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Synthesis of 2-iminothiazolidin-4-ones *via* copper-catalyzed [2 + 1 + 2] tandem annulation†

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In this paper, an efficient synthesis of 2-iminothiazolidin-4-ones through a copper-catalyzed tandem annulation reaction of alkyl amines, isothiocyanates and diazo acetates is presented. Notable advantages of this [2 + 1 + 2] cyclization methodology include readily accessible starting materials, simple operation, mild reaction conditions, high yields, step-economy and diverse functional group tolerance. In addition, the reaction is applicable to the gram scale synthesis and the preparation of bioactive molecules.

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Introduction

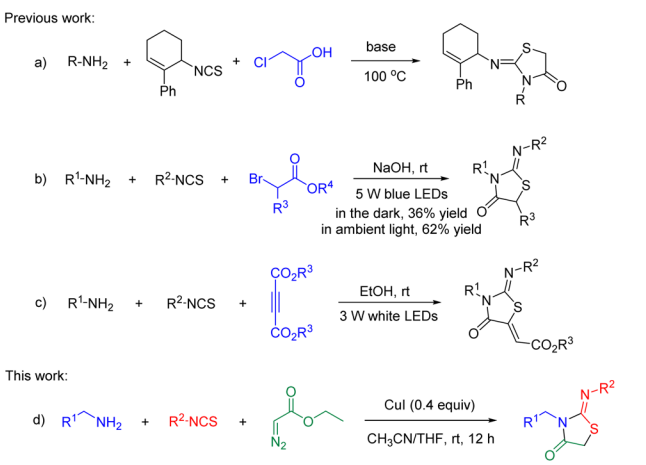
The thiazolidine skeleton, a privileged heterocyclic motif, is ubiquitous in various natural compounds, drug candidates, and pharmacologically active molecules. Specifically, 2-iminothiazolidin-4-one derivatives have attracted much attention due to their broad biological activities[1] and have thus been developed as sphingosine-1-phosphate receptor agonists,[2] carbonic anhydrase IX inhibitors,[3] selective glycogen synthase kinas-3β inhibitors,[4] cell division cycle dual phosphatases inhibitors,[5] entamoeba histolytica inhibitors,[6] and human carbonic anhydrase IX inhibitors.[7] Owing to their pharmaceutical importance, some powerful synthetic methodologies have been developed to access 2-iminothiazolidin-4-ones.[8] In addition, the one-pot three-component cyclization has been successfully explored for the acquisition of 2-iminothiazolidin-4-ones *via* amines, isothiocycanates, with chloroacetic acid[9] (Scheme 1a)/α-bromoesters[10] (Scheme 1b)/alkyl acetylenedicarboxylates[11] (Scheme 1c).

Despite the great progress, the reported methods suffer from several drawbacks such as high temperature, microwave-irradiation, or difficult to scale-up (visible-light-promoted, Scheme 1b and c). Therefore, there is an urgent need to develop concise and scalable methods for the formation of 2-iminothiazolidin-4-ones under mild reaction conditions.

Diazocarbonyl compounds are a class of versatile and easily accessible building blocks containing two functional groups, thereby affording rich chemistry under different reaction conditions.[12] For instance, various cyclopropanations, C–H alkylation, C–X insertion, the Wolff rearrangement, and dipolar cycloaddition reactions have been established.[13] In the past few years, the transition-metal-catalyzed diazocarbonyl compounds have been applied to the assembly of N-heterocycles *via* carbene transfer reactions and such reactions have emerged as a powerful tool in synthetic organic chemistry.[14] Here we designed a novel three-component tandem strategy to prepare the 2-iminothiazolidin-4-ones *via* the copper-catalyzed [2 + 1 + 2] cyclization of alkyl amines, isothiocyanates, and diazo esters (Scheme 1d).

Results and discussion

Our investigations were started with the reaction of phenylmethanamine **1a**, phenyl isothiocyanate **2a**, and ethyl 2-



Scheme 1 One-pot three-component cyclization of 2-iminothiazolidin-4-ones.

