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Functionalization of C–H bonds in acetophenone oximes with arylacetic acids and elemental sulfur†

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Fused thieno[3,2-*d*]thiazoles were synthesized *via* a coupling of acetophenone ketoximes, arylacetic acids, and elemental sulfur in the presence of Li_2CO_3 base. Functionalities including chloro, bromo, fluoro, trifluoromethyl, and pyridyl groups were compatible with reaction conditions. High yields and excellent regioselectivities were obtained even if *meta*-substituted ketoxime acetates were used. Ethyl esters of heteroarylacetic acids were competent substrates, which is very rare in the literature. Our method would offer a convenient protocol to afford polyheterocyclic structures from simple substrates.

Introduction

Although carbonyl groups are ubiquitously found in organic compounds, the use of the functionalities to assist the synthesis of complex molecules is hitherto challenging. Exploiting the presence of aldehyde and ketone groups for selective functionalization of C–H bonds appears to be one of the major targets in organic synthesis over the last decades.[1] Among known reports, methods using N-oxime and isosteric groups to facilitate the functionalization of C–H bonds in carbonyl compounds have emerged.[2] Oxime ester and oxime ether directed, metal-catalyzed transformations of arene carbon–hydrogen bonds into other carbon–carbon and carbon–heteroatom bonds are known. Cleavage of the N–O bond in oximes has been leveraged to stabilize high valent metal intermediates, thus promoting the activation of proximal C–H bonds.[3] In 2008, Liebeskind reported a seminal method for copper-catalyzed coupling of vinyl ketoxime esters and vinylboronic acids to afford highly condensed pyridines.[3a] Functionalization of C–H bonds α to ketone in oximes was also feasible, furnishing N-heterocycles.[3c–f] Notably, most of the known examples often use transition metal catalysis.

Functionalization of C–H bonds in acetophenones with elemental sulfur is a promising metal-free synthetic scheme to conveniently afford sulfur-containing aromatics. Given the importance of five-membered heterocycles such as thiazole and thiophene in organic synthesis and functional materials,[4] developing new methods that allow for the use of simple, commercial substrates to obtain S-heterocycles is demanding. Notably, lack of general substrate scopes is still unsolved. Only a few methods for elemental sulfur-promoted, direct transformation of C–H bonds in acetophenones have been reported.[5] Using prefunctionalized ketoximes have expanded the substrate scope.[6] Deng recently described the annulation of acetophenone oxime acetates and aldehydes or methylazaarenes to afford 2-aryl thienothiazoles (Scheme 1).[6a,b] The successes leaned on the use of copper catalysis or a strong base, thus limiting the compatibility of functional groups. Moreover, the reactions often suffered from the mixture of regioisomeric products when oximes derived from *meta*-substituted acetophenones were used. Herein we report a method for annulation of acetophenone oxime acetates and arylacetic acids. Reactions used such a mild base Li_2CO_3 that many functionalities such as bromide or amine are tolerated. Notably, all of the substrates including those have *meta*-substituents afforded single regioisomers. We also attempted coupling of arylacetate esters, since elemental sulfur mediated decarboxylation is known.[7]

Results and discussion

Our first study focused on the reaction of acetophenone oxime **1a** and phenylacetic acid **2a** to yield 2-phenyl benzothienothiazole **3aa**. The reaction was optimized with respect to bases and solvents. The results are shown in Table 1. In general, inorganic bases were more active than organic bases in our conditions (entries 1–7). Both cesium carbonate and lithium carbonate afforded substantial conversion of reactants (entries 4 and 5). Dissimilar to previous studies,[5a,7] DABCO base was inferior to carbonate bases (entry 7). Polar solvents such as DMF, DMAc, and NMP could not be used for the reaction (entries 8–10). Previous studies have often used DMSO solvent for sulfur-mediated, oxime-assisted annulation of C–H bonds,[6b,6d]

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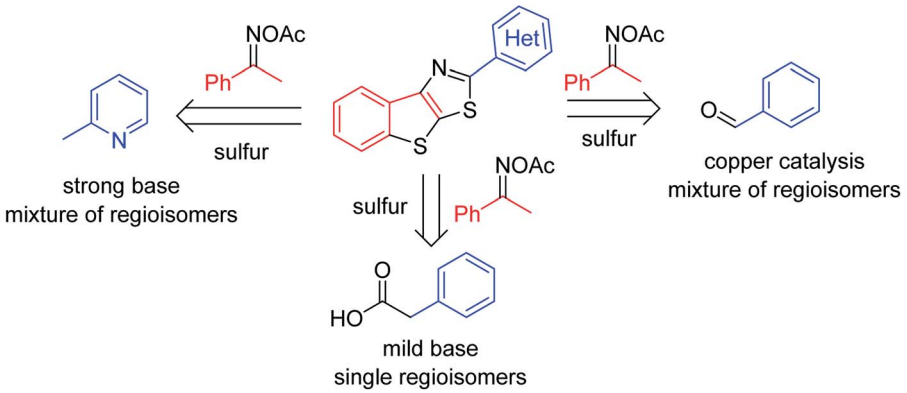


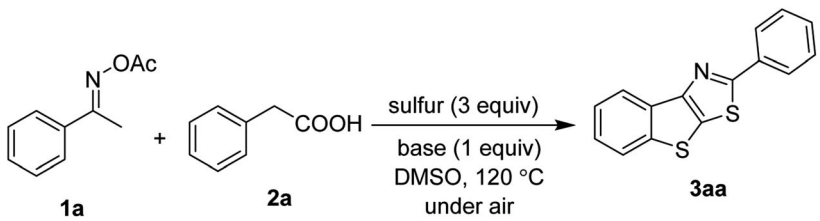
Scheme 1 Retrosynthesis of 2-aryl benzothienothiazoles.

presumably due to oxidative activity. One should be noted that changing the amount of base somewhat impacted the yield of **3aa** (entries 11 and 12). Lastly, a 94% yield of the product was obtained if a diluted reaction mixture was run for 3 h (entry 13).

