ORGANIC LETTERS

2008
Vol. 10, No. 21
4983−4986

Copper Iodide-Catalyzed Cyclization of (*Z*)-Chalcogenoenynes

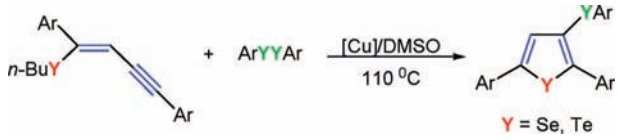
André L. Stein, Diego Alves,* Juliana T. da Rocha, Cristina W. Nogueira, and Gilson Zeni*

Laboratório de Síntese, Reatividade, Avaliação, Toxicológica e Farmacológica de Organocalcogenios-CCNE-UFSM, 97105-900-Santa Maria, RS, Brazil

gzeni@quimica.ufsm.br

Received September 3, 2008

ABSTRACT



We present here our results of the efficient copper-catalyzed cyclizations of chalcogenoenynes and establish a route to obtain 3-substituted chalcogenophenes in good to excellent yields. In addition, the obtained chalcogenophenes were readily transformed to more complex products using the palladium-catalyzed cross-coupling reactions with boronic acids to give Suzuki-type products in good yields.

Chalcogenide compounds have found such wide utility because their effects on an extraordinary number of very different reactions, including many carbon−carbon bond formations,[1] under relatively mild reaction conditions. In addition, they have become attractive synthetic targets because of their chemo-, regio-, and stereoselective reactions,[2] use in a wide variety of functional groups, thus avoiding protection group chemistry, and useful biological activities.[3] The selenium group can be introduced in an organic substrate via both nucleophile and electrophile reagents. After being introduced in an organic substrate, the organoselenium group can easily be removed by selenoxide *syn* elimination[4] and [2,3] sigmatropic rearrangement.[5] Conversely, the carbon−selenium bond can also be replaced by a carbon−hydrogen,[6] carbon−halogen,[7] carbon−lithium,[8] or carbon−carbon bond.[9]

Among chalcogenides, the chalcogenophene derivatives play an important role in organic synthesis because of their excellent electrical properties and environmental stability. Chalcogenophene oligomers are compounds of current interest because many of them show photoenhanced biological activities,[10] and α-type chalcogenophene oligomers, such as 5,2′:5′,2″-terthiophene, produce crystalline, electroconductive polythiophenes on electrochemical polymerizations.[11] Thus, a wide variety of oligomers and related chalcogen compounds including mixed thiophene−pyrrole oligomers have been synthesized mainly with expectation of obtaining excellent

(1) (a) Zeni, G.; Ludtke, D. S.; Panatieri, R. B.; Braga, A. L. *Chem. Rev.* **2006**, *106*, 1032. (b) Zeni, G.; Braga, A. L.; Stefani, H. A. *Acc. Chem. Res.* **2003**, *36*, 731.

(2) (a) Organoselenium Chemistry. In *Topics in Current Chemistry 208*; Wirth, T., Ed.; Springer-Verlag: Heidelberg, 2000. (b) Krief, A. In *Comprehensive Organometallic Chemistry II*; Abel, E. V., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Vol. 11, Chapter 13. (c) Paulmier, C. Selenium Reagents and Intermediates in Organic Synthesis. In *Organic Chemistry Series 4*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1986. (d) Petragnani, N. *Tellurium in Organic Synthesis*; Academic Press: London, 1994.

(3) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255.

(4) (a) Huguet, J. L. *Adv. Chem. Ser.* **1967**, 345. (b) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *22*, 1979.

(5) (a) Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2570. (b) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154.

(6) Sevrin, M.; Vanende, D.; Krief, A. *Tetrahedron Lett.* **1976**, *30*, 2643.

(7) Sevrin, M.; Dumont, W.; Hevesi, L. D.; Krief, A. *Tetrahedron Lett.* **1976**, *30*, 2647.

(8) (a) Seebach, D.; Peleties, N. *Chem. Ber.* **1972**, *105*, 511. (b) Seebach, D.; Beck, A. K. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 806. (c) Reich, H. J.; Shah, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 3250.

(9) Silveira, C. C.; Braga, A. L.; Vieira, A. S.; Zeni, G. *J. Org. Chem.* **2003**, *68*, 662.

