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Copper-Catalyzed Thiolation of Terminal Alkynes Employing Thiocyanate as the Sulfur Source Leading to Enaminone-Based Alkynyl Sulfides under Ambient Conditions

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02308 Read Online

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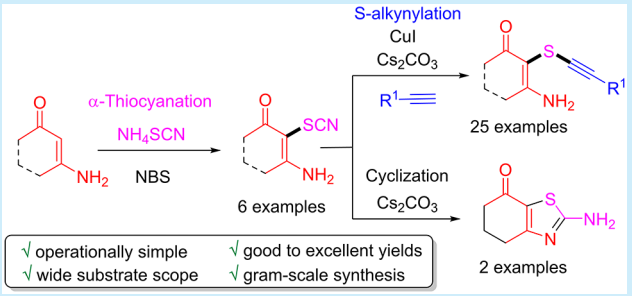
ABSTRACT: A highly efficient protocol for copper-catalyzed thio-alkynylation of enaminone-based thiocyanates with terminal alkynes under mild conditions has been developed. This scalable amino group-directed thio-alkynylation proceeds in the open air with a broad substrate scope and an excellent yield. The demonstrated synthetic transformation creates the opportunity for a wide variety of sulfur-containing useful materials. Gram-scale synthesis and further synthetic transformations of alkynyl sulfides highlight the potential utility of the method.



Alkynes represent a privileged structural motif in synthetic and medicinal chemistry because of their enhanced utility in chemical biology and material science.[1] The unique reactivity of the C(sp)−C(sp) bond makes them valuable precursors in the generation of carbo- and heterocyclic scaffolds ubiquitous in several complex natural products.[2] Among them, the alkynes directly bonded with an atom like N or S are of particular interest due to their ability to influence the chemical transformations. As a consequence, nitrogen-attached alkynes like ynamines and ynamides have been explored in modern synthetic chemistry.[3] Conversely, the synthetic potential of analogous S-alkynes[4] remains untapped despite the omnipresence of organosulfur compounds.[5] This has garnered considerable interest from researchers across the world in recent times for the development of novel and efficient synthetic strategies for alkynyl sulfides.

The classical strategies for constructing the C(sp)−S bond are mainly focused on highly reactive acetylide intermediates with prefunctionalized thiols or activated sulfur-containing leaving groups (Figure 1).[6] Recently developed routes for alkynyl sulfides are Cu(I)-catalyzed coupling of terminal alkynes with thiols in the presence of molecular oxygen (Figure 1A)[6a] and electrophilic alkynylation using alkynyl iodonium salt [ethynylbenziodoxolone (EBX)] as the alkyne transfer reagents (Figure 1B).[6b,c] Selected metal-free or metal-catalyzed coupling strategies for thio-alkynylation with sulfur-containing leaving group include thiosulfonates as the sulfur source with terminal alkynes using CuI as the catalyst and *t*-BuOLi as the base (Figure 1C),[6d] the CuI/Xantphos catalytic system for thiolation with thiosulfonates (Figure 1D),[6e] and transition metal-free *t*-BuOK-mediated coupling of terminal aryl alkynes with thiocyanates (Figure 1E).[6f] Practically, most of the literature methods employ either sensitive or harsh experimental conditions, thus limiting the scope of thio-alkynylation.

To develop an efficient protocol for alkynyl sulfides, we focused our attention on the coupling of terminal alkynes with thiocyanates as the sulfur source utilizing the leaving group ability of CN under ambient reaction conditions (Figure 1F).

