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4-Organochalcogenoyl-*1H*-1,2,3-triazoles: synthesis and functionalization by a nickel-catalyzed Negishi cross-coupling reaction

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ABSTRACT

A general method for the synthesis of triazoles containing selenium and tellurium was accomplished via a CuCAAC reaction between organic azides and a terminal triple bond, generated by in situ deprotection of the silyl group. The reaction tolerates alkyl and arylazides, with alkyl and aryl substituents directly bonded to the chalcogen atom. The products were readily functionalized by a nickel-catalyzed Negishi cross-coupling reaction, furnishing the aryl-heteroaryl products at the 4-position in good yields.

Introduction

Although *N*-heterocycle compounds are broadly distributed in nature, the 1,2,3-triazoles are not found as natural products.[1,2] However, synthetic triazoles, due to their capacity for intermolecular hydrogen bond formation, allow for interactions with biological receptors[3] and have numerous applications, as agrochemical compounds,[4] corrosion inhibitor, dyes,[5] and as ionic liquids.[6]

The main synthesis route to 1,2,3-triazolic compounds is the 1,3-dipolar cycloaddition reaction,[7] which was improved in 2003, when the groups of Sharpless and co-workers[8] and Meldal and co-workers[2] independently introduced the use of copper salts to obtain better yields and good regioselectivity, among several advantages.

These features include the copper catalyzed cycloaddition of azides and alkynes to give triazoles, in the field of click chemistry.[9,10] This kind of reaction can be performed under different conditions, considered non-classical ones, including microwave dielectric heating, ultrasound processing, ionic liquids as the reaction media, and continuous flow processing.[11]

Organochalcogenides have been found to be very important for their biological effects and as intermediates and reagents in organic synthesis.[12] The biological activity of these compounds includes antioxidant,[13] anti-inflammatory,[14] neuroprotective activities as well as cancer prevention,[15] to mention a few. On the other hand, the utility of these compounds is very broad in organic reactions; many are employed for carbon–carbon bond formation under mild conditions.

Interest in the reactions involving organochalcogen compounds has increased because of their chemo-, regio-, and stereoselective properties. Additionally, their compatibility with different functional groups is notable, and they can be used with a wide variety of functional groups, thus avoiding the use of protecting groups.[16]

Organochalcogen species can be introduced as either nucleophiles or electrophiles to other organic molecules, producing useful intermediates for organic synthesis.[17]

The transition metal-catalyzed cross-coupling reaction of organometallics is a methodology widely used by many in the chemical community to produce products prevalent in pharmaceuticals, ligands, and materials. Extensive research has focused on a variety of ways to form C–C bonds using transition metal catalysts.[18]

The nickel-catalyzed Negishi cross-coupling reaction of aryl and vinyl halides/triflates with organozinc reagents represents a powerful tool for the formation of carbon–carbon bonds in view of the ready availability and high functional group compatibility of organozinc compounds.[19] Despite the described Negishi cross-coupling reaction with various azoles (imidazole, oxazole, thiazole, and pyrazole),[20] to the best of our knowledge, no examples using selenium- and tellurium-triazoles as electrophiles in this reaction have been described in the literature.

In this context, we report herein a methodology to obtain 4-organochalcogenoyl-1,2,3-triazoles from copper-catalyzed 1,3-dipolar cycloaddition of terminal organochalcogenoyl-alkynes to azides. We also describe for the first time the catalytic system based on nickel-phosphine to promote Negishi cross-coupling

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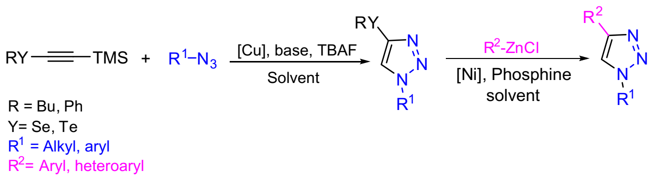


Figure 1. General scheme of the reactions.

reaction with 4-organoselenium- and 4-organotellurium-1,2,3-triazoles (Fig. 1).

