

Turning iprits into green reagents for selective and stereoselective alkylations

Fabio Aricò, Pietro Tundo
Ca' Foscari University of Venice, Department of Environmental Science, Informatics and Statistics
Campus Scientifico, via Torino 155, 30172 Venezia Mestre
email: fabio.arico@unive.it

Nitrogen and sulfur mustards (iprits), namely, bis(2-chloroethyl) sulfide and bis(2-chloroethyl)(ethyl)-amine are infamously known to be cytotoxic vesicant substances that have been used as chemical weapons in several chemical warfares. The toxicity of these compounds is strictly related to their high reactivity that is influenced by the presence of the sulfur or nitrogen atom positioned in *beta* to the terminal chloride group. In fact, mustard compounds readily eliminate the 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 that immediately reacts with a generic nucleophile.

Despite their toxicity, iprits are of great interest as reactive electrophiles. In fact, they have been extensively employed in inorganic and organic synthesis, as well as, in the preparation of numerous pharmaceutical intermediates.

In this view, we have recently reported that substituting a chlorine atom with a carbonate moiety via dialkyl carbonate (DAC) chemistry resulted in a new family of compounds, namely (half-) mustard carbonate (HMC) analogues (Figure 1).

These class of compounds are easily synthesized by methoxycarbonylation reaction and displayed a similar reactivity and kinetic behaviour to their chlorine homologues without showing any evident toxicological properties.

In this presentation it is reported the reactivity of mustard carbonates as novel, green

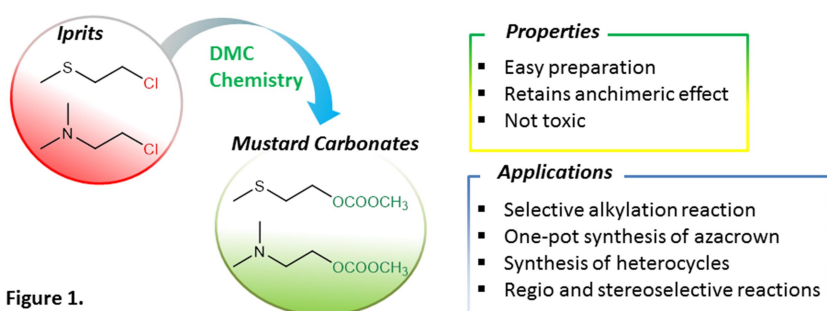


Figure 1.

electrophiles that has been extensively investigated both in autoclave conditions at high temperature (180 °C) under pressure and in the absence of any base, as well as, in neat at lower temperature (150 °C) using a catalytic

amount of a base. The influence of the leaving group on the neighboring effect of sulfur HMCs has then been studied in both autoclave and neat conditions.¹

Besides, symmetrical nitrogen mustard carbonates have been employed as reagent in the preparation of a new family of macrocycles i.e, azacrowns, before not easily accessible.²

Finally, just recently, a new family of nitrogen mustard carbonate analogues has been synthesized starting from parent alcohols so that the resulting HMCs would be anisotropic electrophiles. The reaction of these compounds with selected nucleophiles showed yet another application of HMCs as reagent for regio- and stereoselective alkylation reactions leading to the synthesis of heterocycles via ring expansion reaction.

¹ a) F. Aricò, M. Chiurato, J. Peltier, P. Tundo, *Eur. J. Org. Chem.* **2012**, 3223–3228; b) F. Aricò, S. Evaristo, P. Tundo, *ACS Sustainable Chem. Eng.* **2013**, *1*, 1319-1325; c) F. Aricò, S. Evaristo, P. Tundo, *RSC Adv.* **2014**, *4*, 31071-31078; d) F. Aricò, A. Aldoshin, P. Tundo, *ACS Sustainable Chem. Eng.* **2016**, *4*, 2843-2851.

² F. Aricò, I. Udrea, M. Crisma, P. Tundo, *ChemPlusChem* **2015**, *80*, 471–474.