(10) *Chemistry and Biology of Naturally-Occurring Acetylenes and Related Compounds*; Lain, J., Breteler, H., Arnason, T., Hansen, L., Eds.; Elsevier: Amsterdam, 1988.

(11) (a) Nakayama, J.; Konishi, T. *Heterocycles* **1988**, *27*, 1731. (b) Kuroda, M.; Nakayama, J.; Hoshino, M.; Furusho, N.; Kawata, T.; Ohba, S. *Tetrahedron* **1993**, *49*, 3735.

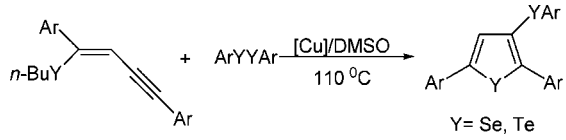
10.1021/ol802060f CCC: $40.75
Published on Web 10/01/2008

precursor compounds for molecular devices and electroconductive polymers. In addition, chalcogenophenes are widely studied agents with a diverse array of biological effects. These include potent antitumor and antiviral activity, as well as efficacy as a maturation inducing agent.[12]

In addition, great progress has been made in carbon−heteroatom bond formation via the cross-coupling reaction of heteroatom compounds with halides using a copper-catalyzed system.[13] These improvements are certainly a consequence of the studies regarding the effects of several ligands, such as aliphatic diamines, 1,10-phenanthroline, amino acids and their derivatives, and others. These important findings allow the use of common organic solvents (dichloromethane, chloroform, toluene, benzene, DMF, and DMSO) and weaker bases (K_2CO_3, Cs_2CO_3, and K_3PO_4), and they also allow the use of not only aryl iodide but also aryl bromides and chlorides. After that, these reactions became more attractive, and nowadays they can be carried out at lower temperatures, under milder conditions, and using a catalytic amount of the copper salts. Besides, the transition-metal-catalyzed reactions of organoselenium compounds have been growing, and highly selective transformations of chalcogen compounds have been developed by using palladium or copper catalysts.[14]

To our knowledge, the use of Cu-catalyzed cyclization of enynes remains unexplored. In this paper, we present our contribution to this field by developing a general and mild protocol for the seleno- and tellurophene synthesis via reaction of enynes with diorganoyl dichalcogenides, catalyzed by CuI. Not only does this method give access to C-3-substituted selenophenes, unavailable by existing one-pot cyclization techniques, but it also holds a promise for a quick assembly of tellurium heterocyclic compounds via a two-component cyclization/coupling strategy (Scheme 1).

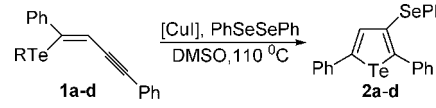
Scheme 1. General Scheme



The starting (*Z*)-chalcogenoenyne **1** was readily available by using the process of hydrochalcogenation of alkynes.[15] Our initial studies on the cyclization have focused on the development of an optimum set of reaction conditions. In this way, the optimization process was performed using telluroenyne **1a** and diphenyl diselenide. Thus, a mixture of **1a** (0.25 mmol) and diphenyl diselenide (1.1 equiv), utilizing DMSO (3 mL) as a solvent at 110 °C, was reacted with different copper salts (10 mol %). The results showed that the cyclization of **1a** was best catalyzed by CuI. Using this catalyst, the desired product **2a** was obtained in 79% yield. Other copper salts such as CuCl, CuCN, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, and $Cu(OTf)_2$ were less effective. Remarkably, diphenyl deselenide alone could not promote this reaction in the absence of the copper catalyst, and **1a** was recovered quantitatively. In comparison, treatment of enyne **1a** with a catalytic amount of CuI in the absence of diphenyl deselenide led to no detectable consumption of the starting material. This observation suggested that a complex PhSe/CuI[16] should be required for the catalytic conversion of **1a** to **2a**. Regarding the influence of the solvent in this cyclization, optimal results were achieved using DMSO. Other solvents (THF, DMF, MeCN, toluene, CH_2Cl_2, and dioxane) gave the desired product **2a** in unacceptable yields (less than 20%).