Organic thiocyanates are considered as highly valuable building blocks leading to functional materials and pharmaceuticals.[7] As a result, several elegant methods for the thiocyanation of $C(sp^2)$−H[8] and $C(sp^3)$−H[9] bonds have been studied extensively. In general, the inorganic thiocyanates such as KSCN, NaSCN, and NH_4SCN are primarily employed to construct a C−SCN bond via thiocyanation.[10] In addition, enaminones play a key role as synthetic intermediates in many conversions leading to the potential pharmaceutical candidates[11] and fused heterocyclic compounds.[12] Thiocyanated enaminones, preferably, offer tremendous synthetic potential, and hence, functionalization of the $C(sp^2)$−H bond of enaminone to the $C(sp^2)$−S bond has been successfully developed.[13] We became interested in exploring the synthetic ability of underutilized thiocyanated enaminones based on our experience with enaminone-based multicomponent reactions.[14] Herein, we report the α-thiocyanation of enaminones and consequential copper-catalyzed C(sp)−S bond formation

Received: July 13, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02308
Org. Lett. XXXX, XXX, XXX−XXX

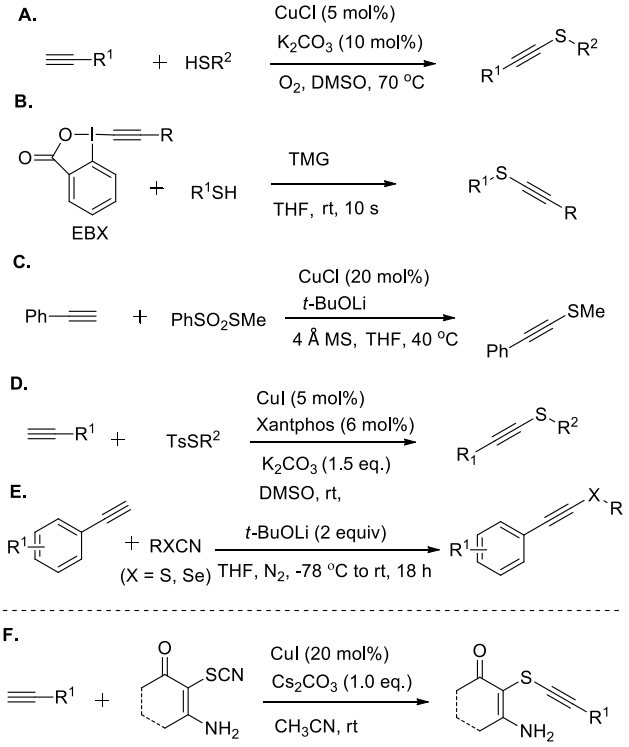


Figure 1. Synthetic strategies for (A–E) S-alkynylation and (F) our approach.

of thiocyanate with terminal alkynes under ambient conditions (Figure 1E). The developed protocol demonstrates an expanded substrate scope, and mechanistic studies reveal the directive role of the amino group in this thio-alkynylation.

We first investigated the regioselective α-thiocyanation of enaminone **2a** with NH_4SCN and *N*-bromosuccinimide (NBS), which successfully provided **3a** in 81% yield (Figure 2). Enaminone **2a** was synthesized from commercially available 1,3-cyclohexanedione **1a**. The preliminary screening of solvents indicated that EtOH could provide a maximum

