperature (180 °C), high pressure (10–15 bar) and a solvent (acetonitrile).

In the present paper, sulfur iprit carbonates were employed in neat, at atmospheric pressure and at lower temperature (150 °C), in the presence of a base (0.2 mol. eq.) 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 sulphur (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.

Furthermore, in 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. Thus, the more acidic is the nucleophile used the less is the need of a base.

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. These results allowed a better understanding of the reaction mechanism and showed the versatility of these safe and green electrophiles for possible future applications.

Experimental

All reagents were ACS grade and were employed without further purification. Mustard carbonate analogues **1–6** and the unsymmetrical carbonate **8** were synthesised and purified as described in our previous paper.[13] Methyl(2-phenoxyethyl)sulfane **11** and (2-ethoxyethoxy)benzene **9** were purified and isolated according to our already published synthetic procedure.[13] The synthesis and characterization of compounds **17**,[23] **20** (ref. 24) and **23** (ref. 25) have already been reported in the literature.

Synthesis of sulphur iprit carbonate analogue

Bis-(2-ethylcarbonate)ethyl sulfide (7). 2,2′-thiodiethanol (5.00 g, 0.04 mol), DMC (75.0 mL, 0.80 mol) and potassium carbonate (11.30 g, 0.08 mol) were placed in a round-bottomed flask equipped with a reflux condenser. While being stirred magnetically, the mixture was heated at reflux temperature for 17 hours. The reaction mixture was then filtered and the solvent was evaporated under vacuum to recover the product as a yellow oil; yield 90% (8.70 g). GC-MS: calcd for $C_{10}H_{18}O_6S$ 266.31; found 265.90. HRMS (TOF-MS ESI): calcd for $C^{10}H^{18}O^6S + Na^+$ 289.7022; found 289.7020. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.30$ (t, $J = 7.6$ Hz, 6H), 2.82 (t, $J = 7.6$ Hz, 4H), 4.18 (q, $J = 7.6$ Hz, 4H), 4.27 (t, $J = 7.6$ Hz, 4H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 14.6$, 30.9, 64.4, 66.7, 155.1 ppm.

Reaction of 2-(methylthio)ethyl methyl carbonate 1 with several nucleophiles[20]

In a typical experiment, a mixture of 2-(methylthio)ethyl methyl carbonate **1** (0.5 g, 2.0 mol. eq.), the nucleophile (1.0 mol. eq.)

and K_2CO_3 (0.2 mol. eq.) was placed in an open vessel and heated at 150 °C while stirring. The reaction was monitored by GC-MS until consumption of the selected nucleophile.

In the experiments involving aromatic diols the reaction mixture was composed of 2-(methylthio)ethyl methyl carbonate **1** (1.50 g, 4.0 mol. eq.), the nucleophile (1.0 mol. eq.) and K_2CO_3 (92.0 mg, 0.4 mol. eq.).

Methyl 2-(4-bromophenoxy)ethyl sulfide (12). Reaction time 5 h. The pure compound was obtained as light yellow oil in 49% (0.20 g) yield by column chromatography on silica gel using as elution mixture dichloromethane–hexane (7 : 3).[26]

4-[2-(Methylthio)ethoxy]benzonitrile (13). Reaction time 5 h. The pure compound was obtained in 71% (0.24 g) yield as white solid by column chromatography on silica gel using as elution mixture pentane–ethyl acetate (8 : 2).[27] Mp 79–80 °C. GC-MS: calcd for $C_{10}H_{11}NOS$ 193.26; found 193.10. HRMS (EI): calcd for $C_{10}H_{11}NOS$ 193.0561; found 193.0560. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.22$ (s, 3H), 2.90 (t, $J = 6.8$ Hz, 2H), 4.20 (t, $J = 6.8$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.59 (d, $J = 8.8$ Hz, 2H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 16.3$, 32.8, 67.8, 104.3, 115.2, 119.1, 134.0, 161.8 ppm.