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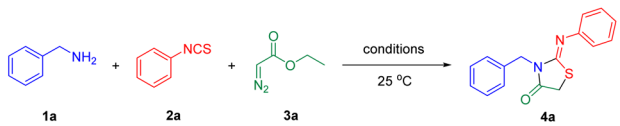
diazoacetate **3a** in CH_3CN at room temperature (25 °C) (Table 1). As shown in Table 1, a brief screening of the copper catalysts and iodine reagents suggested that CuI was the best choice (entries 1–12). In this case, 2-iminothiazolidin-4-one (**4a**) was obtained in 78% yield (entry 5). As expected, no target product was found in the absence of copper catalyst (entry 13). Subsequently, the amount of CuI (Tables S1†), the molar ratio of reactants (Tables S2†), reaction time (Tables S3†) and reaction temperature (Tables S4†) were optimized. However, the yield of **4a** was not improved (see the ESI Tables S1–S4† and Table 1, entry 6). For example, the yield was decreased to 51% when the reaction was carried out in CH_3CN for 6 h (entry 6). Then, the effect of solvents was also investigated (entries 14–19). It was found that the mixture of CH_3CN with THF (v/v = 1 : 1) was a more efficient than other solvent systems, affording **4a** in 85% yield (entry 19). In addition, when the reaction was performed under N_2 or O_2 atmosphere, the transformations proceeded without much difference (entries 20–21), illustrating that the effect of oxygen was insignificant.

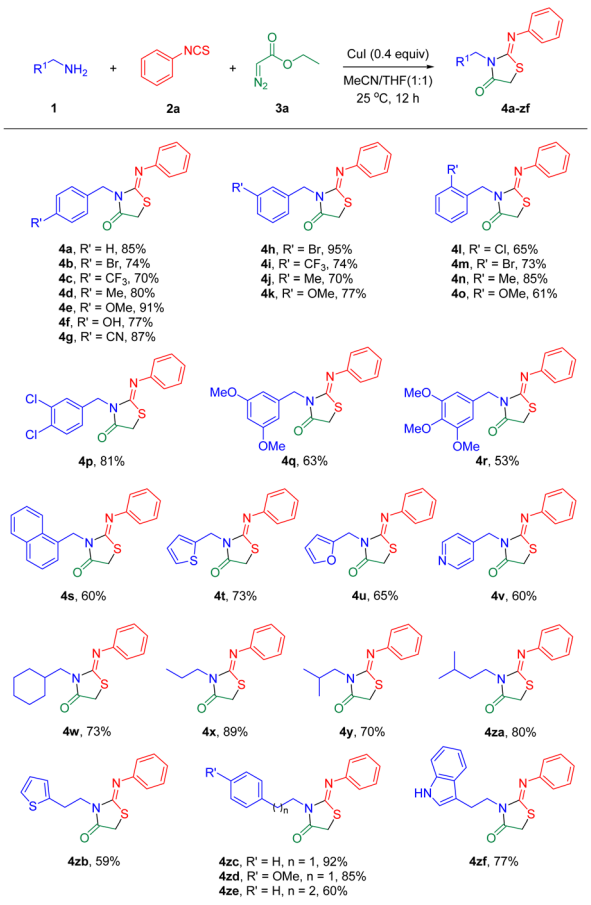
With the optimal reaction conditions in hand, the substrate scope of this transformation was examined. As shown in Scheme 2, the scope of alkyl amines **1** was illustrated and the reaction was performed on the open air conditions at room temperature (25 °C). In general, the results revealed that

Table 1 Screening of reaction conditions[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	$CuCl_2$	CH_3CN	12	38
2	$CuBr_2$	CH_3CN	12	48
3	CuCl	CH_3CN	12	41
4	CuBr	CH_3CN	12	51
5	CuI	CH_3CN	12	78
6	CuI	CH_3CN	6	51
7	$Cu(OAc)_2$	CH_3CN	12	0
8	$Cu(OTf)_2$	CH_3CN	12	31
9	$Cu(TFA)_2$	CH_3CN	12	65
10	NBS	CH_3CN	12	22
11	NIS	CH_3CN	12	42
12	I_2	CH_3CN	12	49
13	—	CH_3CN	12	0
14	CuI	DMF	12	53
15	CuI	Acetone	12	68
16	CuI	EtOH	12	48
17	CuI	$MeNO_2$	12	56
18	CuI	THF	12	82
19	CuI	CH_3CN/THF (1 : 1)	12	85
20[c]	CuI	CH_3CN/THF (1 : 1)	12	81
21[d]	CuI	CH_3CN/THF (1 : 1)	12	78

[a] Reaction conditions: **1a** (0.222 mmol), **2a** (0.185 mmol), **3a** (0.278 mmol) and catalyst (0.4 equiv.) in solvent (2 mL), open to air at room temperature (25 °C). [b] Isolated yield. [c] Reaction under N_2 atmosphere. [d] Reaction under O_2 atmosphere.



