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EFFICIENT ONE-POT SYNTHESIS OF BENZO[*e*]PYRAZOLO-[1,5-*c*][1,3]THIAZINE DERIVATIVES UNDER COPPER-CATALYZED CONDITIONS

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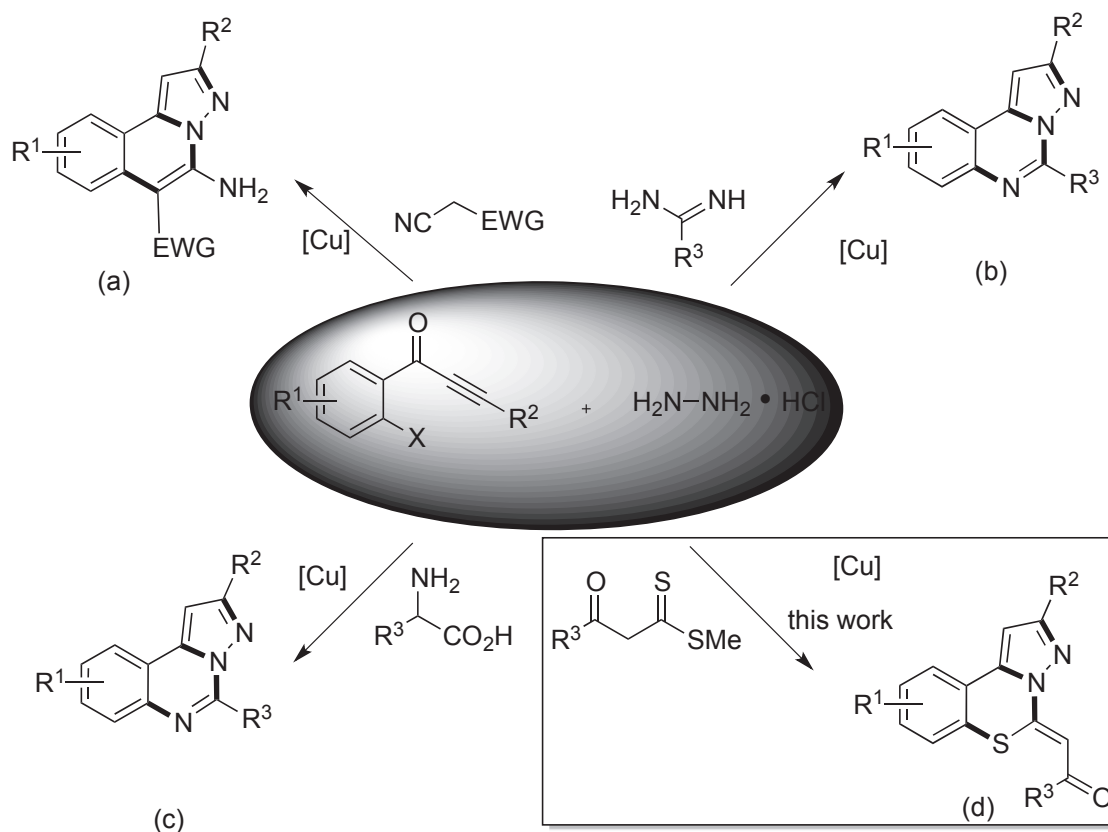
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Abstract – An efficient method has been developed for the synthesis of benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazines via one-pot two-step reactions of readily available substituted 1-(2-halophenyl)-3-alkylprop-2-yn-1-ones, hydrazine hydrochloride and β -oxodithioesters under mild conditions, and the corresponding benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazines were obtained in good to excellent yields. The novel method affords a new strategy for the construction of diverse and useful poly *N,S*-heterocyclic compounds.