Methyl 2-(naphthalen-2-yloxy)ethyl sulfide (14). Reaction time 5 h. The pure compound was obtained in 38% (0.14 g) yield as white crystals by column chromatography on silica gel using as elution mixture hexane–ethyl acetate (7 : 3).[28]

1,4-Bis-[2-(methylthio)ethoxy]benzene (15). Reaction time 5 h. The pure compound was obtained by column chromatography on silica gel using as elution mixture dichloromethane–hexane–acetic acid (8 : 2 : 0.2) yield as a colourless oil in 18% (0.11 g). GC-MS: calcd for $C_{12}H_{18}O_2S_2$ 258.40; found 258.10. HRMS (EI): calcd for $C_{12}H_{18}O_2S_2$ 258.0748; found 258.0744. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.21$ (s, 6H), 2.86 (t, $J = 6.8$ Hz, 4H), 4.11 (t, $J = 6.8$ Hz, 4H), 6.85–6.83 (m, 4H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 16.6$, 33.5, 68.4, 116.0, 153.2 ppm.

4-[2-(Methylthio)ethoxy]anisole (16). A sample of the pure compound was obtained by column chromatography on silica gel using as elution mixture dichloromethane–hexane–acetic acid (8 : 2 : 0.2) as a pale yellow oil in 8% yield (40 mg). GC-MS: calcd for $C_{10}H_{14}O_2S$ 198.07; found 198.01. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.20$ (s, 3H), 2.85 (t, $J = 6.8$ Hz, 2H), 3.76 (s, 3H), 4.10 (t, $J = 6.8$ Hz, 2H), 6.81–6.84 (m, 4H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 16.4$, 33.3, 55.9, 68.4, 114.9, 115.9, 152.8, 154.2 ppm.

2,2′-[2-(Methylthio)ethoxy]biphenyl (18). Reaction time 5 h. The pure compound was obtained by column chromatography on silica gel using as elution mixture dichloromethane–hexane (8 : 2) as a colourless oil in 40% yield (0.33 g). GC-MS: calcd for $C_{18}H_{22}O_2S_2$ 334.50; found 334.20. HRMS: calcd for $C_{18}H_{22}O_2S_2$ 334.1061; found 334.1073. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.97$ (s, 6H), 2.71 (t, $J = 6.8$ Hz, 4H), 4.12 (t, $J = 6.8$ Hz, 4H), 6.97–6.92 (m, 2H), 7.05–6.98 (m, 2H), 7.35–7.23 (m, 4H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 16.3$, 33.3, 69.0, 112.7, 121.0, 128.7, 131.8, 156.4 ppm.

2-[2-(Methylthio)ethoxy]-2′-methoxybiphenyl (19). A sample of the pure compound was obtained by column chromatography on silica gel using as elution mixture dichloromethane–hexane–acetic acid (8 : 2 : 0.2) as a colourless oil in 7% yield (48 mg). GC-MS: calcd for $C_{12}H_{18}O_2S_2$ 274.40; found 274.20. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.98$ (s, 3H), 2.71 (t, $J = 6.8$ Hz, 2H), 3.77 (s, 3H), 4.13 (t, $J = 6.8$ Hz, 2H), 6.95–7.06 (m, 4H), 7.24–7.36 (m, 4H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 16.3$, 33.2, 55.9, 68.9, 110.9, 111.2, 112.8, 120.4, 121.1, 128.0, 128.7, 131.6, 156.3, 157, 2 ppm.

Reaction of 4-cyanophenol with sulphur mustard carbonates

In a typical experiment, a mixture of *p*-cyanophenol (0.5 g, 1.0 mol. eq.) and mustard carbonate (2.0 mol. eq.) was placed in an open vessel equipped with a reflux condenser and heated at 150 °C while stirring. The progress of the reaction was monitored by GC-MS.

In the experiments involving the bis-(2-ethylcarbonate)ethyl sulfide **7** the reaction mixture was composed of *p*-cyanophenol (0.5 g, 2.0 mol. eq.) and the selected mustard carbonate (1.0 mol. eq.).