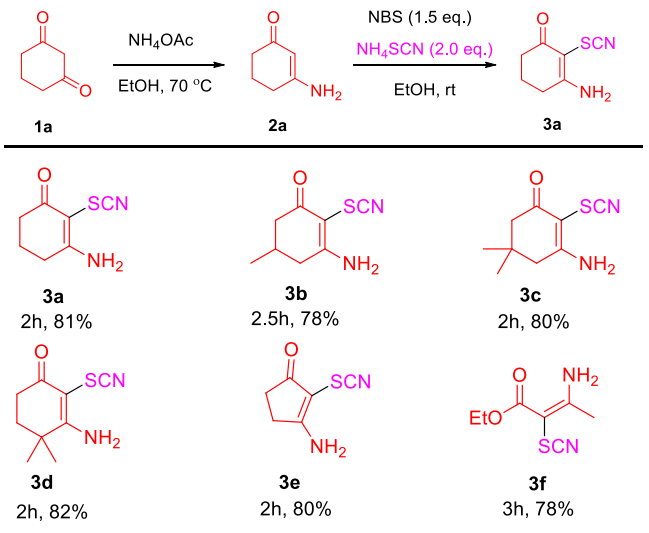


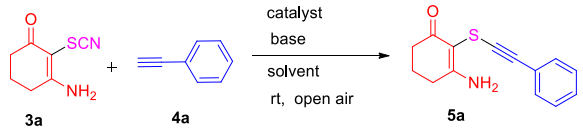
Figure 2. α-Thiocyanation of enaminones. Enaminone (4.50 mmol), NH_4SCN (9.00 mmol), NBS (6.75 mmol), and EtOH (20 mL). Yields refer to isolated yields.

yield of desired product **3a**, while lower yields were observed with solvents like DCE, DCM, and CH_3CN.

The evaluation of other oxidants like oxone and $K_2S_2O_8$ led to desired product **3a** in lower yields. With the optimal reaction conditions in hand, a series of enaminones (**2a–2f**) were successfully transformed to thiocyanated enaminones **3a–3f** in good to excellent yields (78–82%) (Figure 2). Interestingly, the thiocyanation of enaminone with a secondary amine under optimal conditions proceeded to yield 2-iminothiazole **3g**, which is in accord with literature precedent (see the Supporting Information).[15] The attempted thiocyanation of enaminone with tertiary amine also failed to provide any expected product.

With thiocyanated enaminones in hand, we then attempted the thio-alkynylation of derivative **3a** with phenylacetylene **4a** using 20 mol % CuCl and Cs_2CO_3 in CH_3CN at room temperature. Unfortunately, no desired product was observed even after reaction for 3 h (Table 1, entry 1). However, the use

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	base	solvent	time (h)	yield (%)[b]
1	CuCl (20)	Cs_2CO_3	CH_3CN	3	np[c]
2	$Cu(OAc)_2$ (20)	Cs_2CO_3	CH_3CN	1	65
3	$CuSO_4$ (20)	Cs_2CO_3	CH_3CN	3	45
4	CuBr (20)	Cs_2CO_3	CH_3CN	2	60
5	CuI (20)	Cs_2CO_3	CH_3CN	1	87
6	CuI (20)	Cs_2CO_3	EtOH	24	np[c]
7	CuI (20)	Cs_2CO_3	MeOH	24	np[c]
8	CuI (20)	Cs_2CO_3	*i*PrOH	24	43
9	CuI (20)	Cs_2CO_3	DMSO	0.5	62
10	CuI (20)	Cs_2CO_3	DMF	0.5	67
11	CuI (20)	Cs_2CO_3	dioxane	24	62
12	CuI (20)	Cs_2CO_3	acetone	0.5	68
13	CuI (20)	Cs_2CO_3	DCE	24	54
14	CuI (20)	Cs_2CO_3	DCM	24	38
15	CuI (20)	Cs_2CO_3	toluene	24	30
16	CuI (20)	K_2CO_3	CH_3CN	2	72
17	CuI (20)	Na_2CO_3	CH_3CN	2	56
18	CuI (20)	*t*-BuOK	CH_3CN	3	44
19	CuI (20)	DBU	CH_3CN	0.5	55
20	CuI (20)	DABCO	CH_3CN	2	50

[a]Reaction conditions (unless otherwise specified): **3a** (0.59 mmol), **4a** (0.89 mmol), catalyst (0.11 mmol), base (0.59 mmol), solvent (5 mL). [b]Isolated yields. [c]No product.

of 20 mol % $Cu(OAc)_2$ as a catalyst led to desired alkynyl sulfide **5a** in 65% yield (Table 1, entry 2). With similar reaction conditions, expected product **5a** was isolated in 45% and 60% yields with 20 mol % $CuSO_4$ and CuBr, respectively (Table 1, entries 3 and 4, respectively). To our delight, product **5a** was observed in 87% yield with 20 mol % CuI in CH_3CN after reaction for 1 h (Table 1, entry 5). Several silver salts like Ag_2CO_3, AgCl, $AgNO_3$, and $AgOCOCF_3$ failed to yield the desired product. For the solvent, thio-alkynylation with CuI in EtOH and MeOH did not yield any product (Table 1, entries 6 and 7, respectively); however, expected product **5a** was obtained in 43% yield in *i*PrOH (Table 1, entry 8). Alkynyl

