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Phosphine-Catalyzed Construction of Sulfur Heterocycles

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ABSTRACT

A simple and efficient method for constructing sulfur heterocycles was developed using a phosphine-catalyzed tandem umpolung addition and intramolecular cyclization of bifunctional sulfur pronucleophiles on arylpropiolates. The reaction offers a promising route to synthetically useful as well as biologically active heterocycles under neutral conditions.

Sulfur heterocycles continue to receive widespread attention due to their potential biological activity and pharmaceutical significance.[1] Despite the wealth of traditional methods, there is an ongoing search for new, more efficient approaches to form sulfur heterocycles. Among the new synthetic strategies, a series of organocatalyzed reactions induced by phosphines have emerged over the past decade as a powerful approach to construct oxygen or nitrogen heterocycles. Reactions employing electron-deficient multiple bond substrates, in particular, have proven to be very efficient for the straightforward construction of numerous heterocycles.[2] In these reactions, the phosphine catalyst proceeds through the formation of zwiterionic phosphonium intermediate which is able to react either with electrophiles[3] or pronucleophiles[4] to generate umpolung adducts that undergo subsequent cyclization.

In this context, we recently described a phosphine-catalyzed tandem reaction for dioxygenated heterocycles construction.[5] The reaction uses diols or catechols that undergo α-*O*-addition and transesterification on arylpropiolates, both steps being catalyzed by *n*-Bu_3P. This finding stimulated us to explore the reaction with other bifunctional pronucleophiles. One of the crucial points for the success of such approach is chemoselectivity of the first step of the process (e.g., the α-addition step) for only one of the two nucleophiles. For this purpose, we were interested on using bifunctional sulfur nucleophiles to develop a new and simple procedure for sulfur heterocycles preparation (Scheme 1). The strong nucleophilic character of the thiol function should facilitate a chemoselective *n*-Bu_3P-catalyzed α-*S*-addition of the bifunctional nucleophile on the alkyne. The resulting umpolung adduct should then undergo cyclization due to the

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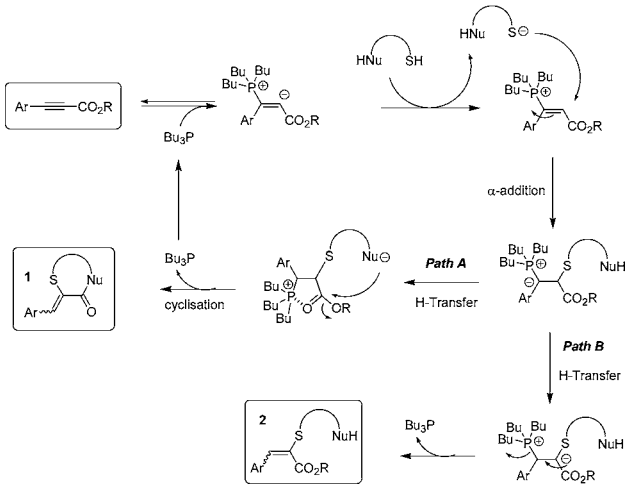
Scheme 1. Proposed Route to Sulfur-Containing Heterocycles **1**



close proximity of the second nucleophile with respect to the ester group (path A, Scheme 1) resulting in the formation of sulfur heterocycle **1**.

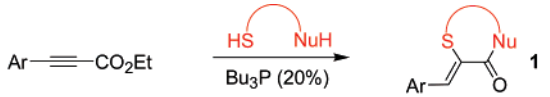
To test the feasibility of this approach, aryl propiolates were reacted with a series of bifunctional sulfur−oxygen or sulfur−nitrogen pronucleophiles in the presence of *n*-Bu_3P.

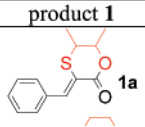
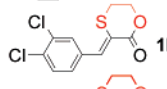
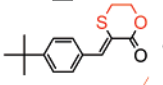
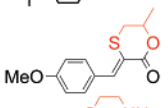
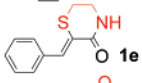
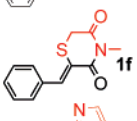
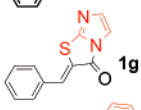
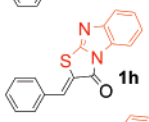
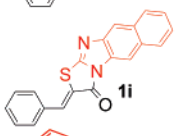
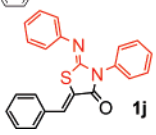
To our delight, the reaction appeared to be applicable for a variety of substrates affording a straighforward route to 5- or 6-membered sulfur-containing rings (Table 1). Mercapto alcohols, amines, or even amides all participated well to give the corresponding arylidene heterocyles **1a**−**f** as pure *Z* isomers in moderate to good yields.[6]

The reaction was also found to proceed successfully when thioureas are used as bifunctional *S*,*N*-pronucleophiles leading to 2-iminothiazolidin-4-ones derivatives **1g**−**j**. The later heterocycles are well-known to display several important biological activities.[7] All of these products were obtained in a very simple manner: just mixing the thioureas in the presence of alkynoate and *n*-Bu_3P afforded the desired heterocycles which are easily recovered by flash chromatography.

It is noteworthy that, in all of these reactions, no Michael-type adduct nor other heterocylic regioisomers were observed. Besides the desired heterocycles, non cyclized α-*S*-adducts **2** (Scheme 1) were the only side products that were detected. The abundance of this byproduct seems to be related to the nature of the aryl group. For certain alkyne substrates it was necessary to help the cyclization by adding catalytic amount of PTSA to get reasonable yields of the desired heterocycle (entries 3 and 4, Table 1).