Since the accomplishment of this reaction probably is dependent on the nature of the group directly linked to the chalcogen atom, we decided to explore this influence using different aryl and alkyl groups, and the results are shown in Scheme 2. A closer inspection of these results revealed that

Scheme 2. Syntheis of Tellurophenes



2a - R = *n*-Bu = 79%, **2b** - R = Et = 44%, **2c** - R = Me = 47%, **2d** - R = Ph = no reaction

the reaction with telluroenynes having an alkyl group bonded at the tellurium atom gave the tellurophene derivatives in good yields, although the yield was lower for telluroenynes with a methyl or ethyl group. Nonetheless, performing the reaction with teluroenyne **1d**, which has an aryl group bonded at the tellurium atom, the desired product was not observed, even under long reaction time. These results demonstrated that the efficiency of the chalcogenophene formation could significantly depend on the steric effects and that this cyclization reaction occurs only with chalcogenenynes having a Y−Csp^3 bond.

Our investigation of the generality and scope of the reaction is summarized in Table 1. Inspection of results demonstrates that the reaction worked well for a variety of diaryl diselenides. Both hindered (**2g** and **2h**) and nonhindred

(12) (a) Srivastava, P. C.; Robins, R. K. *J. Med. Chem.* **1983**, *26*, 445. (b) Streeter, D. G.; Robins, R. K. *Biochem. Biophys. Res. Commun.* **1983**, *115*, 544. (c) Kirsi, J. J.; North, J.; McKernan, P. A.; Murray, B. K.; Canonico, P. G.; Huggins, J. W.; Srivastava, P. C.; Robins, R. K. *Antimicrob. Agents Chemother.* **1983**, *24*, 353. (d) Goldstein, B. M.; Leary, J. F.; Farley, B. A.; Marquez, V. E.; Rowley, P. T. *Blood* **1991**, *78*, 593. (e) Jayaram, H. N.; Dion, R. L.; Glazer, R. I.; Johns, D. G.; Robins, R. K.; Srivastava, P. C.; Cooney, D. A. *Biochem. Pharmacol.* **1982**, *31*, 2371.

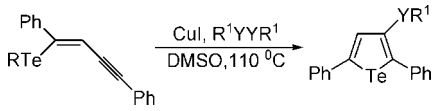
(13) (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (b) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578. (c) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (d) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490. (e) Zhang, D.; Liu, Z.; Yum, E. K.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 251.

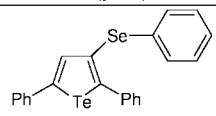
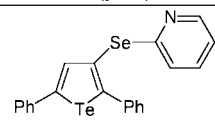
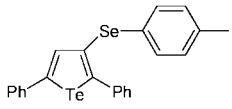
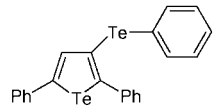
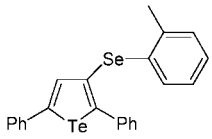
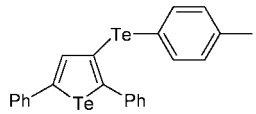
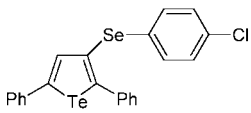
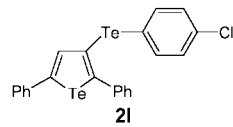
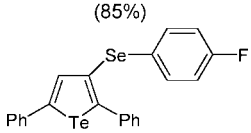
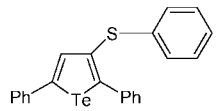
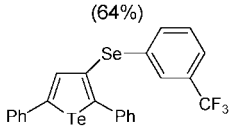
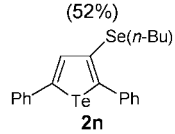
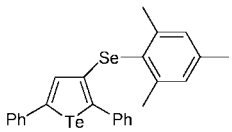
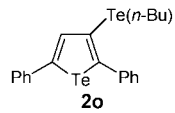
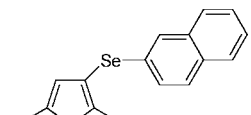
(14) (a) Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. *J. Organomet. Chem.* **2000**, *605*, 96. (b) Beletskaya, I. P.; Ananikov, V. P. *Pure Appl. Chem.* **2007**, *79*, 1041.

(15) Zeni, G.; Stracke, M. P.; Nogueira, C. W.; Braga, A. L.; Menezes, P. H.; Stefani, H. A. *Org. Lett.* **2004**, *6*, 1135.

