

Synthesis of 2-Substituted Benzothio(seleno)phenes and Indoles via Ag-Catalyzed Cyclization/Demethylation of 2-Alkynylthio(seleno)anisoles and 2-Alkynyldimethylanilines

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An Ag-catalyzed cyclization/demethylation of 2-alkynylthio (seleno)anisoles and 2-alkynyldimethylanilines is described and applied for the construction of valuable benzothio(seleno) phenes as well as indoles. Various 2-substituted benzothio (seleno)phenes and indoles were obtained in good to excellent yields under mild reaction conditions with low catalyst loading. An application of this new method is also exemplified with a concise synthesis of a bioactive molecule precursor. Furthermore, a conceivable reaction mechanism is proposed with supports from isotope-exchange experiments.

Introduction

Benzothio(seleno)phenes and indoles are important heterocyclic scaffolds that have been widely found in many pharmaceuticals, natural products, and material science.^[1,2] For example, Zileuton is a market-available drug, which has been widely used for the treatment of asthma.^[3] 2-Butyl-1-(4-carboxybenzyl)-5-[2carboxy-3-(benzo[b]selenophen-1-yl)prop-1-enyl]-1*H*-imidazole is proved to be an excellent AT₁ receptor antagonist.^[4] Ondansetron has been widely used for the suppression of nausea and vomit caused by cancer chemotherapy and radiotherapy^[5] (Figure 1). Therefore, continuous efforts have been directed towards the development of efficient methods for constructing these heterocyclic scaffolds in organic synthesis and medicinal chemistry.

In the past few decades, a variety of concise and robust synthetic methods have been established for the synthesis of substituted benzothio(seleno)phenes^[6,7] and indoles.^[8] Among them, the intramolecular 5-*endo-dig* electrophilic cyclization and demethylation of 2-alkynylthio(seleno)anisoles or 2-alkynyldimethylanilines in the presence of electrophilic reagents (I₂, Br₂, NBS, PhSeCl, ICl, *etc.*), as well as transition-metal catalysts

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	Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202001465	Scl



Figure 1. Representative drugs and biologically active molecules with benzothio(seleno)phene and indole motif.

(Hg(OAc)₂, CuCl₂, CuBr₂, etc.) has been proven to be one of the most efficient and valuable wavs^[6a-k,8a-e] (Scheme 1). For example, by employing this methodology, Flynn's,^[6a] Larock's,^[6b-e,8a-e] Sanz's,^[6i] Wu's,^[6f] Balova's^[8i] and Kesharwani's^[6j,k] groups reported a series of 2,3-disubstituted benzothio(seleno)phenes or indoles, respectively. Ingleson and co-workers have described the preparation of C3-borylated benzofurans and benzothiophenes by using BCl₃ as an electrophilic partner.^[9] Muchalski and co-workers disclosed the synthesis of 2-substituted benzothiophenes from 2-alkynyl thioanisoles by using 1 mol% loading of Au(IPr)OH as a catalyst and 100 mol% AcOH as a protodeauration additive.^[10] Generally, these electrophilic cyclization reactions are very efficient and proceed under very mild reaction conditions with good functional group tolerance. However, in some cases, these protocols still suffer some limitations, such as the use of corrosive halogens or toxic transition-metal salts, the need for a more-than-stoichiometric amount of electrophilic reagents, or the application of expensive catalysts. For these reasons, the development of alternative approaches based on less toxic and cheaper catalysts, such as silver species, will be highly desirable for synthetic organic chemists.

