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Homo- and Heteroannulation of sp^3 C−H Bonds in Acetophenones for Divergent Synthesis of Thienothiazoles

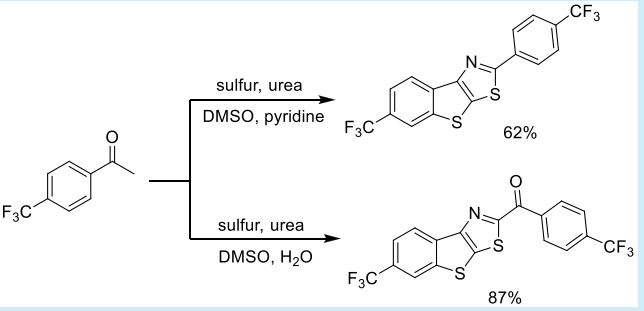
Phuc H. Pham,[†] Khang X. Nguyen,[†] Hoai T. B. Pham,[†,‡] Tung T. Nguyen,*[,†] and Nam T. S. Phan*[,†]

[†]Faculty of Chemical Engineering, HCMC University of Technology, VNU-HCM, 268 Ly Thuong Kiet, District 10, Ho Chi Minh City, Vietnam

[‡]Department of Chemistry, University of Colorado Denver, Denver, Colorado 80204, United States

Supporting Information

ABSTRACT: A synthesis of fused thieno[3,2-*d*]thiazoles via direct functionalization of C(sp^3)−H bonds in acetophenones was reported. The transformation is divergent to afford either 2-phenylbenzo[4,5]thieno[3,2-*d*]thiazoles or benzo[4,5]-thieno[3,2-*d*]thiazol-2-yl(phenyl)methanones. Cross-coupling of acetophenones with C−H bonds in phenylacetic acids, methylazaarenes, and aldehydes was also feasible. Excellent tolerance of functionalities was observed. Our method marks a rare functionalization of C(sp^3)−H bonds in acetophenones to obtain heterocycles in the absence of prefunctionalized oxime esters.



Functionalization of sp^3 C−H bonds α to an aldehyde or ketone group is a fundamental target in organic synthesis.[1] The successes often require the use of strong bases and/or relatively scarce second- or third-row transition metals. Oxime functionality is possibly considered as a masked carbonyl, thus able to help activate the sp^3 C−H bonds under relatively milder conditions.[2] Notably, early examples of ketoxime-assisted, C−H functionalization focused on the synthesis of *N*-heterocycles using copper catalysis. Incorporation of nitrogen atoms in oxime carboxylates into pyridines, pyrroles, and other isosteric, fused heterocycles is favorable due to the formation of an active imine catalyzed by a decomposition of the high valent copper-imine intermediate.[2a] A diastereoselective coupling of oxime acetates and electrophilic ketones has been reported.[2g] Transition metal catalyzed, directed cleavage of sp^2 C−H bonds in carbonyl compounds is well precedented.[3] Meanwhile, oxime-assisted activation of α C(sp^3)−H bonds for synthesis of heterocycles with two heteroatoms is much less developed. Only a few methods for functionalization of α C−H bonds in ketoxime carboxylates with elemental sulfur to afford *S*,*N*-heterocycles is known.[4] Deng and co-workers described a copper-catalyzed annulation of acetophenone oximes, benzaldehydes, and elemental sulfur to derive thienothiazoles.[4a] If oxime acetates of 1-tetralones were used, benzothiazoles were obtained, presumably after oxidative aromatization.[4b] The scope of the substrates that could couple with oximes was later expanded to phenyl-acetylenes and picolines.[4c,d] Despite certain advancements, most of the known examples require the two-step preparation of oxime carboxylates. Perhaps it would be more beneficial if ketones are directly used. The approach somewhat shortens the synthetic schemes, since prefunctionalization of starting materials is thwarted. Our aim is to synthesize thiazoles or isosteres from acetophenones, elemental sulfur, and a nitrogen source since sulfur-mediated activation of α C−H bonds in ketones is known.[5]

Thiophenes and thiazoles are ubiquitously found in a wide range of biologically active natural products, pharmaceutical molecules, agricultural chemicals, and functional organic materials.[6] More importantly, thiophene-fused heteroaromatic systems have many important applications in material science and engineering (Scheme 1). We report herein the homocoupling of acetophenones in the presence of urea and elemental sulfur to afford fused thieno[3,2-*d*]thiazoles that have conventionally required multistep synthesis. Attempts to couple acetophenones with C−H bonds in phenylacetic acids, 2-alkylazaarenes, or aromatic aldehydes were also successful. Our method potentially serves as a general example for metal-free functionalization of sp^3 C−H bonds α to ketones without the use of functionalized oxime carboxylates.

