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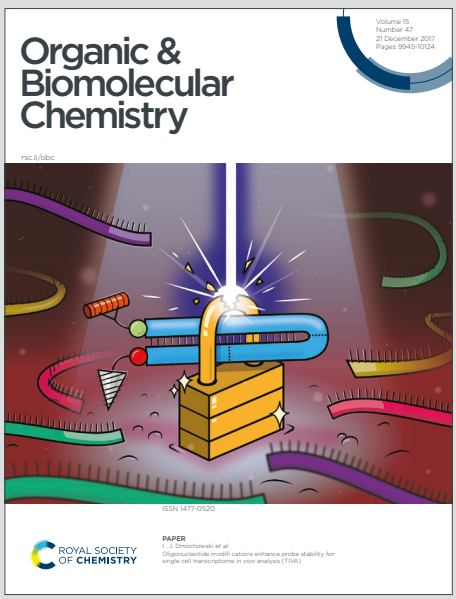

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ARTICLE

A Facile Access to *N*-Sulfonylthioimidates and Their Use for the Transformation to 3,4-Dihydroquinazolines

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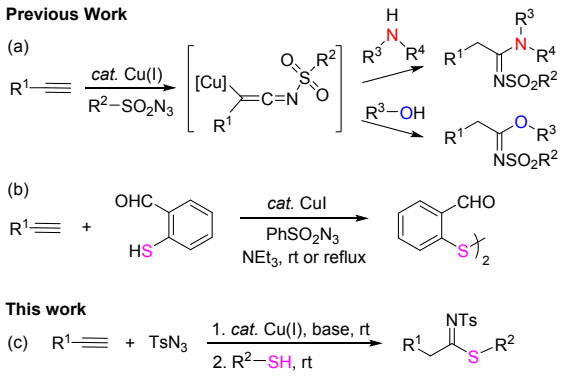
N-sulfonylthioimidates can be efficiently synthesized through one-pot three-component coupling of terminal alkynes, sulfonyl azides, and thiols by using a copper(I) catalyst in the presence of 4-dimethylaminopyridine. The proposed reaction is characterized by mild reaction conditions and tolerance of diverse functional groups. Additionally, the crucial pharmacophore of 3,4-dihydroquinazolines was synthesized using a one-pot synthetic strategy from *N*-sulfonylthioimidates.

Introduction

Thioimidate derivatives are crucial building blocks in organic synthesis[1] and intermediates in medical compounds.[2] Moreover, a thioimidate moiety is present in heterocycles, including benzothiazoles and thiazoles.[3] In addition, an aryl thioimidate scaffold regioselectively reacts with alkynes to form aryl thio azadienes.[4] Therefore, the development of novel methods for thioimidate synthesis remains desirable. Conventional methods for thioimidate synthesis involve thioamide alkylation to yield alkyl thioimidates.[5] However, a major limitation of the aforementioned method is the preparation of thioamide, which is synthesized directly by treating amide groups with P_4S_{10}, B_2S_3, or Lawesson's reagent. These methods require the use of highly toxic reagents or are applied under harsh conditions. To overcome these problems, more recently, numerous synthetic strategies for the organic synthesis of thioimidates have been developed. Examples include copper- or palladium-catalyzed iminothiolation of isocyanides,[1g,6] organoaluminium-promoted Beckmann rearrangement of oxime sulfonates,[7] combination of nitriles with thiols,[8] palladium-catalyzed coupling between aryl halide, thioalkoxide, and isocyanide,[9] radical alkylation of α-nitro thiophenol compounds,[10] combination of hexamethyldisilazane-promoted thiols with nitroalkanes,[11] palladium-catalyzed insertion of isocyanides into the C–S bonds of heteroaryl sulfides,[12] and reaction of secondary thioamides with diaryliodonium salts under metal-free conditions.[13] Although thioimidates can be efficiently synthesized using numerous methods, each of these synthetic protocols has distinct disadvantages. The development of an ideal reaction condition that can be applied feasibly and is scalable for industrial applications is required.