As part of our ongoing interests in the study of new advantageous silver-catalyzed approaches for the synthesis of N/S-containing heterocycles starting from 2-alkynylthioanisoles



Scheme 1. Electrophilic cyclization of 2-alkynylthio(seleno)anisoles.



or 2-alkynylaniline derivatives,^[11] herein we were pleased to report our results on the Ag₂O-mediated synthesis of 2-disubstituted benzothio(seleno)phenes and indoles *via* electro-

Table 1. Optimization of reaction conditions. ^[a]							
Entry	Ph S-Me 1a Catalyst [mol %]	[Ag] (x mol %) Solvent, T (°C) 4 h Solvent	2a T [°℃]	h Yield [%] ^[b]			
1	Ag ₂ O (100)	HOAc	70	79			
2	Ag ₂ O (100)	TFA	70	92			
3	Ag ₂ O (100)	CHCl ₃	70	Trace			
4	Ag ₂ O (100)	DMF	70	N.R			
5	Ag ₂ O (100)	1,4-Dioxane	70	N.R			
6	Ag ₂ O (100)	DCE	70	N.R			
7	Ag₂O (10)	TFA	70	92			
8	$Ag_2O(5)$	TFA	70	90			
9	Ag ₂ O (2.5)	TFA	70	81			
10	AgOTf (10)	TFA	70	70			
11	AgNO ₃ (10)	TFA	70	75			
12	AgOAc (10)	TFA	70	85			
13	AgCl (10)	TFA	25	78			
14	AgBr (10)	TFA	25	80			
15	$Ag_2O(5)$	TFA	25	91			
16	$Ag_2O(5)$	TFA	25	90 ^[c]			
17	Ag ₂ O (1)	TFA	25	82 ^[c]			
[a] Reaction conditions: 1a (0.2 mmol), solvent (2.0 mL), stirred under air. [b] Isolated yield. [c] Reaction time (1.5 h). DCE = 1,2-dichloroethane,							

DMF = N, N-dimethylformamide, TFA = trifluoroacetic acid.



[a] Reaction conditions: 1 or 3 (0.2 mmol), Ag_2O (0.01 mmol), in TFA (2 mL) stirring under air at room temperature (25 °C) for 1.5 h. [b] Two mmol scale.

philic cyclization/demethylation of 2-alkynylthio(seleno)anisoles and 2-alkynyldimethylanilines.

Results and Discussion

In the beginning, methyl(2-(phenylethynyl)phenyl)sulfane (**1 a**) was chosen as the model substrate to optimize the reaction conditions (Table 1). Initially, HOAc was employed as the solvent, and 1.0 equiv. of Ag₂O was used as the catalyst, **2 a** was obtained in 79% yield after being heated at 70 °C in an oil bath for 4 h under air (Table 1, entry 1). Subsequently, various solvents were evaluated, and TFA was found to be the best (entries 2–6). The Ag₂O loading optimization showed 10 mol% of Ag₂O also could give a competitive yield of **2 a** (entries 7–9). By screening other silver catalysts, such as AgOTf, AgNO₃, AgCl, AgBr, and AgOAc, Ag₂O turned out be the most effective one (entries 10–14). Further temperature and Ag₂O loading optimization showed that in the presence of 5 mol% of Ag₂O, **2 a** was obtained in 90% yield after stirring for 1.5 h in TFA at room temperature (entries 13–15).

In order to investigate the generality of this Ag-mediated cyclization process, a series of substrates possessing diverse substituents were tested under the optimized reaction conditions (Table 2). Initially, substrates with variation at the S substituents were first examined. When the methyl group at the S atom was changed to ethyl or phenyl group, 2a was also obtained in 76% and 40% yields, respectively. Afterwards, various substituents on the benzene ring A were examined. Substrates with electron-donating groups such as methyl, ethyl, and methoxyl groups, as well as electron-withdrawing groups such as fluoro, choloro, bromo, nitryl, and formyl groups were tolerated in this reaction without much difference in reactivity, and all delivered the corresponding targeted products (2b-2k)in good to excellent yields. Compounds bearing functional groups such as OMe and halogen atoms on the benzene ring B were also examined and afforded the corresponding products 2I-2n in excellent yields. Terminal alkyne was also examined, unfortunately, no desired product (2o) was detected, which might be attributed to the formation of acetylene silver intermediate to suppress the reaction. Remarkably, this reaction also proceeded efficiently with aliphatic and carboxyl alkynes to give the desired products (2p, 2q, 2u) in excellent yields. In addition, compounds with naphthyl or thienyl were also viable in this reaction (2r, 2s). However, no desired product (2t) was afforded when a pyridyl-based compound was employed, which might be due to the formation of ammonium salt in the strong acid TFA. Moreover, this Ag-mediated cyclization process was also suitable for the preparation of benzoselenophenes stemming from 2-alkynylselenoanisoles 3, as exampled by 4a-4c. It should be noted that this cyclization process was not suitable for the synthesis of benzofurans by employing 1methoxy-2-(phenylethynyl)benzene as the substrate, which might due to the high energy of $C(sp^3)$ –O bond.