Our investigation started with a coupling of acetophenone (**1a**), elemental sulfur, and urea. Based on previous studies,[4,5] DMSO solvent was chosen for the reaction. A roughly 80% yield of two products in a 6:1 molar ratio was detected (Table 1, entry 1). The major product, 2-phenylbenzo[4,5]thieno[3,2-*d*]thiazole (**2a**), was possibly formed through a decarboxylation. In the presence of organic bases, the product distribution was changed. The best yield of the minor product, 2-benzoyl thienothiazole **3a**, was obtained if a catalytic amount

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Scheme 1. Synthesis of Thiophene-Fused Heterocycles

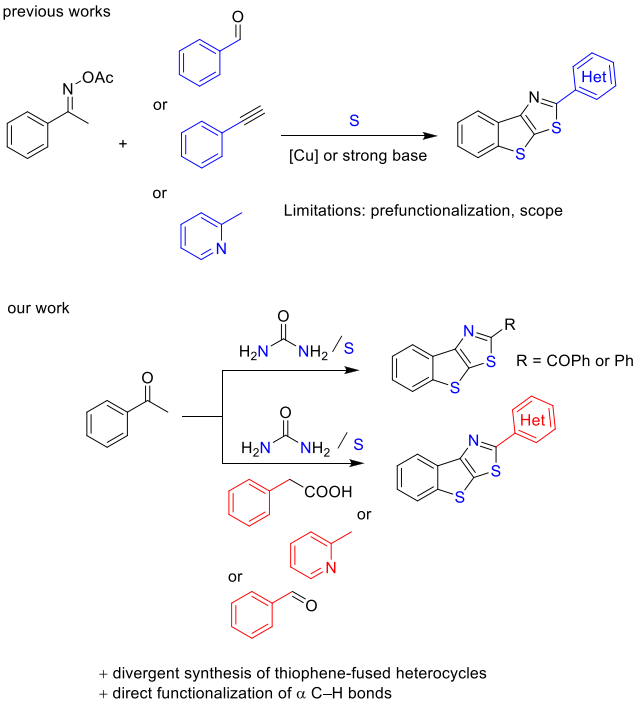
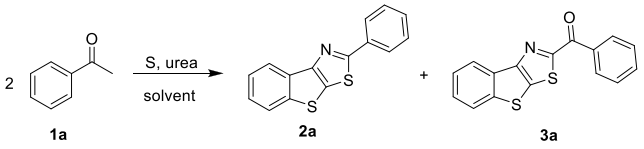


Table 1. Optimization of Reaction Conditions[a]

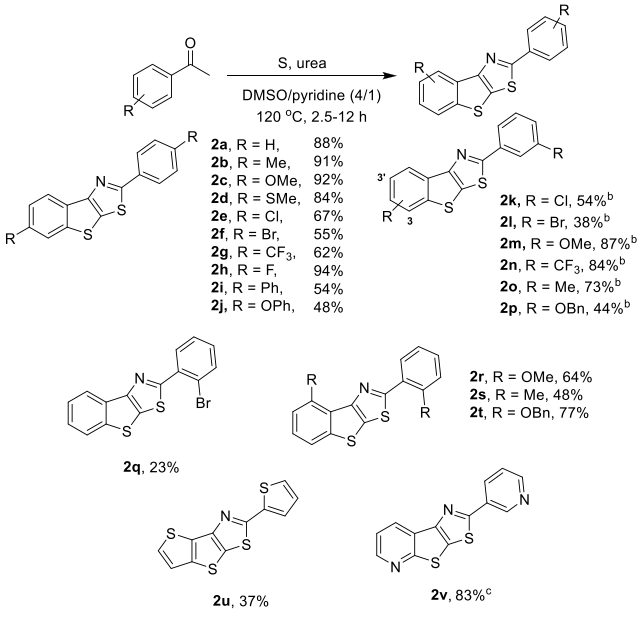


entry	solvent	additive	yield of **2a**, %	yield of **3a**, %
1[b]	DMSO	–	68	11
2[b]	DMSO	DABCO	58	30
3[b]	DMSO	piperidine	47	9
4[b]	DMSO	*N*-methylpiperazine	36	15
5[c]	DMSO	–	83	6
6[d]	DMSO–pyridine	–	94	trace
7[e]	DMSO–H_2O	DABCO	trace	86
8[f]	DMSO–H_2O	–	25	37

