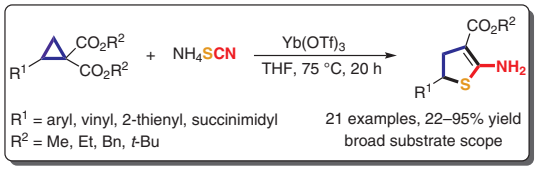
Synlett A. Jacob et al. Letter

(3+2)-Cycloaddition of Donor–Acceptor Cyclopropanes with Thiocyanate: A Facile and Efficient Synthesis of 2-Amino-4,5-dihydrothiophenes

Anu Jacob[a]
Philip Barkawitz[a]
Ivan A. Andreev[b,c]
Nina K. Ratmanova[b]
Igor V. Trushkov[b,c]
Daniel B. Werz*[a]

[a] Technische Universität Braunschweig, Institute of Organic Chemistry, Hagenring 30, 38106 Braunschweig, Germany
d.werz@tu-braunschweig.de
[b] Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Samory Mashela 1, 117997 Moscow, Russian Federation
[c] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky pr. 47, 119991 Moscow, Russian Federation



Received: 21.01.2021
Accepted after revision: 07.02.2021
Published online: 07.02.2021
DOI: 10.1055/a-1385-2385; Art ID: st-2021-b0021-l

Abstract An easy and efficient route to obtain 2-amino-4,5-dihydrothiophenes is presented. A formal (3+2)-cycloaddition of donor–acceptor cyclopropanes and ammonium thiocyanate catalyzed by $Yb(OTf)_3$ delivers the desired products in good to excellent yields. A broad range of functional groups is tolerated during this process.

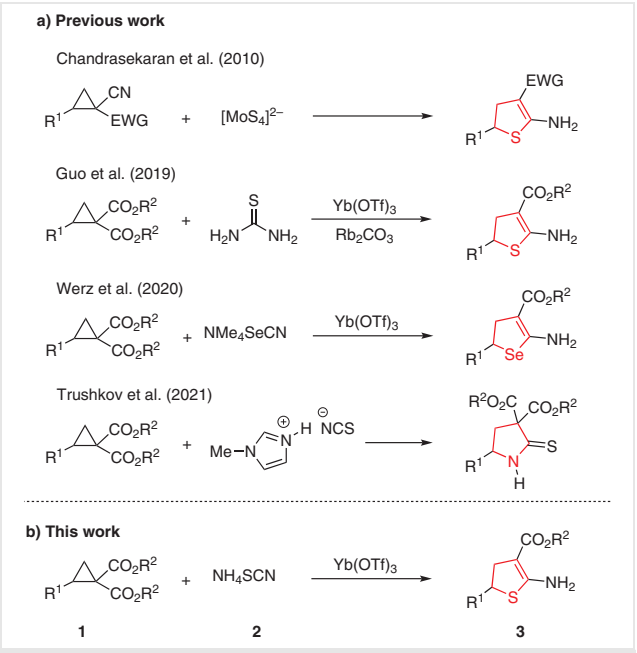
Key words D–A cyclopropanes, dihydrothiophenes, Lewis acid catalysis, thiocyanate, cycloaddition

Donor–acceptor cyclopropanes (DACs) have been widely used as versatile starting materials showing a 1,3-zwitterionic behavior to access carbo- and heterocyclic compounds.[1] The pioneering works on these molecules were unleashed by Wenkert and Reissig in the late 1970s.[2] The field has seen a revival during the past decades when these scaffolds have been utilized not just for the synthesis of various carbo- and heterocycles but also for natural product synthesis.[3] The push–pull effect by the vicinally placed donor and acceptor substituents activates the chemically inert cyclopropane ring to undergo transformations such as ring opening,[4] cycloadditions, and rearrangements.[5] Of these, the most investigated being the cycloadditions with 1,2-, 1,3-, and 1,4-dipoles including dienes,[6] carbonyls,[7] imines,[8] nitrones,[9] alkynes,[10] heterocumulenes,[11] and other dipolarophiles.[12] Less explored are the routes to access heterocycles containing sulfur and selenium starting from DACs.