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Org. Lett. XXXX, XXX, XXX–XXX

sulfide **5a** was obtained with average yields ranging from 62% to 68% in polar solvents like DMSO, DMF, dioxane, and acetone (Table 1, entries 9−12, respectively) and with decreased yields in DCM, DCE, and toluene of 54%, 38%, and 30%, respectively (Table 1, entries 13−15, respectively). Application of inorganic bases like K_2CO_3, Na_2CO_3, and *t*-BuOK and organic bases like DABCO and DBU resulted in lower conversions (Table 1, entries 16−20, respectively).

With the optimized reaction conditions, the substrate scope for this thio-alkynylation was then explored. Both aryl and aliphatic alkyne partners were found to be favorable substrates with thiocyanated enaminones affording efficient creation of alkynyl sulfides (Figure 3). Six-membered thiocyanated

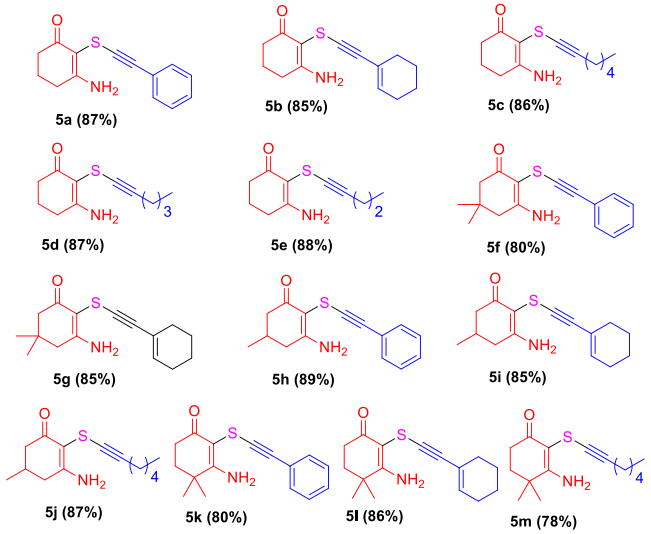


Figure 3. Scope of thiocyanates with terminal alkyne. Conditions: **3** (0.59 mmol), alkyne **4** (0.89 mmol), CuI (0.11 mmol), Cs_2CO_3 (0.59 mmol) and CH_3CN (4.00 mL).

enaminones **3a−3d** were readily amenable to subjected conditions delivering S-alkynylated products **5a−5m** in high to excellent yields (78−87%). For alkynes, thiolations with phenylacetylene **4a**, 1-ethynylcyclohex-1-ne **4b**, 1-heptyne **4c**, 1-hexyne **4d**, and 1-pentyne **4e** proceeded smoothly to furnish alkynyl sulfides **5a−5e**, respectively, in excellent yields (85−88%). The 5,5-dimethyl- substituted **3c** readily reacted with alkyne **4a** and **4b** yielding **5f** and **5g** in 80% and 85% yields, respectively. Similarly, 5-methyl derivative **3b** and 4,4-dimethyl derivative **3d** underwent smooth reaction with alkyne **4a**, **4b**, and **4c** to provide **5h−5m** in very high yields (78−89%). In addition, to extend the scope of the reaction, the thiolation was tested with 3-amino-2-thiocyanatocyclopent-2-enone **3e** with alkynes like phenylacetylene **4a**, 1-ethynylcyclohex-1-ne **4b**, 1-heptyne **4c**, 1-hexyne **4d**, and 1-pentyne **4e**, which afforded alkynyl sulfides **5n−5r**, respectively, in good to excellent yields (75−80%) (Figure 4). The alkynyl sulfides **5s−5y** of the acyclic analogue ethyl 3-amino-2-thiocyanatobut-2-enoate **3f** were also prepared with various alkynes **4a−4f** in high yields (77−91%) (Figure 4).