[a]Acetophenone **1a** (0.2 mmol), additive (0.02 mmol), 120 °C under air for 12 h. Yields are GC yields using diphenyl ether as the internal standard. Please see Supporting Information for details. [b]Urea (0.8 mmol), sulfur (0.4 mmol), DMSO (0.2 mL). [c]Urea (0.6 mmol), sulfur (0.25 mmol). [d]Urea (0.6 mmol), sulfur (0.32 mmol), DMSO/pyridine (v/v 4:1, total 0.25 mL), 2.5 h. [e]Urea (0.15 mmol), sulfur (0.7 mmol), DMSO/H_2O (v/v 20:1, total 1.05 mL). [f]Urea (0.6 mmol), sulfur (0.25 mmol), DMSO/H_2O (v/v 2:1, total 0.3 mL). Abbreviation: DABCO = 1,4-diazabicyclo[2.2.2]octane.

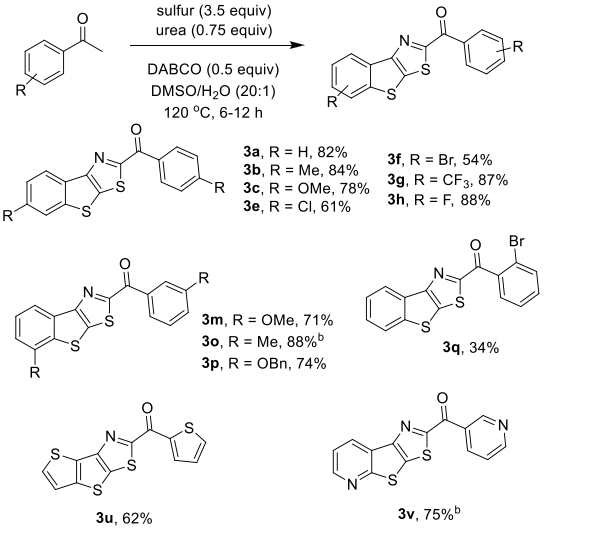
of DABCO was added (entry 2). Running the reaction in the presence of secondary amines gave sluggish mixtures (entries 3 and 4). Decreasing the amount of urea and sulfur afforded a better yield of product **2a** (entry 5). Using cosolvents also impacted the yields of products. Full conversion of acetophenone to the product **2a** was obtained if a 4:1 solvent mixture of DMSO/pyridine was used (entry 6). On the other hand, the reaction proceeded to afford an 86% yield of **3a** in wet DMSO and catalytic DABCO (entry 7). Lastly, omitting DABCO gave a 1:1 molar ratio of the products, proving the importance of the base with regard to diversifying the reaction pathways (entry 8).

Scheme 2. Synthesis of 2-Arylbenzo[4,5]-thieno-[3,2-*d*]-thiazoles[a]



[a]Acetophenones (0.2 mmol), urea (0.6 mmol), sulfur (0.31 mmol, 32 g/mol), DMSO (0.2 mL), pyridine (0.05 mL), 120 °C. Yields are isolated yields. Please see the Supporting Information for details. [b]Isolated as a regioisomer mixture at C3 and C3′. [c]Isolated as a 8:1 regioisomeric product.

Scheme 3. Synthesis of Benzo[4,5]thieno[3,2-*d*]thiazol-2-yl(phenyl)-methanones[a]



[a]Acetophenones (0.2 mmol), urea (0.15 mmol), sulfur (0.7 mmol, 32 g/mol), DABCO (0.1 mmol), DMSO (1 mL), H_2O (0.05 mL), 120 °C. Yields are isolated yields. [b]Isolated as a regioisomeric product.

The reaction scope with respect to the synthesis of 2-aryl thienothiazoles is presented in Scheme 2. The conditions were compatible with many functionalities such as methoxy (**2c**, **2m**), methylthio (**2d**), halogen (**2e**, **2f**, and **2h**), trifluoromethyl (**2g**), and protected phenol (**2j**, **2p**, **2t**) groups. Similar to the copper-catalyzed system,[4a] *meta*-substituted

