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Sulfur Incorporation: Copper-Catalyzed Cascade Cyclization of 1,7-Enynes with Metal Sulfides toward Thieno[3,4-*c*]quinolin-4(5*H*)-ones

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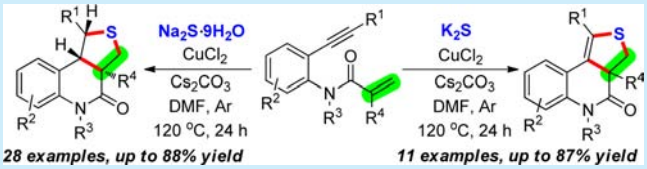
Supporting Information

ABSTRACT: A novel copper-catalyzed cascade cyclization of 1,7-enynes with metal sulfides is described. This sulfur-incorporation method provides straightforward access toward the important thiophene-fused quinolin-4(5*H*)-one scaffold through cyclization and double C−S bond formation cascade, and the chemoselectivity of this 1,7-enyne cyclization toward 1,3,3a,9b-tetrahydrothieno[3,4-*c*]quinolin-4(5*H*)-ones and 3,3a-dihydrothieno[3,4-*c*]quinolin-4(5*H*)-ones can be controlled by varying the sulfur resources.



Metal-catalyzed 1,*n*-enyne cyclization processes have proven to be powerful and frequently utilized methods for constructing complex, functionalized polycyclic ring systems in an atom- and step-economical manner.[1−4] In this field, cycloisomerization, skeletal rearrangement, and metathesis are excellent strategies for the 1,*n*-enyne cyclizations that have been well-documented.[1,2] However, the majority of these strategies are triggered by interaction among a noble transition metal, a π-orbital of acetylene, and a π-orbital of alkene, thereby limiting the distance between the acetylene and the alkene in 1,*n*-enynes (often 1,6-enynes) due to a combination of entropic factors and the presence of nonbonding interactions in the transition state.[1−4] Finding a means to realize remote 1,*n*-enyne cyclization using inexpensive transition-metal catalysts, such as copper salts,[1l,3] remains an important challenge. Recently, a new 1,*n*-enyne cascade cyclization strategy catalyzed by transition-metal catalysts using additional reagents was developed and is especially attractive for impressively increasing structural complexity;[4] however, such successes are much less abundant. Moreover, approaches for the cyclization of remote 1,7-enynes using inexpensive copper catalysts are lacking.

Sulfur-containing heterocyclic compounds are widespread in natural products and synthetic compounds of high utility in pharmaceutical, agrochemical, and materials chemistry.[5] As a result, the development of new efficient and selective routes to sulfur-containing heterocyclic compounds remains a continuous hot topic in synthesis and industry. A typical procedure includes the incorporation of sulfur atoms from metal sulfides into organic frameworks for building the sulfur-containing heterocyclic ring scaffold by copper-catalyzed cross-coupling tandem reactions.[6] We reasoned that metal sulfides may be used as additional reagents to initiate copper-catalyzed 1,*n*-enyne cascade cyclization.[6] Herein, we report an unprecedented copper-catalyzed cascade cyclization of 1,7-enynes with metal sulfides for one-pot synthesis of important thieno[3,4-*c*]quinolin-4(5*H*)-ones[7] through double C−S bond formation. Notably, the chemoselectivity toward 1,3,3a,9b-tetrahydrothieno[3,4-*c*]quinolin-4(5*H*)-ones or 3,3a-dihydrothieno[3,4-*c*]quinolin-4(5*H*)-ones can be controlled by simply changing the sulfur resources ($Na_2S·9H_2O$ or K_2S). To the best of our knowledge, this method represents the first 1,*n*-enyne cascade cyclization using metal sulfides as the addition reagents through incorporation of a sulfur atom into the product system.

