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Selenium compounds in Click Chemistry: copper catalyzed 1,3-dipolar cycloaddition of azidomethyl arylselenides and alkynes

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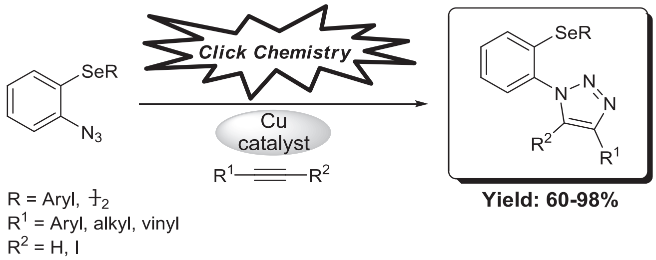
ABSTRACT

We described herein the use of selenium compounds in Click Chemistry by copper catalyzed 1,3-dipolar cycloaddition of azidomethyl arylselenides with alkynes. The reactions were performed under mild conditions reacting azidomethyl arylselenides with a range of terminal alkynes using catalytic amount of $Cu(OAc)_2.H_2O$/sodium ascorbate and the corresponding 1-(arylseleno-methyl)-1,2,3-triazoles were obtained in high yields. The reaction time of these reactions could be reduced to a few minutes using microwave irradiation.

1. Introduction

1,2,3-Triazoles, classic nitrogen heterocyclic compounds, are an important class of molecules, which display a broad spectrum of biological activities.[1] These compounds are also widely employed in various fields of chemistry, such as in the research and modulation of drug candidates,[2] development of new materials,[3] design of new catalysts,[4] among others.[5] There is a variety of methods available in the literature for the preparation of 1,2,3-triazoles. The most attractive way to prepare these compounds involves the thermal 1,3-dipolar cycloaddition of azides with alkynes, pioneered by Huisgen.[6] Independently, Sharpless[7] and Meldal[8] not only popularized this reaction but also discovered a copper-catalyzed version for this useful transformation. The development of the copper-catalyzed azide–alkyne cycloaddition (CuAAC) process was a definitive advance in triazole synthesis, and represents the most effective reaction of 'Click Chemistry'.[9]

On the other hand, organoselenium compounds are attractive synthetic targets. They can promote transformations with high levels of selectivity,[10,11] can be used as ionic liquids,[12] in asymmetric reactions,[10b,13] exhibit fluorescent properties[14] and are often linked to interesting biological activities.[15] The versatility and applicability of organoselenium compounds in organic chemistry is well described in a great number of reviews[10] and books.[11] Among organoselenium compounds, those containing nitrogen atoms in their structure are of special interest. This class of molecules have been employed in various organic transformations, for instance, in asymmetric synthesis.[10b,13] Consequently, the search for new and efficient methods for the synthesis of nitrogen-functionalized organoselenium compounds, more specifically organoselenium–triazoles, remains a challenge in organic chemistry. A number of examples for the synthesis of selenium-containing 1,2,3-triazole compounds has been reported,[16] and recently, a CuAAC protocol was published for the synthesis of arylseleno-1,2,3-triazoles in excellent yields under mild reaction conditions, starting from azido arylselenides (Scheme 1).[16d]



Scheme 1. CuAAC synthesis of arylseleno-1,2,3-triazoles.

However, to the best of our knowledge, methodologies involving CuAAC for the synthesis of organoselenium–triazoles are scarce and have not been well explored. In this sense, and due to our interest correlated to CuAAC protocol for the synthesis

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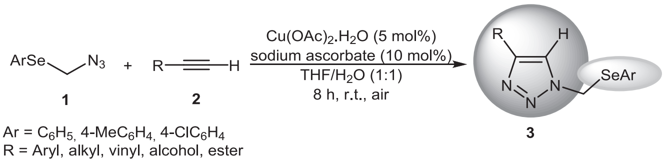
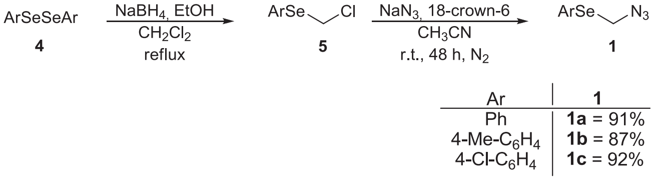
organoselenium–triazoles, we describe herein the copper catalyzed 1,3-dipolar cycloaddition of azidomethyl arylselenides **1** with terminal alkynes to obtain 1-(arylseleno-methyl)-1,2,3-triazoles **3** (Scheme 2).



Scheme 2. Synthesis of 1-(arylseleno-methyl)-1,2,3-triazoles **3**.

2. Results and discussion

Initially, our studies were focused on the synthesis of azidomethyl arylselenides **1**, the starting materials for the synthesis of the selenium-triazoles **3**. Thus, phenylselenolate, generated in situ by the reaction of diphenyl diselenide **4a** with $NaBH_4/EtOH$, reacted with methylene chloride at reflux, affording chloromethyl phenylselenide **5a** in satisfactory yield (Scheme 3).[17] This compound was easily converted to azidomethyl phenylselenide **1a** in excellent yield after reaction with sodium azide and 18-crown-6 in CH_3CN at room temperature.[18] This protocol was extended to the chloro- and methyl–arylselenide **5b** and **5c**, giving the products **1b** and **1c** in 87% and 92% yield, respectively (Scheme 3).



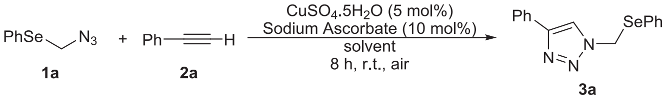
Scheme 3. Synthesis of azidomethyl arylselenides **1**.