(16) (a) Taniguchi, N. *J. Org. Chem.* **2007**, *72*, 1241. (b) Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, *69*, 915.

Table 1. Telluroenynes Cyclization Catalized by CuI/ArYYAr[a]



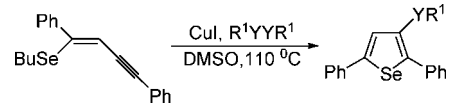
entry	product (yield)[b]	entry	product (yield)[b]
1	 **2a** (79%)	9	 **2i** (59%)
2	 **2b** (72%)	10	 **2j** (76%)
3	 **2c** (62%)	11	 **2k** (74%)
4	 **2d** (85%)	12	 **2l** (79%)
5	 **2e** (64%)	13	 **2m** (52%)
6	 **2f** (65%)	14	 **2n** (42%)
7	 **2g** (65%)	15	 **2o** (56%)
8	 **2h** (58%)		

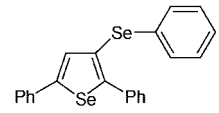
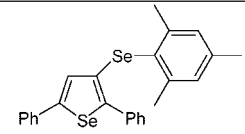
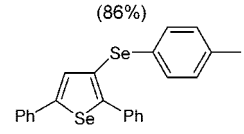
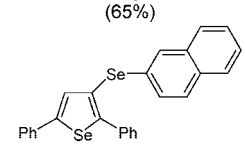
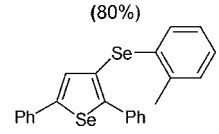
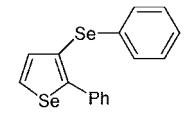
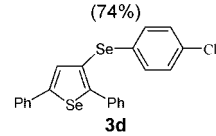
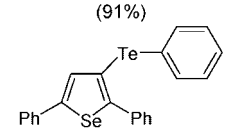
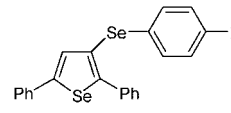
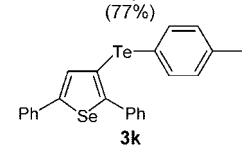
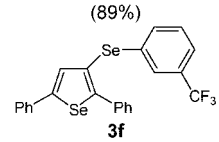
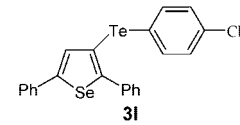
[a] Reaction conditions: telluroenyne (0.5 mmol), diorganoyl dichalcogenide (1.1 equiv), CuI (10 mol %) in DMSO (3 mL) at 110 °C for 10 h. [b] Yields of isolated products.

(**2a**) diaryl diselenides gave the desired tellurophene in good yields. A closer inspection of the results revealed that the reaction is not sensitive to electronic effects of the substituents in the aromatic ring. For example, diaryl diselenides with a CF_3 substituent (**2f**) or with a Cl (**2d**) gave similar yields than diaryl diselenides with a methyl group (**2b**). It is worth mentioning that, through our methodology, it was possible to prepare highly functionalized selenophenes, using as substrate not only diaryl diselenides (**2a**−**2i**) but also diaryl ditelurides (**2j**,**2k**) and sulfide (**2m**). Notably, dialkyl diselenide (**2n**) and dialkyl ditelluride (**2o**) delivered the desired tellurophenes in moderated yields.

In an attempt to broaden the scope of our methodology, the possibility of performing the reaction with selenoenynes instead of telluroenynes was also investigated. Thus, the standard reaction condition applied to prepare the telluroenynes was also tested for selenoenynes (Table 2). The reaction is tolerant of both electron-donating and electron-

Table 2. Selenoenynes Cyclization Catalized by CuI/ArYYAr[a]



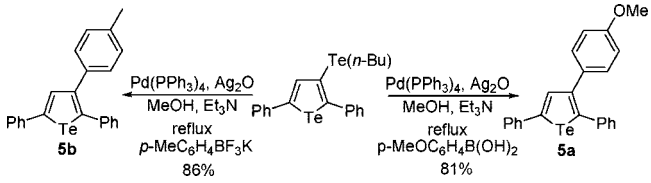
entry	product (yield)[b]	entry	product (yield)[b]
1	 **3a** (86%)	7	 **3g** (65%)
2	 **3b** (80%)	10	 **3h** (56%)
3	 **3c** (74%)	11	 **3i** (91%)
4	 **3d** (89%)	12	 **3j** (77%)
5	 **3e** (89%)	13	 **3k** (73%)
6	 **3f** (82%)	14	 **3l** (78%)

[a] Reaction conditions: selenoenyne (0.5 mmol), diorganoyl dichalcogenide (1.1 equiv), CuI (10 mol %) in DMSO (3 mL) at 110 °C for 10 h. [b] Yields of isolated products.

withdrawing groups on the aromatic ring, including sensitive chlorine. Excellent yield was also obtained in cyclization of the terminal selenoenynes which gave selenophene **3i** with no substituent at the 5 position.