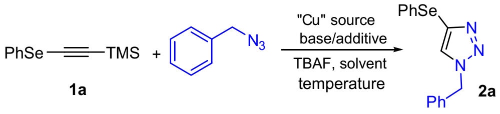
Results

The terminal alkyne was obtained through the deprotection of the silyl group. This synthesized compound is novel in the literature and represents an excellent building block because of the presence of the chalcogen atom.

Initially, we focused our attention on the optimization of the reaction conditions. In this way, we investigated some parameters in the procedure, such as different copper loading salts, bases, additives, and solvents (Table 1). For this purpose, we employed trimethyl(phenylselanylethynyl)silane **1a** as the source of a terminal triple bond and benzylazide as a standard reagent. In the first test, a mixture of **1a** (0.5 mmol), benzylazide (0.6 mmol), and CuI (1 equiv), using THF as the solvent, was reacted at room temperature for 3 h in the absence of a base.

As shown in Table 1, using these conditions, product **2a** was obtained in only 23% yield (entry 1). On the other hand, in the presence of a base (PMDTA), the desired product was isolated in 60%

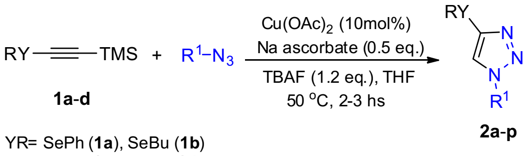
Table 1
Effect of reaction conditions on CuAAC



Entry	[Cu] (equiv)	Base or additive (1.1 equiv)	Solvent	Yield[a] (%)
1	CuI (1.0)	—	THF	23
2	CuI (1.0)	PMDTA	THF	60
3	CuI (0.1)	PMDTA	THF	72
4	CuI (0.05)	PMDTA	THF	Trace
5	CuCN (0.1)	PMDTA	THF	24
6	$CuSO_4·5H_2O$ (0.1)	PMDTA	THF	Trace
7	$Cu(Oac)_2$ (0.1)	PMDTA	THF	75
8	CuBr (0.1)	PMDTA	THF	70
9	CuCl (0.1)	PMDTA	THF	64
10	$Cu(OAc)_2$ (0.1)	Na ascorbate	THF	78
11	$Cu(OAc)_2$ (0.1)	Et_3N	THF	35
12	$Cu(OAc)_2$ (0.1)	Na ascorbate	MeCN	36
13	$Cu(OAc)_2$ (0.1)	Na ascorbate	DMSO	74
14	$Cu(OAc)_2$ (0.1)	Na ascorbate	MeOH	62
15	$Cu(OAc)_2$ (0.1)	Na ascorbate	H_2O	45
16	$Cu(OAc)_2$ (0.1)	Na ascorbate	Dioxane	70
17	$Cu(OAc)_2$ (0.1)	Na ascorbate	Dioxane	59[e]
18	$Cu(OAc)_2$ (0.1)	Na ascorbate	THF	83[b]
19	$Cu(OAc)_2$ (0.05)	Na ascorbate	THF	63[b]
20	$Cu(OAc)_2$ (0.1)	Na ascorbate	THF	80[b,c]
21	$Cu(OAc)_2$ (0.1)	Na ascorbate	THF	64[b,d]

[a] Yields are given for isolated products.
[b] Reaction carried out at 50 °C.
[c] Reactions were performed using 0.5 equiv of Na ascorbate.
[d] Reaction performed using 0.1 equiv of Na ascorbate.
[e] Reaction carried out at 80 °C.

