Thiophosgene

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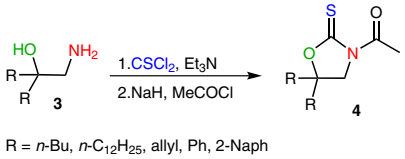
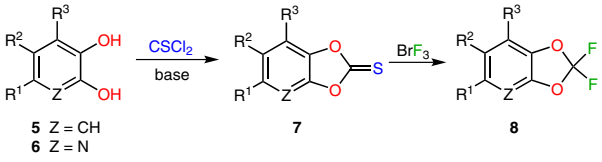
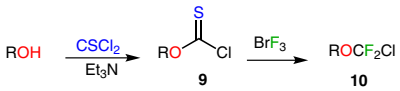
Roxana Martínez Pascual was born in 1980 in Oaxaca, Mexico. She graduated from Benemérita Universidad Autónoma de Puebla in 2003 and received her M.Sc. degree in organic chemistry in 2006. Currently, she is working under the supervision of Dr. Sara Montiel Smith. Her Ph.D. research project focuses on the development of novel methodologies to construct steroidal heterocyclic frameworks with the aim of finding new bioactive molecules.

Introduction

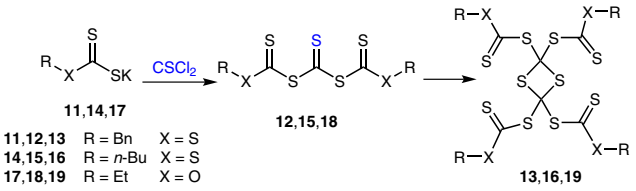
Thiophosgene, also known as thiocarbonyl chloride, is a red-orange liquid with a strong and suffocating odor. Thiophosgene is irritant to eyes (lachrymatory), skin and respiratory tracts; nevertheless, it is less toxic than phosgene. Thiophosgene reacts with nucleophilic sites in a number of functional groups like amines, alcohols, phenols, thiols, oximes, among others. A variety of heterocycles can be constructed when there are two nucleophiles close. As a consequence, thiophosgene has many applications in organic synthesis. It can be used to prepare isothiocyanates which serve as important scaffolds to provide compounds such as thioureas, thiazoles[1,2] or thiocarbamates.[3] Besides, thiones,[4] oxadiazolones,[5] thiocarbonates,[6] chlorothioformates,[7] and heptathiodicarbonates[8] can be synthetized with the employment of this reagent.

Thiophosgene was first prepared in small amounts in 1870 by Rathke;[9] then in 1887, Klason[10] developed a more efficient methodology via reduction of trichloromethanesulfenyl chloride with zinc.

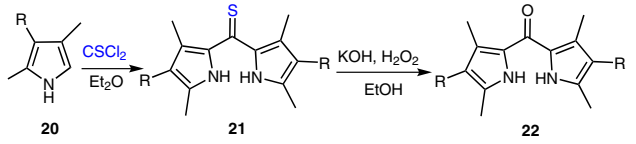
Table 1 Use of Thiophosgene

(A) Recently, in the search of novel selective antitumor agents with more selectivity to destroy malignant cells, a group of optically active amines **1** were converted into isothiocyanates **2** using a solution of thiophosgene. Isothiocyanates were used as intermediates in the synthesis of a series of active thioureas and 2-aminobenzothiazoles evaluated in biological tests.[1]	
(B) Figadère and co-workers[4] described the formation of a group of achiral 5,5-disubstituted *N*-acetyloxazolidine-2-thiones **4** using different amino alcohols **3**, thiophosgene and Et_3N in THF and subsequent acetylation on the nitrogen. The yields reported in the first step range from 20 to 44%. These heterocycles were studied as achiral auxiliaries in the *C*-glycosylation of lactol acetates.	 R = *n*-Bu, *n*-$C_{12}H_{25}$, allyl, Ph, 2-Naph
(C) In 2011, Rozen's group[6] reported a novel methodology for preparing aromatic difluoromethylene dioxides **8** from deactivated or mildly deactivated aromatic rings (**5**,**6**) using bromine trifluoride (BrF_3). In order to introduce the fluorides without radical side reactions, they rationalized the inclusion of sulfur as a soft base using cyclic thiocarbonates **7** as intermediates, which were obtained by the reaction of aromatic derivatives with thiophosgene in 90–95% yields.	 **5** Z = CH **6** Z = N
(D) Hagooly et al.[7] described a methodology to afford $ROCF_2Cl$ ethers **10**, avoiding the formation of trifluoromethyl ethers as byproducts. First, the alcohol dissolved in Et_3N reacted with a solution of thiophosgene forming the respective chlorothioformates **9** in 80–95% yields. Then, the reaction of BrF_3 with chlorothioformates provided the desired products in short reaction times.	

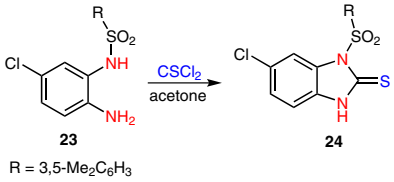
(E) In 2013,[8] Weber et al. described the utility of thiophosgene in the synthesis of four-membered 1,3-dithietane rings in the search of a new pathway to form heptathiodicarbonates as potential RAFT reagents. The potassium salts **11**, **14** and **17** were treated with thiophosgene resulting in the formation of products characterized as **13**, **16** and **19**. Either the yields of the global reaction or the isolation of intermediates (**12** and **18**) depended on the solvent and the mode of addition of thiophosgene.



(F) In the synthesis of BODIPYs, Wang et al.[11] used the formation of dipyrrylketones **22** as the key step; such compounds were obtained in two stages: first, the reaction of pyrrole derivatives **20** and thiophosgene to get the corresponding dipyrrylthioketones **21** in 40 and 43% yield and then a subsequent oxidative hydrolysis.



(G) With the aim of finding new active molecules as potent HIV-1 TR inhibitors, Monforte and co-workers[12] designed a synthesis of a series of novel benzimidazolones and analogues. In this group of compounds, a derivative with a thiocarbonyl moiety **24** was synthesized; this product was obtained by the reaction of **23** with thiophosgene in acetone in 14% yield and showed high inhibitory potency.



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