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[3 + 2]-Annulation of Prop-2-ynylsulfonium Salts: Access to Hydroindol-5-ones Containing a Methylthio Group

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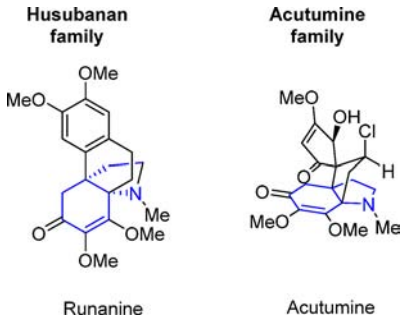
Supporting Information

ABSTRACT: An unprecedented [3 + 2]-annulation of prop-2-ynylsulfonium salts and *p*-quinamines was developed, affording a series of hydroindol-5-ones with a methylthio group in moderate to good yields under mild conditions. In this reaction, the prop-2-ynylsulfonium salt acts as a novel C_2 synthon and sulfide does not serve as a leaving group, which provides facile access to organosulfur compounds.

Hydroindol-5-one scaffolds exist widely in the polycyclic alkaloids isolated from medicinal herbs. Hasubanan and acutumine alkaloids are representative examples (Scheme 1).[1]

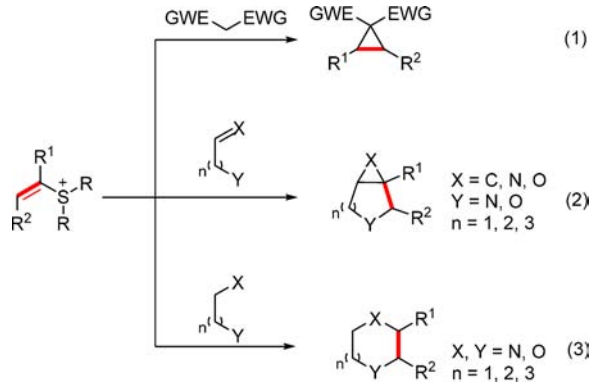
Scheme 1. Representative Polycyclic Alkaloids Containing Hydroindol-5-one Scaffolds



These densely functionalized small molecules exhibit promising biological properties. For example, acutumine alkaloid has selective T-cell cytotoxicity and antiamnesic activity.[2] Therefore, the synthesis of such structures has been of interest to the chemical community for many years.[3]

As C_1 synthons, sulfur ylides have been widely used as methylene-transfer reagents in the construction of three-membered ring compounds with C = X (X = C, N, O, etc.) double bonds.[4] In recent years, Aggarwal's, Xiao's, and other groups have reported the significant application of sulfur ylides as C_2 synthons. According to their research, vinylsulfonium salts could react with active methylene compounds containing electron-withdrawing groups to give substituted cyclopropane derivatives (Scheme 2, eq 1).[5] Upon reaction with *α*-, *β*-, and *γ*-aminoaldehydes, hydroxyaldehydes, or similar olefins or imines, epoxide-, cyclopropane-, or aziridine-fused heterocycles can be obtained, which also provides a key strategy for the total synthesis (Scheme 2, eq 2).[6] When amino alcohols or diamines are used in the reaction with vinylsulfonium salts, a series of heterocycles containing nitrogen and oxygen atoms can be constructed (Scheme 2, eq 3).[7] For all the reactions mentioned above, vinylsulfonium salts are directly used or generated in situ. Therefore, the development of new kinds of sulfur ylides as C_2 synthons and their applications in more reaction types are underexplored.

Scheme 2. Application of Vinylsulfonium Salts as C_2 Synthons



It has been reported that prop-2-ynylsulfonium salts could transform into allenic sulfonium salts and react with enolate anions of *β*-diketones to afford substituted furans (Scheme 3).[8] Inspired by their previous work and on the basis of our continuous interest in exploring new reactions of sulfur ylides,[9] we developed a novel [3 + 2]-annulation reaction[10] of prop-2-ynylsulfonium salts and *p*-quinamines[11] to generate S-containing hydroindol-5-ones. In this reaction, sulfide does not serve as leaving group compared with traditional reactions of sulfur ylides, which provides the possibility for the

