Tetrahedron Letters 59 (2018) 1080–1083

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of (arylselanyl)- and (arylsulfenyl)-alkyl-1,2,3-triazolo-1,3,6-triazonines *via* a copper-catalyzed multicomponent reaction

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ARTICLE INFO

Article history:
Received 7 November 2017
Revised 12 January 2018
Accepted 23 January 2018
Available online 31 January 2018

Keywords:
Azonines
Copper
Nitrogen heterocycles
Organochalcogen compounds
1,2,3-Triazoles

ABSTRACT

An efficient copper-catalyzed multicomponent reaction was developed for the synthesis of (arylselanyl)- or (arylsulfenyl)-alkyl-1,2,3-triazolo-1,3,6-triazonines. The products were obtained in moderate to excellent yields *via* the reaction of *o*-phenylenediamine, 2-azidobenzaldehyde and different arylchalcogenyl alkynes using catalytic copper iodide in 1,4-dioxane at 100 °C. The reactions tolerated a range of substituents on the arylchalcogenyl alkynes and proved to be an efficient methodology for the combinatorial synthesis of new selenium or sulfur-containing triazonine derivatives.

Nine-membered *N*-heterocycles are an important class of compounds, which are present in several natural and synthetic bioactive molecules.[1] The azonines represent a significant class of medium-sized heterocyclic rings that are found in alkaloids, such as laurifonine, laurifine and laurifinine, obtained from the leaves of *Cocculus laurifolia*.[2] A number of important pharmacological properties have been attributed to benzoazonines, including the ability to stimulate the central nervous system (CNS)[3] and activate the protein kinase C (Teleocidin A and B) (Fig. 1).[4] These medium-sized heterocycles also possess antitumor,[5] antimalarial[6] and antihypertensive activities,[7] and are antagonists for cholecystokinin (CCK) receptors.[8]

Despite the important pharmacological activities attributed to this class of compounds, few methods to prepare benzoazonines have been reported.[9] Transition metal-catalyzed reactions have been employed as an efficient strategy to access various carbocycles and heterocycles. Transition-metal catalyzed C—*N* bond coupling has been established as a useful tool in modern organic synthesis, delivering by a variety of processes, a broad range of complex structures in high yields and selectivity.[10] For example, Selvaraju and Sun recently described the highly efficient copper-catalyzed tandem synthesis of 1,2,3-triazoloquinazolinones *via* sequential one-pot 1,2,3-triazole (CuAAC) formation followed by aerobic intramolecular C—H amidation (Scheme 1A).[11]

Therefore, multicomponent reactions (MCRs) offer an efficient route to produce complex molecular structures from simple and readily available substrates. Transition metal-catalyzed MCRs, including CuI-catalyzed protocols, are of high importance because in most cases they have excellent catalytic efficiency.[12] As an example, we recently reported the synthesis of fused 1,2,3-triazolo-1,3,6-triazonines using a copper-catalyzed MCR *via* sequential formation of an imine, 1,2,3-triazole and C—*N* bond.[13] The products were obtained in 34–98% yield from 2-azidobenzaldehydes, substituted diaminobenzenes and a range of terminal alkynes in the presence of catalytic CuI (Scheme 1B).

On the other hand, an important class of molecules with increased interest are organoselenium compounds.[14] These compounds are considered as attractive synthetic targets, owing to their special structural motifs and unique reactivity – organoselenium compounds serve as highly powerful and valuable building blocks in the synthesis of natural products,[15] selective transformations,[16] as well as chiral catalysts[17] and ionic liquids.[18] Additionally, these compounds are often linked to pharmacological activities.[19] Considering the aforementioned characteristics, there is significant interest in the development of methods for the synthesis and chemical modification of organoselenium compounds.