2-Aminodihydrothiophenes and -thiophenes were previously accessed through various routes, but syntheses starting from DACs are rather scant.[13] These moieties are often found in many biologically relevant molecules,[14] setting up the need for more efficient and simple ways to access them. In 2010, Chandrasekaran and co-workers utilized tetrathiomolybdate as the sulfur transfer agent to doubly activated cyclopropanes to obtain dihydrothiophenes.[15] Srinivasan et al. introduced a two-step route to access tetrasubstituted thiophene by a (3+3)-cycloaddition of DACs with in situ generated mercaptoacetaldehyde.[16] In 2017, the synthesis of highly substituted tetrahydrothio- and tetrahydroselenophenes via a (3+2)-cycloaddition of DACs with thio- and selenoketones, respectively, was reported by our group.[17] Later in 2018, a similar transformation using thionoester was disclosed by Yazaki and Ohshima.[18] An $Yb(OTf)_3$-catalyzed (3+2)-cycloaddition involving DACs and thiourea to obtain dihydrothiophenes was disclosed by Guo and co-workers in 2019.[19] Very recently, our group successfully prepared dihydroselenophenes via a (3+2)-cycloaddition of DACs and tetramethylammonium selenocyanate (Scheme 1a).[20]

Very recently, Trushkov and co-workers made use of protic ionic liquids with thiocyanate anion (Scheme 1a).[21] With electron-rich DACs, the protic ionic liquid served as a reagent, catalyst, and solvent and converted the three-membered ring into pyrrolidine-2-thiones. This result is noteworthy since the ambident thiocyanate anion attacks the three-membered ring with the less nucleophilic nitrogen atom. Inspired by these investigations and our previous results with selenocyanate, we were interested in whether we can find conditions that enable the sulfur terminus of thiocyanate anion to attack the electrophilic carbon of the DAC. Such an initial step should lead – analogously to the selenium congeners – to thiophene derivatives (Scheme 1b).

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Scheme 1 a) Previously reported routes to access sulfur- and selenium-containing heterocycles utilizing DACs. b) New route to access dihydrothiophenes from DACs.

Table 1 Optimization of Reaction Conditions[a]

Entry	Reagent	Lewis acid	Solvent	Temp (°C)	Yield (%)[b]
1	KSCN	$Sc(OTf)_3$	THF	25	–
2	KSCN	$Yb(OTf)_3$	THF	25	–
3	KSCN	$Yb(OTf)_3$	THF	75	–
4	KSCN	$Yb(OTf)_3$	DME	75	–
5	NH_4SCN	$Sc(OTf)_3$	DME	50	20
6	NH_4SCN	$Yb(OTf)_3$	DME	50	32
7	NH_4SCN	$Yb(OTf)_3$	THF	50	45
8	NH_4SCN	$Yb(OTf)_3$	THF	75	60[c]
9	NH_4SCN	$Yb(OTf)_3$[d]	THF	75	89[c]

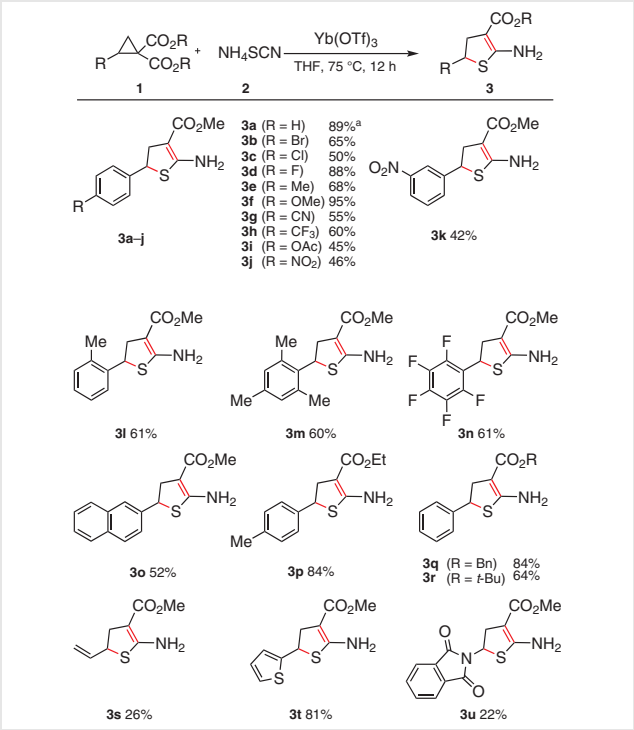
[a] Reaction conditions: **1a** (100 µmol), **2** (200 µmol), Lewis acid (10 mol%), solvent (1 mL), under Ar, 4 h.
[b] Yields refer to purified and isolated products.
[c] The reaction was stirred for 12 h.
[d] The catalyst loading was increased to 30 mol%.