Azidomethyl arylselenides **1a**–**c** obtained as described above appear to be highly promising substrates for the CuAAC protocol to obtain selenium–triazol derivatives. This class of compounds[16b,19a] has a large synthetic importance since they combine the well known reactivity of the azido group[20] with that of the selenium-containing group.[10,11]

After that, we turned out our attention to the application of the obtained azidomethyl arylselenides **1a**–**c** in the synthesis of 1-(arylseleno-methyl)-1,2,3-triazoles **3**, using a copper-catalyzed 1,3-dipolar cycloaddition reaction. Generally, these reactions require the generation of Cu(I) species in situ starting from $CuSO_4\cdot 5H_2O$ and sodium ascorbate in aqueous medium.[7a] In view of this, firstly we studied the reaction of azidomethyl phenylselenide **1a** (0.3 mmol) with phenylacetylene **2a** (0.3 mmol) in the presence of $CuSO_4.5H_2O$ (5 mol %) and sodium ascorbate (10 mol %) in a mixture of different solvents (2 mL) (Table 1).

Checking the Table 1, it is possible to verify that the reaction afforded the selenium-triazole **3a** in good yields using a variety of organic solvents in combination with H_2O. When we used mixtures of $MeOH/H_2O$, *t*-$BuOH/H_2O$, CH_2Cl_2/H_2O, Et_2O/H_2O, acetone/H_2O and THF/H_2O, good yields were obtained of the desired product **3a** (Table 1, entries 1–6). Optimal result was achieved using a mixture of THF/H_2O (1:1) as solvent (Table 1, entry 6). A remarkable feature of this reaction was the H_2O dependence in the selenium-triazole synthesis. Reactions using a mixture of THF/H_2O (1:0.5) or just THF, gave poor yields of the desired product **3a** (Table 1, entries 7–8). This may be due to the increased solubility of sodium ascorbate and copper salt in this solvent.[16d] However, when the reaction was performed only in H_2O, the formation of product **3a** was not observed (Table 1, entry 9). It is important to note that the reactions are not air sensitive, allowing the preparation of the respective triazole **3a** in an open atmosphere (Table 1, entry 10).

Table 1
Study of the solvent effect on CuAAC of azidomethyl arylselenide **1a**

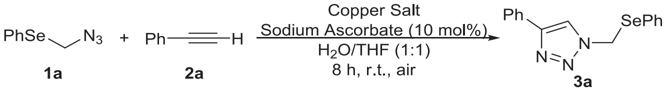


Entry	Solvent (Ratio)	Isolated yield **3a** (%)
1	$MeOH/H_2O$ (1:1)	80
2	*t*-$BuOH/H_2O$ (1:1)	83
3	$CH_2Cl_2/H_2O/$ (1:1)	77
4	Et_2O/H_2O (1:1)	82
5	acetone/H_2O (1:1)	79
6	THF/H_2O (1:1)	88
7	THF/H_2O (1:0.5)	47
8	THF	Traces
9	H_2O	nd
10	THF/H_2O (1:1)[a]	86

[a] Reaction under argon atmosphere.

We observed that the nature of the copper salt and its amount were critical for the success of the reaction. As shown in Table 2, different copper salts, such as $CuSO_4\cdot 5H_2O$, $CuBr_2$, $Cu(OTf)_2$, $Cu(OAc)_2\cdot H_2O$, and CuO nanoparticles, exhibited a moderate to good catalytic activity (Table 1, entries 1–5). Among the conditions tested, the best result was obtained using $Cu(OAc)_2.H_2O$ (5 mol %), which gave the product **3a** in excellent yield (Table 2, entry 5). It is significant to note that when the amount of catalyst was reduced from 5 mol % to 1 mol %, a decrease in the yield was observed (Table 1, entries 5–7). The analysis of the obtained results indicated that the best reaction conditions were found to be use azidomethyl phenylselenide **1a** (0.3 mmol), phenylacetylene **2a** (0.3 mmol) in presence of $CuSO_4.5H_2O$ (5 mol %), sodium ascorbate (10 mol %) in a mixture of THF/H_2O (1:1, 2 mL) at room temperature under air atmosphere for 8 h.

Table 2
Influence of copper salt in the CuAAC of azidomethyl arylselenide **1a** and phenylacetylene **2a**



Entry	Copper salt (mol %)	Isolated yield **3a** (%)
1	$CuSO_4\cdot 5H_2O$ (5%)	88
2	$CuBr_2$ (5%)	70
3	$Cu(OTf)_2$ (5%)	65
4	CuO·NPs (5%)	75
5	$Cu(OAc)_2\cdot H_2O$ (5%)	94
6	$Cu(OAc)_2\cdot H_2O$ (3%)[a]	87
7	$Cu(OAc)_2\cdot H_2O$ (1%)[b]	80

[a] 6 mol % of sodium ascorbate was used.
[b] 2 mol % of sodium ascorbate was used.

To extend the scope of the reaction, a range of terminal alkynes were reacted with azidomethyl phenylselenide **1a** under the optimized reaction conditions. Thus, terminal alkynes with a variety of substituents, including aryl, alkyl, vinyl, alcohol, and ester were successfully employed in these reactions and the corresponding products were obtained in high yields (Table 3, entries 1–11). Good results were achieved when dialkyne **2l** was reacted with two different amounts of azidomethyl phenylselenide **1a**. When we used 0.3 mmol of compound **1a**, the respective alkynyl selenium–triazole **3l** (Table 3, entry 12) was obtained in 68% yield with traces of bis-