Scope of arylacetic acids was then investigated and presented in Scheme 2. Electron-rich (**3ab**, **3ae**) and electron-poor (**3ah**, **3ai**) substrates were all active. *ortho*-Substituted phenylacetic acids afforded the thienothiazoles in high yields (**3ac**). It should be noted that the transformation was scalable, up to 2 mmol run without a significant loss of the yield (**3aa**). Halogenated arylacetic acids were competent substrates (**3ag**, **3ah**), thus are useful for further cross-coupling functionalization. Our first attempts to incorporate heteroaryl acetic acids failed to give the thienothiazoles. Fortunately, the uses of ethyl ester derivatives afforded the desired products in good yields. Such decarboxylation coupling of arylacetates has not been discussed in previous studies.[7] In our conditions, ethyl esters of pyridyl acetates were found to be active regardless of the relative position (**3aj**, **3ak**, **3al**).

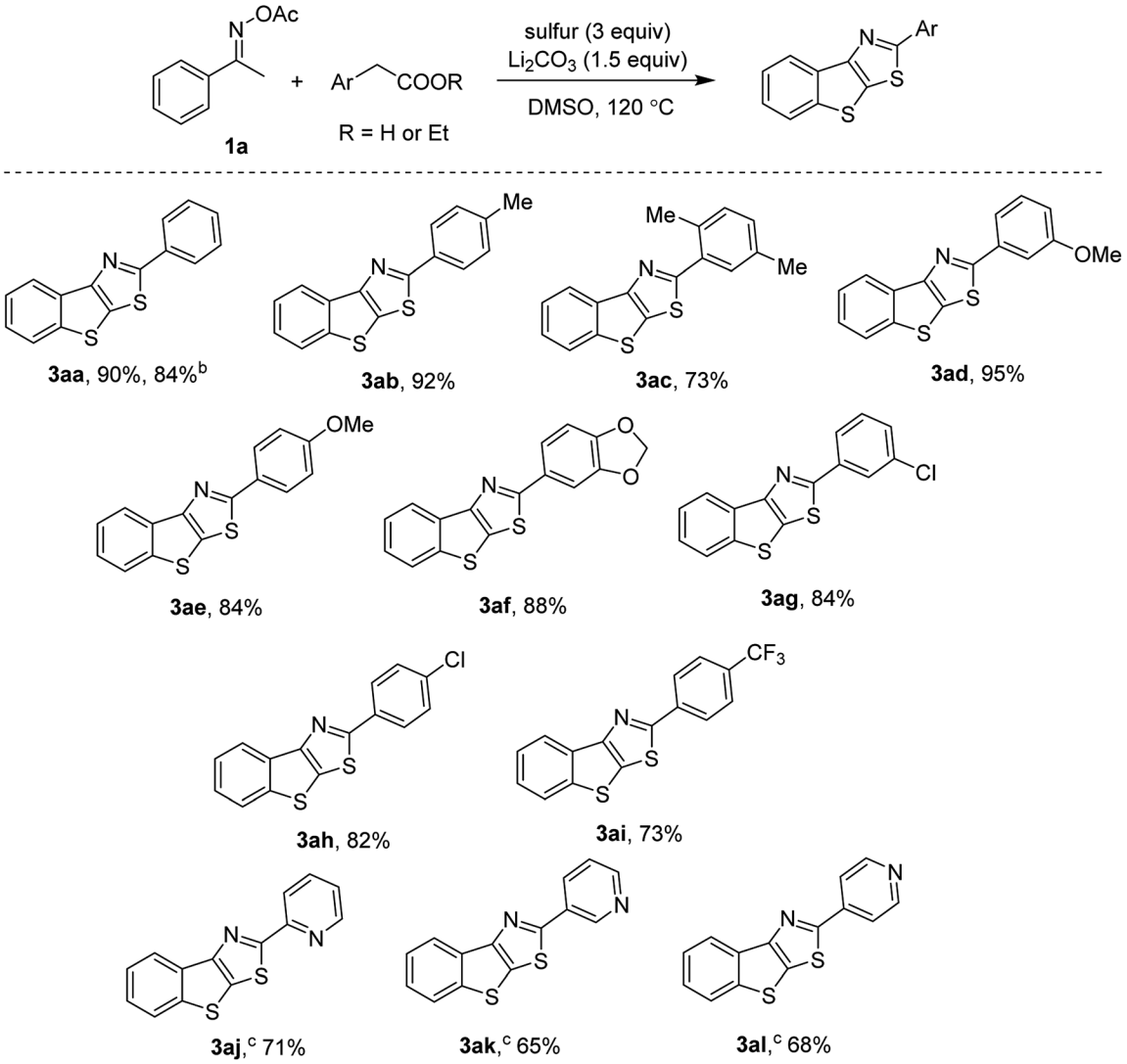
Derivatives of ketoxime acetates could couple with phenylacetic acid **2a** as well. Scope of the methyl oximes is presented in Scheme 3. Our conditions were compatible with many functionalities such as methoxy (**3ca**), chloro (**3da**), bromo (**3ea**, **3fa**) and fluoro (**3ga**) groups. The most acidic C–H bonds were

Table 1 Effect of bases and solvents[a]