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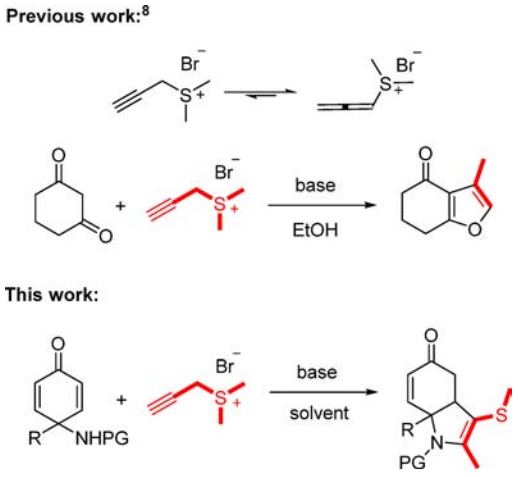
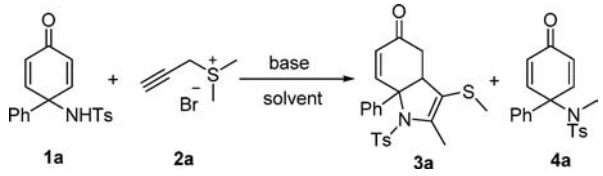
Scheme 3. Reactions of Prop-2-ynylsulfonium Salts



construction of organosulfur compounds with biological and chemical properties.[12]

At the outset of this investigation, we employed *p*-quinamine **1a** with prop-2-ynylsulfonium salt **2a** in the presence of Cs_2CO_3 (2 equiv) in CH_3CN at room temperature. The reaction gave the [3 + 2]-annulation product **3a** in 41% yield as well as *N*-methyl product **4a** in 17% yield after 3 h (Table 1, entry 1). When the reaction time was extended to 24 h, pleasingly, the yield of **3a** improved to 53% (Table 1, entry 2). Subsequent screening of bases showed that K_2CO_3 could give a better yield of 58% (Table 1, entries 3–8). Solvents such as DCM, DCE, DBM, and $CHCl_3$ all proceeded with the desired

Table 1. Screening of the Reaction Conditions[a]



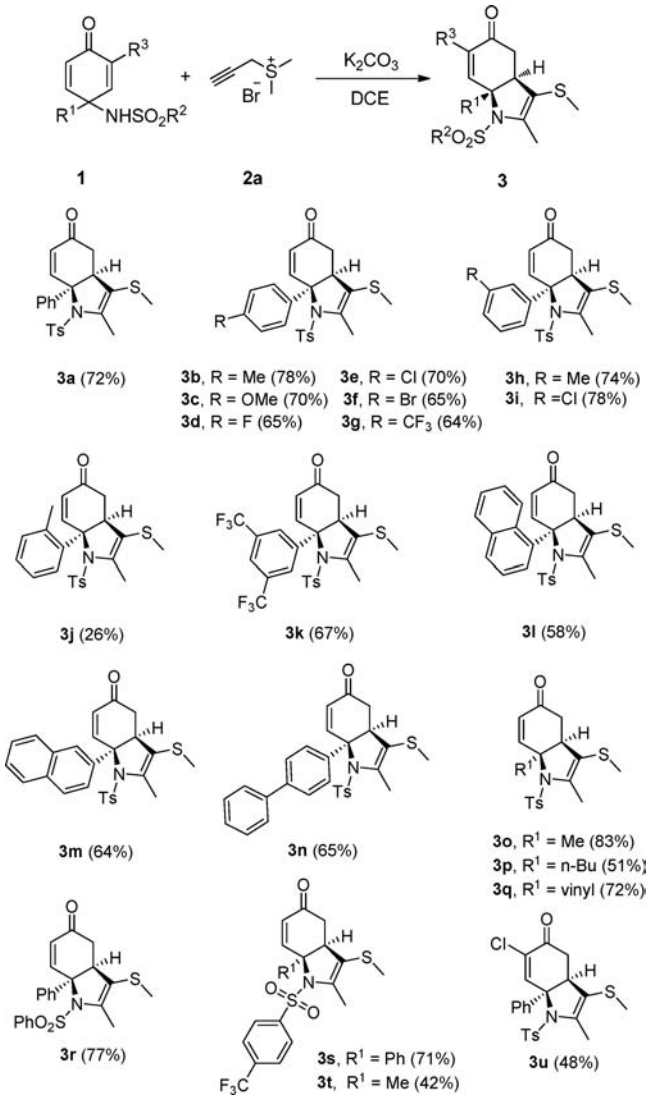
					yield[b] (%)	
entry	base	solvent	time (h)	1a/2a/base	3a	4a
1	Cs_2CO_3	CH_3CN	3	1:2:2	41	17
2	Cs_2CO_3	CH_3CN	24	1:2:2	53	18
3	K_2CO_3	CH_3CN	24	1:2:2	58	13
4	Et_3N	CH_3CN	24	1:2:2	52	NP
5	DABCO	CH_3CN	24	1:2:2	26	trace
6	K_3PO_4	CH_3CN	24	1:2:2	49	28
7	NaOH	CH_3CN	24	1:2:2	41	15
8	KOH	CH_3CN	24	1:2:2	43	22
9	K_2CO_3	DCM	24	1:2:2	68	trace
10	K_2CO_3	DCE	24	1:2:2	72	trace
11	K_2CO_3	DBM	24	1:2:2	59	trace
12	K_2CO_3	$CHCl_3$	24	1:2:2	52	trace
13[c]	K_2CO_3	DCE	24	1:2:2	69	NP
14	K_2CO_3	DCE	24	1:1.5:2	68	trace
15	K_2CO_3	DCE	24	1:3:2	67	trace
16	K_2CO_3	DCE	24	1:2:1.5	68	trace
17	K_2CO_3	DCE	24	1:2:3	73	trace