Table 1. Preparation of Sulfur Heterocycles[a]



entry	conditions	product **1**	yield (%)[b]
1	Toluene 25 °C – 12 h	 **1a**	77
2	Toluene 25 °C – 12 h	 **1b**	52
3	Toluene 25 °C – 2 h[c]	 **1c**	57
4	Toluene 25 °C – 2 h[c]	 **1d**	47
5	Toluene 70 °C –3 h	 **1e**	69
6	Toluene 110 °C –12 h	 **1f**	65
7	Toluene 70 °C –8 h	 **1g**	91
8	MeOH 70 °C – 12 h	 **1h**	53
9	MeOH 70 °C – 12 h	 **1i**	47
9	Toluene 90 °C –4 h	 **1j**	62

[a] Reactions conducted under argon; the concentration of the substrates was 0.5 M. [b] Isolated yields. [c] In these reactions, 10% of PTSA were added after 2 h at 25 °C and the mixture was heated at 110 °C for 1 h to help the cyclization step.

The structures of compounds **1a**−**j** were assigned by comparison to published NMR data[8] and further proven by the X-ray crystallography of a representative product **1e**.

Finally, we have undertaken the preparation of arylidene rhodanine derivatives. The rhodanine (2-thioxo-4-thiazolidinone) heterocyle is an interesting core for the development of biologically active molecules. Arylidene rhodanine-based molecules, in particular, are known to possess multiple biological activities through the inhibition of numerous targets such as HCV NS3 protease,[9] β-lactamase,[10] PMT1

(6) The reaction conducted with aromatic amino thiols produced the desired cyclic products with only poor yields (~15%).

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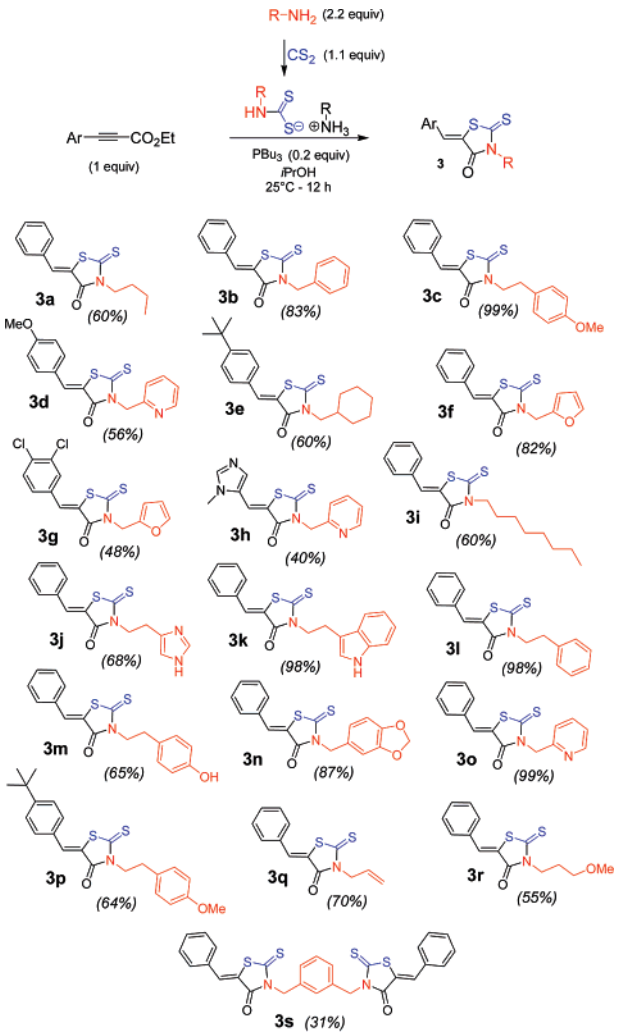
Scheme 2. Phosphine Catalyzed Reaction of Dithiocarbamates with Aryl Propiolates Leading to Rhodanine Derivatives[a]



[a] Isolated yields.

manosyl transferase,[11] and PRL-3 and JSP-1 phosphatases.[12] Classical methods for their preparation need several steps and generally involve the preparation of the rhodanine moiety followed by a Knoevenagel condensation with aldehydes.[13] We were convinced that such compounds would be easily obtained in a one-pot process through the reaction of dithiocarbamates (prepared in situ from amines and CS_2) and arylpropiolates in the presence of Bu_3P. As hoped, this reaction was found to proceed successfully at room temperature with a variety of substrates (Scheme 2).

Although the procedure showed some limitations (dithiocarbamates prepared from hindered or aromatic amines did not afford the desired cyclized product; only the α-*S*-adduct was observed), it presents many advantages over previous ones. Besides the fact that the reaction is trivial to run, an added bonus is the easy of product recovery. In many cases the rhodanine products precipitate in *i*-PrOH and are obtained in good yields as pure *Z*-isomer[14] after simple filtration and washing. This reaction is therefore well adapted to the preparation of libraries of these biologically actives compounds.

In conclusion, we have developed a simple and practical method for the preparation of arylidene sulfur-containing heterocyles via *n*-Bu_3P-catalyzed tandem α-*S*-addition and intramolecular cyclization. This strategy offers a straightforward way for constructing various heterocycles that are found in many biologically active products. The reaction should be successfully extended to the preparation of others interesting heterocyles.

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Supporting Information Available: Experimental procedures for synthesis and full characterization for compounds; ^{1}HNMR and ^{13}CNMR spectra of products **1a**−**l** and **3a**−**s**. RX structure of product **1e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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