To begin with, the model DAC **1a** and KSCN were reacted in the presence of 10 mol% of $Sc(OTf)_3$ in THF as solvent under inert conditions (Table 1, entry 1). After various attempts, KSCN was proved to be an unsuitable reagent for the desired transformation. Further investigations were carried out using NH_4SCN as a thiocyanate source. With 10 mol% of $Sc(OTf)_3$ as Lewis acid catalyst and DME as a solvent, the desired product was obtained in 20% yield (entry 5). Further trials with $Yb(OTf)_3$ as catalyst and DME as solvent yielded 32% of **3a** (entry 6). Switching the solvent to THF increased the product formation up to 45% (entry 7). Tuning the reaction conditions by increasing the temperature to 75 °C proved to be successful and delivered the product in 60% yield (entry 8). An increased catalyst loading of 30 mol% was found to deliver the product in 89% yield (entry 9).

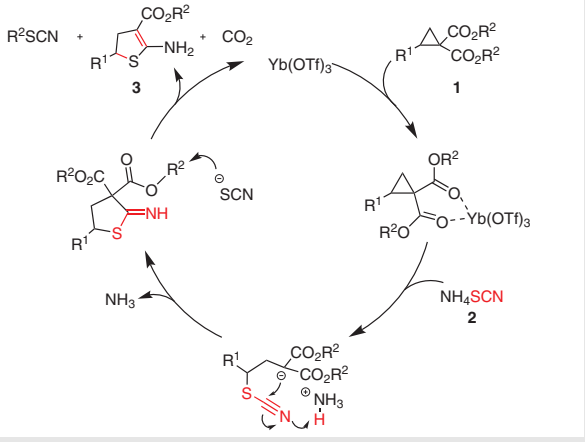
With the optimized conditions in hand, the generality of the synthetic methodology was explored utilizing ammonium thiocyanate **2** and diversely substituted DACs. The *para*-substituted aryl cyclopropanes underwent the desired transformation in fair to excellent yields to deliver the corresponding products **3a–j** (Scheme 2). DACs with an electron-withdrawing nitro group at the *meta* position of the aryl donor **1k** showed poor performance in the transformation to the desired product with only 42% yield. The sterically demanding substrate **1l** gave the corresponding product **3l** in 61% yield. The mesityl donor containing DAC **1m** afforded the product **3m** in 60% yield. The highly electron-deficient perfluorophenyl DAC **1n** furnished the corresponding product **3n** in a moderate yield of 61%. Enlarging the electron-donating π-system to the naphthyl group had no beneficial effect and afforded the product **3o** in 52% yield. Changing the ester type from methyl to ethyl and benzyl had almost no effect on the yield; only with the sterically encumbered *tert*-butyl residue, the yield was slightly lower (**3r**, 64% yield). However, the transformation gave only poor yields when a vinyl group (**3s**, 26% yield) or nitrogen-derived residue were installed as a donor (**3u**, 22% yield). In contrast, excellent conversion was observed with the DAC containing the thienyl donor delivering product **3t** in 81% yield.

A plausible mechanistic scenario for this transformation is proposed in Scheme 3. $Yb(OTf)_3$ coordinates to the acceptor moieties, thereby weakening the C–C bond in the DAC. The activated ring undergoes an S_N2-like attack by the nucleophilic thiocyanate ion leading to the ring opening. Unfortunately, we were unable to prove the inversion in this case because we did not get any separation of the two enantiomeric products by our HPLC methods. The emerging malonate anion attacks the nitrile carbon of the thiocyanate, resulting in a kinetically favored five-membered ring. Excess thiocyanate ion, which is required, captures the alkyl moiety from one of the ester groups, leading to decarboxylation, followed by the formation of product **3**.

In summary, a simple and straightforward method to synthesize 2-amino-4,5-dihydrothiophenes is reported.[22] The formal (3+2)-cycloaddition reaction of DACs and ammonium thiocyanate was catalyzed by the action of $Yb(OTf)_3$. Numerous functional groups are tolerated in this transformation.



