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Copper(I)-Catalyzed Oxidative Coupling between 2-Aminobenzothiazole and Terminal Alkyne: Formation of Benzothiazine

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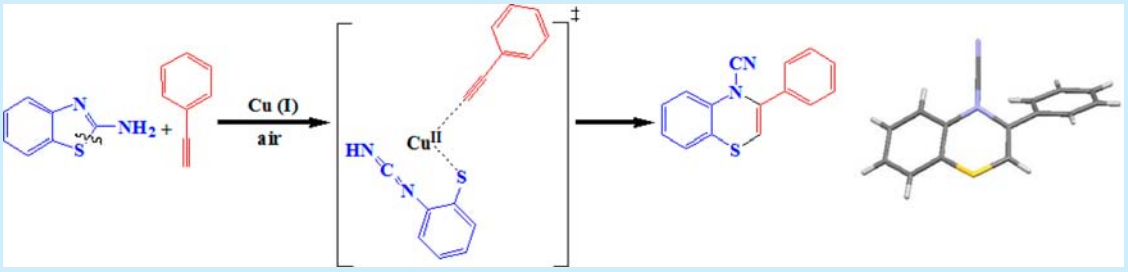
Supporting Information



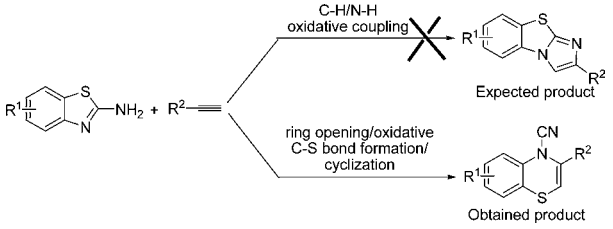
ABSTRACT: An unprecedented formation of benzothiazine during copper(I)-catalyzed oxidative coupling of 2-aminobenzothiazole and terminal alkyne in air has been observed. This unique transformation possibly occurs through the ring opening of 2-aminobenzothiazole and subsequent oxidative coupling with alkyne followed by intramolecular cyclization. A variety of substituted benzo[*b*][1,4]thiazine-4-carbonitriles are obtained by this protocol.

Metal-catalyzed direct functionalization of a C−H bond is a powerful tool to construct C−C and C−heteroatom bonds in an efficient and straightforward way.[1] Specifically, oxidative cross-dehydrogenative coupling reactions provide convenient access to a wide range of heterocyclic frameworks.[2] Despite extensive progress in this field, the selective cross-coupling reaction involving terminal alkyne is still challenging due to the inevitable homocoupling of terminal alkyne through Glaser−Hay coupling.[3] However, few elegant methods have been reported for the oxidative C−H functionalization of terminal alkynes.[4] In this context, oxygen is found to be the most compatible oxidant from both environmental and economical points of view.[5]

Recently, we have synthesized various imidazo[1,2-*a*]pyridine derivatives by the coupling of 2-aminopyridine with ketones and nitroalkenes.[6] We found that 2-aminopyridine is an effective coupling partner for oxidative amination in the presence of air. Stimulated by the recent advancement on oxidative coupling reactions using terminal alkynes,[4b,c] we envisaged that the coupling between 2-aminobenzothiazole and terminal alkyne would afford the imidazobenzothiazole (Scheme 1). However, the unprecedented formation of benzo[1,4]thiazine-4-carbonitriles was observed possibly through the ring opening of 2-aminobenzothiazole/oxidative coupling with alkyne/intramolecular cyclization.

Benzo[1,4]thiazine is considered a promising unit in the field of pharmaceuticals and agrochemicals.[7] This moiety shows a wide range of biological activities in vivo and in vitro, such as antibacterial,[8] antidiabetic,[9] antiarrhythmic,[10] antitumor,[11] and neurodegenerative diseases.[12] Due to the presence of a fold along the nitrogen sulfur axis, the benzo[1,4]thiazine moiety shows some structural specificities and activities similar to the phenothiazines which are well-known as antipsychotic and antihistaminic drugs.[13] On the other hand, cyanamides are conveniently used as important intermediates in the synthesis of herbicides[14] and key precursors in the synthesis of various heterocyclic molecules.[15] These are also useful against the tumor growth activities.[16]

Scheme 1. Oxidative Coupling between 2-Aminobenzothiazole and Alkyne



Herein we report the synthesis of benzothiazines by the coupling of 2-aminobenzothiazole with alkynes in the presence of CuI under ambient air (Scheme 2). To the best of our knowledge, this is the first report of oxidative ring expansion of 2-aminobenzothiazole to benzo[*b*][1,4]thiazine-4-carbonitrile.