To the best of our knowledge, the synthesis of selenium or sulfur functionalized fused 1,2,3-triazolo-1,3,6-triazonines has

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https://doi.org/10.1016/j.tetlet.2018.01.072
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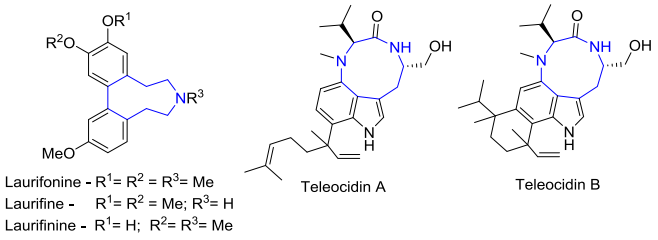
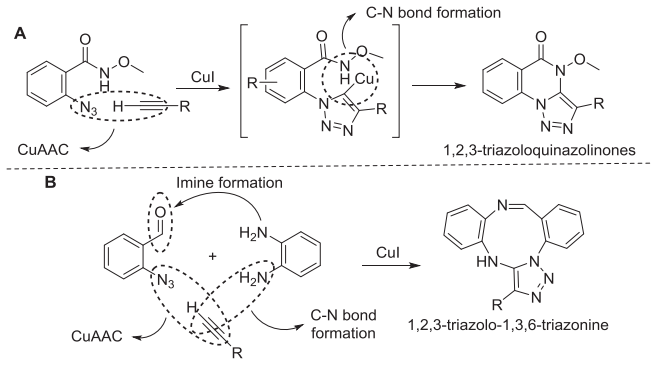
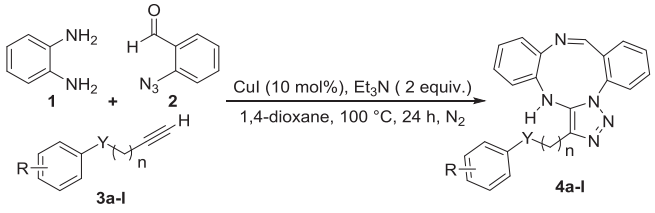


Fig. 1. Selected examples of bioactive benzoazonines.



Scheme 1. Recent examples of the copper-catalyzed tandem synthesis of *N*-heterocycles.



Scheme 2. General reaction scheme.

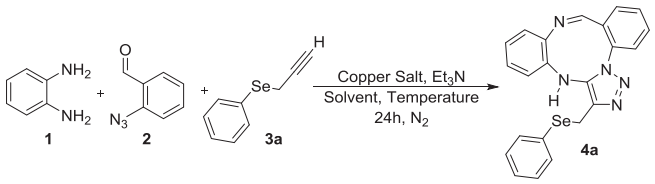
not yet been explored. In this sense, and due to our interest in the preparation of nitrogen-functionalized organoselenium compounds, herein we describe the synthesis of (arylselanyl)- or (arylsulfenyl)-alkyl-1,2,3-triazolo-1,3,6-triazonines **4** by a copper-catalyzed MCR (Scheme 2).

To determine the best reaction conditions, initially a mixture of *o*-phenylenediamine **1** (0.5 mmol), 2-azidobenzaldehyde **2** (0.5 mmol) and phenyl propargylselenide **3a** (0.5 mmol) in DMSO (1.0 mL) was stirred under an N_2 atmosphere at 100 °C in the presence of CuI (10 mol%) as a catalyst and Et_3N (2.0 equiv.) as a base.[13] Under these conditions, the desired (phenylselanyl)-alkyl-1,2,3-triazolo-1,3,6-triazonine **4a** was obtained in 79% yield after 24 h (Table 1, entry 1).

To improve the yield, we then examined the influence of the reaction temperature (Table 1, entries 2–5). Thus, when the reactions were performed at 60, 80, 120 and 150 °C, a decrease in the yield of product **4a** was observed. Next, the reaction was screened using different solvents, such as toluene, DMF and 1,4-dioxane (Table 1, entries 6–8). The nature of the solvent was observed to notably influenced the reaction and the use of toluene or DMF provided poor yields of the desired product **4a** (Table 1, entries 6–7). However, a good result was achieved when 1,4-dioxane was used, with the desired product **4a** obtained in 84% yield after 24 h (Table 1, entry 8).