To examine the role of copper in this thio-alkynylation, an experiment was conducted with thiocyanated enaminone **3a** and alkyne **4a** under standard conditions without CuI as a catalyst. Interestingly, 2-amino-5,6-dihydrobenzo[*d*]thiazol-7(4*H*)-one **6a** was obtained in quantitative yield after reaction for 1.5 h at room temperature (Scheme 1). Similarly,

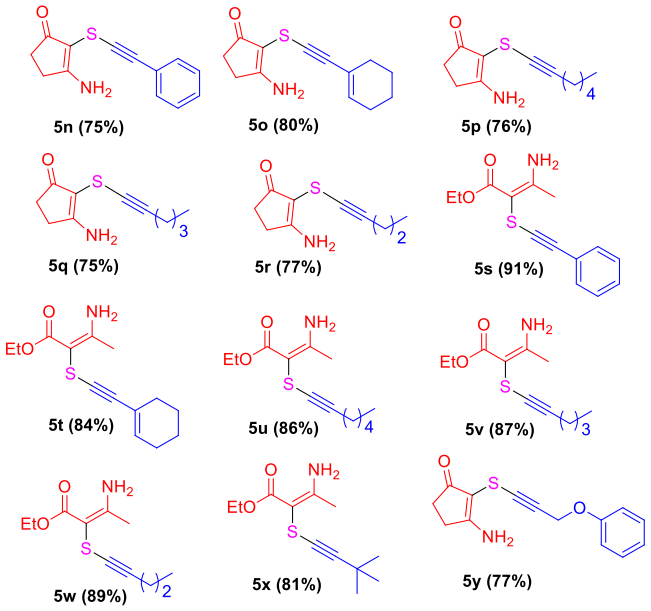
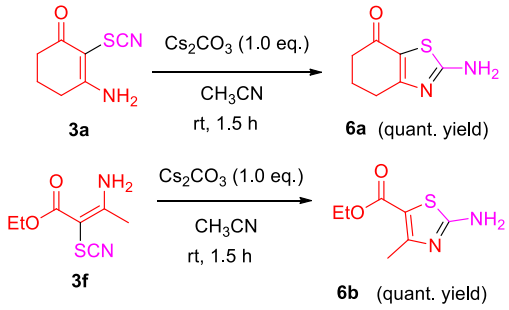


Figure 4. Scope of thiocyanates with terminal alkyne. Conditions: **3** (0.59 mmol), alkyne **4** (0.89 mmol), CuI (0.11 mmol), Cs_2CO_3 (0.59 mmol), and CH_3CN (4.00 mL).

Scheme 1. Reaction of Thiocyanates without CuI[a]



[a]Reaction conditions: **3a** (0.59 mmol), Cs_2CO_3 (0.59 mmol), and CH_3CN (5.0 mL).

compound **3f** was also converted to ethyl 2-aminomethylthiazole-5-carboxylate **6b** in quantitative yield with standard reaction conditions. This cyclization could happen only in the absence of copper, which otherwise generates acetylide with terminal alkyne leading to thio-alkynylation. Products **6a** and **6b** appear to be a medicinally relevant scaffold that could be readily utilized as a potential drug precursor. These valuable intermediates and their derivatives could easily be obtained in high yields with the current approach.