INTRODUCTION

N-Heterocycles and *S*-heterocycles play the key roles in pharmaceutical and agrochemical industries.^{1,2} Pyrazoles represent an important structural motif frequently found in man-made biologically active compounds such as celecoxib, fipronil, lonazolac, viagra, although they are rarely found in natural products.³ Thiazine derivatives show various biological and medical functions.⁴ For example, they exhibit antibacterial,⁵ antimalarial,⁶ antiretroviral activities,⁷ and some of them are investigated as cell growth inhibitors,⁸ promising inhibitors of nitric oxide synthase,⁹ endogenous natriuretic factors.¹⁰ However, methods for the synthesis of pyrazolothiazines are very limited.¹¹ Additionally, dithioester was a good partner when some *S*-heterocycles were synthesized.¹² So, it provides us opportunities for developing novel procedures for the synthesis of this kind of derivatives.

In our previous works, we successfully employed 1-(2-halophenyl)-3-arylprop-2-yn-1-ones, hydrazine hydrochloride and other nitrogen sources to construct *N*-fused heterocycles under mild copper-catalyzed conditions (Scheme 1).¹³⁻¹⁵ And we found that pyrazoles could be easily constructed by 1-(2-halophenyl)-3-arylprop-2-yn-1-ones and hydrazine hydrochloride. Following this strategy, we herein wish to report a convenient and efficient one-pot synthesis of pyrazolothiazines under copper-catalyzed conditions.



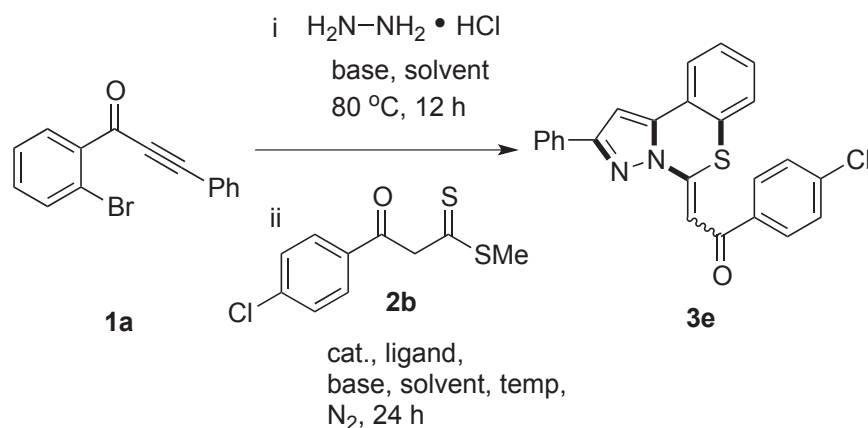
Scheme 1. Strategies for constructing heterocycles using 1-(2-halophenyl)-3-arylprop-2-yn-1-ones and hydrazine hydrochloride

RESULTS AND DISCUSSION

Initially the reaction of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**1a**), hydrazine hydrochloride and methyl 3-(4-chlorophenyl)-3-oxopropanedithioate (**2b**) was chosen as the model to optimize reaction conditions including copper-catalysts, ligands, bases, solvents and temperature under nitrogen atmosphere. As shown in Table 1, the reaction of the three components is a one-pot two-step process: coupling of **1a** with hydrazine hydrochloride in MeCN first led to intermediate **I** in the presence of Cs_2CO_3 at 80 °C for 12 h, and then treatment of **1a** with **2b** provided the target product (**3e**) under copper catalysis for 24 h (see Schemes 2 and 3). First, four ligands (20 mol% amount relative to **1a**) were screened applying 10 mol% of CuI as the catalyst, Cs_2CO_3 as the base, MeCN as the solvent under nitrogen atmosphere (entries 1-4), the reaction was performed at 80 °C for the first step and at 100 °C for the second step, and the highest yield (89%) was obtained in the absence of ligand (entry 4). When CuBr (entry 5) and $\text{Cu}(\text{OAc})_2$ (entry 6) were used as the catalysts, and low yields were obtained. No desired product was observed without copper catalyst (entry 7). Other bases were also examined (entries 8-10), and they showed the inferior results. DMF, DMSO, 1,4-dioxane and toluene were used as the solvents (entries 11-14), and they were inferior to MeCN (entry 4). Lower reactivity was observed when temperature was decreased to 80 °C (entry 15). When the amount of **2b** was decreased to 1.5 eq. (relative to **1a**), a lower yield was

obtained (entry 16).