Scheme 2 Substrate scope with respect to DACs. *Reagents and conditions*: **1** (100 µmol), **2** (200 µmol), $Yb(OTf)_3$ (30 mol%), THF (1 mL), at 75 °C under Ar, 12 h; yields refer to purified and isolated products. [a] Large scale: 81% yield for 1.5 mmol of starting material.



Scheme 3 Plausible reaction mechanism

Funding Information

A DAAD fellowship to A.J. is gratefully acknowledged.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1385-2385.

References and Notes

(1) (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Agrawal, D.; Yadav, V. K. *Chem. Commun.* **2008**, 6471. (c) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (d) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504. (e) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804. (f) Werz, D. B.; Biju, A. T. *Angew. Chem. Int. Ed.* **2020**, *59*, 3385. (g) Pirenne, V.; Muriel, B.; Waser, J. *Chem. Rev.* **2021**, *121*, 227. (h) Xia, Y.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2021**, *60*, in press DOI: 10.1002/anie.202006736.

(2) (a) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778. (b) Piers, E.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 791. (c) Reissig, H.-U.; Hirsch, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 813. (d) Brückner, C.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 588. (e) Lim, D. S. W.; Anderson, E. A. *Synthesis* **2012**, *44*, 983.

(3) Gharpure, S. J.; Nanda, L. N. *Tetrahedron Lett.* **2017**, *58*, 711.

(4) (a) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809. (b) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2558. (c) de Nanteuil, F.; Loup, J.; Waser, J. *Org. Lett.* **2013**, *15*, 3738. (d) Garve, L. K. B.; Barkawitz, P.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2014**, *16*, 5804. (e) Ivanov, K. L.; Villemson, E. V.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V.; Melnikov, M. Y. *Chem. Eur. J.* **2015**, *21*, 4975. (f) Xia, Y.; Lin, L.; Chang, F.; Fu, X.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 13748. (g) Kaicharla, T.; Roy, T.; Thangaraj, M.; Gonnade, R. G.; Biju, A. T. *Angew. Chem. Int. Ed.* **2016**, *55*, 10061. (h) Das, S.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2016**, *18*, 5576. (i) Garve, L. K. B.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2017**, *56*, 9226. (j) Lücht, A.; Patalag, L. J.; Augustin, A. U.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2017**, *56*, 10587. (k) Wallbaum, J.; Garve, L. K. B.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2017**, *19*, 98. (l) Das, S.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2017**, *56*, 11554. (m) Ivanov, K. L.; Bezzubov, S. I.; Melnikov, M. Y.; Budynina, E. M. *Org. Biomol. Chem.* **2018**, *16*, 3897. (n) Das, S.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 4053. (o) Richmond, E.; Vuković, V. D.; Moran, J. *Org. Lett.* **2018**, *20*, 574. (p) Augustin, A. U.; Jones, P. G.; Werz, D. B. *Chem. Eur. J.* **2019**, *25*, 11620. (q) Lücht, A.; Sobottka, S.; Patalag, L. J.; Jones, P. G.; Reissig, H.-U.; Sarkar, B.; Werz, D. B. *Chem. Eur. J.* **2019**, *25*, 10359. (r) Kreft, A.; Lücht, A.; Grunenberg, J.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2019**, *58*, 1955. (s) Boichenko, M. A.; Andreev, I. A.; Chagarovskiy, A. O.; Levina, I. I.; Zhokhov, S. S.; Trushkov, I. V.; Ivanova, O. A. *J. Org. Chem.* **2020**, *85*, 1146.

(5) (a) Schneider, T. F.; Kaschel, J.; Awan, S. I.; Dittrich, B.; Werz, D. B. *Chem. Eur. J.* **2010**, *16*, 11276. (b) Kaschel, J.; Schneider, T. F.; Kratzert, D.; Stalke, D.; Werz, D. B. *Angew. Chem. Int. Ed.* **2012**, *51*, 11153. (c) Kaschel, J.; Schmidt, C. D.; Mumby, M.; Kratzert, D.; Stalke, D.; Werz, D. B. *Chem. Commun.* **2013**, *49*, 4403. (d) Schmidt, C. D.; Kaschel, J.; Schneider, T. F.; Kratzert, D.; Stalke, D.; Werz, D. B. *Org. Lett.* **2013**, *15*, 6098. (e) Shim, S. Y.; Choi, Y.; Ryu, D. H. *J. Am. Chem. Soc.* **2018**, *140*, 11184. (f) Ivanova, O. A.; Chagarovskiy, A. O.; Shumsky, A. N.; Krasnobrov, V. D.; Levina, I. I.; Trushkov, I. V. *J. Org. Chem.* **2018**, *83*, 543. (g) Ortega, A.; Manzano, R.; Uria, U.; Carrillo, L.; Reyes,

E.; Tejero, T.; Merino, P.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 8225. (h) Lücht, A.; Jones, P. G.; Werz, D. B. *Eur. J. Org. Chem.* **2019**, 5254.