Entry	Base	Solvent	Yield of **3aa**, %
1	K_2CO_3	DMSO	52
2	Na_2CO_3	DMSO	78
3	*t*BuOK	DMSO	29
4	Cs_2CO_3	DMSO	81
5	Li_2CO_3	DMSO	84
6	*N*-Methylmorpholine	DMSO	53
7	DABCO	DMSO	78
8	Li_2CO_3	DMF	8
9	Li_2CO_3	DMAc	n.d.
10	Li_2CO_3	NMP	n.d.
11[b]	Li_2CO_3	DMSO	64
12[c]	Li_2CO_3	DMSO	93
13[c,d]	Li_2CO_3	DMSO	94[c]

[a] Oxime acetate **1a** (0.15 mmol), phenylacetic acid **2a** (0.1 mmol), elemental sulfur (0.3 mmol), base (0.1 mmol), solvent (0.5 mL), 120 °C for 6 h under air. Yields of **3aa** are GC yields using diphenyl ether internal standard. [b] 0.05 mmol Li_2CO_3. [c] 0.15 mmol Li_2CO_3. [d] 1 mL DMSO, 3 h. Abbreviation: DABCO = 1,4-diazabicyclo[2.2.2]octane.

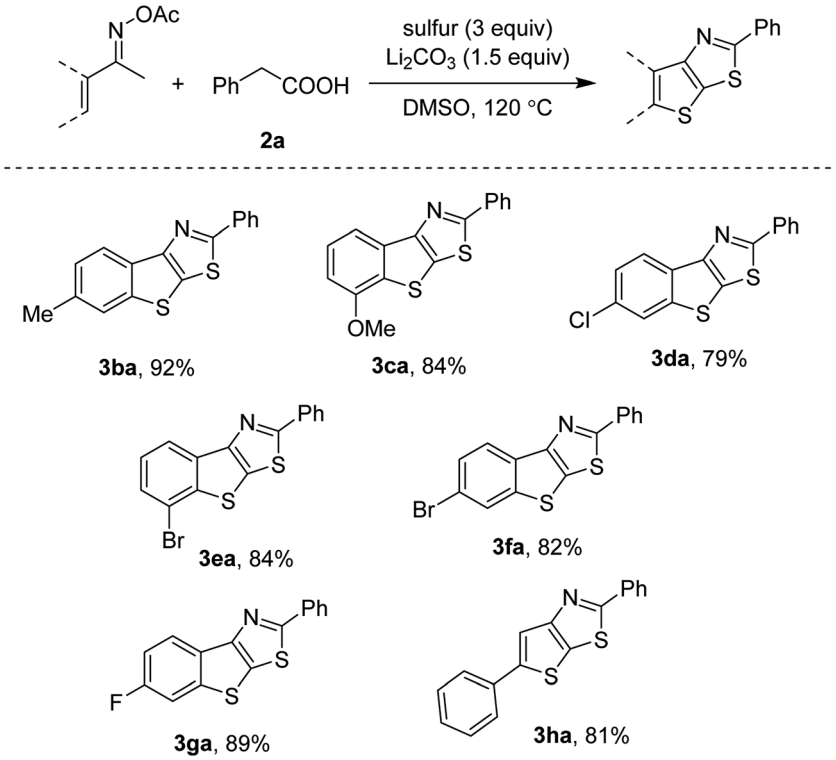


Scheme 2 Annulation of arylacetic acid derivatives[a]. [a]**1a** (0.3 mmol), arylacetic acids (0.2 mmol), sulfur (0.6 mmol, 32 g mol^{-1}), Li_2CO_3 (0.3 mmol), DMSO (1 mL), 120 °C, 3–12 h. Yields are isolated yields. [b]2 mmol scale. [c]Ethyl esters of arylacetic acids (0.2 mmol) were used.

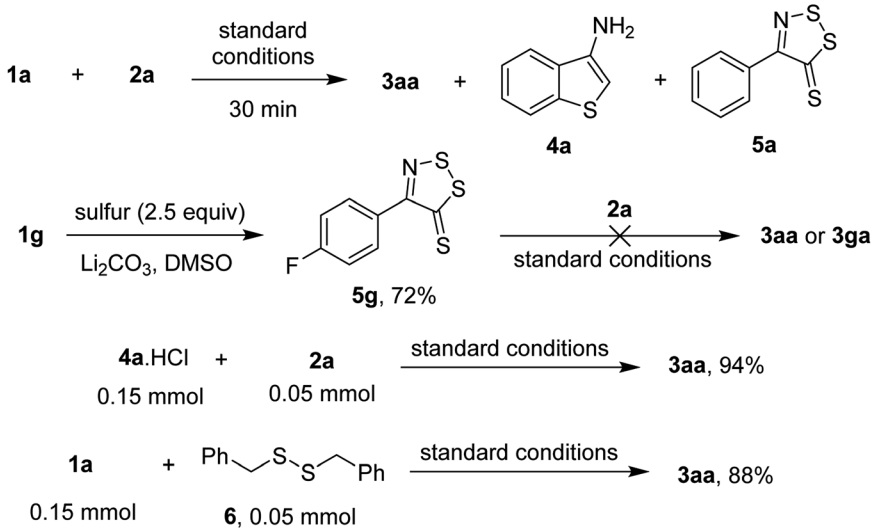
functionalized if *meta*-substituted ketoxime esters were used (**3ca, 3ea**). It should be noted that such substrates often suffered from the forging of regioisomeric mixtures.[6a,b] Since the bromo-substituted acetophenone oximes furnished the thienothiazoles in high yields (**3ea**, **3fa**), our transformation is somewhat useful for further functionalization. Vinyl ketoxime esters were active, thus affording a trisubstituted thienothiazole in 81% yield (**3ha**).