4-[2-(Phenylthio)ethoxy]benzonitrile (24). Reaction time 24 h. The pure compound was obtained by column chromatography on silica gel using as elution mixture dichloromethane–hexane–acetic acid (8 : 2 : 0.5) as a light yellow solid in 66% yield (0.77 g). Mp 76–77 °C. GC-MS: calcd for $C_{15}H_{13}NOS$ 255.33; found 255.10. HRMS (EI): calcd for $C_{15}H_{13}NOS$ 255.0717; found 255.0721. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.30$ (t, $J = 6.8$ Hz, 2H), 4.17 (t, $J = 6.8$ Hz, 2H), 6.92–6.85 (m, 2H), 7.28–7.21 (m, 1H), 7.35–7.29 (m, 2H), 7.45–7.39 (m, 2H), 7.59–7.53 (m, 2H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 32.8$, 67.0, 104.5, 115.2, 119.2, 126.9, 129.2, 130.2, 134.0, 134.9, 161.6 ppm.

4-[3-(Methylthio)propoxy]benzonitrile (25). Reaction time 21 h. The pure compound was obtained by column chromatography on silica gel using as elution mixture dichloromethane–hexane (7 : 3) in 21% yield (0.18 g) as a light yellow oil. GC-MS: calcd for $C_{11}H_{13}NOS$ 207.30; found 207.10. HRMS: calcd for $C_{11}H_{13}NOS$ 207.0717; found 207.0714. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.20$–2.02 (m, 5H), 2.68 (t, $J = 6.8$ Hz, 2H), 4.11 (t, $J = 7.2$ Hz, 2H), 6.94 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 15.8$, 28.6, 30.7, 66.7, 104.2, 115.4, 119.4, 134.2, 162.4 ppm.

4-[4-(Methylthio)butoxy]benzonitrile (26). Reaction time 7 h. The pure compound was obtained by column chromatography on silica gel using as elution mixture dichloromethane–hexane (7 : 3) in 25% yield (0.23 g) as a colourless oil. GC-MS: calcd for $C_{12}H_{15}NOS$ 221.32; found 221.10. HRMS: calcd for $C_{12}H_{15}NOS$ 221.0874; found 221.0866. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.84$–1.72 (m, 2H), 1.99–1.85 (m, 2H), 2.11 (s, 3H), 2.57 (t, $J = 6.8$ Hz, 2H), 4.03 (t, $J = 6.4$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 7.57 (d, $J = 8.8$ Hz, 2H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 15.7$, 25.7, 28.2, 34.0, 68.0, 104.1, 115.4, 119.6, 134.2, 162.5 ppm.

Bis[2-(4-cyanophenoxy) ethyl] sulfide (27). Reaction time 21 h. The pure compound was obtained by column chromatography on silica gel using as elution mixture dichloromethane–ethyl acetate (98 : 2) in 54% yield (0.37 g) as a white solid. Mp 110–111 °C. HRMS (EI): calcd for $C_{18}H_{16}N_2O_2S$ 324.0932; found 324.0940. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.05$ (t, $J = 6.8$ Hz, 4H), 4.23 (t, $J = 6.8$ Hz, 4H), 6.94 (d, $J = 8.0$ Hz, 4H), 7.59 (d, $J = 8.0$ Hz, 4H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 31.6$, 68.3, 104.5, 115.2, 119.0, 134.1, 161.6 ppm.

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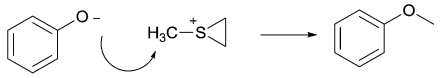
18 The amount of base/catalyst used, *i.e.* 0.2 eq. mol, was selected so to minimize decomposition of the starting carbonate **8**. Experiments conducted reacting the half-mustard carbonate analogues and 1 eq. mol of base at 150 °C showed a rapid decomposition of the carbonate.

19 In order to exclude that anisole was formed by direct methylation of the methylthio moiety of the compound **1** (see figure below), 2-(methylthio)ethyl ethyl carbonate ($CH_3SCH_2CH_2OCOOCH_2CH_3$) was prepared and reacted with phenol.



The reaction led mainly to the alkylated product (87%) with traces of phenetole (12%), meanwhile anisole was present only in traces (1%). This excludes the attack of the nucleophile on the methyl of the charged cyclic intermediate.

20 Alkylated products **12–16**, **18**, **19** have been isolated as pure compounds and fully characterized. Compounds **17** and **20** were present just in traces and identified only by GC-MS (ESI†). (Phenylsulfonyl)acetonitrile derivatives **21–23** were identified only by GC-MS analysis (ESI†) attempts to isolate them as pure products by column chromatography were not successful due to their similar Rf.

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