[a]Unless otherwise noted, reactions of **1a** (0.20 mmol) and **2a** were carried out in 2 mL of the solvent at 20 °C. [b]Isolated yields. [c]The reaction temperature was 10 °C.

products, among which DCE gave the best yield of 72% of **3a** with a trace amount of **4a** (Table 1, entry 10). Lowering the reaction temperature to 10 °C gave a lower yield of 69% (Table 1, entry 13). Changing the loading of prop-2-ynylsulfonium salt **2a** and bases did not give better yields (Table 1, entries 14–17).

The generality of this prop-2-ynylsulfonium salts involved [3 + 2]-cycloaddition reaction was examined. As summarized in Scheme 4, a wide range of *p*-quinamines can be employed in

Scheme 4. Scope of the Reactions[a,b]



[a]Reactions of **1** (0.20 mmol) and **2a** (0.40 mmol) were carried out in the presence of K_2CO_3 (0.40 mmol) in 2 mL of 1,2-dichloroethane. [b]Isolated yields are shown.

this transformation. *p*-Quinamines bearing either electron-rich or electron-deficient substituents at the para and meta position of the benzene ring were well-tolerated, producing the desired products in good to high yields (**3b–i**). However, when *p*-quinamine with Me at the ortho position of the benzene ring was employed in the reaction, a reduced yield of 26% was obtained, probably because of steric hindrance (**3j**). Substrates **1** with a 3,5-bis(trifluoromethyl)-substituted phenyl ring could also be transformed into the corresponding product in 67%

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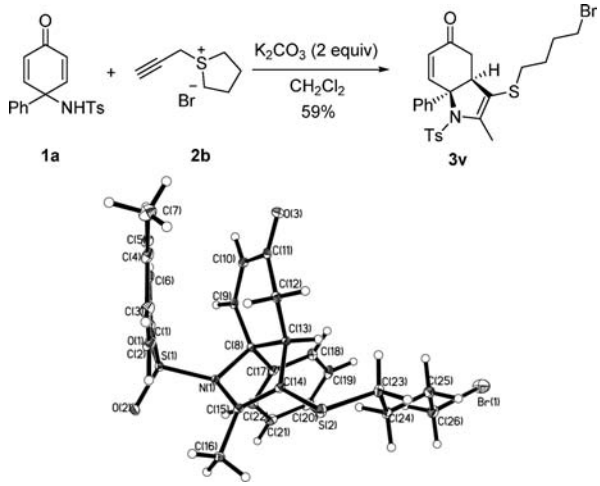
yield (**3k**). Further investigation showed that *p*-quinamines bearing naphthyl groups or a biphenyl group (**3l–n**) were also efficient for the transformation. Different alkyl groups were also introduced into substrates **1**. The yields decreased with the increase of the chain R^1 length because of steric hindrance (**3o–q**). The protecting group of the sulfamide functional group could also be changed and worked well in the reaction (**3r–t**). *p*-Quinamine with R^3 = Cl was also a suitable substrate for this conversion, producing the corresponding cycloaddition product in moderate yield (**3u**).