Table 1. Copper-catalyzed synthesis of 1-(4-chlorophenyl)-2-(2-phenyl-5*H*-benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazin-5-ylidene)ethan-1-one (**3e**) via one-pot two step reaction of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**1a**), hydrazine hydrochloride and methyl 3-(4-chlorophenyl)-3-oxopropanedithioate (**2b**): optimization of conditions^a

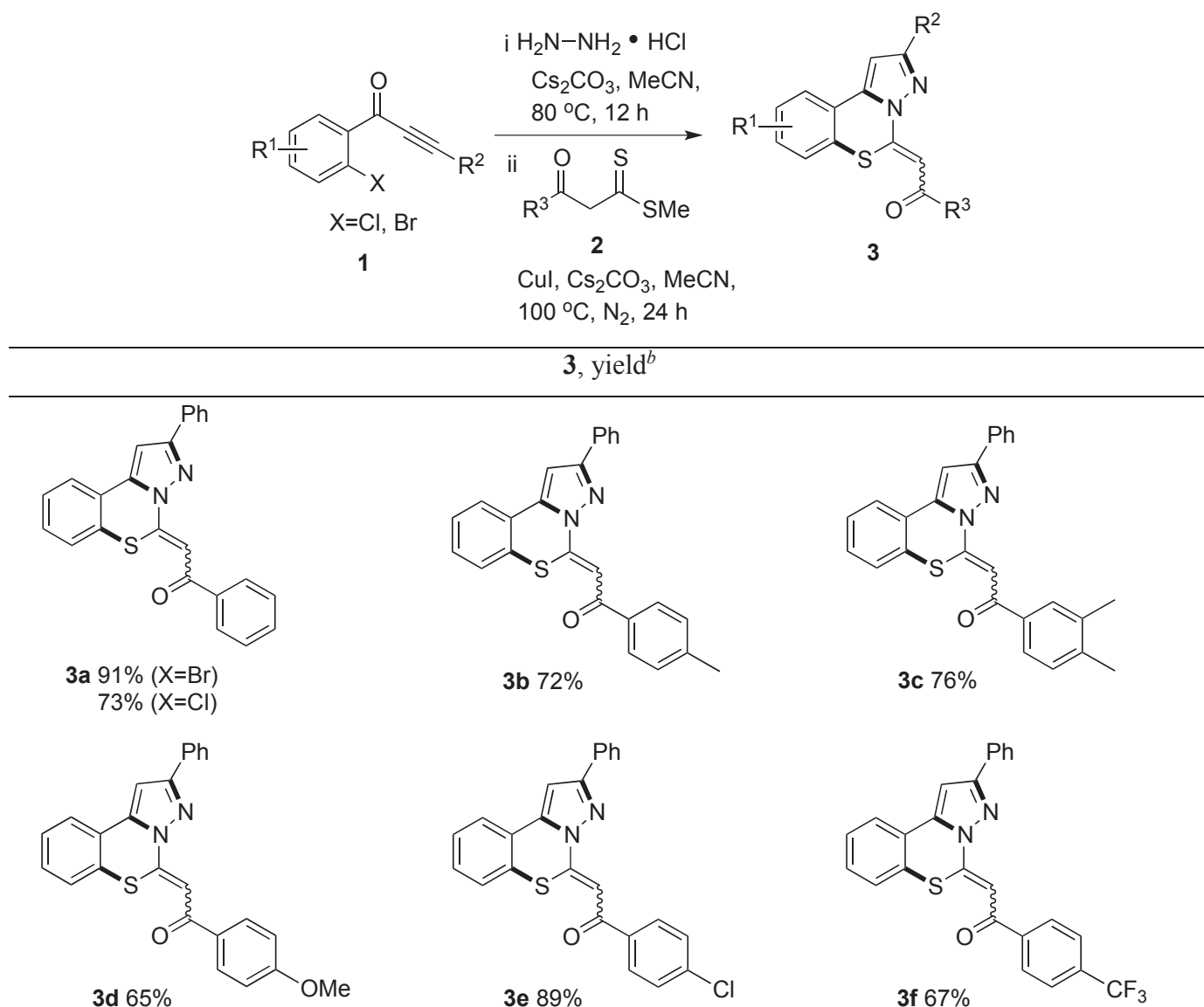


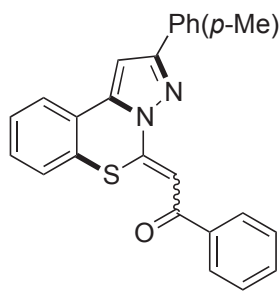
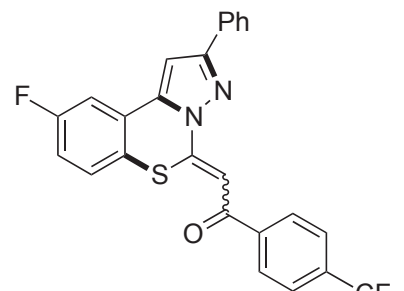
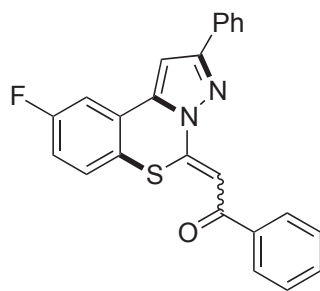
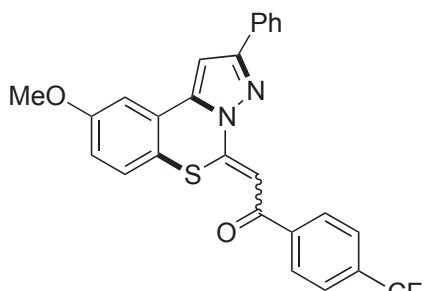
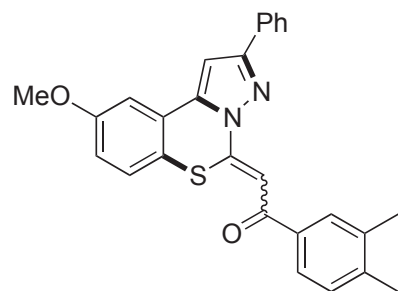
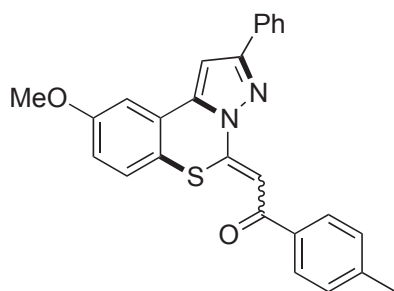
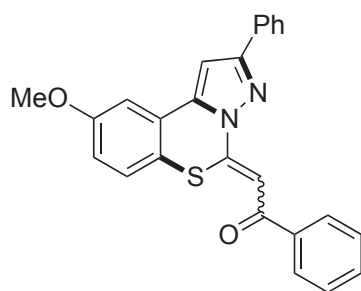
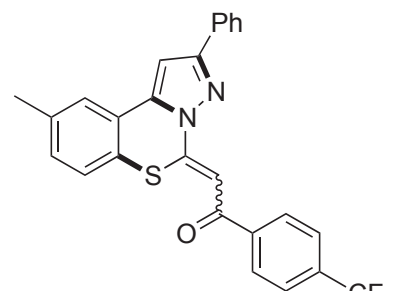
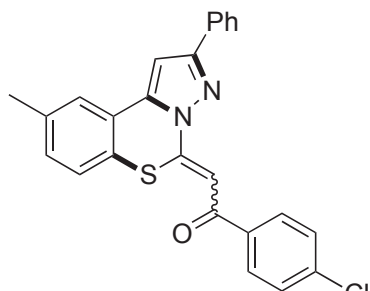
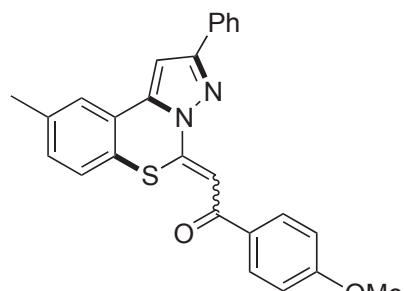