We believe that this approach to chalcogenophenes should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting functionalities into other substituents. For instance, the resulting tellurophene **2o** should be a particularly useful intermediate in many transition-metal-catalyzed processes, such as Sonogashira, Suzuki, Stille, Heck, and Ullmann cross-couplings.[1] In view of this, the potential of tellurophene derivatives as precursors for increasing molecular complexity via palladium-catalyzed reactions has been briefly investigated (Scheme 3). For example, compound **2o** underwent

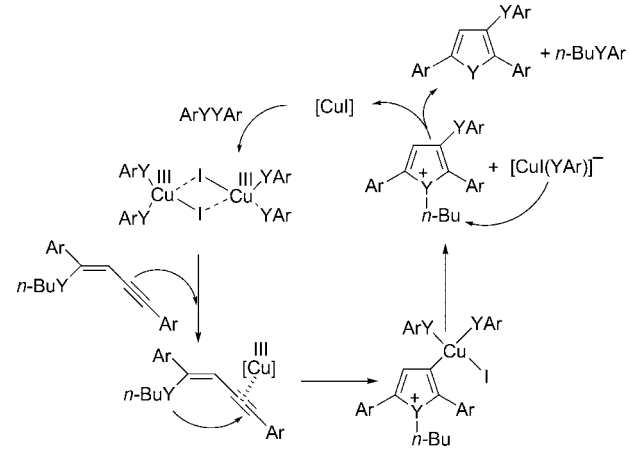
Scheme 3. Suzuki Cross-Coupling of Selenophenes



palladium cross-coupling with boronic acids,[17] and aryltrifluoroborates[18] gave the corresponding 3-aryltellurophenes **5a** and **5b** in excellent yields.

Our working mechanism for the copper-catalyzed conversion of chalcogenoenynes to chalcogenophene is based on experimental data obtained: (1) in all cases, we isolated the BuYAr as byproduct; (2) the reaction does not work with Cu(0) catalyst; (3) no product was obtained when a sp^2 carbon was bonded to the chalcogen atom; and (4) no product was obtained in the absence of both copper salt and dichalcogenides, then it could involve (a) CuI into the Y−Y bond to give a Cu(III)-tetracoordinated square-planar selenolate,[19] (b) alkyne coordination to the metal center to give the cationic organo-Cu(III) complex, (c) anti-attack of the chalcogen atom on the activated triple bond to produce the chalcogen salt, (d) the Cu(I) anionic complex formations $[CuI(YAr)]^-$, and (e) nucleophilic attack of selenolate anion on the alkyl group bonded to the chalcogen atom (Scheme 4).

Scheme 4. Proposed Reaction Mechanism



In conclusion, we have described simple and efficient copper-catalyzed cyclizations of chalcogenoenynes and established a route to obtain 3-substituted chalcogenophene in good to excellent yields. In addition, using the reactions with boronic acid, we were able to convert chalcogenophenes to Suzuki-type products in good yields. We believe that this approach to chalcogenophenes should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting tellurium and selenium functionalities into other substituents. A scale-up experiment was carried out to show the practicability of the method to provide chalcogenophenes having different substituents. Preliminary mechanistic studies support the proposed mechanism, and the results of additional investigations that are ongoing in our laboratory will be reported in due course.

Acknowledgment. We are grateful to CNPq, CAPES (SAUX), and FAPERGS for financial support. CNPq is also acknowledged for a fellowship (to G.Z. and A.L.S.).

OL802060F

(17) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(18) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.
(19) Vicente, J.; Herrero, P. G.; Sánchez, Y. G.; Jones, P. G.; Bautista, D. *Eur. J. Inorg. Chem.* **2006**, 115.