To further broaden the scope of the reaction, tetrahydrothiophene sulfonium salt **2b** was employed in the reaction in the presence of K_2CO_3 in dichloromethane at room temperature. Ring-opened product **3v** with a Br atom at the terminal of the chain was obtained in 59% yield (Scheme 5). The structure and stereochemistry of **3v** were characterized by a combination of NMR, HRMS, and single-crystal X-ray analysis.[13]

Scheme 5. Reaction of 1a and 1-(Prop-2-yn-1-yl)tetrahydro-1*H*-thiophene-1-ium Bromide

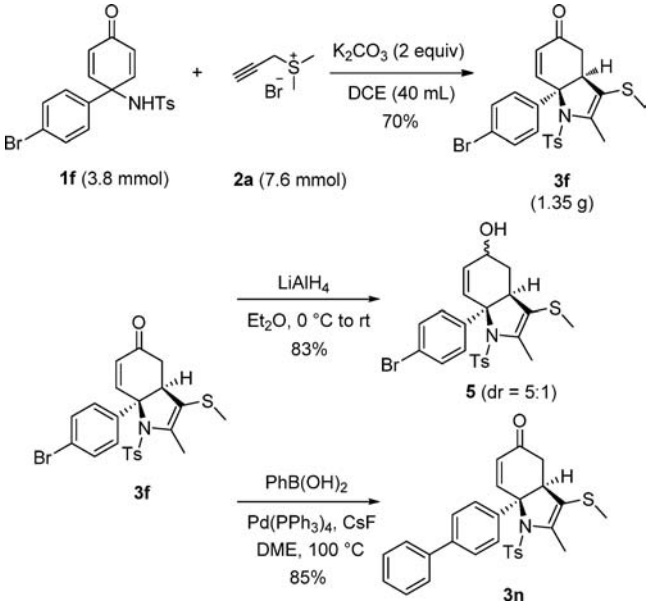


To investigate the synthetic utility of this reaction, a gram-scale version of the reaction using substrates **1f** and **2a** was carried out, and compound **3f** was obtained in 70% yield (Scheme 6). Some transformations were conducted using product **3f**. Upon treatment of **3f** with $LiAlH_4$ in Et_2O, reduction product **5** was generated in 83% yield with 5:1 diastereoselectivity. Moreover, product **3n** could also be obtained from **3f** via a Suzuki cross-coupling reaction in 85% yield.

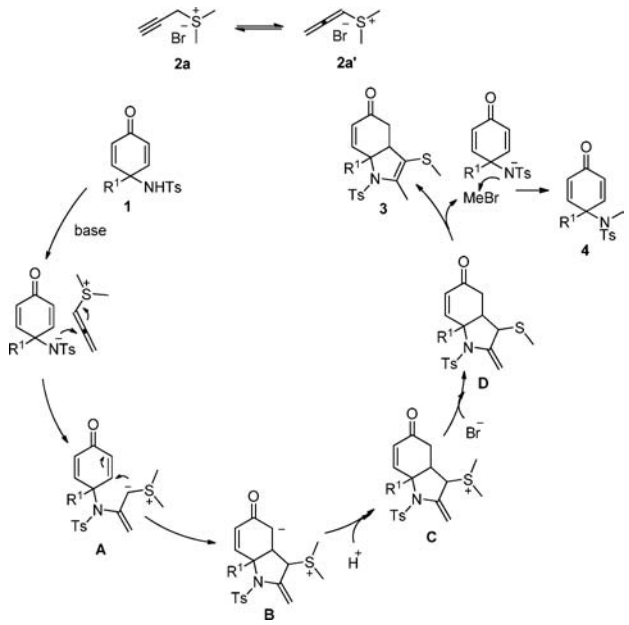
A possible mechanism is depicted in Scheme 7. Prop-2-ynylsulfonium salt **2a** first isomerizes into allenic sulfonium salt **2a′**. Conjugate addition of the N anion to **2a′** generates intermediate **A**, which then undergoes intramolecular nucleophilic addition to form intermediate **B**. Subsequent protonation of **B** give intermediate **C**. The methyl group of the Me_2S sulfonium would be attacked by Br^- to yield intermediate **D**,[14] which then undergoes double-bond isomerization to afford the final product **3**. The Br^- of MeBr proceeds via nucleophilic substitution by the N anion to generate *N*-methyl product **4**.