Next, the reaction was screened using different copper salts, such as CuBr, CuCl and $CuCl_2$; however, low yields of azonine **4a** were obtained (Table 1, compare entry 8 with 9–11). Unfortunately, when the catalyst loading was reduced from 10 to 5 mol%,

Table 1
Reaction conditions optimization.[a]



Entry	Catalyst	Solvent	Temperature °C	Yield **4a** (%)
1	CuI	DMSO	100	79
2	CuI	DMSO	80	65
3	CuI	DMSO	60	20
4	CuI	DMSO	120	75
5	CuI	DMSO	150	50
6	CuI	Toluene	100	20
7	CuI	DMF	100	23
8	CuI	1,4-Dioxane	100	84
9	CuBr	1,4-Dioxane	100	40
10	CuCl	1,4-Dioxane	100	41
11	$CuCl_2$	1,4-Dioxane	100	nd[b]
12	CuI	1,4-Dioxane	100	52[c]

[a] Reagents and conditions: *o*-phenylenediamine **1** (0.5 mmol), 2-azidobenzaldehyde **2** (0.5 mmol), copper catalyst (10 mol%), phenyl propargylselenide **3a** (0.5 mmol), Et_3N (1.0 mmol), solvent (1.0 mL), N_2 atmosphere, 24 h.
[b] nd: not detected.
[c] Reaction performed with CuI (5 mol%).

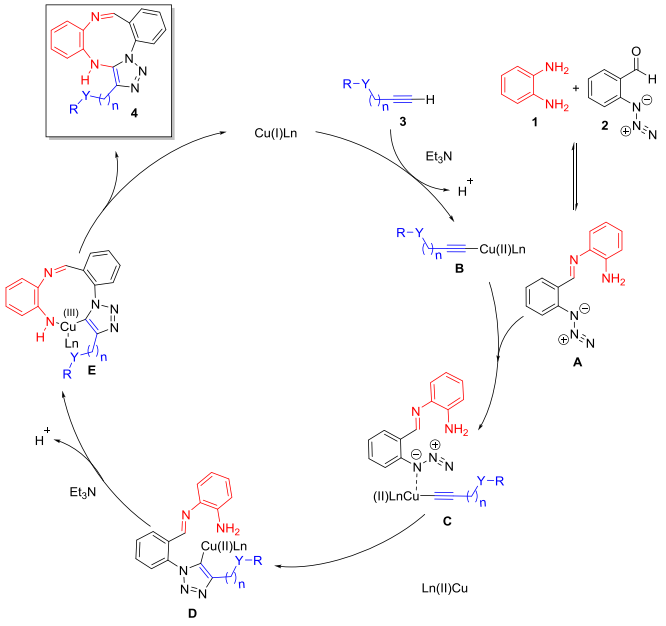


Fig. 2. Proposed mechanism.

a significant decrease in the yield of product **4a** was observed (Table 1, entry 12). This could be explained, at least in part, by complexation between the copper ion with intermediate **A**, formed during the reaction (see Fig. 2, for a plausible mechanism).[20]

In order to verify the scope and limitations of this protocol, the generality of our method was explored by extending the optimized reaction conditions (Table 1, entry 8) to other substituted propargyl selenides **3b–h** (Table 2). Firstly, varying the substituents on the aromatic ring of selanyl alkynes **3** was evaluated to determine the influence of electron-donating (–Me, –OMe) and electron-withdrawing groups (–F, $–CF_3$). The corresponding (arylselanyl)-alkyl-1,2,3-triazolo-1,3,6-triazonines **4b–h** were obtained in 45–81% yield (Table 2, entries 2–6). As shown in Table 2, electronic effects