Recently, the modified copper-catalyzed alkyne-azide cycloaddition (CuAAc) of a highly reactive ketenimine intermediate for the preparation of various molecules,[14] such as amides,[15] amidines,[16] imidates,[17] coumarins,[18] quinolines,[19] thiophenes,[20] dihydropyrimidin-4-ones,[21] oxindoles,[21] 4-substituted pyridines,[22] and cyclohexadienones,[23] has received research attention. The reaction mechanism proceeds through the formation of sulfonyl copper triazole, which can be formed through the CuAAc pathway.[14] Subsequently, the Dimroth rearrangement leads to the formation of a diazoimino copper intermediate, which is converted to the ketenimine intermediate through the Wolff rearrangement. A nucleophilic group can be employed to attack the electrophilic ketenimine intermediate to obtain corresponding products (Scheme 1a). However, Wang's group found that the reaction of aryl thiol molecules through a CuAAc strategy yields a disulfide byproduct (Scheme 1b); although they reported that the reaction could be performed to produce aryl thioimidates by using potassium aryl thiolate derivatives.[24] They proposed that sulfonyl azide might be reduced to sulfonyl amide and nitrogen gas by thiols in the presence of triethylamine (TEA), and thiols were oxidized to disulfide derivatives.[24-25] Thus, we developed a novel synthetic strategy for thioimidate synthesis with the use of mild and feasible reaction conditions. In this paper, the synthesis of *N*-



Scheme 1. Copper-catalyzed multicomponent reaction of alkyne, sulfonyl azide, and diverse nucleophiles.

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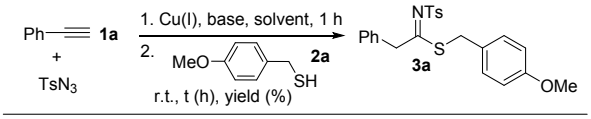
sulfonylthioimidates through a new multicomponent reaction, tosyl triazole–mediated denitrogenative thiolation, is proposed. Recently, our group developed a method for thiol group formation that involves the lanthanide(III)-catalyzed *S*-deacetylation of thioacetates.[26] We now report the successful preparation of *N*-sulfonylthioimidates through a one-pot two-step reaction, in which freshly prepared thiols are directly reacted with ketenimine intermediates, which are formed using alkyne and tosyl azide under copper (I) catalyst conditions (Scheme 1c).

Results and discussion

The model of the one-pot three-component reaction of thioimidate synthesis was optimized using phenylacetylene **1a**, tosyl azide (TsN_3), and thiol molecule **2a** by employing a copper(I) catalyst under different base and solvent conditions (Table 1). Initially, to prevent the reduction of tosyl azide to tosyl amide ($TsNH_2$) by thiol molecule,[24] alkyne **1a** with tosyl azide was reacted in a copper(I) iodide catalytic system for 1 h to produce ketenimine intermediates, and the freshly prepared thiol molecule **2a** was subsequently added to the reaction mixture. The reactivity of the one-pot two-step reaction was assessed using the reported reaction conditions,[14] including bases, (triethylamine and potassium carbonate), solvents (tetrahydrofuran, acetonitrile, dimethylformamide, and dichloromethane), and copper(I) sources (CuI and CuCl) (Table 1, entries 1–8). The results revealed that the reaction proceeds unfavorably, and the major product is disulfide. Chang et al. reported a range of base additives suitable for accelerating ketenimine intermediate formation.[27] Inspired by the use of aryl thiolates as a substitute for thiols in thiochromene synthesis,[24] we considered the base used in this reaction to be a potentially crucial factor. To determine the optimal base, reaction conditions were set according to the use of aromatic bases, including imidazole (entry 9), pyridine (entry 10), 2,6-lutidine (entry 11), and 4-dimethylaminopyridine (DMAP, entry 12). We found that the reaction could proceed favorably in the presence of the CuI catalyst with 1 equivalent of DMAP and 3 equivalents of the thiol molecule **2a** at room temperature to obtain a satisfactory yield of the desired *N*-sulfonylthioimidate **3a** (80%). Therefore, DMAP was selected as the base for optimal reactivity.