To explore the possible mechanism of the transformation, some control experiments were performed (Scheme 4). Running the reaction of acetophenone oxime ester **1a** and phenylacetic acid **2a** afforded some heterocyclic intermediates such as **4a** and **5a** after 30 min (detected by GC-MS). Since **2a** unsuccessfully coupled with dithiazolethiones, such as **5g**, under standard conditions, the observed species (*i.e.* **5a**) was likely a resting state than an intermediate of the transformation. Meanwhile, reaction of 3-aminobenzothiophene hydrochloride (**4a**·HCl) afforded a quantitative yield of the desired thienothiazole **3aa**. We speculated that the conversion of **1a** to **4a** likely proceeded through a single electron cyclization, since the reaction was slowed down in the presence of radical quenchers such as TEMPO or 1,1-diphenylethylene.[5b] Meanwhile, functionalization of phenylacetic acid was likely triggered by the formation of dibenzyl sulfide intermediate.[7a] The annulation of acetophenone oxime **1a** with disulfide **6** furnished **3aa** in 88% yield which was in comparison with the standard run.

With the information in hands, we briefly proposed a possible mechanism (Scheme 5), commencing with a sulfur-mediated decarboxylative sulfuration of phenylacetic acid **2a** to afford the benzylic polysulfide intermediate **A**. The interaction between $S_3^{\bullet-}$, formed by heating elemental sulfur in DMSO under basic conditions, and ketoxime acetate **1a** delivered the iminosulfur radicals **A** or **B**, by which elimination of a disulfur moiety afforded radical **C** followed by a SET cyclization to furnish 3-aminobenzothiophene **4a**. Such radical cyclization is supported by the results of intermolecular competition



Scheme 3 Scope of ketoxime acetates[a]. [a]Ketoxime acetates (0.3 mmol), phenylacetic acid **2a** (0.2 mmol), sulfur (0.6 mmol, 32 g mol^{-1}), Li_2CO_3 (0.3 mmol), DMSO (1 mL), 120 °C, 3–12 h. Yields are isolated yields.



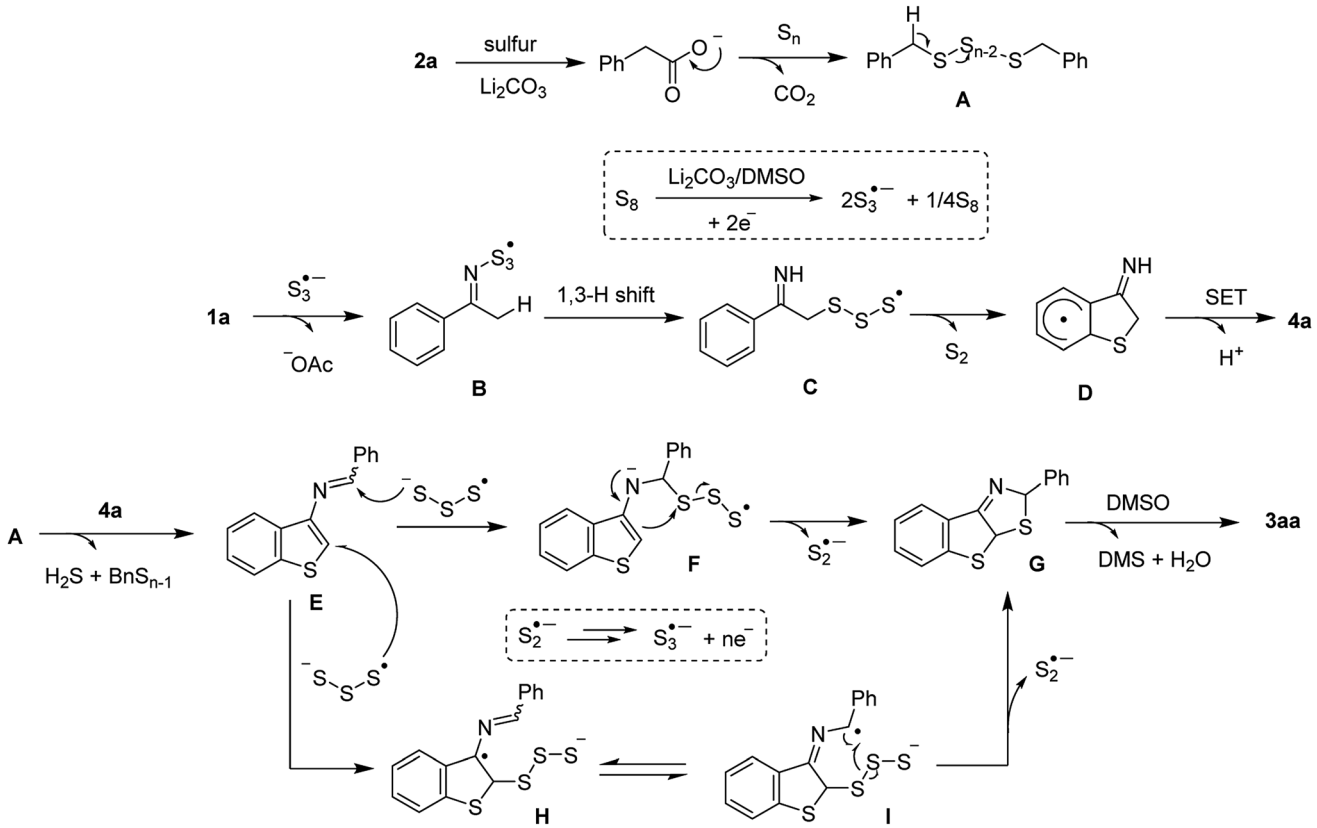
Scheme 4 Mechanistic consideration.

reactions and regioselectivity of *meta*-substituted ketoxime substrates Condensation of this species with the polysulfide **A** then afforded an iminobenzothiophene **E**. An addition of $S_3^{\bullet-}$ to **E** would give the intermediates **F** or **H**. Subsequent cyclizations and cleavages of S–S bond afforded **G** followed by a further oxidation, in the presence of DMSO, to afford **3aa**.