Table 2
Synthesis of 4-organochalcogenoyl-*1H*-1,2,3-triazoles



1a-d **2a-p**

YR= SePh (**1a**), SeBu (**1b**)
TeBu (**1c**), TePh (**1d**)
R1= Aryl, alkyl

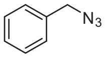
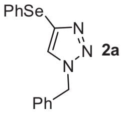
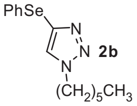
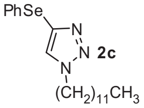
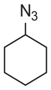
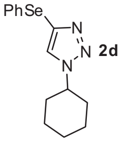
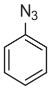
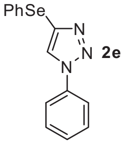
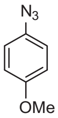
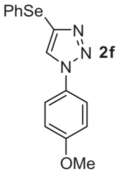
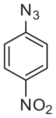
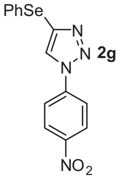
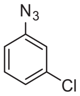
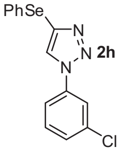
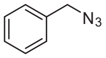
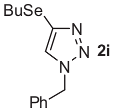
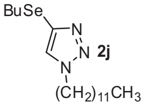
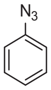
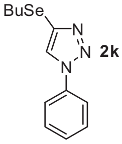
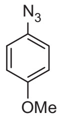
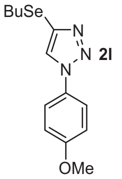
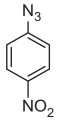
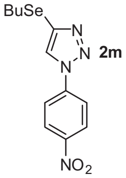
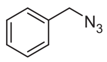
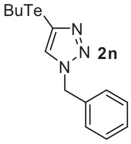
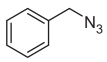
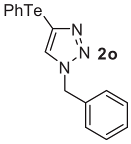
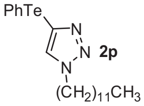
Entry	Azide	Product	Yield[a] (%)
1		 **2a**	80
2	$CH_3(CH_2)_5$-N_3	 **2b**	77
3	$CH_3(CH_2)_{11}$-N_3	 **2c**	76
4		 **2d**	65
5		 **2e**	60
6		 **2f**	73
7		 **2g**	42
8		 **2h**	53
9		 **2i**	75
10	$CH_3(CH_2)_{11}$-N_3	 **2j**	68
11		 **2k**	55

Table 2 (*continued*)

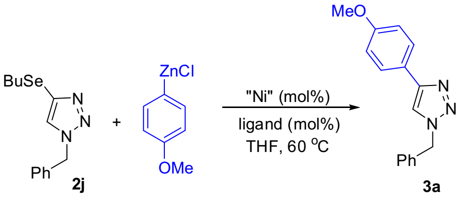
Entry	Azide	Product	Yield[a] (%)
12		 **2l**	65
13		 **2m**	51
14		 **2n**	50[b]
15		 **2o**	58[b]
16	$CH_3(CH_2)_{11}$-N_3	 **2p**	60[b]

[a] Yields are given for isolated products. The reaction times vary between two and three hours.

[b] Conditions: acetylene (0.5 mmol), THF (4 mL), organic azide (0.55 mmol), CuI (0.5 mmol), PMDTA (0.55 mmol, 0.11 mL), and TBAF (0.6 mmol).

Table 3

Optimization of the nickel-catalyzed Negishi reaction



2j **3a**

Entry	Catalyst (mol %)	Ligand (mol %)	Yield (%)
1	$Ni(acac)_2$ (5)	DPE-Phos (10)	68
2	$NiCl_2(PPh_3)_2$ (5)	DPE-Phos (10)	77
3	$NiCl_2(PPh_3)_2$ (5)	—	51
4	$NiBr_2$ (5)	DPE-Phos (10)	69
5	$NiCl_2$(dppf) (5)	DPE-Phos (10)	54
6	$NiCl_2$(dppe) (5)	DPE-Phos (10)	47
7	$NiCl_2(PPh_3)_2$ (5)	X-Phos (10)	72
8	$NiCl_2(PPh_3)_2$ (5)	S-Phos (10)	15
9	$NiCl_2(PPh_3)_2$ (5)	Ru-Phos (10)	57
10	$NiCl_2(PPh_3)_2$ (5)	PCy_3 (10)	81
11	$NiCl_2(PPh_3)_2$ (2.5)	PCy_3 (5)	46

yield (entry 2). As can be seen in the initial experiments, the base plays an important role in the reaction.

Concerning the amount of the copper salt, the reaction was carried out in a catalytic system, reducing the amount of CuI to 10 mol %; this change increased the yield of the product to 72% (entry 3). Other copper salts were tested, such as CuCN, $CuSO_4$, $Cu(OAc)_2$, CuBr, and CuCl, however, some of them were less effective (Table 1, entries 4–6). Comparable results were obtained using $Cu(OAc)_2$, CuBr, and CuCl (entries 7–9).