To extend the scope of thioimidate formation, the aforementioned optimization conditions of the one-pot three-component reaction were used to synthesize several functionalized thioimidates by treating organic alkynes with tosyl azide, thiol molecules, and DMAP in the copper(I) iodide catalytic system. Various structurally and electronically tuned organic thiol molecules were investigated under these optimized conditions (Table 2). Benzylic thiol molecules with electron-donating groups, such as *p*-OMe (**2a**), *m*-OMe (**2c**), *o*-OMe(**2d**), *p*-Me (**2e**), and naphthalene (**2f**) derivatives, formed the desired thioimidate products (**3a**–**3f**) with satisfactory yields (66%–81%). Moreover, a reaction with an electron-withdrawing group of benzylic thiol molecules, such as *p*-F (**2g**), *p*-Cl (**2h**), *p*-Br (**2i**), and *p*-NO_2 (**2j**), produced satisfactory yields (66%–88%).

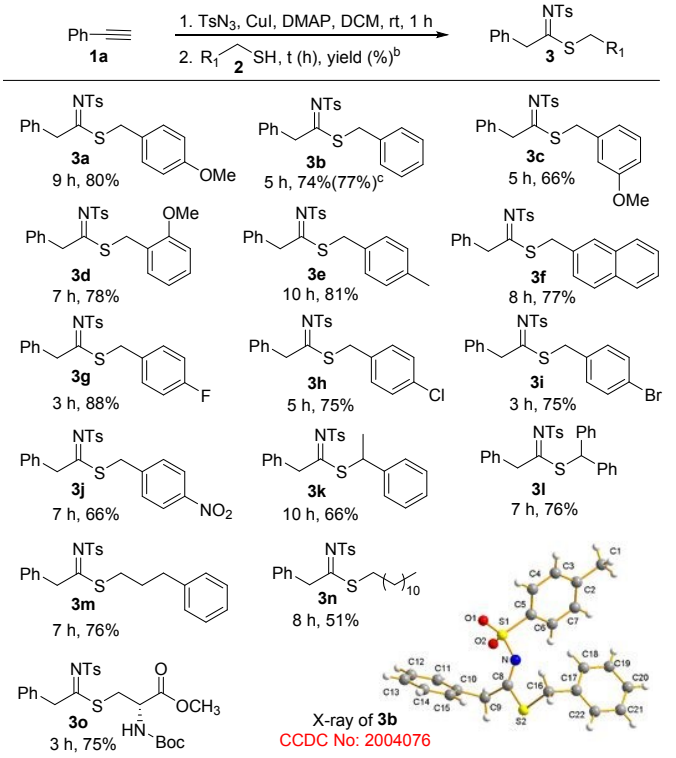
Table 1. Optimization of the reaction conditions



entry	solvent	base	t (h)	yield (%)[e]
1[a]	THF	Et_3N	4	4
2[a]	ACN	Et_3N	4	5
3[a]	DMF	Et_3N	2	N.D.
4[a]	DCM	Et_3N	3	6
5[a]	DCM	K_2CO_3	4	N.D.
6[b]	DCM	Et_3N	8	6
7[c]	DCM	Et_3N	6	8
8[d]	DCM	Et_3N	8	N.R.
9[c]	DCM	Imidazole	8	4
10[c]	DCM	Pyridine	9	18
11[c]	DCM	2,6-Lutidine	9	15
12[c]	DCM	DMAP[f]	9	80 (39)[g]

[a] Conditions: phenylacetylene (1.0 equiv), TsN_3 (1.2 equiv), CuI (0.1 equiv), base (1.0 equiv), and thiol (1.5 equiv) under nitrogen atmosphere. [b] Thiol (3.0 equiv). [c] CuI (0.2 equiv), and thiol (3.0 equiv). [d] CuCl (0.2 equiv), and thiol (3.0 equiv). [e] Isolated yield. [f] When DMAP was used 0.3 equiv, the reaction yield was only 25% [g] When thiol **2a** was used 1.5 equiv. N.D. = not detected. N.R. = no reaction.