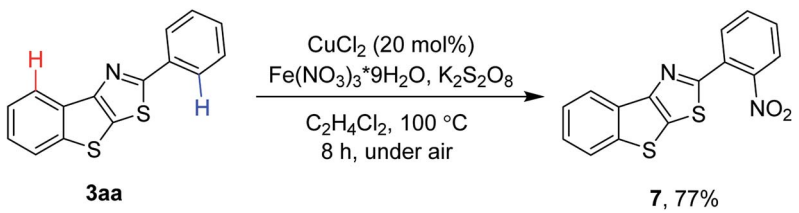
It is perhaps more synthetically useful if late stage functionalization of 2-aryl benzothienothiazoles was possible. The presence of the chelating nitrogen in thiazole would help achieve the regioselective functionalization of C–H bonds (Scheme 6). Thus, thiazole-directed nitration of C–H bonds was achievable in the presence of $CuCl_2$ catalyst and $Fe(NO_3)_3 \cdot 9H_2O$ as a nitrating source, affording the product **7** in 77% yield.[8]

Conclusions

In summary, we have developed a method for synthesis of fused thieno[3,2-*d*]thiazoles. The transformation only required Li_2CO_3



Scheme 5 Plausible mechanism.



Scheme 6 Directed C–H functionalization of 2-phenyl benzothienothiazole[a]. [a]Condition: **3aa** (0.2 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (0.4 mmol), anhydrous $CuCl_2$ (20 mol%), $K_2S_2O_8$ (0.4 mmol), 1,2-dichloroethane (3 mL), 100 °C, 8 h. Yield is isolated yield.

base to promote the coupling of C–H bonds in acetophenone oxime acetates with arylacetic acids and elemental sulfur. A number of functional groups were tolerant of reaction conditions. Reactions of ethyl arylacetates were also feasible, affording heteroaryl thienothiazoles in good yields. Ongoing projects will focus on selective C–H functionalization directed by the thieno-fused thiazole directing group.

Experimental section

General information

All reagents and starting materials were obtained commercially and used as received without any further purification unless otherwise noted. Gas chromatographic (GC) analyses were performed using a Shimadzu GC 2010-Plus equipped with a flame ionization detector (FID) and an SPB-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). The GC yield was calculated using diphenyl ether as the internal standard. GC-MS analyses were analyzed on a Shimadzu GCMS-QP2010Ultra with a ZB-5MS column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). MS spectra were compared with the spectra gathered in the NIST library. The ^{1}H NMR and ^{13}C NMR were recorded on Bruker AV 500 spectrometers using residual solvent peak as a reference. HR-MS spectra were recorded by an Agilent HPLC 1200 Series coupled to Bruker micrOTOF-QII. Molecular mass of elemental sulfur is 32 g mol^{-1}, unless otherwise noted. Compounds **4a**·HCl[6a] and **6** (ref. 7*a*) were synthesized following the known procedures.

General procedure A. To a 8 mL screw-cap vial was added ketoxime acetate (0.3 mmol), arylacetic acid or ester (0.2 mmol), elemental sulfur (19 mg, 0.6 mmol), Li_2CO_3 (22 mg, 0.3 mmol),

and DMSO (1 mL). The vial was tightly capped and heated at 120 °C for 3 h. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with ethyl acetate (5 mL). Organic compounds were extracted with $NaHCO_3$ (5% aqueous solution, 2 × 2.0 mL), dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column chromatography on silica gel with dichloromethane/hexane eluent to give the pure product.

*2-Phenylbenzo[4,5]thieno[3,2-d]thiazole (**3aa**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), phenylacetic acid **2a** (27 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 2 : 1), 48 mg (90%) of a white solid was obtained. This compound is known.[6a] R_f = 0.53 (hexane/dichloromethane = 2 : 1). Mp = 137–139 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.28 (d, J = 7.9 Hz, 1H), 8.08–8.03 (m, 2H), 7.85 (d, J = 8.1 Hz, 1H), 7.53–7.45 (m, 4H), 7.44–7.39 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.6, 156.1, 142.8, 134.0, 130.8, 130.5, 130.3, 129.1, 126.6, 125.1, 125.1, 123.3, 121.8.

*Procedure for the synthesis of **3aa** in 2 mmol scale.* To a 50 mL Schlenk tube was added acetophenone ketoxime acetate **1a** (531 mg, 3 mmol), phenylacetic acid **2a** (272 mg, 2 mmol), elemental sulfur (192 mg, 6 mmol, 32 g mol^{-1}), Li_2CO_3 (222 mg, 3 mmol), and DMSO (10 mL). The tube was sealed with septum and placed into a sand bath preheated to 120 °C. After 6 h, the mixture was cooled to room temperature and poured onto cold water. The precipitates were then extracted into ethyl acetate (3 × 30 mL). The organic phase was washed with saturated $NaHCO_3$ solution (2 × 10 mL) and brine (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (gradient dichloromethane/hexane from 1 : 8 to 1 : 2) to afford the desired product 449 mg of **3aa** (84%) as a white solid. The spectrum information was consistent with that reported in the small scale.

*2-(p-Tolyl)benzo[4,5]thieno[3,2-d]thiazole (**3ab**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), *p*-tolylacetic acid **2b** (30 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 3 : 1), 52 mg (92%) of a white solid was obtained. This compound is known.[6a] R_f = 0.38 (hexane/dichloromethane = 3 : 1). Mp = 167–169 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.26 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.1 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.39 (dd, J = 11.2, 4.1 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.9, 156.0, 142.8, 140.6, 131.4, 130.6, 130.4, 129.8, 126.5, 125.08, 125.06, 123.4, 121.9, 21.5.