To probe the reaction mechanism of thio-alkynylation, several control experiments were conducted (Scheme 2. First, the reaction of thiocyanate **3a** was performed with internal alkyne 1,4-diphenylbuta-1,3-diyne and diethyl acetylenedicarboxylate (Scheme 2G), which resulted in no reaction indicating the role of acetylide with terminal alkyne during product formation. To investigate the directive effect of the NH_2 group in alkynylation, 2-thiocyanatocyclohexane-1,3-dione **7** was treated with phenylacetylene **4a** under standard conditions, which also failed to provide any expected product (Scheme 2H). Similarly, the reaction of 4-thiocyanatoaniline **8** with phenylacetylene **4a** remained unfruitful (Scheme 2I). The failure of these substrates to undergo reaction with terminal

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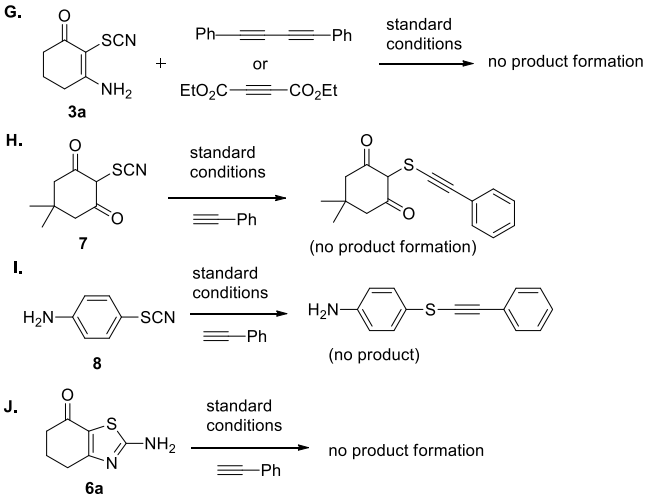
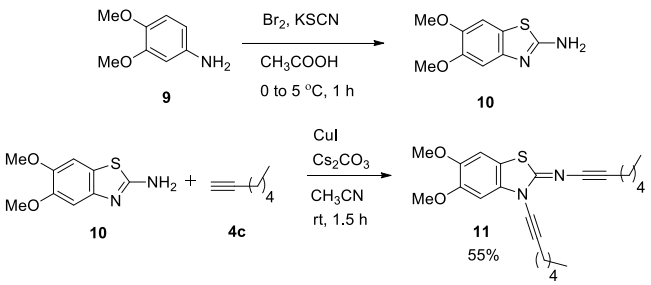
Scheme 2. Control Experiments



alkyne underlines the possible directive role of NH_2 in copper-catalyzed thio-alkynylation. To further understand this thio-alkynylation, we tested the reaction of 2-amino-5,6-dihydrobenzo[*d*]thiazol-7(4*H*)-one **6a** with phenylacetylene **4a**, which again failed to provide any product (Scheme 2J). Finally, we set out to perform thio-alkynylation with 2-thiocyanatoaniline to assess the directive effect. However, during the thiocyanation of 3,4-dimethoxyaniline **9** with bromine and KSCN, 5,6-dimethoxybenzo[*d*]thiazol-2-amine **10** was isolated rather than the expected product. In addition, the treatment of compound **10** with 1-heptyne **4c** provided unexpected dialkynylated product **11** in 55% yield after reaction for 1.5 h (Scheme 3). The use of even equimolar

Scheme 3. Alkynylation of Benzo[*d*]thiazol-2-amine 10[a]



[a]Reaction conditions: **9** (3.26 mmol), Br_2 (3.26 mmol), and KSCN (6.53 mmol); **10** (0.47 mmol), **4c** (0.71 mmol), CuI (0.11 mmol), Cs_2CO_3 (0.47 mmol), and CH_3CN (5.0 mL).

alkyne also led to the same product. To the best of our knowledge, this kind of dialkynylation has not been documented and needs to be subjected to further mechanistic studies. The fact that alkynylation was observed with only benzo[*d*]thiazol-2-amine **10** and not with 2-amino-5,6-dihydrobenzo[*d*]thiazol-7(4*H*)-one **6a** points to the nature of the difference in reactivity between the two substrates.