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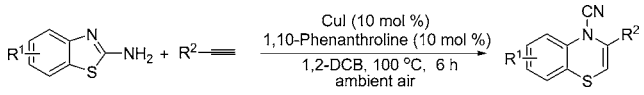
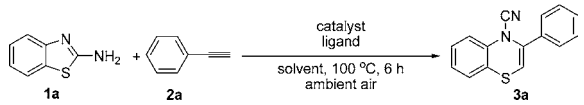
Scheme 2. Formation of Benzo[*b*][1,4]thiazine-4-carbonitrile



We started our investigation with the reaction of 2-aminobenzothiazole **1a** (0.5 mmol) and phenylacetylene **2a** (0.6 mmol) in the presence of CuCl (10 mol %) and 1,10-phenanthroline (10 mol %) in 1,2-DCB (1,2-dichlorobenzene) at 100 °C under aerobic conditions (Table 1, entry 1).

Table 1. Optimization of the Reaction Parameters[a]



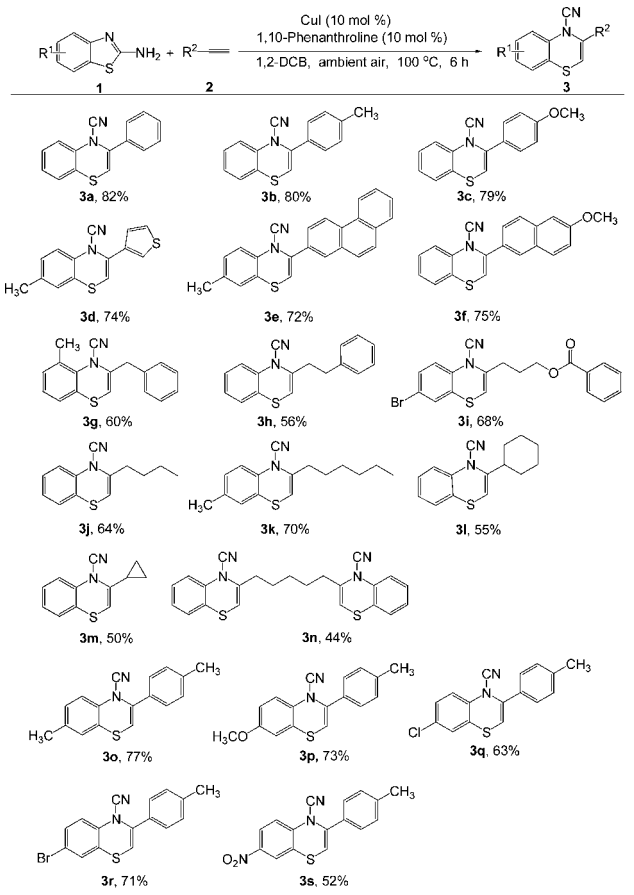
entry	catalyst	ligand	solvent	yield[b] (%)
1	CuCl	1,10-phenanthroline	1,2-DCB	68
2	CuBr	1,10-phenanthroline	1,2-DCB	76
3	CuI	1,10-phenanthroline	1,2-DCB	82 (84)[c]
4	$CuBr_2$	1,10-phenanthroline	1,2-DCB	
5	$Cu(OAc)_2·H_2O$	1,10-phenanthroline	1,2-DCB	
6	$FeCl_3$	1,10-phenanthroline	1,2-DCB	
7	$PdCl_2$	1,10-phenanthroline	1,2-DCB	
8	CuI		1,2-DCB	trace
9	CuI	bipyridine	1,2-DCB	22
10	CuI	L-proline	1,2-DCB	trace
11	CuI	DMEDA	1,2-DCB	15
12	CuI	TMEDA	1,2-DCB	12
13	CuI	bathophenanthroline	1,2-DCB	80
14	CuI	bathocuproine	1,2-DCB	trace
15	CuI	neocuproine	1,2-DCB	trace
16	CuI	1,10-phenanthroline	DMF	60
17	CuI	1,10-phenanthroline	DMSO	64
18	CuI	1,10-phenanthroline	dioxane	25
19	CuI	1,10-phenanthroline	toluene	28

[a]Reaction conditions (unless otherwise specified): **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (0.05 mmol), ligand (0.05 mmol), solvent (2 mL), 100 °C. [b]Yields of the isolated product. [c]Reaction was performed using O_2 balloon.