(6) (a) Ivanova, O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Kaplun, A. E.; Trushkov, I. V.; Melnikov, M. Y. *Adv. Synth. Catal.* **2011**, *353*, 1125. (b) Zhu, W.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032. (c) Budynina, E. M.; Ivanova, O. A.; Chagarovskiy, A. O.; Grishin, Y. K.; Trushkov, I. V.; Melnikov, M. Y. *J. Org. Chem.* **2015**, *80*, 12212. (d) Ma, C.; Huang, Y.; Zhao, Y. *ACS Catal.* **2016**, *6*, 6408. (e) Dey, R.; Banerjee, P. *Org. Lett.* **2017**, *19*, 304. (f) Blom, J.; Vidal-Albalat, A.; Jørgensen, J.; Barløse, C. L.; Jessen, K. S.; Iversen, M. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 11831. (g) Ahlburg, N. L.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2020**, *22*, 6404.

(7) (a) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642. (b) Benfatti, F.; de Nanteuil, F.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 4844. (c) Sabbatani, J.; Maulide, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 6780. (d) Kreft, A.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2018**, *20*, 2059.

(8) (a) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242. (b) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196. (c) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688. (d) Wang, D. C.; Xie, M. S.; Guo, H. M.; Qu, G. R.; Zhang, M. C.; You, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 14111. (e) Preindl, J.; Chakrabarty, S.; Waser, J. *Chem. Sci.* **2017**, *8*, 7112.

(9) (a) Young, I. S.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3023. (b) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764. (c) Kang, Y. B.; Sun, X. L.; Tang, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3918.

(10) (a) Yadav, V. K.; Sriramurthy, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 2669. (b) Rakhmankulov, E. R.; Ivanov, K. L.; Budynina, E. M.; Ivanova, O. A.; Chagarovskiy, A. O.; Skvortsov, D. A.; Latyshev, G. V.; Trushkov, I. V.; Melnikov, M. Y. *Org. Lett.* **2015**, *17*, 770. (c) Racine, S.; Hegedüs, B.; Scopelliti, R.; Waser, J. *Chem. Eur. J.* **2016**, *22*, 11997.

(11) (a) Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A. II.; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314. (b) Sun, Y.; Yang, G.; Chai, Z.; Mu, X.; Chai, J. *Org. Biomol. Chem.* **2013**, *11*, 7859. (c) Gladow, D.; Reissig, H.-U. *J. Org. Chem.* **2014**, *79*, 4492.

(12) (a) Lebold, T. P.; Leduc, A. B.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3770. (b) Xu, H.; Hu, J. L.; Wang, L.; Liao, S.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 8006. (c) Su, Z.; Qian, S.; Xue, S.; Wang, C. *Org. Biomol. Chem.* **2017**, *15*, 7878. (d) Petzold, M.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2019**, *58*, 6225.

(13) (a) Gewald, K.; Schinke, E.; Böttcher, H. *Chem. Ber.* **1966**, *99*, 94. (b) Furukuwa, M.; Nagato, K.; Kojima, Y.; Hayashi, S. *Chem. Pharm. Bull.* **1972**, *20*, 2262. (c) Hesse, S.; Perspicace, E.; Kirsch, G. *Tetrahedron Lett.* **2007**, *48*, 5261. (d) Huang, Y.; Dömling, A. *Mol. Diversity* **2011**, *15*, 3. (e) Adib, M.; Soheilizad, M.; Daryasaraei, S. R.; Mirzaei, P. *Synlett* **2015**, *26*, 1101. (f) Suzuki, I.; Sakamoto, Y.; Seo, Y.; Ninomaru, Y.; Tokuda, K.; Shibata, I. *J. Org. Chem.* **2020**, *85*, 2759.