*2-(2,5-Dimethylphenyl)benzo[4,5]thieno[3,2-d]thiazole (**3ac**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), 2,5-dimethylphenylacetic acid **2c** (33 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 2 : 1), 43 mg (73%) of a white solid was obtained. R_f = 0.44 (hexane/dichloromethane = 2 : 1). Mp = 174–176 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.23 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.51 (s, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.36–7.32 (m, 1H), 7.16 (d, J = 7.8 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 2.56 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.5, 155.3, 142.7, 135.8, 133.8, 132.9, 131.5, 131.3, 130.65, 130.61, 129.5, 129.1, 125.1, 123.4, 121.9, 20.92, 20.91. HRMS (ESI+) m/z calculated for $C_{17}H_{14}NS_2^+$ $(M + H)^+$ 296.0562, found 296.0564.

*2-(3-Methoxyphenyl)benzo[4,5]thieno[3,2-d]thiazole (**3ad**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), 3-methoxyphenylacetic acid **2d** (33 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 5 : 1), 57 mg (95%) of a white solid was obtained. This compound is known.[6a] Mp = 123–125 °C R_f = 0.26 (hexane/dichloromethane = 5 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.28 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.65–7.62 (m, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.40 (ddd, J = 13.7, 10.4, 4.5 Hz, 2H), 7.01 (dd, J = 8.2, 2.5 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.4, 160.1, 156.1, 142.8, 135.3, 130.9, 130.6, 130.1, 125.17, 125.13, 123.4, 121.9, 119.2, 116.5, 111.4, 55.5.

*2-(4-Methoxyphenyl)benzo[4,5]thieno[3,2-d]thiazole (**3ae**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), 4-methoxyphenylacetic acid **2e** (33 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 2 : 1), 50 mg (84%) of a white solid was obtained. This compound is known.[6a] Mp = 124–126 °C. R_f = 0.27 (hexane/dichloromethane = 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.26 (d, J = 7.9 Hz, 1H), 8.03–7.95 (m, 2H), 7.84 (d, J = 8.1 Hz, 1H), 7.53–7.47 (m, 1H), 7.43–7.38 (m, 1H), 7.03–6.98 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.6, 161.4, 155.9, 142.8, 130.6, 129.9, 128.1, 127.0, 125.05, 124.99, 123.4, 121.8, 114.4, 55.9.

*2-(Benzo[d][1,3]dioxol-5-yl)benzo[4,5]thieno[3,2-d]thiazole (**3af**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), 3,4-(methylenedioxyphenyl)acetic acid **2f** (36 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 1 : 1), 55 mg (88%) of a white solid was obtained. R_f = 0.31 (hexane/dichloromethane = 1 : 1). Mp = 140–142 °C ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.29 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.08 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.3, 155.7, 149.6, 148.4, 142.8, 130.5, 130.1, 128.4, 125.11, 125.09, 123.4, 121.9, 121.2, 108.7, 106.9, 101.7. HRMS (ESI+) m/z calculated for $C_{16}H_{10}NO_2S_2^+$ $(M + H)^+$ 312.0147, found 312.0149.

*2-(3-Chlorophenyl)benzo[4,5]thieno[3,2-d]thiazole (**3ag**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), 3-chlorophenylacetic acid **2g** (34 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 2 : 1), 51 mg (84%) of a white solid was obtained. This compound is known.[6a] Mp = 162–164 °C. R_f = 0.45 (hexane/dichloromethane = 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.31 (d, J = 7.8 Hz, 1H), 8.11 (s, 1H), 7.96–7.92 (m, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.49–7.44 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 168.7, 156.2, 142.9, 135.6, 135.2, 131.4, 130.4, 130.3, 130.2, 126.5, 125.3, 124.7, 123.4, 121.9. One carbon signal could not be located.

*2-(4-Chlorophenyl)benzo[4,5]thieno[3,2-d]thiazole (**3ah**, Scheme 2): following the general procedure A.* Acetophenone oxime

acetate **1a** (53 mg, 0.3 mmol), 4-chlorophenylacetic acid **2h** (34 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 2 : 1), 50 mg (82%) of a white solid was obtained. This compound is known.[6a] Mp = 160–161 °C. R_f = 0.48 (hexane/dichloromethane = 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.19 (d, J = 7.8 Hz, 1H), 7.94–7.89 (m, 2H), 7.77 (d, J = 8.1 Hz, 1H), 7.46–7.41 (m, 1H), 7.41–7.32 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 169.1, 156.2, 142.8, 136.2, 132.5, 131.1, 130.4, 129.3, 127.7, 125.3, 125.2, 123.4, 121.9.

*2-(4-Trifluoromethylphenyl)benzo[4,5]thieno[3,2-d]thiazole (**3ai**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), 4-(trifluoromethyl)phenylacetic acid **2i** (41 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 3 : 1), 49 mg (73%) of a white solid was obtained. This compound is known.[6c] Mp = 124–126 °C. R_f = 0.37 (hexane/dichloromethane = 3 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.28 (d, J = 8.0 Hz, 1H), 8.17 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 168.4, 156.5, 142.9, 137.1, 131.9, 130.5 (q, J = 276.9 Hz), 128.1, 126.7, 126.1 (q, J = 3.7 Hz), 125.5, 125.3, 124.9, 123.4, 122.8, 121.9.

*2-(Pyridin-2-yl)benzo[4,5]thieno[3,2-d]thiazole (**3aj**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), ethyl 2-pyridylacetate **2j** (33 mg, 0.2 mmol). After column chromatography (gradient hexane/ethyl acetate from 10 : 1 to 2 : 1), 38 mg (71%) of a white solid was obtained. This compound is known.[6a] Mp = 194–196 °C. R_f = 0.63 (hexane/ethyl acetate = 2 : 1). ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 8.70 (d, J = 3.8 Hz, 1.0 Hz), 8.27 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 7.6 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.04 (t, J = 7.0 Hz, 1H), 7.59–7.50 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ 171.9, 155.7, 151.1, 150.3, 143.2, 138.4, 134.6, 130.4, 125.9, 125.91, 125.87, 124.5, 121.4, 119.7.