We propose a speculative reaction mechanism for the formation of alkynyl sulfide based on the outcome of reactions and control experiments (Figure 5). Two different reactions could be operative on the basis of the presence or absence of copper salt in the reaction. In the presence of copper, the reaction likely proceeds via the initial generation of copper acetylide **I** as indicated in the control experiment. Then, the

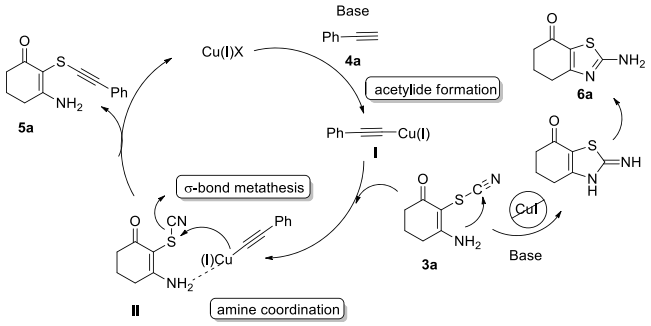
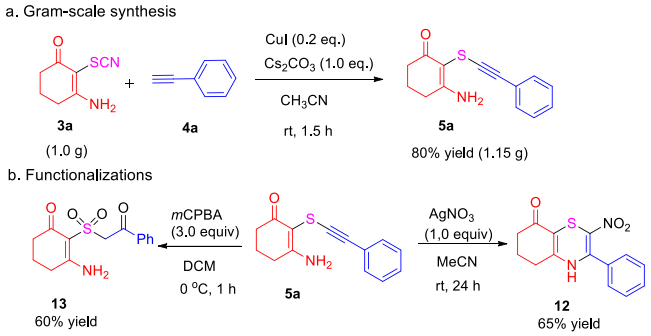


Figure 5. Plausible mechanism.

directive coordination of acetylide **I** with an amino group of **3a** subsequently follows σ-bond metathesis via SN_2 type attack on thiocyanate in structure **II** knocking out CN to yield product **5a**. Without a copper catalyst, the amino group of **3a** nucleophilically attacks SCN in intramolecular fashion leading to formation of product **6a** apparently.

To evaluate the efficacy of the reaction, a gram-scale synthesis of **5a** was conducted with 1.0 g (5.00 mmol) of thiocyanate **3a** and phenylacetylene **4a** furnishing 1.15 g of thioalkyne **5a** with 80% yield (Scheme 4a). Advantageously,

Scheme 4. Gram-Scale Synthesis and Further Transformations



the unpleasant odor generally observed as part of the thiolation reaction is not realized with the current protocol. In addition, few synthetic transformations of alkynyl sulfides were also performed (Scheme 4b). The treatment of compound **5a** with 1.0 equiv of $AgNO_3$ provided nitro compound **12** in 65% yield by annulative nitration.[16] Similarly, substrate **5a** was easily oxidized to corresponding sulfones **13** in 60% yield upon treatment with *m*-CPBA at 0 °C for 1 h. These simple transformations outline the versatility and usefulness of the methods reported herein.

In summary, we have successfully developed α-thiocyanation of enaminone and consequential copper-catalyzed alkynylation using thiocyanates with terminal alkynes. The method utilizes ambient reaction conditions with a wide substrate scope and gives ready access to biologically relevant sulfur-containing privileged scaffolds that are useful for developing new drug candidates and materials. Further exploration of studies for the synthesis of sulfur-containing heterocyclic scaffolds and detailed mechanistic studies of reactions are currently underway.

https://dx.doi.org/10.1021/acs.orglett.0c02308
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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02308.

Experimental procedures, analytical data, and NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge Dr. S. J. S. Flora, Director, NIPER, Raebareli, for his support of this research program. C.R., A.P., S.K.S., R.D., and S.V. thank the Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, Government of India, for providing fellowships. The authors are thankful to Central Instrumentation Facility (CIF), NIPER, Raebareli, for spectral data. NIPER, Raebareli, communication NIPER-R/Communication/117.

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