As described in the literature, sodium ascorbate is considered to be a convenient additive for in situ reducing agents to generate catalytically active Cu(I).[21–23] This justifies the result found with the combination of $Cu(OAc)_2$ and sodium ascorbate (entry 10).

Additionally, we investigated the reaction behavior with different solvents, including CH_3CN, DMSO, MeOH, Dioxane, and H_2O; however THF gave the best results (Table 1, entries 10, 12–17).

In order to improve the results, we changed the temperature to 50 °C. This approach increased the yield of triazole **2a** to 83% (entry 18) in a shorter reaction time.

With the optimized conditions in hand, $Cu(OAc)_2$ (10 mol %), sodium ascorbate (0.5 equiv) at 50 °C in THF, we explored the generality of the protocol using different organic azides and acetylenes. The results are summarized in Table 2.

Analysis of Table 2 shows that, in general, all of the reactions proceeded under mild conditions, with a simple methodology, easy isolation, and acceptable yields.

Aliphatic azide derivatives were employed as substrates; the corresponding products were obtained in good yields (Table 2, entries 1–4). However, we found a limitation in our methodology when we attempted to react sodium azide as the dipole partner, since no triazole product was obtained.

The reaction was sensitive to the electronic effects of the substituents on the aromatic ring of the azide. For example, an organic azide containing an electron-donating group (OMe) gave a better result than neutral and electron-withdrawing groups in the aromatic ring (Table 2, entries 5–8).

Additionally, we tried to broaden the scope of the methodology by performing the reaction with other acetylene derivatives containing YR = SeBu-*n* (**1b**), TeBu-*n* (**1c**), and TePh (**1d**). The substrate containing the SeBu group furnished the corresponding product in lower yields compared to SePh derivatives (Table 2, entries 9–13).

Unfortunately, substrate **1c** did not behave as the analogs **1a** and **1b** under the conditions described, and the triazole was obtained in only 20% yield. Thus, we attempted to find different conditions compatible with the TeR substrate. In this way, we submitted compounds **1c** and **1d** to different conditions (Table 1, entry 2), furnishing the corresponding products in moderate yields (Table 2, entries 14–16).

During the reaction of **1c**, the formation of a black precipitate was observed, probably composed of elemental tellurium. GC/MS monitoring showed the formation of byproducts such as butyl iodide and the corresponding hydrogenated triazole from the detelluration reaction.

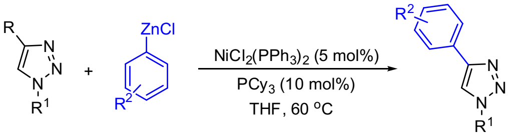
The synthesized products appeared as potential precursors to explore the functionalization of triazole scaffolds. Since selenium and tellurium functionalities have the ability to be converted into other substituents,[17] the possibility of employing these substrates as useful intermediates in cross-coupling reactions was investigated.[24]

Knochel and coworkers developed Pd-catalyzed cross-coupling reactions with thiomethyl-substituted *N*-heterocycles with various organozinc reagents, using $Pd(OAc)_2$/S-Phos as the catalytic system.[25] Additionally, the same authors described an additional protocol by changing the catalytic system to $Ni(acac)_2$/DPE-Phos.[26]

Following this, the ability of selenium and tellurium derivatives was investigated under Ni-catalyzed cross-coupling reaction with organozinc reagents.