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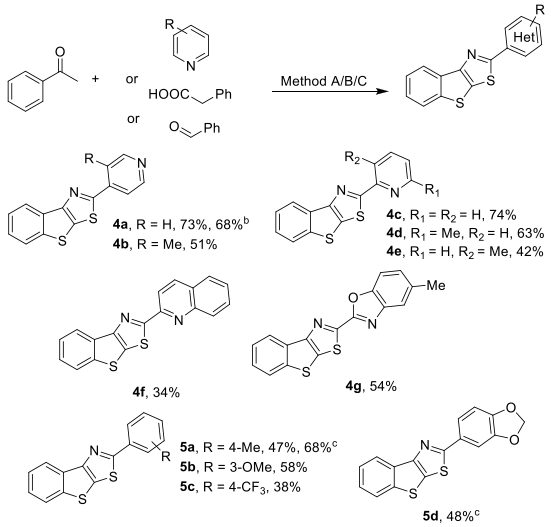
Scheme 4. Coupling of Acetophenone and Methylazaarenes, Phenylacetic Acids, and Aromatic Aldehydes[a]



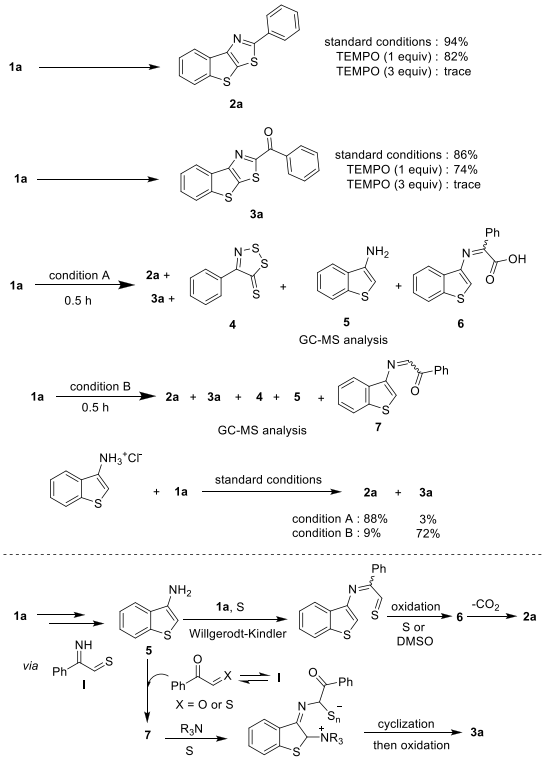
[a]Method A: Acetophenone (0.1 mmol), 2- or 4-methylazaarenes (0.2 mmol), urea (0.15 mmol), sulfur (0.3 mmol, 32 g/mol), NaOAc (0.1 mmol), DMSO (1 mL), 120 °C for 12 h. Method B: Acetophenone (0.4 mmol), phenylacetic acids (0.2 mmol), NH_4OAc (0.4 mmol), sulfur (0.7 mmol, 32 g/mol), DABCO (0.2 mmol), DMSO (1 mL), 120 °C for 12 h. Method C: Acetophenone (0.2 mmol), urea (0.2 mmol), DMSO (0.5 mL), 80 °C for 0.5 h, then aldehyde (0.1 mmol), sulfur (0.5 mmol, 32 g/mol), 120 °C for 12 h. Yields are isolated yields. Please see the Supporting Information for details. [b]4-Ethylpyridine was used. [c]Method C was used to afford the product.

acetophenones afforded the regioisomeric products (**2k**–**2m**, **2q**). Substituents *ortho* to the ketone group apart from the bromo group successfully coupled with elemental sulfur and urea (**2r**, **2s**, **2t**). Nucleophilic substitution of sulfur possibly occurred,[7] thus yielding a monobromo derivative of 2-phenylbenzo[4,5]thieno[3,2-*d*]thiazole when 2′-bromoacetophenone was used (**2q**). The reaction of thiophenyl- and pyridyl-methyl ketones gave tetraheterocyclic products in moderate to good yields (**2u** and **2v**).

Synthesis of benzo[4,5]thieno[3,2-*d*]thiazol-2-yl(phenyl)-methanone was next studied. The scope of the acetophenones is described in Scheme 3. Notably, 50 mol % of DABCO was used to completely convert all of the acetophenones. Good yields of the products were obtained regardless of electronic properties of acetophenones. Functional groups such as halogens (**3e**, **3f**, **3h**), trifluoromethyl (**3g**), and protected alcohol (**3q**) were tolerant of reaction conditions. *meta*-Substituted acetophenones were competent substrates (**3m**, **3o**, **3p**). However, reactions of 2-acetylaryl halides failed to yield the 2-benzoyl thienothiazoles.[8] The homocoupling of 2′-bromoacetophenone, elemental sulfur, and urea afforded a debrominative product in low yield (**3q**). Heteroaryl ketones were capable of furnishing the products in good yields (**3u** and **3v**). It should be noted that the transformations were easy to scale up while still furnishing the thienothiazoles in good yields.[8]