Furthermore, product **2I**, a key intermediate of polymerization inhibitor^[6a] and Reloxifene,^[12] was obtained in 79% yield in 10 mmol scale through this Ag-mediated cyclization protocol



in one step (Scheme 2), demonstrating the synthetic applicability of this method.

Importantly, with modification on the reaction conditions (see *supporting information*), this Ag-mediated cyclization process was successfully applied to the synthesis of indole derivatives. It was found that the reactions in TFA gave no desired products under the typical conditions by using 2-alkynyldimethylanilines instead of 2-alkynylthioanisoles. However, when a DMF solution of the *N*,*N*-dimethyl-2-(arylethynyl) aniline substrates **5**, 1.0 equiv. of *p*-toluenesulfonic acid monohydrate (*p*-TSA·H₂O) and 5 mol% of Ag₂O were heated at 60 °C in an oil bath for 12 h, the corresponding 2-aryl substituted indoles **6** could be obtained in good to excellent yields (Table 3, **6a–6g**, 86%–96%).

In order to investigate the reaction mechanism, an isotopelabeling experiment was performed by using deuterated TFA (*d*-TFA) as the solvent under the optimized reaction conditions (Scheme 3a). Gladly, a significant deuterium-labeling product *d*-**2a** was obtained, and the byproduct methyl 2,2,2-trifluoroacetate was detected by gas chromatography-mass spectrometry (GC-MS) from the reaction mixtures (see *supporting information*



Scheme 2. Synthetic applications.







Scheme 3. Mechanism study.

for detail). This result illustrated that TFA is likely to act as an electrophilic reagent. Therefore, a tentative mechanism for the reaction was proposed for the Ag-mediated cyclization process (Scheme 3b). Initially, the coordination of silver catalyst with the alkyne that is followed by an *anti*-attack from sulfur gives the cationic intermediate **II**. Subsequently, the methyl group is released and captured by 2,2,2-trifluoroacetate (CF₃COO⁻), to form methyl 2,2,2-trifluoroacetate (CF₃COOMe) along with the desired product **2a**, and a silver species is released and reenters the catalytic cycle.

Conclusion

In summary, we have successfully developed an efficient protocol for the construction of valuable benzothio(seleno) phenes as well as indoles through an Ag-catalyzed cyclization/ demethylation process. Various 2-substituted benzothio(seleno) phenes and indoles were obtained in good to excellent yields under mild reaction conditions with low catalyst loading. Furthermore, the current protocol was successfully applied to the synthesis of a raloxifene precursor and a polymerization inhibitor. A conceivable reaction mechanism is proposed and supported by isotope-exchange experiments.

Experimental Section

General Procedures for the Preparation of Benzothio(seleno) phenes

A mixture of Ag₂O (2.3 mg, 0.01 mmol), 2-Alkynylthioanisole derivatives $\mathbf{1}^{[6c]}$ or 2-alkynylselenoanisole derivatives $\mathbf{3}^{[6c]}$ (0.2 mmol) and CF₃COOH (2.0 mL) in a Schlenk tube was stirred at room temperature for 1.5 hours. Upon completion, the reaction mixture was quenched with NaOH (1 M, 10 mL) aqueous solution, and then extracted by DCM (2×10 mL). The organic layer was dried over



 Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt (100:1~50:1, v/v) as the eluent to give the corresponding products.