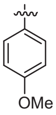
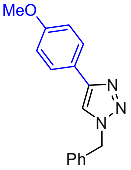
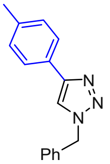
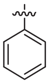
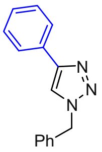
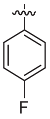
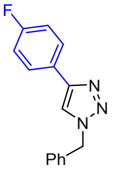
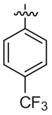
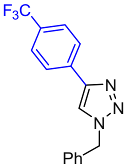
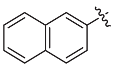
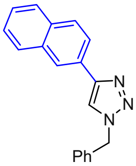
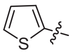
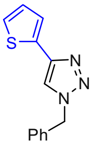
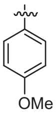
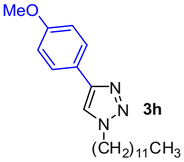
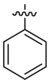
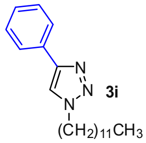
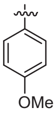
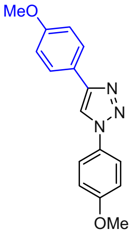
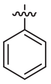
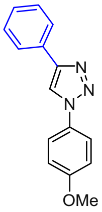
Initially, we started by employing $Ni(acac)_2$ and DPE-Phos as the catalytic system, and used compound **2j** as the electrophilic partner. The arylated product was obtained in 68% yield (Table 3, entry 1). The simple change of the catalyst to $NiCl_2(PPh_3)_2$ provided the product **3a** in 77% yield (Table 3, entry 2). The reaction in the

Table 4
Synthesis of 4-aryl-*1H*-1,2,3-triazoles by a nickel-catalyzed Negishi cross-coupling reaction



3a-k

R = SeBu, R^1 = Bn **2j**
R = SeBu, R^1 = $(CH_2)_{11}CH_3$ **2k**
R = SeBu, R^1 = 4-OMe(C_6H_4) **2m**
R = TeBu, R^1 = Bn **2o**

Entry	Triazole	Organozinc	Product	Yield[a] (%)
1	2j 2o		 **3a**	81 51
2	2j 2o		 **3b**	73 43
3	2j 2o		 **3c**	71 42
4	2j		 **3d**	54
5	2j		 **3e**	60
6	2j		 **3f**	83
7	2j		 **3g**	62[b]
8	2k		 **3h**	70
9	2k		 **3i**	63
10	2m		 **3j**	52
11	2m		 **3k**	73

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[a] Yields are given for isolated products. The reaction times vary between two and three hours.

[b] The organozinc reagent was obtained from thiophene using the methodology described previously.

absence of the ligand DPE-Phos furnished the product in moderate yield (Table 3, entry 3).

Since the preliminary tests were successful, a survey was performed to find the optimal conditions, by changing the catalyst and the ligand. Other nickel salts such as $NiBr_2$, $NiCl_2$(dppf), and $NiCl_2$(dppe) were less effective (Table 3, entries 4–6). Additionally, the influence of the phosphine ligand was investigated; thus, we used Buchwald phosphine [27] in order to increase the yield of the arylated product (Table 3, entries 7–9). However, the ligands tested were less efficient compared to PCy_3 (Table 3, entry 10).

A detailed analysis of Table 3 shows that the optimal conditions for the coupling reaction were achieved using $NiCl_2(PPh_3)_2$ (5 mol %) and PCy_3 (10 mol %) in heated THF.

We explored the generality of our method by applying these conditions to different organozinc reagents, including selenium and tellurium triazole derivatives. The results are summarized in Table 4.

Inspection of Table 4 shows that the reaction worked well for avariety of organozinc reagents, including aryl and heteroaryl derivatives. However, poor yields were achieved for 4-organotellurium-*1H*-1,2,3-triazoles.With alkylzinc reagent was not observed coupling product.

Conclusions

In summary, using the click chemistry concept, we have developed an efficient route to synthesize different 4-organoselenium- and 4-organotellurium-*1H*-1,2,3-triazoles via 1,3-dipolar cycloaddition employing organochalcogen acetylenes in moderate to good yields. For the first time, 4-organoselenium-*1H*-1,2,3-triazoles were successfully subjected to a nickel-catalyzed Negishi cross-coupling reaction, as the electrophile, obtaining different triazoles in moderate to good yields. All the obtained compounds are interesting as a final product or as a building block for organic synthesis. Further applications of this practical nickel-catalyzed Negishi cross-coupling reaction with 4-organoselenium-*1H*-1,2,3-triazoles and mechanistic investigations are underway in our laboratory.

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