Our initial investigations focused on the cascade cyclization of *N*-methyl-*N*-(2-(phenylethynyl)phenyl)methacrylamide (**1a**) with $Na_2S·9H_2O$ for reaction condition optimization (Table 1). 1,7-Enyne **1a** was found to furnish the desired 1,3,3a,9b-tetrahydrothieno[3,4-*c*]quinolin-4(5*H*)-one **2a** in 83% yield together with only a trace of another 3,3a-dihydrothieno[3,4-*c*]quinolin-4(5*H*)-one product **3a** upon exposure to $CuCl_2$, Cs_2CO_3, $Na_2S·9H_2O$, and argon in DMF at 120 °C (entry 1). However, the absence of bases decreased the yield from 83% to 31% (entry 2). In light of these results, the effect of bases was examined: a series of other bases, including Na_2CO_3, CsOAc, CsF, and ^{t}BuOK, could favor the reaction, albeit with lower reactivity (entries 3−6). The amount of $CuCl_2$ was subsequently examined, and the results showed that 20 mol % of $CuCl_2$ was preferred (entry 1 vs entries 7 and 8). Other copper salts, such as $CuBr_2$, $Cu(OAc)_2$, and CuCl, also displayed high catalytic activity for the reaction, although they were inferior to $CuCl_2$ (entry 1 vs entries 9−11). It should be noted that CuCl, a Cu(I) salt, is also effective for the reaction, delivering **2a** in 75% yield (entry 11). Among the effects of other reaction parameters, including solvents (entries 12−14) and the reaction temperatures (entries 15 and 16), examined, it was found that DMF at 120 °C led to the optimized process (entry 1). We were surprised to find that by changing from $Na_2S·9H_2O$ to anhydrous Na_2S

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Table 1. Screening of Optimal Conditions[a]

					yield (%)	
entry	[Cu] (mol %)	base	solvent	temp (°C)	2a	3a
1	$CuCl_2$	Cs_2CO_3	DMF	120	83	trace
2	$CuCl_2$		DMF	120	31	trace
3	$CuCl_2$	Na_2CO_3	DMF	120	45	trace
4	$CuCl_2$	CsOAc	DMF	120	30	trace
5	$CuCl_2$	CsF	DMF	120	47	trace
6	$CuCl_2$	^{t}BuOK	DMF	120	36	trace
7[b]	$CuCl_2$	Cs_2CO_3	DMF	120	75	trace
8[c]	$CuCl_2$	Cs_2CO_3	DMF	120	82	trace
9	$CuBr_2$	Cs_2CO_3	DMF	120	80	trace
10	$Cu(OAc)_2$	Cs_2CO_3	DMF	120	60	trace
11	CuCl	Cs_2CO_3	DMF	120	75	trace
12	$CuCl_2$	Cs_2CO_3	DMA	120	66	trace
13	$CuCl_2$	Cs_2CO_3	DMSO	120	10	trace
14	$CuCl_2$	Cs_2CO_3	toluene	120	33	trace
15	$CuCl_2$	Cs_2CO_3	DMF	100	53	trace
16	$CuCl_2$	Cs_2CO_3	DMF	130	81	trace
17[d]	$CuCl_2$	Cs_2CO_3	DMF	120	15	65
18[e]	$CuCl_2$	Cs_2CO_3	DMF	120	trace	77
19[f]	$CuCl_2$	Cs_2CO_3	DMF	120	trace	35
20[g]	$CuCl_2$	Cs_2CO_3	DMF	120	80	trace

[a]Reaction conditions: **1a** (0.2 mmol), $Na_2S·9H_2O$ (1.2 mmol), [Cu] (20 mol %), base (0.6 mmol), and solvent (2 mL) under argon atmosphere for 24 h. The dr value is about 21:4 determined by ^{1}H NMR analysis of the crude product (*trans* (1-Ph/9*b*-H), *trans* (3*a*-Me/9*b*-H)-isomer is major, and *cis* (1-Ph/9*b*-H), *trans* (3*a*-Me/9*b*-H)-isomer is minor). [b][Cu] (10 mol %). [c][Cu] (30 mol %). [d]Anhydrous Na_2S (1.2 mmol). [e]K_2S (1.2 mmol) instead of $Na_2S·9H_2O$. [f]PhSSPh (1.2 mmol) instead of $Na_2S·9H_2O$. [g]**1a** (1 g, 3.64 mmol) and solvent (10 mL) for 72 h.

(entry 17), K_2S (entry 18), or PhSSPh (entry 19) the chemoselectivity of the cyclizaiton was shifted from product **2a** toward another product **3a** in 65%, 77%, and 35% yield, respectively. Gratifyingly, a 1 g (3.64 mmol) scale reaction of 1,7-enyne **1a** is successfully performed with $Na_2S·9H_2O$, giving **2a** in high yield (entry 20).