Intriguingly, the unexpected formation of benzo[1,4]thiazine **3a** was observed in 68% yield within 6 h. No improvement in the yield was observed on further heating. Then we screened different Cu catalysts like CuBr, CuI, $Cu(OAc)_2·H_2O$, $CuBr_2$; among them, CuI furnished the optimum yield (Table 1, entry 3). However, the reaction did not proceed at all in the presence of Cu(II) salts (Table 1, entries 4 and 5). Use of other metal catalysts like iron or palladium also failed to perform the reaction (Table 1, entries 6 and 7). Only a trace amount of product was formed in absence of ligand (Table 1, entry 8). Different ligands like bipyridine, TMEDA, DMEDA, bathocuproine, neocuproine, etc., were also tested (Table 1, entries 9−15). 1,10-Phenanthroline was found to be the most effective ligand for this reaction. Choice of solvent is also important. Various common solvents like DMF, DMSO, dioxane, and toluene were screened, but they are not as effective as 1,2-DCB (Table 1, entries 16−19). Further, the effect of catalyst loading was also checked, and it was observed that the product yield was decreased to 44% in the presence of 5 mol % of catalyst, whereas no significant increment was observed using 15 mol % of catalyst. The reaction was also performed using various oxidants like DDQ, *p*-benzoquinone, potassium persulfate, etc. (see the Supporting Information), but these oxidants were ineffective in this coupling reaction. Aerobic oxygen was found to be the most suitable oxidant for this transformation. Moreover, the use of molecular oxygen did not improve the yield of the product. No considerable improvement of the yield was observed on increasing the temperature from 100 to 120 °C. Finally, 10 mol % of CuI along with 10 mol % of 1,10-phenanthroline in 1,2-DCB at 100 °C under ambient air afforded the optimum 82% yield of the product within 6 h (Table 1, entry 3).

Under the optimized reaction conditions, we examined a variety of substrates to show the generality of this methodology (Scheme 3). Arylalkynes having substitutions like methyl and

Scheme 3. Synthesis of Benzo[*b*][1,4]thiazine-4-carbonitriles: Scope of the Reaction[a]



[a]Reaction conditions: 0.5 mmol of **1**, 0.6 mmol of **2**, CuI (0.05 mmol), 1,10-phenanthroline (0.05 mmol), 1,2-DCB (2 mL), 100 °C, 6 h, ambient air. Isolated yields.

methoxy afforded the desired products in excellent yields (**3a**−**c**). Heterocyclic alkyne such as 3-ethynylthiophene was well tolerated under the standard conditions, providing 74% yield (**3d**). Polyaromatic alkynes like 2-ethynyl-6-methoxynaphthalene and 2-ethynylphenanthrene also furnished good yields (**3e** and **3f**). Both 1-(prop-2-ynyl)benzene and 1-(but-3-ynyl)-benzene smoothly participated in this reaction (**3g** and **3h**). Moreover, aliphatic alkynes like ethynylcyclohexane, hexyne, and octyne furnished the corresponding products in moderate to good yields (**3j**−**l**). It is notable that ethynylcyclopropane also reacted effectively under the present optimized conditions (**3m**).

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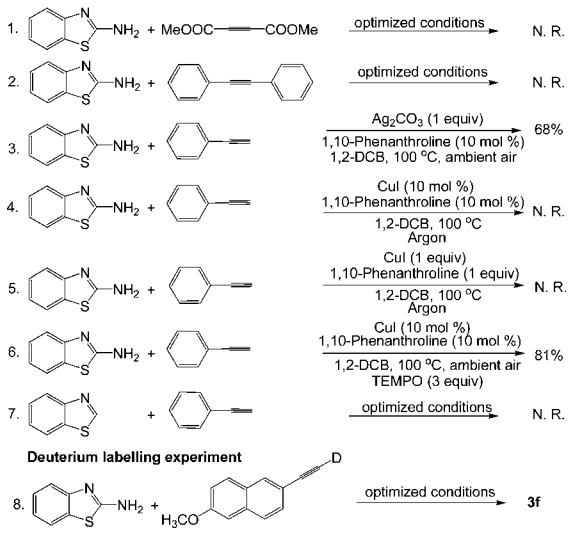
Interestingly, bis-benzothiazine moiety (**3n**) was also obtained in moderate yield. Various 2-aminobenzothiazoles having electron-donating and electron-withdrawing substituents like −Me, −OMe, $-NO_2$, and halogens (−Cl, −Br) reacted well to afford the desired products in moderate to good yields (**3o**−**3s**). However, 2-aminothiazole did not afford the desired product under the present reaction conditions.