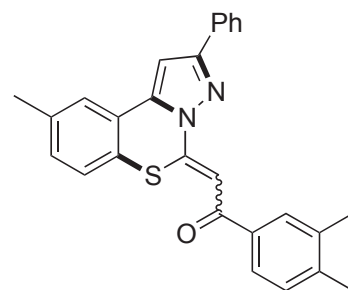
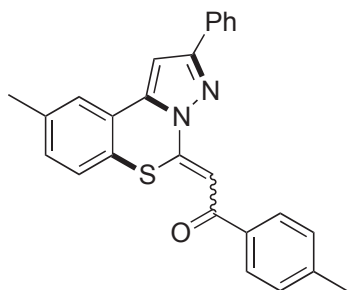
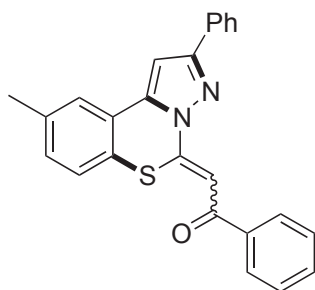
entry	cat.	ligand	base	solvent	temp. ($^\circ\text{C}$) ^c	2b (eq.) ^d	yield (%) ^b
1	CuI	<i>L</i> -proline	Cs_2CO_3	MeCN	100	2.5	43
2	CuI	DMEDA	Cs_2CO_3	MeCN	100	2.5	55
3	CuI	1,10-phen	Cs_2CO_3	MeCN	100	2.5	86
4	CuI	-	Cs_2CO_3	MeCN	100	2.5	89
5	CuBr	-	Cs_2CO_3	MeCN	100	2.5	43
6	$\text{Cu}(\text{OAc})_2$	-	Cs_2CO_3	MeCN	100	2.5	41
7	-	-	Cs_2CO_3	MeCN	100	2.5	0
8	CuI	-	NaOAc	MeCN	100	2.5	37
9	CuI	-	K_3PO_4	MeCN	100	2.5	34
10	CuI	-	NaOEt	MeCN	100	2.5	trace
11	CuI	-	Cs_2CO_3	DMF	100	2.5	68
12	CuI	-	Cs_2CO_3	DMSO	100	2.5	29
13	CuI	-	Cs_2CO_3	dioxane	100	2.5	21
14	CuI	-	Cs_2CO_3	toluene	100	2.5	39
15	CuI	-	Cs_2CO_3	MeCN	80	2.5	52
16	CuI	-	Cs_2CO_3	MeCN	100	1.5	66