After determining the optimal reaction conditions, we turned our attention to investigating the scope of this cascade cyclization protocol by examining the enyne component with $Na_2S·9H_2O$ (Figure 1) or K_2S (Figure 2). As shown in Figure 1, 1,7-enyne with a free N−H bond was not a viable substrate for this cascade cyclization reaction (**2b**). Although 1,7-enyne having an *N*-allyl group was successfully reacted with $Na_2S·9H_2O$, $CuCl_2$, and Cs_2CO_3, removal of the allyl group took place leading to **2b** in 58% yield. Use of *N*-Bn-substituted 1,7-enyne delivered **2d** in 64% yield. 1,7-Enyne bearing a substituent, including Me, MeO, F, Cl, and Br, on the aromatic ring at the terminal alkyne performed well in the cascade cyclization under these optimal conditions, providing **2e−l** in good yields. Interestingly, the cascade process could generate heteroaryl-containing products **2m−u** when the heteroaryl groups, pyridinyl and thiophene-yl, are directly attached at the terminal alkyne. We were delighted to find that the reaction also accommodated several substituents,

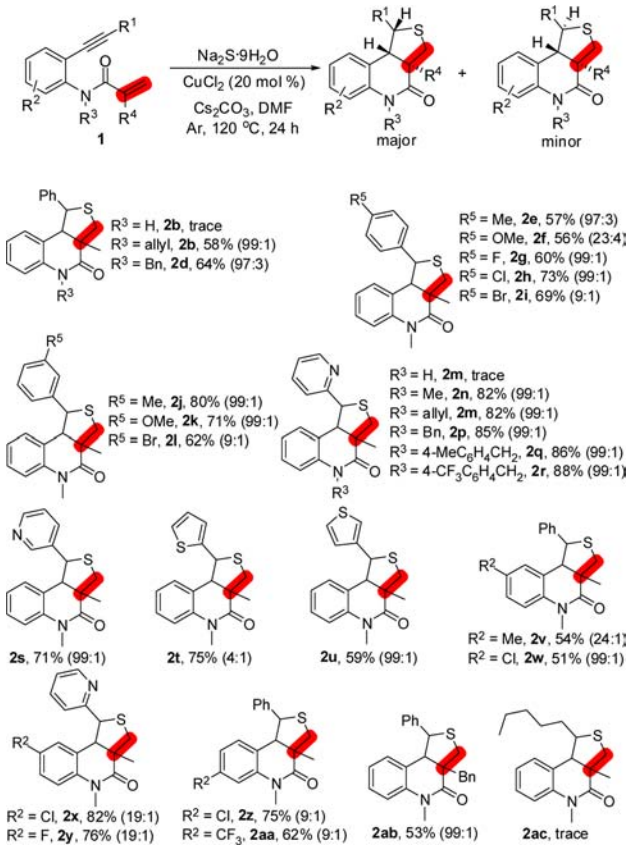

Figure 1. Cyclization of 1,7-enynes (**1**) with $Na_2S·9H_2O$. Reaction conditions: **1** (0.2 mmol), $Na_2S·9H_2O$ (1.2 mmol), $CuCl_2$, (20 mol %), Cs_2CO_3 (0.6 mmol), and DMF (2 mL) under argon atmosphere for 24 h. The dr value is given in the parentheses determined by ^{1}H NMR analysis of the crude product. The diastereoisomers are determined by 2D NMR analysis of products **2i** and **2s**: *trans* (1-R^1/9*b*-H), *trans* (3*a*-R^4/9*b*-H)-isomer is major and *cis* (1-R^1/9*b*-H), *trans* (3*a*-R^4/9*b*-H)-isomer is minor.