Some crossover experiments were performed to gain insight on the mechanism of the reaction as shown in Scheme 4. Internal

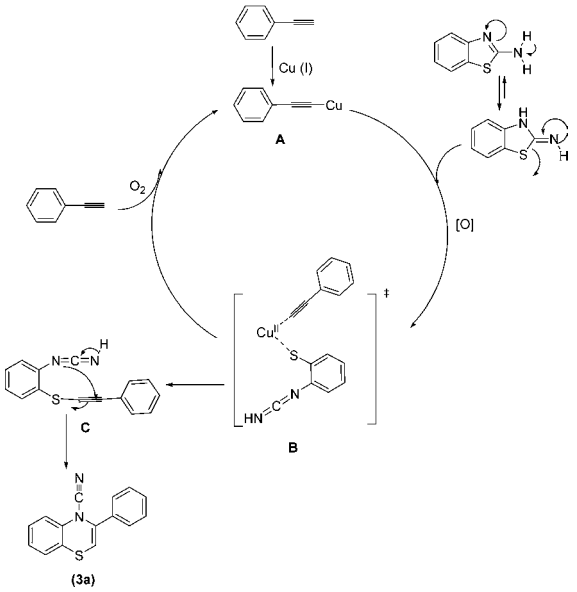
Scheme 4. Control Experiments



alkynes such as dimethyl but-2-ynedioate (entry 1) and 1,2-diphenylethyne (entry 2) failed to afford the corresponding benzothiazines under the optimized reaction conditions. Accordingly, we anticipated that copper acetylide might be the key intermediate in this reaction. This assumption was further supported by the reaction with silver carbonate (entry 3), where reaction possibly proceeded through the formation of silver acetylide.[4b] The reaction did not proceed at all under an argon environment (entry 4), even when a stoichiometric amount of copper salt was used (entry 5). These results suggest that oxygen is necessary for this transformation. The reaction proceeded with equal ease in the presence of a radical scavenger TEMPO (entry 6), which indicates that the reaction does not proceed through a radical pathway. Benzothiazole failed to react with phenylacetylene under the optimized reaction conditions (entry 7), indicating that ring opening occurs in the presence of an amino group in benzothiazole. Notably, the reaction of 2-aminobenzothiazole with deuterated alkyne furnished the product **3f** in 72% yield without accompanying any deuterated product (entry 8).

On the basis of these crossover experiments, a probable mechanistic path has been suggested in Scheme 5. Initially the Cu−acetylide complex **A** is formed by the reaction of terminal alkyne with CuI. This Cu−acetylide **A** reacts with 2-aminobenzothiazole, and probably ring opening of thiazole moiety takes place at this stage with assistance of Cu catalyst.[17] Presumably, the intermediate **B** is formed through the oxidative addition of sulfur nucleophiles and Cu−acetylide complex with the aid of O_2.[4e] Subsequently, the intermediate **B** is reductively eliminated to produce the alkyne−sulfide **C**, and the Cu−acetylide **A** is regenerated in the presence of O_2 and phenylacetylene to complete the catalytic cycle. Finally, 6-*endo*-

Scheme 5. Probable Mechanism



dig cyclization of intermediate **C** occurs to afford the product **3a**. Aerobic oxygen plays an important role in facilitating the formation of the intermediate **B**. It is worth mentioning that no homodimerization of terminal alkynes occurred under the present reaction conditions.

The X-ray crystallographic analysis was performed to confirm the structure of the product as shown in Figure 1.[18]

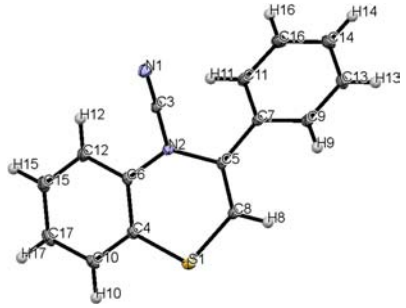


Figure 1. X-ray crystal structure of 3-phenyl-4*H*-benzo[*b*][1,4]thiazine-4-carbonitrile (**3a**).

In summary, the unprecedented formation of benzo[*b*][1,4]-thiazine-4-carbonitrile was observed by a copper-catalyzed coupling of 2-aminobenzothiazoles and terminal alkynes under ambient air. This unique transformation shows broad substrate scope with regard to both alkynes and 2-aminobenzothiazoles and a wide range of functional group tolerance. Most importantly, this new methodology provides a rare moiety of benzo[*b*][1,4]thiazine-4-carbonitrile that is not readily accessible by conventional methods. Preliminary mechanistic studies indicate that the reaction possibly proceeds through the ring opening of thiazole moiety followed by sequential oxidative coupling with alkyne and intramolecular cyclization to afford the products. We believe our findings will gain much importance in organic synthesis, medicinal chemistry, and material science.

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■ ASSOCIATED CONTENT

Supporting Information

Additional data, spectral data of all compounds, and scanned spectra of all compounds. 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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(18) Further information can be found in the CIF file. This crystal was deposited in the Cambridge Crystallographic Data Centre and assigned as CCDC 975531.