^a Reaction conditions: (**1a**) (0.25 mmol), hydrazine hydrochloride (0.375 mmol), (**2b**) (0.625 mmol), catalyst (0.025 mmol), ligand (0.05 mmol), base (0.75 mmol), solvent (2 mL), under nitrogen atmosphere. Reaction time (12 h for the first step; 24 h for the second step). ^b Isolated yield from **1a** to **3e**. ^c For the second step. ^d Relative to **1a**.

As shown in Table 2, the substrate scope of the one-pot two-step reactions was investigated, and the examined substrates provided moderate to good yields. For compound **1**, the substrates with electron-withdrawing groups showed higher reactivity than those with electron-donating groups. The substrate with a C–Cl bond, 1-(2-chlorophenyl)-3-phenylprop-2-yn-1-one, also gave the target product (**3a**) in 73% yield. For substrate **2**, substituents bearing either electron-withdrawing or electron-donating groups gave good yields. Interestingly, no extra ligand and additive were required in the reactions above. The reactions could tolerate some functional groups in the substrates including ether (**3d**, **3j**, **3m–p**), C–Cl bond (**3e**, **3k**), C–F bond (**3q**, **3r**), CF₃ (**3f**, **3l**, **3p**, **3r**). In addition, we cannot get the desired product when R² are alkyl groups.

