A New Thiazole Synthesis by Cyclocondensation of Thioamides and Alkynyl(Aryl)Iodonium Reagents

Peter Wipf* and Srikanth Venkatraman

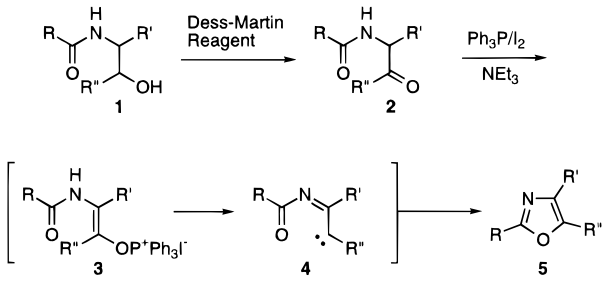
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received August 30, 1996

Many biologically active natural products contain oxazole and thiazole moieties, five-membered heterocycles derived from cyclodehydrated serine, threonine, and cysteine residues.[1] In spite of the long tradition in the synthesis of these heterocycles,[2] standard protocols lack the broad range of functional group tolerance and the stereospecificity that is required for complex natural product synthesis. As part of our program in heterocyclic chemistry, we have recently developed[3] a modern version of the Robinson−Gabriel synthesis for the preparation of highly substituted oxazoles and demonstrated its utility in total synthesis.[4] We assume that in this method after oxidation of the β-hydroxy amide **1** with Dess−Martin reagent to give ketone **2** and exposure to triphenylphosphine/iodine, a carbene is formed as the reactive intermediate before ring closure (Scheme 1).[3] In an attempt to apply this concept to the synthesis of thiazoles, it occurred to us that the crucial carbene intermediate could be prepared by an addition of a thioamide **8** to a readily available alkynyl(aryl)iodonium salt **9** (Scheme 2). At the onset of this project, it was not clear to us if the regioselectivity of the addition would ultimately favor thiazoles of type **6** or **7**. We now report our preliminary data on the realization of this novel thiazole synthesis.

Addition−elimination sequences of carbon, nitrogen, oxygen, and some sulfur nucleophiles to alkynyliodonium salts to form free carbenes are well documented.[5,6] Instead of the more common alkynyl(phenyl)iodonium triflates **9**, we decided to use the corresponding mesylates **10** because of their, in our hands, improved tendency to crystallize. In analogy to the method of Stang et al.,[7] mesylates were prepared from commercially available iodobenzene diacetate by sequential treatment with NaOH, methanesulfonic anhydride, TMSCN, and alkynyl stannanes, followed by crystallization from Et_2O. The careful purification of alkynyliodonium salt proved necessary to achieve consistent yields. After mixing mesylate

Scheme 1



Scheme 2

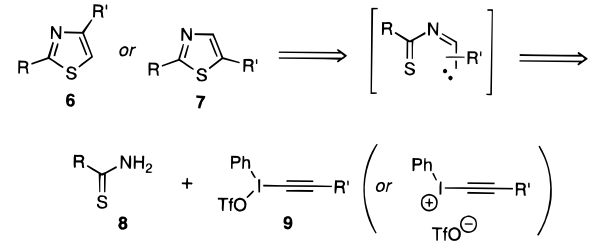


Table 1

Entry	Thioamide	Alkynyl(phenyl)iodonium salt	Thiazole	Yield[a] [%]
1	**8a**	**10a**	**6a**	57[b]
2	**8b**	**10b**	**6b**	54[c]
3	**8c**	**10b**	**6c**	62[d]
4	**8d**	**10a**	**6d**	32[d]
5	**8b**	**10a**	**6e**	62[e]

[a] Yields are based on alkynyl(phenyl)iodonium mesylate and refer to isolated, fully characterized products. [b] Reaction in Et_2O in the presence of K_2CO_3. [c] Reaction in MeOH in the presence of Et_3N. [d] Reaction in EtOAc in the presence of Et_3N. [e] Reaction in MeOH in the presence of K_2CO_3.

10a with thioamide **8a** in Et_2O in the presence of solid K_2CO_3, the desired thiazole **6a** was indeed formed cleanly after 3 h as the only significant nonpolar component in the reaction mixture besides starting materials. Table 1 summarizes further results with this thioamide−alkynyliodonium cyclocondensation strategy. Generally, a range of solvents (Et_2O, EtOAc, MeOH) and bases such as carbonate or triethylamine could be used. For the preparation of 2-aminothiazole **6b**, thiourea (**8b**) and (phenylacetylene)(phenyl)iodonium mesylate **10b** were reacted in methanol in the presence of 1 equiv of triethylamine (entry 2). Synthesis of the biazole **6c** was readily accomplished from thioamide **8c** and **10b** in 62% yield (entry 3). Directly linked oxazole−thiazole units

(1) (a) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (b) Lewis, J. R. *Nat. Prod. Rep.* **1995**, 135. (c) Wipf, P.; Venkatraman, S. *Synlett*, in press.

(2) Reviews: (a) Liebscher, J. In *Heteroarenes III*, Houben-Weyl, 4th ed.; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1994; Part 2, Vol. E8b, pp 1−398. (b) Hassner, A.; Fischer, B. *Heterocycles* **1993**, *35*, 1441. (c) Lang-Fugmann, S. In *Heteroarenes III*, Houben-Weyl, 4th ed.; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1993; Part 1, Vol. E8a, pp 891−1019.

(3) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.

(4) (a) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558. (b) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1995**, *60*, 7224. (c) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157. (d) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1996**, *61*, 6517.

(5) Review: Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274.

(6) (a) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3135. (b) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 93. (c) Schildknegt, K.; Bohnstedt, A. C.; Feldman, K. S.; Sambandan, A. *J. Am. Chem. Soc.* **1995**, *117*, 7544. (d) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K. *J. Org. Chem.* **1995**, *60*, 7722 and references cited therein.