Table 2. Thioimidate formation by using various organic thiol molecules.[a]



[a] Conditions: Phenylacetylene **1a** (1.0 equiv), TsN_3 (1.2 equiv), CuI (0.2 equiv), DMAP (1.0 equiv) and thiol (3.0 equiv) in DCM under nitrogen atmosphere. [b] Isolated yield. [c] Gram scale (**1a**, 9.79 mmol)

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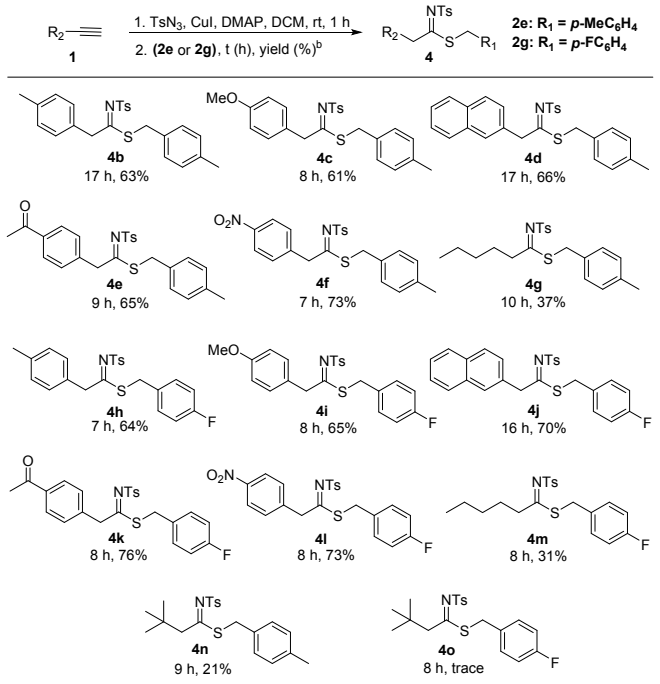
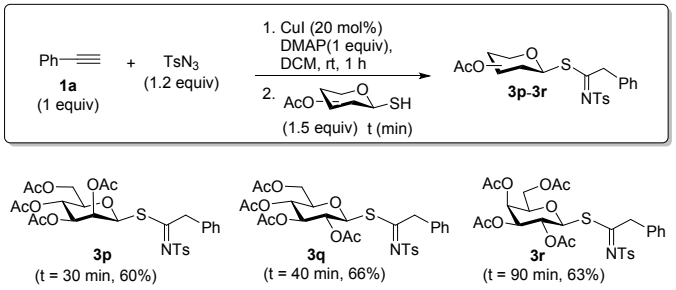
Additionally, reactions involving branched chain thiol molecules (**2k** and **2l**), medium-length alkyl chain thiol molecules (**2m** and **2n**), and the biological molecules of cysteine derivatives **2o** achieved favorable results, and the obtained yield of corresponding products (**3k**–**3o**) was 51%–76%. Moreover, we applied these reaction conditions to gram-scale procedures and achieved a satisfactory yield of desired thioimidate **3b**. The structure and (E)-geometry of thioimidate **3b** was confirmed using *X*-ray crystal analysis (Table 2).[28] Based on the successful results presented in Table 2, we used aromatic thiol molecules with electron-donating (**2e**) and electron-withdrawing (**2g**) groups and treated these molecules with diverse organic alkynes for thioimidate synthesis (Table 3). A wide range of alkynes was easily converted into the corresponding thioimidate adducts (**4b**–**4o**), and for most of them (**4b**–**4f** and **4h**–**4l**), satisfactory reaction yields (61%–76%) were obtained. Therefore, this aryl system exhibited high functional group tolerance, and aromatic alkynes with electron-donating (**1b**–**1d**) and electron-withdrawing (**1e**–**1f**) groups were successfully employed in this synthetic strategy. In contrast to the aryl alkynes, the aliphatic 1-hexyne (**1g**) was treated with thiol molecules **2e** and **2g**, which resulted in the formation of the desired products **4g** and **4m** with yields of 37% and 31%, respectively. However, treatment of the stereo-hindered aliphatic alkyne (**1h**) with **2e** and **2g** led to the formation of **4n** with a low reaction yield (21%) and traces of **4o**.