Scheme 2 Scope of RCH_2NH_2[a,b]. [a]Reaction conditions: **1** (0.222 mmol), **2a** (0.185 mmol), **3a** (0.278 mmol) and CuI (0.4 equiv.) in CH_3CN/THF (1 : 1) (2 mL), open to air at room temperature (25 °C). [b]Yields of isolated products.

benzylamines **1b–1o** bearing either an electron-donating group (CH_3, OCH_3, and OH) or an electron-withdrawing group (Cl, Br, CF_3, and CN) on the *para*-/*meta*-/*ortho*-position of the aromatic ring reacted with phenyl isothiocyanate **2a** and ethyl 2-diazoacetate **3a** smoothly to furnish products **4b–4o** in good to excellent yields. Moreover, disubstituted and trisubstituted benzylamines were able to undergo this transformation to afford the desired products **4p–4r** in moderate to good isolated yields. Further, naphthalen-1-ylmethanamine, thiophen-2-ylmethanamine, furan-2-ylmethanamine, and pyridin-4-ylmethanamine were applicable to this reaction system providing **4s–4v** in moderate yields. When cyclohexylmethanamine and aliphatic amines were employed as competent partners with **2a** and **3a**, the corresponding products **4w–4za** were obtained in good yields. To our delight, the use of 2-(thiophen-2-yl)ethan-1-amine, 2-phenylethan-1-amine, and 3-phenylpropan-1-amine also generated the desired 2-iminothiazolidin-4-ones **4zb–4ze** in 59–92% yields. Notably, tryptamine afforded product **4zf** in 77% yield. However, aniline failed to give the desired product, which might be due to the conjugation effect between the aromatic ring and the nitrogen atom.

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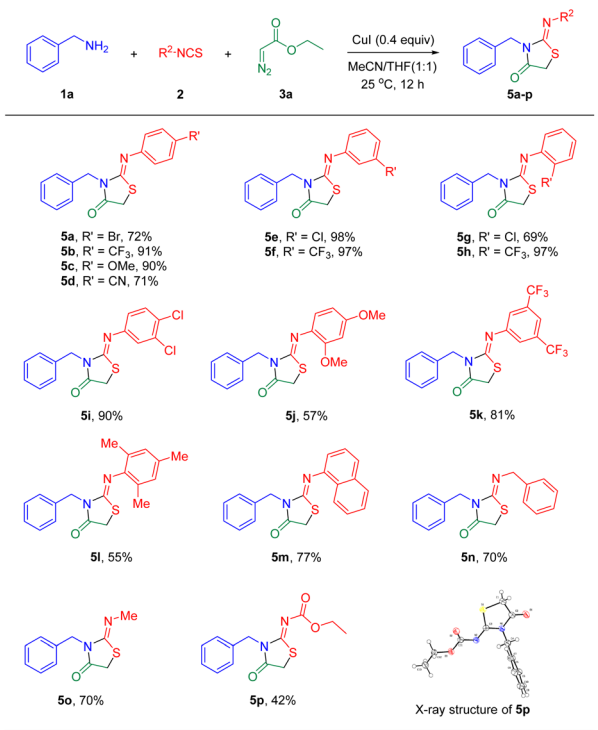
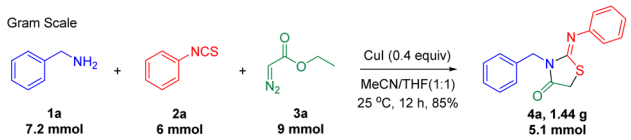
The scope of isothiocyanates under similar conditions was then investigated, and the results are summarized in Scheme 3. As expected, isothiocyanatobenzenes containing –Cl, –Br, –CF_3, –OCH_3, –CN groups at the *para*-, *meta*-, or *ortho*-position reacted well with phenylmethanamine **1a** and ethyl 2-diazoacetate **3a**, producing the desired cyclization products **5a–5h** in moderate to excellent yields. Furthermore, disubstituted and trisubstituted isothiocyanatobenzenes provided the desired products **5i–5l** as well. For 1-napthyl isothiocyanate, the target product **5m** was formed in 77% yield, whereas (isothiocyanatomethyl) benzene gave the corresponding product **5n** in 70% yield. In addition, aliphatic isothiocyanates were tried. To our delight, isothiocyanatomethane demonstrated comparable reactivity and provided the desired product **5o** in 70% yield. Notably, the CuI catalyzed [2 + 1 + 2] tandem annulation of **1a**, *o*-ethyl carbonisothiocyanatidate **2p**, and ethyl 2-diazoacetate **3a** at room temperature (25 °C) afforded the 2-iminothiazolidin-4-one **5p** in 42% yield. The geometry of the imine double bond at **5p** was determined *via* X-ray crystallographic analysis (see the ESI† for details). Further, other substituted diazo compounds were screened under the standardized protocol. However, ethyl 2-diazo-3-oxo-3-phenylpropanoate, ethyl 2-diazo-3-oxobutanoate, or ethyl 2-diazo-2-phenylacetate couldn't be transformed into the target product because of a steric hindrance effect.