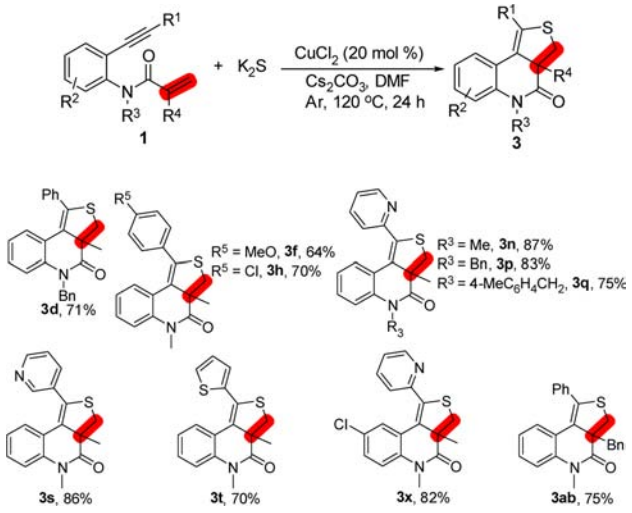

Figure 2. Cyclization of 1,7-enynes (**1**) with K_2S. Reaction conditions: **1** (0.2 mmol), K_2S (1.2 mmol), $CuCl_2$ (20 mol %), Cs_2CO_3 (0.6 mmol), and DMF (2 mL) under argon atmosphere for 24 h.

including Me, Cl, F, and CF_3, on the aryl of the *N*-(2-ethynylarylyl) moiety, giving the corresponding products **2v−aa** in 51−82% yields. Finally, 1,7-enyne with a Bn group at the 2

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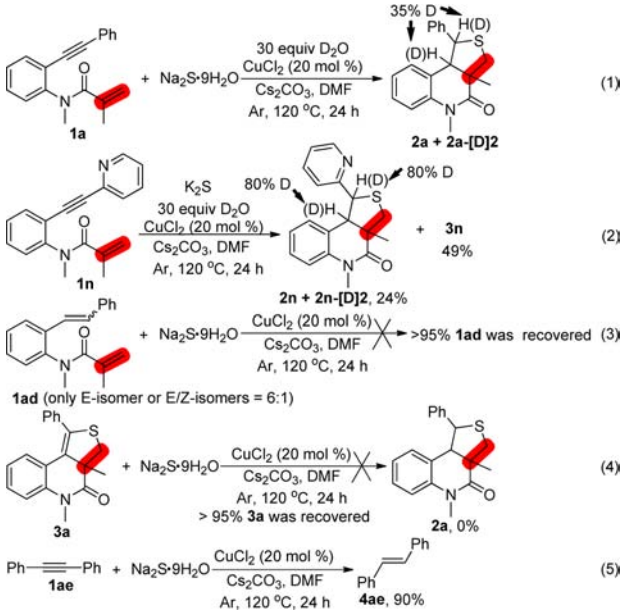
position of the acrylamide moiety is effective for the construction of **2ab** in moderate yield. Importantly, halide motifs are accommodated by the reaction conditions and provide further opportunities for additional modifications of the thieno[3,4-*c*]quinolin-4(5*H*)-one scaffold (**2g–i,l,w–z**). However, aliphatic alkyne has no reactivity for the reaction (**2ac**).

Next, we set out to exploit the scope of this cascade cyclization reaction using K_2S as the sulfur resource (Figure 2). To our delight, analogous 1,7-enyne with a *N*-Bn group instead of the *N*-Me group was also converted into dihydrothieno[3,4-*c*]quinolin-4(5*H*)-one **3d** in 71% yield. We obtained good yields of **3f** and **3h** from 1,7-enynes with a *p*-MeC_6H_4 or a *p*-ClC_6H_4 group at the terminal alkynes. A range of heteroaryl alkynes could be successfully accommodated by the reaction with K_2S, $CuCl_2$, and Cs_2CO_3 (**3n**, **3p**, **3q**, **3s**, and **3t**), and even a Cl-substituted enyne worked well to form **3x** in high yield. Notably, a 1,7-enyne with a Bn group at the 2 position of the acrylamide moiety was also viable for constructing **3ab** in good yield.

In light of the results of Table 1 and Figures 1 and 2, the chemoselectivity toward products **2** and **3** was based on the sulfur resource, $Na_2S{\cdot}9H_2O$ or K_2S, suggesting that the hydrogen atoms in the new formed C–H bonds of **2** may be from H_2O.[8] To verify these, two control experiments with D_2O were investigated (eqs 1 and 2; Scheme 1).[9] As expected, deuterium