It is perhaps more general if our methods are applied for cross-coupling of sp^3 C–H bonds. Previous studies reported examples for using elemental sulfur to functionalize sp^3 C–H bonds in phenylacetic acids and 2-/4-methylazaarenes.[4d] To our delight, coupling of acetophenones and activated C–H bonds is possible. The scope of substrates is shown in Scheme 4. Moderate to good yields of 2-hetarylbenzo[4,5]thieno[3,2-*d*]thiazoles were obtained if 2-picoline and isosteres were used. 2,6-Lutidine coupled with acetophenone to afford a single isomer derived from monofunctionalization (**4d**). Functionalization of sp^3 C–H bonds in 4-ethylpyridine occurred with a loss of alkyl carbon. The conditions were compatible to convert 2-methylbenzoxazole, which was unactive in the presence of strong base,[4d] to the product (**4g**). Methylene C–H bonds in phenylacetic acids could also be used to couple with acetophenone. Reactions required ammonium acetate as the nitrogen source, affording the thienothiazoles in moderate yields (**5a**–**5c**). Using modified reaction conditions, attempts to couple acetophenones and aromatic aldehydes were successful (**5a** and **5e**).

Scheme 5. Mechanistic Considerations and Possible Mechanism[a]



[a]Condition A: acetophenone (0.2 mmol), urea (3 equiv), sulfur (0.15 equiv), DMSO/pyridine (v/v 4:1), 120 °C. Condition B: acetophenone (0.2 mmol), urea (0.75 equiv), sulfur (3.5 equiv), DABCO (0.5 equiv), DMSO/H_2O (v/v 20:1), 120 °C.

Some experiments related to mechanistic consideration are shown in Scheme 5. Adding a radical quencher such as TEMPO to the reaction mixtures decreased the yields. During the reaction courses, some intermediates could be detected, such as a dithiazole thione **4**, 3-aminobenzothiophene **5**, and its imine derivatives. Since **4** was inactive to couple with acetophenone **1a** under the standard conditions, this adduct was more likely a resting state than an intermediate of the transformation.[4c] Meanwhile, the reaction of **5** and **1a** afforded the products in high yield, somewhat showing that the adduct was possibly a key intermediate.[8] Based on the results in hand, a proposed mechanism is presented in Scheme 5. We hypothesized that **5** was formed through an aromatic radical cyclization of acetophenone **1a**. Thus, different regioselectivities were observed with regard to electron-withdrawing or

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electron-donating substituents at the *meta* position of acetophenone. Condensation of 3-aminobenzothiophene **5** with the second acetophenone molecule produced an imine, followed by Willgerodt−Kindler type sulfuration and oxidation to afford an iminoyl phenylacetic acid intermediate **6**. Decarboxylation of **6** afforded the product **2a**. On the other hand, "wet" DMSO facilitated the hydrolysis of the imino ethanethial intermediate **I**, which was involved in the formation of 3-aminobenzothiophene. Imine condensation of the hydrolysis product and **5** yielded the intermediate **7**. The presence of a hindered amine as DABCO facilitated the Baylis−Hillman type sulfuration, followed by cyclization and oxidation to furnish 2-benzoyl thienothiazole **3a**.

In conclusion, we have developed a new metal-free synthesis of fused thieno[3,2-*d*]thiazoles using the three-component reaction between acetophenones, urea, and elemental sulfur. The conditions could be divergent to obtain either 2-phenylbenzo[4,5]thieno[3,2-*d*]thiazoles or benzo[4,5]thieno-[3,2-*d*]thiazol-2-yl(phenyl)methanones. Cross-coupling of α C−H bonds in acetophenones with other activated sp^3 C−H bonds in phenylacetic acids and 2-methylazaarenes was also feasible. Reactions were compatible with many functionalities such as halogens, methylthio, trifluoromethyl, and protected alcohol groups. Attempts to expand the scope of the transformation with regard to reagents for C−H/C−H cross-coupling are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03414.

Details of optimization studies, general procedures, and characterization data of unknown compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tungtn@hcmut.edu.vn.
*E-mail: ptsnam@hcmut.edu.vn.

ORCID

Phuc H. Pham: 0000-0002-7086-6948
Khang X. Nguyen: 0000-0003-3336-1390
Tung T. Nguyen: 0000-0002-0912-9981
Nam T. S. Phan: 0000-0002-5928-7638

Notes

The authors declare no competing financial interest.

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(8) Please see the Supporting Information for the list of unreacting substrates, more mechanistic experiments, and procedures for large scale runs.

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