As shown in Scheme 4, the present method can be performed in gram scale. In addition, this tandem annulation was used to furnish bioactive molecules (Scheme 5). For instance, the



Scheme 3 Scope of isothiocyanate compounds[a,b]. [a]Reaction conditions: **1a** (0.222 mmol), **2** (0.185 mmol), **3a** (0.278 mmol) and CuI (0.4 equiv.) in CH_3CN/THF (1 : 1) (2 mL), open to air at room temperature (25 °C). [b]Yields of isolated products.

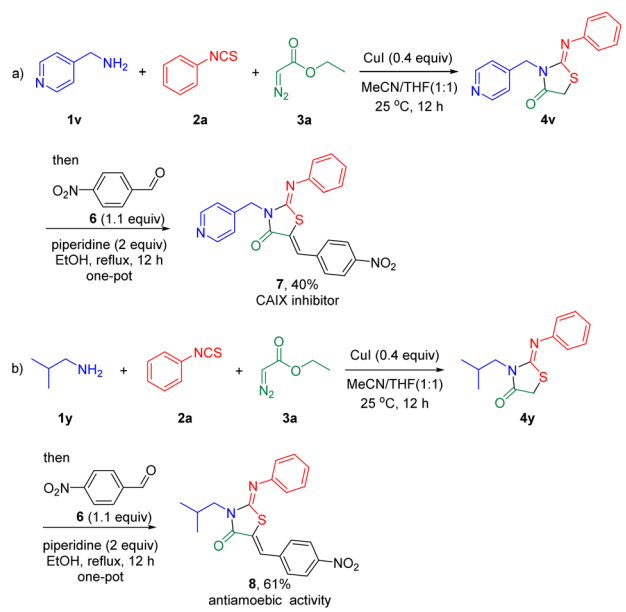


Scheme 4 Gram scale.

reaction of **1v**, phenyl isothiocyanate **2a**, ethyl 2-diazoacetate **3a**, and 4-nitrobenzalde **6** led to **7**, a human carbonic anhydrase IX inhibitor,[7] in 40% yield *via* a one-pot annulation (Scheme 5a). Similarly, an entamoeba histolytica inhibitor[6] **8** was obtained in 61% yield (Scheme 5b).

To gain insight into the mechanism of this reaction, we carried out some control experiments (Scheme 6). Addition of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), or 1,1-diphenylethylene (DPE), showed no significant effects on the yield of the desired product **4a** (eqn (1)–(3)), indicating that a radical pathway is unlikely in this reaction. Furthermore, the reaction of 1-benzyl-3-phenylthiourea **9** (ref. 10, 11 and 15) with ethyl 2-diazoacetate **3a** carried out under the standard conditions provided **4a** in 76% isolated yield, implying that **9** might be a reasonable intermediate in this transformation (eqn (4)). However, when 1-benzyl-3-phenylthiourea **9** was used as the substrate in the absence of CuI, no desired product **4a** was detected, suggesting that CuI is essential to the reaction (eqn (5)).