(14) (a) Meltzer, H. Y.; Fibiger, H. C. *Neuropsychopharmacology* **1996**, *14*, 83. (b) Li, X.; Conklin, D.; Pan, H. L.; Eisenach, J. C. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 950. (c) Walburger, A.; Koul, A.; Ferrari, G.; Nguyen, L.; Prescianotto-Baschong, C.; Huygen, K.; Klebl, B.; Thompson, C.; Bacher, G.; Pieters, J. *Science* **2004**, *304*, 1800. (d) Podolin, P. L.; Callahan, J. F.; Bolognese, B. J.; Li, Y. H.; Carlson, K.; Davis, T. G.; Mellor, G. W.; Evans, C.; Roshak, A. K. *J. Pharmacol. Exp. Ther.* **2005**, *312*, 373. (e) Kalariya, P. D.; Patel, P. N.; Kavya, P.; Sharma, M.; Garg, P.; Srinivas, R.; Talluri, M. V. N. K. *J. Mass Spectrom.* **2015**, *50*, 1222.

(15) Gopinath, P.; Chandrasekaran, S. *J. Org. Chem.* **2011**, *76*, 700.

(16) Sathishkannan, G.; Srinivasan, K. *Chem. Commun.* **2014**, *50*, 4062.

(17) (a) Augustin, A. U.; Sensse, M.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2017**, *56*, 14293. (b) Augustin, A. U.; Busse, M.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2018**, *20*, 820.

(18) Matsumoto, Y.; Nakatake, D.; Yazaki, R.; Ohshima, T. *Chem. Eur. J.* **2018**, *24*, 6062.

(19) Xie, M.-S.; Zhao, G.-F.; Qin, T.; Suo, Y.-B.; Qu, G.-R.; Guo, H.-M. *Chem. Commun.* **2019**, *55*, 1580.

(20) Jacob, A.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2020**, *22*, 8720.

(21) Andreev, I. A.; Ratmanova, N. K.; Augustin, A. U.; Ivanova, O. A.; Levina, I. I.; Khrustalev, V. N.; Werz, D. B.; Trushkov, I. V. *Angew. Chem. Int. Ed.* **2021**, *60*, in press DOI: 10.1002/anie.202016593.

(22) **General Procedure for the Preparation of 2-Amino-dihydrothiophenes (3)**

Cyclopropane diester **1** (100 μmol, 1.00 equiv), ammonium thiocyanate **2** (200 μmol, 2.00 equiv), and ytterbium triflate (19 mg, 30.0 μmol, 0.30 equiv were dissolved in THF (1 mL). The solution was stirred at 75 °C for 12 h. The solvent was removed, and the residue was purified by flash column chromatography.

Methyl 2-Amino-5-(4-chlorophenyl)-4,5-dihydrothiophene-3-carboxylate (3c)

Colorless solid; yield 50%; mp 146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 2 H), 7.31–7.27 (m, 2 H), 6.08 (s, 2 H), 4.79 (dd, *J* = 8.5, 6.9 Hz, 1 H), 3.69 (s, 3 H), 3.40 (dd, *J* = 14.3, 8.5 Hz, 1 H), 3.10 (dd, *J* = 14.2, 6.9 Hz, 1 H). ^{13}C NMR (156 MHz, $CDCl_3$): δ = 166.5, 161.9, 140.2, 133.5, 128.8, 128.4, 90.4, 50.5, 50.4, 41.4. HRMS (ESI): *m/z* calcd for $C_{12}H_{12}ClNO_2S$ [M + Na]: 292.0175; found: 292.0172.

Methyl 2-Amino-5-(*p*-tolyl)-4,5-dihydrothiophene-3-carboxylate (3e)

Colorless solid; yield 68%; mp 100 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.2 Hz, 2 H), 7.15–7.10 (m, 2 H), 6.06 (s, 2 H), 4.83 (t, *J* = 8.0 Hz, 1 H), 3.68 (s, 3 H), 3.37 (dd, *J* = 14.2, 8.5 Hz, 1 H), 3.14 (dd, *J* = 14.2, 7.6 Hz, 1 H), 2.33 (s, 3 H). ^{13}C NMR (156 MHz, $CDCl_3$): δ = 166.6, 162.3, 138.4, 137.5, 129.3, 127.0, 90.8, 51.3, 50.4, 41.4, 21.0. HRMS (ESI): *m/z* calcd for $C_{13}H_{15}NO_2S$ [M + Na]: 272.0721; found: 272.0717.