Table 2. One-pot two-step synthesis of benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives under copper-catalyzed conditions^a

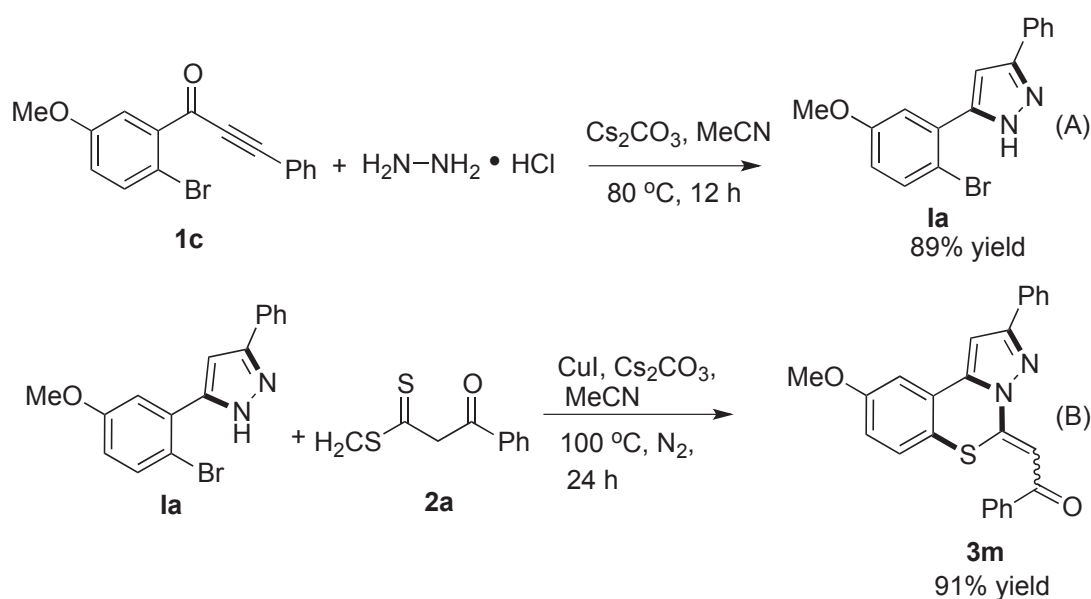




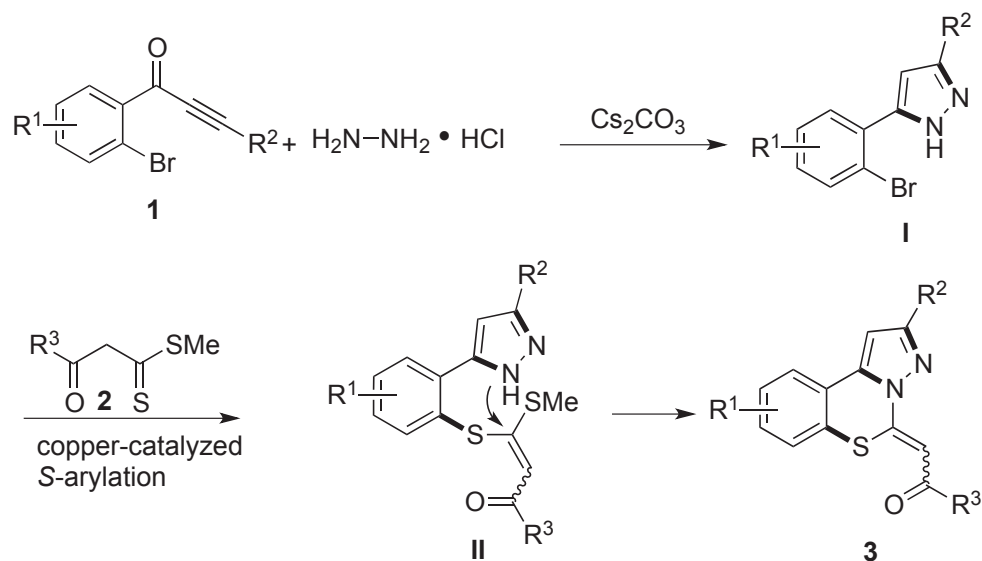
^a Reaction conditions: substituted 1-(2-bromophenyl)-3-alkylprop-2-yn-1-one (**1**) (0.25 mmol), hydrazine hydrochloride (0.375 mmol), β -oxodithioesters (**2**) (0.625 mmol), CuI (0.025 mmol), Cs_2CO_3 (0.75 mmol), MeCN (2 mL) 100 °C (for the second step), under nitrogen atmosphere. Reaction time (12 h for the first step; 24 h for the second step). ^b Isolated yield from **1** to **3**.