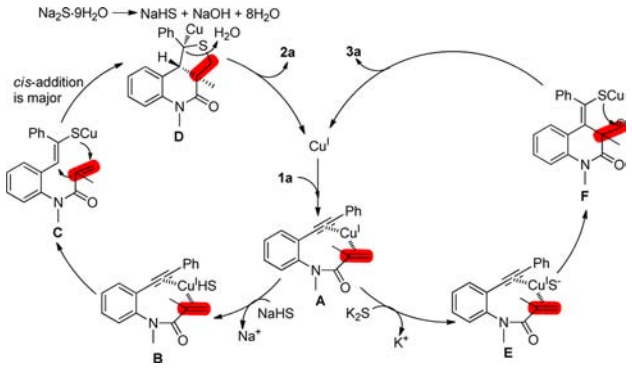
Scheme 1. Control Experiments



atoms were incorporated into **2a**, and K_2S combined with D_2O could deliver deuterated product **2n**-$[\mathbf{D}]_2$ along with **3n**. The results of eq 3 show that alkene **1ad** is not a suitable substrate for the reaction.[8e] Notably, product **3a** cannot be hydrogenated by the $Na_2S{\cdot}9H_2O/CuCl_2/Cs_2CO_3$ system (eq 4). This suggests that the hydrogenation reaction is not a sole step during the whole cyclization process.[8] Using 1,2-diphenylethyne (**1ae**) to react with $Na_2S{\cdot}9H_2O$ under the optimal conditions only afforded (*E*)-1,2-diphenylethene (**4ae**), a hydrogenation product, implying that the addition of S atom takes place at the acrylate unit (eq 5).[8] Notably, CuCl showed high catalytic activity for the reaction (entry 11; Table 1). The results suggest that the Cu(I) species plays a major role in the current reaction.

The mechanisms outlined in Scheme 2 were proposed for this cascade cyclization reaction.[2–4,7,8] Initially, coordination of the

Scheme 2. Possible Mechanisms



active Cu^I species with the C–C triple bond and the C–C double bond in 1,7-enyne **1a** afforded intermediate **A**. In the presence of $Na_2S{\cdot}9H_2O$, intermediate **A** readily reacts with NaHS,[8] in situ generated from $Na_2S{\cdot}9H_2O$, to provide intermediate **B**, followed by addition to form intermediate **C**. *cis*-Nucleophilic cyclization of intermediate **C** gives intermediate **D**. Finally, protonation of intermediate **D** via *trans*-addition of H_2O to the C–Cu bond delivers *trans,trans*-**2a** as the major isomer and regenerates the active Cu^I species. Using K_2S reacted intermediate **A** forms intermediate **E**. Nucleophilic addition and cyclization of intermediate **E** take place to afford intermediate **F**, followed by the second nucleophilic cyclization of intermediate **F** to give **3a**.

In summary, we have illustrated the first Cu-catalyzed cascade cyclization of 1,7-enynes by incorporating a sulfur atom into the product system using metal sulfides as sulfur resources. This method proceeds through 1,7-enyne cyclization and double C–S bond formation cascade and provides a valuable one-pot assembly of thieno[3,4-*c*]quinolin-4(5*H*)-ones from a broad range of enynes with good yields and excellent functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

Descriptions of experimental procedures for compounds and analytical characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews: (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, 1995. (c) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.

dx.doi.org/10.1021/ol5025162 | *Org. Lett.* 2014, 16, 5838–5841

(d) Trost, B. M. *Chem.—Eur. J.* **1998**, *4*, 2405. (e) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (f) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (g) Zhang, L.; Sun, J.; Kozmin, S. *Adv. Synth. Catal.* **2006**, *348*, 2271. (h) Zhang, Z.; Zhu, G.; Tong, X.; Wang, F.; Xie, X.; Wang, J.; Jiang, L. *Curr. Org. Chem.* **2006**, *10*, 1457. (i) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (j) Marco-Contelles, J.; Soriano, E. *Chem.—Eur. J.* **2007**, *13*, 1350. (k) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (l) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (m) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (n) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371. (o) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 2899. (p) Wille, U. *Chem. Rev.* **2013**, *113*, 813. (q) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (r) Xu, P.-F.; Wang, W. *Catalytic Cascade Reactions*; John Wiley & Sons: Hoboken, NJ, 2013.

(2) For special reviews on the 1,7-enyne cyclization via the cycloisomerisation, skeletal rearrangement, or metathesis strategies, see: (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (b) Fairlamb, I. J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1048. (c) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, *4*, 371. (d) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (e) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55.