General Procedures for the Preparation of Indoles

A mixture of Ag₂O (2.3 mg, 0.01 mmol), N,N-dimethyl-2-(1-alkynyl) anilines derivatives **5**^[13] (0.2 mmol), 4-methylbenzenesulfonic acid hydrate (38.1 mg, 0.2 mmol) and DMF (2.0 mL) in a Schlenk tube was stirred 60 °C in an oil bath for 12 hours. Upon completion, the reaction mixture was quenched with H₂O (50 mL) and then extracted by AcOEt (2×5 mL). The organic layer was washed with brine (20 mL) and then dried over Na₂SO₄. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt (100:1, *v/v*) as the eluent to give the corresponding products.

Acknowledgements

We gratefully thank the financial support from NSFC (Grant No. 21801240), the Youth Foud of Shaoxing University (No. 20185019), the Zhejiang Provincial Natural Science Foundation of China (No. LQ21B020005), as well as the Public Projects of Zhejiang Province of China (No. LGG19B020002).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Benzothiophenes · Cyclization · Indoles · Heterocycles · Homogeneous catalysis · Synthetic methods

- a) Z. H. Qin, I. Kastrati, R. E. P. Chandrasena, H. Liu, P. Yao, P. A. Petukhov, J. L. Bolton, G. R. J. Thatcher, J. Med. Chem. 2007, 50, 2682–2692; b) A. M. Isloor, B. Kalluraya, K. S. Pai, Eur. J. Med. Chem. 2010, 45, 825–830; c) I. Osaka, S. Shinamura, T. Abe, K. Takimiya, J. Mater. Chem. C. 2013, 1, 1297–1304; d) M. Pieroni, E. Azzali, N. Basilico, S. Parapini, M. Zolkiewski, C. Beato, G. Annunziato, A. Bruno, F. Vacondio, G. Costantino, J. Med. Chem. 2017, 60, 1959–1970; e) P. Arsenyan, E. Paegle, S. Belyakov, I. Shestakova, E. Jaschenko, I. Domracheva, J. Popelis, Eur. J. Med. Chem. 2011, 46, 3434–3443.
- [2] a) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* 2013, *18*, 6620–6662; b) T. V. SravanthiS, L. Manju, *Eur. J. Pharm. Sci.* 2016, *91*, 1–10; c) J. A. Homern, J. Sperry, *J. Nat. Prod.* 2017, *80*, 2178–2187; d) D. Goyal, A. Kaur, B. Goyal, *ChemMedChem.* 2018, *13*, 1275–1299; e) G. Luo, L. Chen, A. Easton, A. Newton, C. Bourin, E. Shields, K. Mosure, M. G. Soars, R. J. Knox, M. Matchett, R. L. Pieschl, D. J. Post-Munson, S. Wang, J. Herrington, J. Graef, K. Newberry, D. V. Sivarao, A. Senapati, L. J. Bristow, N. A. Meanwell, L. A. Thompson, C. Dzierba, *J. Med. Chem.* 2019, *62*, 831–856.
- [3] a) P. Thalanayar Muthukrishnan, M. Nouraie, A. Parikh, F. Holguin, *Pulm. Pharmacol. Ther.* 2020, 60, 101872–101894; b) H. Liu, J. Liu, R. B. van Breemen, G. R. Thatcher, J. L. Bolton, *Chem. Res. Toxicol.* 2005, 18, 162–173.
- [4] M. K. Staples, R. L. Grange, J. A. Angus, J. Ziogas, N. P. H. Tan, M. K. Taylor, C. H. Schiesser, Org. Biomol. Chem. 2011, 9, 473–479.
- [5] J. A. Generali, D. J. Cada, Hosp. Pharm. 2009, 44, 670-671.
- [6] a) B. L. Flynn, P. Verdier-Pinard, E. Hamel, Org. Lett. 2001, 3, 651–654;
 b) D. W. Yue, R. C. Larock, J. Org. Chem. 2002, 67, 1905–1909; c) T. Kesharwani, S. A. Worlikar, R. C. Larock, J. Org. Chem. 2006, 71, 2307–