*2-(Pyridin-3-yl)benzo[4,5]thieno[3,2-d]thiazole (**3ak**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), ethyl 3-pyridylacetate **2k** (33 mg, 0.2 mmol). After column chromatography (gradient hexane/ethyl acetate from 10 : 1 to 2 : 1), 35 mg (65%) of a white solid was obtained. This compound is known.[6c] R_f = 0.57 (hexane/ethyl acetate = 2 : 1). Mp = 122–124 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.21 (bs, 1H), 8.63 (bs, 1H), 8.29 (d, J = 7.8 Hz, 1H), 8.21 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.40–7.34 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.5, 156.5, 150.4, 147.2, 142.9, 134.0, 131.7, 130.3, 125.5, 125.3, 124.0, 123.5, 122.0. One carbon signal could not be located.

*2-(Pyridin-4-yl)benzo[4,5]thieno[3,2-d]thiazole (**3al**, Scheme 2): following the general procedure A.* Acetophenone oxime acetate **1a** (53 mg, 0.3 mmol), ethyl 4-pyridylacetate **2l** (33 mg, 0.2 mmol). After column chromatography (gradient hexane/ethyl acetate from 4 : 1 to 1 : 1), 36 mg (68%) of a yellow solid was obtained. This compound is known.[6a] R_f = 0.64 (hexane/ethyl acetate = 1 : 1). Mp = 170–172 °C. ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 8.76 (dd, J = 4.5, 1.5 Hz, 2H), 8.20 (d, J = 7.7 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.00 (dd, J = 4.5, 1.5 Hz, 2H), 7.57 (td, J = 7.5, 1.0 Hz, 1H), 7.51 (td, J = 7.5 Hz, 1.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ 167.8, 155.7, 151.3, 143.4, 140.4, 134.4, 130.1, 126.2, 125.9, 124.6, 121.6, 120.4.

*6-Methyl-2-phenylbenzo[4,5]thieno[3,2-d]thiazole (**3ba**, Scheme 3): following the general procedure A.* 4-Methylacetophenone oxime acetate **1b** (57 mg, 0.3 mmol), phenylacetic acid **2a** (27 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 2 : 1), 52 mg (92%) of a white solid was obtained. This compound is known.[6a] R_f = 0.41 (hexane/dichloromethane = 2 : 1). Mp = 126–128 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.15 (d, J = 8.1 Hz, 1H), 8.04 (dd, J = 8.0, 1.4 Hz, 2H), 7.63 (s, 1H), 7.47 (tdd, J = 6.9, 4.6, 2.5 Hz, 3H), 7.32 (d, J = 8.1 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.4, 156.1, 143.1, 135.3, 134.1, 130.2, 129.8, 129.1, 128.3, 126.7, 126.6, 123.3, 121.4, 21.6.

*5-Methoxy-2-phenylbenzo[4,5]thieno[3,2-d]thiazole (**3ca**, Scheme 3): following the general procedure A.* 3-Methoxyacetophenone oxime acetate **1c** (62 mg, 0.3 mmol), phenylacetic acid **2a** (27 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 1 : 1), 50 mg (84%) of a white solid was obtained. This compound is known.[6a] R_f = 0.42 (hexane/dichloromethane = 1 : 1). Mp = 132–134 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.00 (dd, J = 8.0 Hz, 1.5 Hz, 2H), 7.87 (d, J = 8.0 Hz, 1H), 7.44–7.38 (m, 4H), 6.83 (d, J = 8.0 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.7, 154.3, 149.6, 133.8, 131.9, 131.4, 130.9, 130.4, 129.1, 126.6, 126.5, 114.6, 105.5, 55.7.

*6-Chloro-2-phenylbenzo[4,5]thieno[3,2-d]thiazole (**3da**, Scheme 3): following the general procedure A.* 4-Chloroacetophenone oxime acetate **1d** (63 mg, 0.3 mmol), phenylacetic acid **2a** (27 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 2 : 1), 48 mg (79%) of a white solid was obtained. This compound is known.[6a] Mp = 186–188 °C. R_f = 0.52 (hexane/dichloromethane = 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.12 (d, J = 8.4 Hz, 1H), 7.98 (dd, J = 7.8, 1.6 Hz, 2H), 7.76 (d, J = 1.7 Hz, 1H), 7.44–7.39 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 171.2, 155.3, 143.7, 133.8, 131.1, 131.0, 130.5, 129.2, 129.0, 126.7, 125.9, 123.0, 122.5.

*5-Bromo-2-phenylbenzo[4,5]thieno[3,2-d]thiazole (**3ea**, Scheme 3): following the general procedure A.* 3-Bromoacetophenone oxime acetate **1e** (77 mg, 0.3 mmol), phenylacetic acid **2a** (27 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 2 : 1), 58 mg (84%) of a white solid was obtained. This compound is known.[6a] Mp = 176–178 °C. R_f = 0.48 (hexane/dichloromethane = 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.28 (d, J = 7.8 Hz, 1H), 8.08 (dd, J = 7.7, 1.5 Hz, 2H), 7.60 (d, J = 7.7 Hz, 1H), 7.56–7.50 (m, 3H), 7.44 (t, J = 7.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 171.0, 144.1, 133.8, 132.1, 131.5, 130.6, 129.2, 127.9, 126.7, 126.5, 120.7, 116.4. One carbon signal could not be located.