(3) For papers on the copper-catalyzed cyclization of 1,*n*-enynes, see: (a) Fehr, C.; Farris, I.; Sommer, H. *Org. Lett.* **2006**, *8*, 1839. (b) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901. (c) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531. (d) Fehr, C.; Magpantay, I.; Arpagaus, J.; Marquet, X.; Vuagnoux, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7221. (e) Fehr, C.; Vuagnoux, M.; Buzas, A.; Arpagaus, J.; Sommer, H. *Chem.—Eur. J.* **2011**, *17*, 6214. (f) Fehr, C.; Vuagnoux, M.; Sommer, H. *Chem.—Eur. J.* **2011**, *17*, 3832. (g) Wang, Z.-Q.; Zhang, W.-W.; Gong, L.-B.; Tang, R.-Y.; Yang, X.-H.; Liu, Y.; Li, J.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8968.

(4) For papers on the cyclization of 1,7-enynes with additional reagents, including alkoxycyclization with alcohols, see: (a) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2003**, *9*, 2627. (b) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M.; Genét, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706. Cyclization with aldehydes: (c) Schelwies, M.; Moser, R.; Dempwolff, A. L.; Rominger, F.; Helmchen, G. *Chem.—Eur. J.* **2009**, *15*, 10888. Oxidative cyclization with acetic acid: (d) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836. (e) Lyons, T. W.; Sanford, M. S. *Tetrahedron* **2009**, *65*, 3211. (f) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906. (g) Tsujihara, T.; Takenaka, K.; Onitsuka, K.; Hatanaka, K.; Sasai, H. *J. Am. Chem. Soc.* **2009**, *131*, 3452. Pauson–Khand-type cyclization with CO: (h) Geis, O.; Schmalz, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 911. (i) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32. (j) Rodríguez-Rivero, M.; Adrio, J.; Carretero, J. C. *Eur. J. Org. Chem.* **2002**, 2881. (k) Ingate, S. T.; Marco-Contelles, J. L. *Org. Prep. Proced. Int.* **1998**, *30*, 123. Carboxylative cyclization with CO_2: (l) Takimoto, M.; Mizuno, T.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **2005**, *46*, 5173. (m) Takimoto, M.; Mizuno, T.; Mori, M.; Sato, Y. *Tetrahedron* **2006**, *62*, 7589. Borylative cyclization with $B_2(pin)_2$: (n) Pardo-Rodríguez, V.; Buñuel, E.; Collado-Sanz, D.; Cárdenas, D. J. *Chem. Commun.* **2012**, *48*, 10517. Cyclization with $ArSO_2Cl$: (o) Deng, G.-B.; Wang, Z.-Q.; Xia, J.-D.; Qian, P.-C.; Song, R.-J.; Hu, M.; Gong, L.-B.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 1535. Oxidative cyclization with *t*-BuONO: (p) Liu, Y.; Zhang, J.-L.; Song, R.-J.; Qian, P.-C.; Li, J.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 9017.

(5) For selected reviews, see: (a) Lednicer, D. *The Organic Chemistry of Drug Synthesis*; Wiley Interscience: New York, 1999; Vol. *6*, p 187. (b) Roncali, J. *Chem. Rev.* **1992**, *92*, 711. (c) Zaumseil, J.; Sirringhaus, H. *Chem. Rev.* **2007**, *107*, 1296. (d) Mishra, A.; Ma, C.-Q.; Bäuerle, P. *Chem. Rev.* **2009**, *109*, 1141. (e) Hartough, H. D.; Hochgesang,F. P.; Blicke, F. F. *Chemistry of Heterocyclic Compounds: Thiophene and its Derivatives*; John Wiley & Sons: Hoboken, 2008. (f) Mishra, R.; Jha, K. K.; Kumar, S.; Tomer, I. *Pharma Chem.* **2011**, *3*, 38. (g) Sałat, K.; Moniczewski, A.; Librowski, T. *Mini Rev. Med. Chem.* **2013**, *13*, 335.