Table 3. Thioimidates formation by using various organic alkyne molecules.[a]



[a] Conditions: Alkyne (1.0 equiv), TsN_3 (1.2 equiv), CuI (0.2 equiv), DMAP (1.0 equiv) and thiol (3.0 equiv) in DCM under nitrogen atmosphere. [b] Isolated yield.

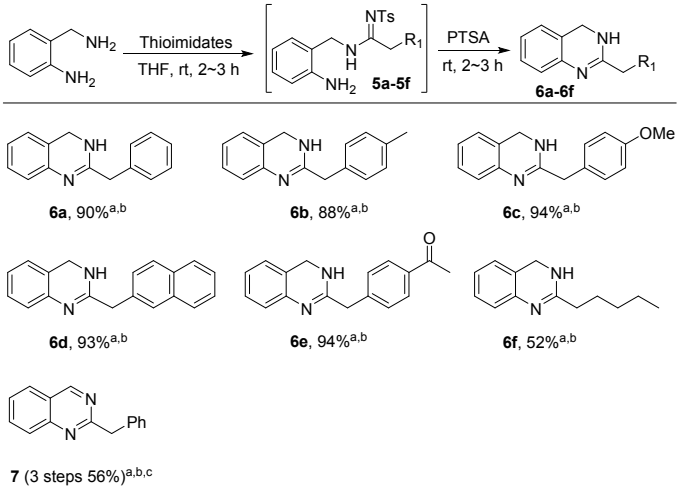
Furthermore, to determine the applicability of the one-pot three-component reaction, we explored the possibility of conducting this reaction with carbohydrates. In particular, glycosyl thioimidates were selected as the anomeric leaving group of glycosyl donors and temporary masking group of glycosyl acceptors.[29] Thus, we conducted the reaction by using phenylacetylene **1a**, tosyl azide, and β-1-mercapto glycosides (**2p**–**2r**). Scheme 2 displays the results. With the use of 3 equivalents of thiol molecules, the yield of the desirable products of the reaction decreased and disulfide byproducts were obtained in major yields. To suppress byproduct formation, we used 1.5 equivalents of **2p**–**2r**, which led to the formation of the desired glycosyl 1-thioimidate **3p**–**3r** with satisfactory yields (60%-–66%). Notably, the configuration of newly formed glycosyl thioimidates was determined using nuclear magnetic resonance spectroscopy, and no α-anomer was obtained under these reaction conditions.



Scheme 2. Thioimidates formation by using β-1-mercapto glycosides.