*6-Bromo-2-phenylbenzo[4,5]thieno[3,2-d]thiazole (**3fa**, Scheme 3): following the general procedure A.* 4-Bromoacetophenone oxime acetate **1f** (77 mg, 0.3 mmol), phenylacetic acid **2a** (27 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 2 : 1), 57 mg (82%) of a white solid was obtained. This compound is known.[6a] Mp = 188–190 °C. R_f = 0.42 (hexane/dichloromethane = 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.55 (d, J = 7.8 Hz, 2H), 8.15 (d, J = 8.4 Hz, 1H),

7.79 (s, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.44 (dd, J = 8.4, 1.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.1, 156.2, 144.1, 138.8, 134.8, 133.9, 132.2, 131.2, 129.0, 128.5, 126.3, 123.2, 122.8.

*6-Fluoro-2-phenylbenzo[4,5]thieno[3,2-d]thiazole (**3ga**, Scheme 3): following the general procedure A.* 4-Fluoroacetophenone oxime acetate **1g** (59 mg, 0.3 mmol), phenylacetic acid **2a** (27 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 2 : 1), 51 mg (89%) of a white solid was obtained. This compound is known.[6c] Mp = 140–142 °C. R_f = 0.35 (hexane/dichloromethane = 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.21 (dd, J = 9.0 Hz, 5.0 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1.5 Hz, 2H), 7.53–7.46 (m, 3H), 7.25 (d, J = 10 Hz, 2.5 Hz, 1H, overlapping with $CHCl_3$ signal). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 171.0, 160.8 (d, $^1J_{C-F}$ = 245.6 Hz), 155.3, 143.6 (d, $^3J_{C-F}$ = 10.0 Hz), 133.9, 130.4, 129.8 (d, $^4J_{C-F}$ = 2.9 Hz), 129.1, 127.1, 126.6, 122.7 (d, $^3J_{C-F}$ = 9.2 Hz), 113.8 (d, $^2J_{C-F}$ = 23.9 Hz), 110.0 (d, $^2J_{C-F}$ = 25.8 Hz).

*2,5-Diphenylthieno[3,2-d]thiazole (**3ha**, Scheme 3): following the general procedure A.* (2*E*,3*E*)-4-Phenylbut-3-en-2-one *O*-acetyl oxime **1h** (61 mg, 0.3 mmol), phenylacetic acid **2a** (27 mg, 0.2 mmol). After column chromatography (hexane/dichloromethane = 4 : 1), 47 mg (81%) of a white solid was obtained. This compound is known.[6a] Mp = 195–197 °C. R_f = 0.31 (hexane/dichloromethane = 4 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.92 (dd, J = 8.0 Hz, 1.0 Hz, 2H), 7.63 (s, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.42–7.34 (m, 5H), 7.27 (t, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.7, 161.6, 147.8, 134.4, 133.8, 130.5, 129.5, 129.1, 128.2, 126.7, 125.8, 114.8. One carbon signal could not be located.

*4-(4-Fluorophenyl)-5H-1,2,3-dithiazole-5-thione (**5g**, Scheme 4).* To an 8 mL screw-cap vial was added 4-fluoroacetophenone ketoxime acetate **1g** (71 mg, 0.4 mmol), Li_2CO_3 (15 mg, 0.2 mmol), elemental sulfur (32 mg, 1 mmol), and DMSO (0.5 mL). The vial was stirred at 120 °C for 12 h. Upon completion of the reaction, the mixture was cooled to room temperature, and $NaHCO_3$ (5% aqueous solution, 2 mL) was added. The organic components were consequently extracted into ethyl acetate (3 × 2 mL), washed with brine (2 × 1 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/dichloromethane 10 : 1) to afford 66 mg (72%) of a brown solid. This compound is known.[9] R_f = 0.72 (hexane/dichloromethane 2 : 1). Mp = 150–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.98–7.95 (m, 2H), 7.16–7.12 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 207.9, 166.7, 164.0 (d, $^1J_{C-F}$ = 251.9 Hz), 131.7 (d, $^3J_{C-F}$ = 8.5 Hz), 127.5 (d, $^4J_{C-F}$ = 3.5 Hz), 115.2 (d, $^2J_{C-F}$ = 21.7 Hz).

2-(2-Nitrophenyl)benzo[4,5]thieno[3,2-d]thiazole (7, Scheme 6). To a 25 mL Schlenk tube was added 2-phenylbenzo[4,5]thieno[3,2-*d*]thiazole (53 mg, 0.2 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (162 mg, 0.4 mmol), anhydrous $CuCl_2$ (5.4 mg, 0.04 mmol), $K_2S_2O_8$ (108 mg, 0.4 mmol), and 1,2-dichloroethane (3 mL). The reaction mixture was stirred at 100 °C for 8 h in an oil bath. After cooling to room temperature, the mixture was diluted with chloroform (15 mL) and filtered through a short pad of silica gel. The organic layer was washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. After column chromatography (hexane/dichloromethane 1 : 1), 48 mg (77%) of a yellow solid was obtained. R_f = 0.2 (hexane/dichloromethane 1 : 1). Mp = 187–189 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.21 (dd, J = 7.5, 1.5 Hz, 1H), 7.86 (dd, J = 8.0, 1.0 Hz, 1H), 7.77 (dd, J = 7.5 Hz, 1.5 Hz, 1H), 7.74 (dd, J = 8.0, 1.0 Hz, 1H), 7.49–7.42 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 169.1, 155.2, 140.8, 135.4, 135.3, 132.9, 131.7, 131.5, 130.4, 126.5, 125.7, 124.7, 124.3, 121.8. HRMS (ESI+) *m*/*z* calculated for $C_{15}H_9N_2O_2S_2^+$ $(M + H)^+$ 313.0100, found 313.0104. One carbon signal could not be located.

Conflicts of interest

The authors declare no competing financial interest.

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