(6) For selected papers, see: (a) Gronowitz, S.; Timari, G. *J. Heterocycl. Chem.* **1990**, *27*, 1501. (b) Ombetta, J. E.; Lyet, S.; Xicluna, A.; Robert, J. F.; Panouse, J. J. *Ann. Pharm. Fr.* **1989**, *46*, 377. (c) El-Abadelah, M. M.; Nazer, M. Z.; Okasha, S. F.; Calas, M.; Bompart, J.; Mion, P. *Eur. J. Med. Chem.* **1998**, *33*, 33. (d) Shinkwin, A. E.; Whish, W. J. D.; Threadgill, M. D. *Bioorg. Med. Chem.* **1999**, *7*, 297. (e) Koerber, S. C.; Rizo, J.; Struthers, R. S.; Rivier, J. E. *J. Med. Chem.* **2000**, *43*, 819. (f) Pereillo, J. M.; Maftouh, M.; Andrieu, A.; Uzabiaga, M. F.; Fedeli, O.; Savi, P.; Pascal, M.; Herbert, J. M.; Maffrand, J. P.; Picard, C. *Drug Metab. Dispos.* **2002**, *30*, 1288. (g) Buchstaller, H.-P.; Siebert, C. D.; Steinmetz, R.; Frank, I.; Berger, M. L.; Gottschlich, R.; Leibrock, J.; Krug, M.; Steinhilber, D.; Noe, C. R. *J. Med. Chem.* **2006**, *49*, 864. (h) Zhao, G.; Iyengar, R. R.; Judd, A. S.; Cool, B.; Chiou, W.; Kifle, L.; Frevert, E.; Sham, H.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3254. (i) Lindvall, M.; McBride, C.; McKenna, M.; Gesner, T. G.; Yabannavar, A.; Wong, K.; Lin, S.; Walter, A.; Shafer, C. M. *ACS Med. Chem. Lett.* **2011**, *2*, 720. (j) M. Poduval, K.; Burrezo, P. M.; Casado, J.; Navarrete, J. T. L.; Ortiz, R. P.; Kim, T.-H. *Macromolecules* **2013**, *46*, 9220. (k) Goerlitzer, K.; Gabriel, B.; Jomaa, H.; Wiesner, J. *Pharmazie* **2006**, *61*, 901. (l) McCauley, J. A.; Rajapakse, H. A.; Greshock, T. J.; Sanders, J.; Kim, B.; Rada, V. L.; Kern, J. T.; Stevenson, H. H.; Bilodeau, M. T. Preparation of thieno[3,4-*c*]pyridin-4(5*H*)-one derivatives as inhibitors of Leucine-rich repeat kinase. PCT Int. Appl. WO 2012058193 A1 20120503, 2012.

(7) Na_2S: (a) Shvartsberg, M. S.; Ivanchikova, I. D. *ARKIVOC* **2003**, 87. (b) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222. (c) Li, C.-L.; Zhang, X.-G.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 7037. K_2S: (d) You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930. (e) Zhang, X.; Zeng, W.; Yang, Y.; Huang, H.; Liang, Y. *Org. Lett.* **2014**, *16*, 876. KSCN: (f) Ke, F.; Qu, Y.; Jiang, Z.; Li, Z.; Wu, D.; Zhou, X. *Org. Lett.* **2011**, *13*, 454. $Na_2S_2O_3$: (g) Qiao, Z.; Liu, H.; Xiao, X.; Fu, Y.; Wei, J.; Li, Y.; Jiang, X. *Org. Lett.* **2013**, *15*, 2594. (h) Qiao, Z.; Wei, J.; Jiang, X. *Org. Lett.* **2014**, *16*, 1212.

(8) For selected papers on the use of $Na_2S{\cdot}9H_2O$ as the reducing agent: (a) Shiao, M.-J.; Lai, L.-L.; Ku, W.-S.; Lin, P.-Y.; Hwu, J.-R. *J. Org. Chem.* **1993**, *58*, 4742. (b) Steinbach, J.; Mäding, P.; Füchtner, F.; Johannsen, B. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 33. (c) Yadav, G. D.; Lande, S. V. *Adv. Synth. Catal.* **2005**, *347*, 1235. (d) He, Q.; Wang, C.; Jiang, Q.; Shen, Y. *Chin. J. Org. Chem.* **2009**, *29*, 105. (e) Chen, Z.; Luo, M.; Wen, Y.; Luo, G.; Liu, L. *Org. Lett.* **2014**, *16*, 3020.

(9) The detailed data, including the deuterium-labeled experiments (Figure S1) and 2D NMR analysis of products **2i** and **2s**, are summarized in the Supporting Information.

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