(7) (a) Zhdankin, V. V.; Crittell, C. M.; Stang, P. J.; Zefirov, N. S. *Tetrahedron Lett.* **1990**, *31*, 4821. (b) Bachi, M. D.; Bar-Ner, N.; Crittell, C. M.; Stang, P. J.; Williamson, B. L. *J. Org. Chem.* **1991**, *56*, 3912.

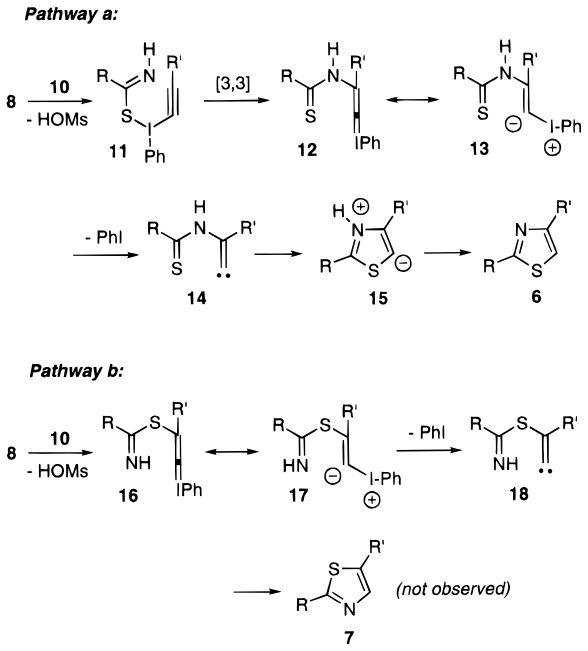
S0022-3263(96)01681-7 CCC: $12.00

of this type are important building blocks of cytotoxic natural products.[1c] Similarly, the peptidyl thiazole **6d** was obtained from *N*-protected valine−alanine thioamide **8d** (entry 4). Peptide-linked thiazoles such as **6d** are found in many marine natural products.[8]

The formation of thiazoles **6** in a single reaction step from alkynyl(aryl)iodonium salts and thioamides can be rationalized mechanistically by a thiophilic attack of the hypervalent iodine atom on the sulfur atom of the thiocarbonyl group.[9] This is in contrast to the common Michael addition−carbene formation−rearrangement reaction pathway of these species,[5,6] where addition of the nucleophile to the carbon atom of the alkynyliodonium compound followed by elimination of iodobenzene provides a direct route to a carbene (Scheme 3, path b). The latter reaction course can be excluded in our case, because it would provide thiazoles **7** of inversed C(4),C(5)-substitution pattern.[10] Therefore, we propose a novel room-temperature polyhetero-Claisen rearrangement[11] of the primary addition product **11** that provides the *N*-alkenylated thioamide **12**. The groups of Ochiai and Norton have recently reported a reductive iodonio-Claisen rearrangement of allenyl(aryl)iodanes to yield *o*-propargyliodoarenes,[12] but no hetero-Claisen rearrangement of the type shown in Scheme 3 has yet been noted. Subsequent 1,1-elimination of **12** to give carbene **14** and iodobenzene is expected[5] to be fast and lead to the observed heterocycle **6** after cycloaromatization.

In summary, a novel thiazole synthesis based on the cyclocondensation of hypervalent alkynyliodonium salts and thioamides has been developed.[13] Yields based on iodonium salts as limiting reagents range from 32 to 62%, and quite highly functionalized building blocks for natural products synthesis are readily prepared by this convergent, single-step process. The postulated reaction mechanism that is supported by the regiochemistry of the isolated thiazole products involves the thiophilic attack of the iodonium atom on the thioamide, followed by an unusual room-temperature polyhetero-Claisen rearrangement and 1,1-elimination of iodobenzene. The resulting carbene cyclizes to form the five-membered heterocycle in analogy to our earlier postulated mechanism for the cyclodehydration of β-keto amides to oxazoles. We plan to investigate the details of the polyhetero-Claisen rearrangement as well as further applications of this reaction concept in heterocycle synthesis.

Scheme 3



Acknowledgment. This work was supported by the National Institutes of Health (AI/GM34914). We gratefully acknowledge additional support from the A. P. Sloan and the Camille Dreyfus Foundations and Merck, Pharmacia & Upjohn, and Zeneca Co.

Supporting Information Available: Experimental procedures and compound characterization data (13 pages).

JO961681C

(8) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771.

(9) For an example of the direct alkylation of alkynyl(aryl)iodonium salts on iodine by organolithium reagents, see: Margida, A. J.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 4703.

(10) The assigned regiochemistry of the thiazoles was confirmed by comparison with commercially available **6b** and independently prepared **6a**. An alternative, third mechanism involving the direct Michael addition of the thioamide nitrogen on the alkynyl(aryl)iodonium species, is unlikely since the thioamide sulfur atom is far more nucleophilic: Walter, W.; Voss, J. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, 1970; Part 1, pp 383−475.

(11) Blechert, S. *Synthesis* **1989**, 71.

(12) (a) Ochiai, M.; Ito, T.; Takaoka, Y.; Masaki, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1319. (b) Gately, D. A.; Luther, T. A.; Norton, J. R.; Miller, M. M.; Anderson, O. P. *J. Org. Chem.* **1992**, *57*, 6496. (c) Ochiai, M.; Ito, T. *J. Org. Chem.* **1995**, *60*, 2274.

(13) The cyclocondensation of α-halocarbonyl compounds with thioamides is known as the Hantzsch thiazole synthesis.[2] Since we also use a thioamide as starting material, our method can be considered, in a distant sense, as a variation of the Hantzsch synthesis.