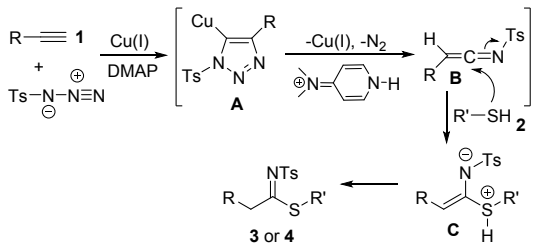
Subsequently, the practical potential of thioimidates for the synthesis of heterocycles was investigated. A 3,4-dihydroquinazoline core is a biologically crucial pharmacophore, and various derivatives with the key moiety exhibit anticancer,[30] antidepressant,[31] and trypanothione reductase inhibition[32] activities. Therefore, several synthetic methods for pharmacophore synthesis have been developed.[33] Because we considered that the key molecular skeleton of C2-substituted 3,4-dihydroquinazolines could be synthesized through the intramolecular cyclization of precursors obtained using the sequential *N*-functionalization of 2-aminobenzylamine with thioimidates, we developed a one-pot two-step route for the synthesis of crucial pharmacophores (Table 4). The intramolecular cyclization of 2-aminobenzyl amidines (**5a**–**5f**), which were obtained using 2-aminobenzyl amine and thioimidates, was readily achieved by employing *p*-toluenesulfonic acid. Under the proposed conditions, C2-substituted 3,4-dihydroquinazolines were obtained in satisfactory to excellent yields (52%–94%). We purified compound **5a** after the first step, and the results revealed that regioselective amidine formation was observed for benzylic amine over phenyl amine, leading to a 95% yield of 2-aminobenzyl amidines **5a**. Because thioimidates were employed in 3,4-dihydroquinazoline synthesis, we conducted C2-substituted quinazoline synthesis by using one-pot three-step reaction. After the sequential two-step reaction, an acid agent was removed, and then oxidation was induced through the addition of iodobenzenediacetate (PIDA) in tetrahydrofuran. The one-pot operation was successfully applied for three procedures to obtain a satisfactory yield of the desired C2-substituted quinazoline **7**.

Table 4. Synthesis of C2-substituted 3,4-dihydroquinazolines.



[a] Condition: Thioimidates (1.0 equiv) and 2-aminobenzylamine (1.2 equiv) in THF were stirred under nitrogen atmosphere for 2~3 h, then added *p*-toluenesulfonic acid monohydrate (2.0 equiv) to the reaction mixture. [b] Isolated yield. [c] After getting crude **6a**, an acid was removed through extraction, then the crude **6a** in THF was added iodobenzenediacetate (3 equiv) at rt for 3 h.

On the basis of literature reports,[14,15,19,34] a proposed reaction mechanism is shown in Scheme 3. The reaction can be rationalized as being initiated by the copper(I)-catalyzed [3+2] cycloaddition of sulfonyl azide and alkynes **1**, followed by the release of N_2 to form the intermediate ketenimine **B** (*via* **A**). Then, the nucleophilic thiols **2** attacked the electron deficient central carbon of ketenimine **B** lead to the construction of *N*-sulfonylthioimidates **3** or **4**.



Scheme 3. Possible mechanism route to N-sulfonylthioimidates.

Conclusions

In summary, *N*-sulfonylthioimidates can efficiently be prepared through the one-pot three-component reaction of terminal alkynes, TsN_3, and freshly prepared thiols under the action of a copper(I) catalyst in the presence of DMAP as the base. The developed method provides advantages such as efficiency, a wide substrate scope, considerably mild reaction conditions, and high tolerance toward diverse functional groups. Moreover, the method can be manipulated to obtain a satisfactory yield of the crucial pharmacophores of C2-substituted 3,4-dihydroquinazolines by using a range of substrates under ambient reaction conditions.

Conflicts of interest

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There are no conflicts of interest to declare.

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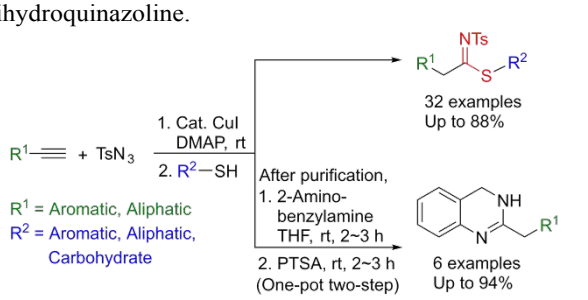
N-sulfonylthioimidates can be synthesized via terminal alkynes, sulfonyl azide, and thiols using a copper(I) catalyst in the presence of 4-dimethylaminopyridine. Subsequently, it can be transformed to crucial pharmacophores of 3,4-dihydroquinazoline.



Broad substrate scope High efficiency Crucial synthetic intermediate