2312; d) S. Mehta, J. P. Waldo, R. C. Larock, J. Org. Chem. 2009, 74, 1141-1147; e) B. Nakamura, T. Sato, M. Terada, Y. Yamamoto, Org. Lett. 2007, 9, 4081-4083; f) W. D. Lu, M. J. Wu, Tetrahedron 2007, 63, 356-362; g) T. Kashiki, S. Shinamura, M. Kohara, E. Miyazaki, K. Takimiya, M. Ikeda, H. Kuwabara, Org. Lett. 2009, 11, 2473-2475; h) C. L. Li, X. G. Zhang, R. Y. Tang, P. Zhong, J. H. Li, J. Org. Chem. 2010, 75, 7037-7040; i) R. Sanz, V. Guilarte, E. Hernando, A. M. Sanjuán, J. Org. Chem. 2010, 75, 7443-7446; j) T. Kesharwani, J. Craig, C. D. Rosario, R. Shavnore, C. Kornman, Tetrahedron Lett. 2014, 55, 4373-4376; k) S. Kim, N. Daha, T. Kesharwani, Tetrahedron Lett. 2013, 54, 6812-6816; I) D. J. Faizi, A. J. Davis, F. B. Meany, S. A. Blum, Angew. Chem. Int. Ed. 2016, 55, 14286-14290; Angew. Chem. 2016, 128, 14498-14502; m) J. Sheng, C. Fan, J. Wu, Chem. Commun. 2014, 50, 5494-5496; n) L. M. Ye, L. Qian, Y. Y. Chen, X. J. Zhang, M. Yan, Org. Biomol. Chem. 2017, 15, 550-554; o) L. L. Sun, C. L. Deng, R. Y. Tang, X. G. Zhang, J. Org. Chem. 2011, 76, 7546-7550; p) D. Yang, K. Yan, W. Wei, L. Tian, Q. Li, J. You, H. Wang, RSC Adv. 2014, 4, 48547-48553; q) Y. Masuya, M. Tobisu, N. Chatani, Org. Lett. 2016, 18, 4312-4315; r) L. Gao, B. Chang, W. Qiu, L. Wang, X. Fu, R. Yuan, Adv. Synth. Catal. 2016, 358, 1202-1207; s) D. Wan, Y. Yang, X. Liu, M. Li, S. Zhao, J. You, Eur. J. Org. Chem. 2016, 2016, 55-59; t) J. Chen, H. Xiang, L. Yang, X. Zhou, RSC Adv. 2017, 7, 7753-7757; u) T. Kunz, P. Knochel, Angew. Chem. Int. Ed. 2012, 51, 1958-1961; Angew. Chem. 2012, 124, 1994-1997; v) S. Yugandar, S. Konda, H. Ila, Org. Lett. 2017, 19, 1512-1515; w) B. Wu, N. Yoshikai, Angew. Chem. Int. Ed. 2013, 52, 10496-10499; Angew. Chem. 2013, 125, 10690-10693; x) D. P. Hari, T. Hering, B. König, Org. Lett. 2012, 14, 5334-5337; y) X. Xie, P. Li, Q. Shi, L. Wang, Org. Biomol. Chem. 2017, 15, 7678-7684; z) L. Wang, H. Wang, W. Meng, X.-H. Xu, Y. Huang, Chin. Chem. Lett. 2020, DOI: 10.1016/ j.cclet.2020.02.040.