According to these experimental results, a plausible reaction mechanism for the copper-catalyzed tandem annulation reaction is suggested in Scheme 7. First, the reaction of alkyl amine (**1**) and isothiocyanate (**2**) gives intermediate **A**.[10,11,15] Next, the



Scheme 5 The synthesis of 2-iminothiazolidin-4-one derivatives of bioactive molecules[a]. [a]Reaction conditions: **1** (0.222 mmol), **2a** (0.185 mmol), **3a** (0.278 mmol) and CuI (0.4 equiv.) in CH_3CN/THF (1 : 1) (2 mL), open to air at room temperature (25 °C). Isolated yields.

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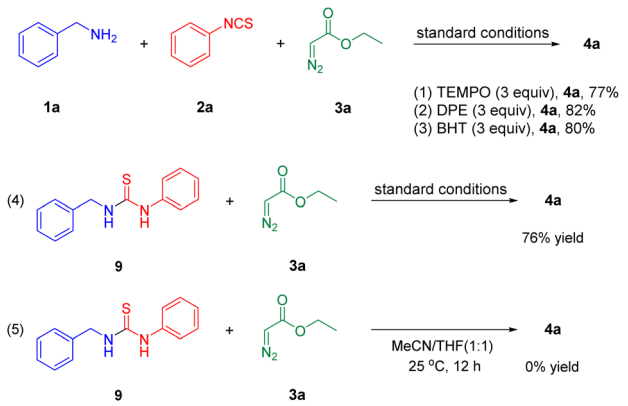
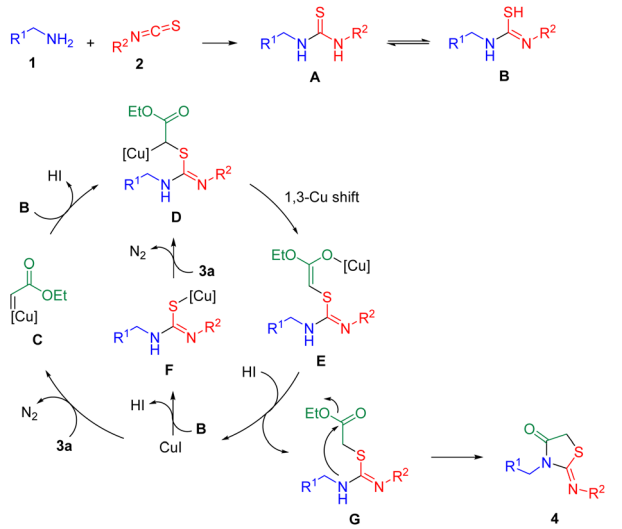


Scheme 6 Mechanistic studies.



Scheme 7 Proposed reaction mechanism.

intermediate **B** is obtained from **A** *via* isomerization.[10,16] Then the coordination of **3a** to the catalyst (CuI) affords the active Cu(I) carbene intermediate **C** through the extrusion of one N_2 molecule.[17] Subsequently, nucleophilic attack of intermediate **B** on Cu(I) carbene intermediate **C** forms intermediate **D**, which further generates intermediate **E** through 1,3-Cu shift. Intermediate **E** is protonated to produce intermediate **G** with concomitant regeneration of CuI catalyst. Finally, **G** undergoes an intramolecular ammonolysis/cyclization to yield the desired product **4**. In the meantime, it is also possible that CuI first reacts with intermediate **B** to provide intermediate **F**, followed by metal carbene generation *via* its reaction with **3a** to give **D**.

Conclusions

In conclusion, we have explored a novel copper-catalyzed tandem annulation reaction of alkyl amines, isothiocyanates, and diazo esters for the construction of 2-iminothiazolidin-4-ones under mild reaction conditions. This transformation represents a copper-catalyzed C–S/C–N bond formation strategy in a one-pot protocol without the requirement of any external bases, ligands, or oxidants. It shows wide functional group tolerance, high yields, and high step economy. In addition, this protocol is applicable to the gram scale synthesis and the preparation of bioactive molecules with such structural motif, which may facilitate the research of such bioactive molecules in medicinal chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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