In conclusion, we have developed a method to construct hydroindol-5-ones containing a methylthio group via [3 + 2] annulation of prop-2-ynylsulfonium salts and *p*-quinamines. Prop-2-ynylsulfonium salts can isomerize into allenic sulfonium salts and act as a novel C_2 sython in the reaction, which broadens the chemistry of sulfur ylides. Moreover, sulfides do not serve as leaving groups compared with traditional reactions, which provides access to organosulfur compounds. Further studies applying this method to the synthesis of molecules with biological activity are underway in our laboratory.

Scheme 6. Gram-Scale Synthesis and Further Transformation of 3f



Scheme 7. Plausible Reaction Mechanism



■ ASSOCIATED CONTENT

Supporting Information

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Experimental details, characterization data for new compounds, NMR spectra, and X-ray crystal structure of **3v** (PDF)
Crystallographic data for **3v** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Parsons, A. F.; Palframan, M. J. Erythrina and Related Alkaloids. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier: Amsterdam, 2010; Vol. *68*, pp 39−81. (b) Barbosa-Filho, J. M.; Da-Cunha, E. V. L.; Gray, A. I. Alkaloids of the Menispermaceae. In *The Alkaloids, Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier: Oxford, 2000; Vol. *54*, pp 1−190.

(2) (a) Yu, B.-W.; Chen, J.-Y.; Wang, Y.-P.; Cheng, K.-F.; Li, X.-Y.; Qin, G.-W. *Phytochemistry* **2002**, *61*, 439. (b) Qin, G.-W.; Tang, X.-C.; Lestage, P.; Caignard, D.-H.; Renard, P. PCT Int. Appl. WO 2004000815, 2003.

(3) (a) Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6674−6675. (b) Herzon, S. B.; Calandra, N. A.; King, S. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8863−8866. (c) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 9447−9451. (d) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Chem. Sci.* **2011**, *2*, 1086−1089. (e) Navarro, R.; Reisman, S. E. *Org. Lett.* **2012**, *14*, 4354−4357.

(4) (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341−2372. (b) Dai, L.-X.; Hou, X.-L.; Zhou, Y.-G. *Pure Appl. Chem.* **1999**, *71*, 369−376. (c) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611−620. (d) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841−5883. (e) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937−948. (f) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278−1293. (g) Li, G.-C.; Wang, L.-Y.; Huang, Y. *Chin. J. Org. Chem.* **2013**, *33*, 1900−1918.

(5) (a) Lin, H.; Shen, Q.-L.; Lu, L. *J. Org. Chem.* **2011**, *76*, 7359−7369. (b) Kasai, N.; Maeda, R.; Furuno, H.; Hanamoto, T. *Synthesis* **2012**, *44*, 3489−3495. (c) Ishikawa, T.; Kasai, N.; Yamada, Y.; Hanamoto, T. *Tetrahedron* **2015**, *71*, 1254−1260.