- [7] a) H. Zang, J. G. Sun, X. Dong, P. Li, B. Zhang, Adv. Synth. Catal. 2016, 358, 1746–1752; b) J. Xu, X. Yu, J. Yan, Q. Song, Org. Lett. 2017, 19, 6292–6295; c) J. Yan, J. Xu, Y. Zhou, J. Chen, Q. Song, Org. Chem. Front. 2018, 5, 1483–1487; d) W. Liu, Y.-Q. Hu, X.-Y. Hong, G. X. Li, X. B. Huang, W. X. Gao, M. C. Liu, Y. Xia, Y. B. Zhou, H. Y. Wu, Chem. Commun. 2018, 54, 14148–14151; e) X. Gong, M. Wang, S. Ye, J. Wu, Org. Lett. 2019, 21, 1156–1160; f) X. Y. Yuan, F. L. Zeng, H. L. Zhu, Y. Liu, Q. Y. Lv, X. L. Chen, L. Peng, B. Yu, Org. Chem. Front. 2020, 7, 1884–1889; g) S. C. Lu, B. Wu, S. P. Zhang, Y. L. Gong, S. Xu, RSC Adv. 2020, 10, 19083–19087.
- [8] a) R. C. Larock, E. K. Yum, M. D. Refvik, J. Org. Chem. 1998, 63, 7652-7662; b) D. Yue, R. C. Larock, Org. Lett. 2004, 6, 1037–1040; c) T. Yao, D. Yue, R. C. Larock, J. Org. Chem. 2005, 70, 9985-9989; d) D. Yue, T. Yao, R. C. Larock, J. Org. Chem. 2006, 71, 62-69; e) Y. Chen, F. Shi, R. C. Larock, J. Org. Chem. 2009, 74, 6802-6811; f) K. Krüger, A. Tillack, M. Beller, Adv. Synth. Catal. 2008, 350, 2153-2167; g) X. Zeng, R. Kinjo, B. Donnadieu, G. Bertrand, Angew. Chem. Int. Ed. 2010, 49, 942-945; Angew. Chem. 2010, 122, 954-957; h) J. McNulty, K. Keskar, Eur. J. Org. Chem. 2014, 1622-1629; i) N. A. Danilkina, A. E. Kulyashova, A. F. Khlebnikov, S. Bräse, I. A. Balova, J. Org. Chem. 2014, 79, 9018-9045; j) Y. Gao, G. Lu, P. Zhang, L. Zhang, G. Tang, Y. Zhao, Org. Lett. 2016, 18, 1242-1245; k) J. Meesin, M. Pohmakotr, V. Reutrakul, D. Soorukram, P. Leowanawat, C. Kuhakarn, Org. Biomol. Chem. 2017, 15, 3662-3669; I) S. W. Tao, J. Y. Zhou, R. Q. Liu, Y. M. Zhu, J. Org. Chem. 2019, 84, 8121-8130; m) G. K. Zhao, C. Roudaut, V. Gandon, M. Alami, O. Provot, Green Chem. 2019, 21, 4204-4210; n) J. S. S. Neto, G. Zeni, Org. Biomol. Chem. 2020, 18, 4906-4915; o) A. M. Garkhedkar, B. S. Gore, W. P. Hu, J. J. Wang, Org. Lett. 2020, 22, 3531-3536.
- [9] A. J. Warner, A. Churn, J. S. McGough, M. J. Ingleson, Angew. Chem. Int. Ed. 2017, 56, 354–358; Angew. Chem. 2017, 129, 360–364.
- [10] C. C. Dillon, B. Keophimphone, M. Sanchez, P. Kaur, H. Muchalski, Org. Biomol. Chem. 2018, 16, 9279–9284.
- [11] a) T. Cai, J. Liu, H. Zhang, X. Wang, J. Feng, R. Shen, Y. Gao, Org. Lett. 2019, 21, 4605–4608; b) Y. Gao, G. Lu, P. Zhang, L. Zhang, G Tang, Y. Zhao, Org. Lett. 2016, 18, 1242–1245.
- [12] P. S. Shinde, S. S. Shinde, A. S. Renge, G. H. Patil, A. B. Rode, R. R. Pawar, *Lett. Org. Chem.* 2009, 6, 8–10.
- [13] X.-F. Xia, N. Wang, L. Zhang, X.-R. Song, X.-Y. Liu, Y.-M. Liang, J. Org. Chem. 2012, 77, 9163–9170.

Manuscript received: November 8, 2020

Revised manuscript received: December 1, 2020

Accepted manuscript online: December 3, 2020