As shown in Scheme 2, we attempted two control experiments in order to explore the copper-catalyzed one-pot two-step reaction mechanism. Coupling of 1-(2-bromo-5-methoxyphenyl)-3-phenylprop-2-yn-1-one (**1c**) with hydrazine hydrochloride in the presence of Cs_2CO_3 led to 5-(2-bromo-5-methoxyphenyl)-3-phenyl-1*H*-pyrazole in 89% yield (**1a**) (Scheme 2A), whose structure was confirmed by NMR and MS. Copper-catalyzed reaction of **1a** with methyl 3-oxo-3-phenylpropanedithioate (**2a**) provided product **3m** in 91% yield under the standard condition (Scheme 2B). Therefore, a possible mechanism on the copper-catalyzed three-component reactions of substituted 1-(2-bromophenyl)-3-phenylprop-2-yn-1-ones, hydrazine hydrochloride and β -oxodithioesters leading to benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives (**3**) is proposed in Scheme 3. First, coupling of substituted 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**1**) with hydrazine hydrochloride provides **I** in the presence of base (Cs_2CO_3). Copper-catalyzed coupling of **I** with β -oxodithioesters (*S*-arylation) gives **II**, intramolecular nucleophilic substitution reaction in **II** leads to the target product (**3**).

In summary, we have developed a convenient and efficient copper-catalyzed method for the synthesis of benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives from the readily available starting materials. The reactions were performed under mild conditions, and no extra ligand and additive were required. In addition, pyrazoles were not pre-synthesized. This convenient and economical approach to benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives is expected to find wide application in academic and industrial research.



Scheme 2. (A) Coupling of 1-(2-bromo-5-methoxyphenyl)-3-phenylprop-2-yn-1-one (**1c**) with hydrazine hydrochloride leading to 5-(2-bromo-5-methoxyphenyl)-3-phenyl-1*H*-pyrazole (**1a**). (B) Copper-catalyzed reaction of **1a** with methyl 3-oxo-3-phenylpropanedithioate (**2a**) leading to **3m**



Scheme 3. Possible mechanism for synthesis of benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives (3)

EXPERIMENTAL

All reactions were carried out under nitrogen atmosphere. Proton and carbon magnetic resonance spectra (¹H NMR and ¹³C NMR) were recorded using tetramethylsilane (TMS) in the solvent of CDCl₃ as the internal standard (¹H NMR: TMS at 0.00 ppm, CDCl₃ at 7.26 ppm; ¹³C NMR: CDCl₃ at 77.0 ppm).

General procedure for synthesis of compounds 3a-s.

Substituted 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (0.25 mmol), hydrazine hydrochloride (0.5 mmol), Cs₂CO₃ (0.5 mmol, 163 mg), dried MeCN (3 mL) were added to a 25 mL t-shaped tube with a magnetic stirrer under nitrogen atmosphere. The mixture was allowed to stir under nitrogen atmosphere at 80 °C for 12 h. After cooled to room temperature, β-oxodithioester (0.625 mmol), Cs₂CO₃ (0.25 mmol, 82 mg), CuI (0.025 mmol, 5 mg) were added to this 25 mL t-shaped tube with a magnetic stirrer under nitrogen atmosphere. The mixture was allowed to stir under nitrogen atmosphere at 100 °C for 24 h. After cooled to room temperature, the resulting solution was concentrated via rotary evaporation, and the residue was purified by column chromatography on silica gel to provide the desired product (3a-s).

ACKNOWLEDGEMENTS

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