(6) (a) Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7066−7069. (b) Unthank, M. G.; Tavassoli, B.; Aggarwal, V. K. *Org. Lett.* **2008**, *10*, 1501−1504. (c) Catalán-Muñoz, S.; Müller, C. A.; Ley, S. V. *Eur. J. Org. Chem.* **2010**, *2010*, 183−190. (d) Fritz, S. P.; West, T. H.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2012**, *14*, 6370−6373. (e) Fritz, S. P.; Matlock, J. V.; McGarrigle, E. M.; Aggarwal, V. K. *Chem. - Eur. J.* **2013**, *19*, 10827−10831. (f) Matlock, J. V.; Fritz, S. P.; Harrison, S. A.; Coe, D. M.; McGarrigle, E. M.; Aggarwal, V. K. *J. Org. Chem.* **2014**, *79*, 10226−10239.

(7) (a) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784−3786. (b) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 257−260. (c) An, J.; Chang, N.-J.; Song, L.-D.; Jin, Y.-Q.; Ma, Y.; Chen, J.-R.; Xiao, W.-J. *Chem. Commun.* **2011**, *47*, 1869−1871. (d) Fritz, S. P.; Mumtaz, A.; Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Eur. J. Org. Chem.* **2011**, *2011*, 3156−3164. (e) Yar, M.; Fritz, S. P.; Gates, P. J.; McGarrigle, E. M.; Aggarwal, V. K. *Eur. J. Org. Chem.* **2012**, *2012*, 160−166. (f) Matlock, J. V.; Svejstrup, T. D.; Songara, P.; Overington, S.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2015**, *17*, 5044−5047.

(8) (a) Kanematsu, K.; Aso, M.; Sakamoto, M.; Urakawa, N.; Kanemastsu, K. *Heterocycles* **1990**, *31*, 1003−1006. (b) Aso, M.; Ojida, A.; Yang, G.; Cha, O.-J.; Osawa, E. *J. Org. Chem.* **1993**, *58*, 3960−3968. (c) Ojida, A.; Tanoue, F.; Kanematsu, K. *J. Org. Chem.* **1994**, *59*, 5970−5976.

(9) (a) Xie, P.-Z.; Wang, L.-Y.; Yang, L.-H.; Li, E.-Q.; Ma, J.-Z.; Huang, Y.; Chen, R.-Y. *J. Org. Chem.* **2011**, *76*, 7699−7705. (b) Gao, F.; Huang, Y. *Adv. Synth. Catal.* **2014**, *356*, 2422−2428. (c) Jia, P.-H.; Huang, Y. *Org. Lett.* **2016**, *18*, 2475−2478.

(10) For reported vinylsulfonium salts involved [3 + 2] reactions, see: (a) McGarrigle, E. M.; Fritz, S. P.; Favereau, L.; Yar, M.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3060−3063. (b) An, J.; Yang, Q.-Q.; Wang, Q.; Xiao, W.-J. *Tetrahedron Lett.* **2013**, *54*, 3834−3837.

(11) (a) Tello-Aburto, R.; Kalstabakken, K. A.; Harned, A. M. *Org. Biomol. Chem.* **2013**, *11*, 5596−5604. (b) Pantaine, L.; Coeffard, V.; Moreau, X.; Greck, C. *Org. Lett.* **2015**, *17*, 3674−3677.

(12) (a) *Sulfur Compounds: Advances in Research and Application*; Acton, A. Q., Ed.; Scholarly Editions: Atlanta, 2012. (b) Block, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1135−1178. (c) Takimiya, K.; Osaka, I.; Mori, T.; Nakano, M. *Acc. Chem. Res.* **2014**, *47*, 1493−1502.

(13) CCDC 1489814 (**3v**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) (a) Shao, Q.-Y.; Li, C.-B. *Synlett* **2008**, 2317−2320. (b) Palillero, A.; Teran, J. L.; Gnecco, D.; Juarez, J. R.; Orea, M. L.; Castro, A. *Tetrahedron Lett.* **2009**, *50*, 4208−4211. (c) Kantam, M. L.; Mahendar, K.; Sreedhar, B.; Choudary, B. M. *Tetrahedron* **2010**, *66*, 5042−5052. (d) Li, K.; Hu, J.; Liu, H.; Tong, X.-F. *Chem. Commun.* **2012**, *48*, 2900−2902. (e) Zhang, Q.; Liu, X.; Xin, X.-Q.; Zhang, R.; Liang, Y.-J.; Dong, D.-W. *Chem. Commun.* **2014**, *50*, 15378−15380.

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