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SHORT COMMUNICATION

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One-Pot Synthesis of 4-Substituted 1*H*-[1,2,3]triazolo[4,5-*c*]quinolines Through CuO-Promoted Tandem Cyclization Reactions of (*E*)-3-(2-Bromoaryl)-1-arylprop-2-en-1-ones with Sodium Azide

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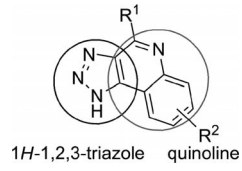
Keywords: Domino reactions / Nitrogen heterocycles / Copper / Azides / Cyclization

A facile and efficient protocol for the synthesis of 4-substituted-1*H*-[1,2,3]triazolo[4,5-*c*]quinolines through a CuO-promoted tandem cyclization reaction has been developed. This method allows for the construction of two heterocyclic rings in a one-pot reaction of readily available (*E*)-3-(2-bromoaryl)-1-arylprop-2-en-1-ones and sodium azide without the addition of any additive. A series of triazole-fused N-heterocyclic compounds could be prepared in moderate to good yields.

Introduction

1*H*-[1,2,3]Triazolo[4,5-*c*]quinolines (Scheme 1) contain the skeleton of 1,2,3-triazoles and quinolines. 1,2,3-Triazoles derivatives are an important class of organic compounds with regard to their various biological and pharmacological properties.[1] Moreover, they have wide applications in biological science, materials chemistry, medicinal chemistry, and synthetic organic chemistry.[2] Quinoline derivatives are also important biologically active motifs and are ubiquitous in both natural products[3] and active pharmaceutical ingredients (APIs).[4] However, molecules containing both the 1,2,3-triazole and quinoline frameworks have not been synthesized thus far. Additionally, it is highly needed to develop novel, structurally diverse molecules for drug discovery and related fields, and herein we want to design and synthesize novel triazole-fused N-heterocyclic compounds by using readily available starting materials.

In the past decade, azides have been used by us and others in a diverse array of cycloaddition and multicomponent reactions for the synthesis of various N-containing compounds.[5,6] Our group has also been endeavoring to synthesize 1,2,3-triazole derivatives by using sodium azide to avoid the preparation of organic azides.[7] Inspired by previous work,[5–8] we envisioned an efficient one-pot, copper-promoted tandem cyclization reaction of readily available (*E*)-3-(2-bromoaryl)-1-arylprop-2-en-1-ones with two molecules of sodium azide to synthesize 4-substituted-1*H*-[1,2,3]triazolo[4,5-*c*]quinolines by the formation of two heterocyclic rings without the addition of any additive. In this system, the oxidative reaction and reductive amination could proceed simultaneously.



Scheme 1. Structure of a fused compound containing the 1,2,3-triazole and quinoline skeletons.

Results and Discussion

In an initial attempt, we selected (*E*)-3-(2-bromophenyl)-1-phenylprop-2-en-1-one (**1a**) as a model substrate to probe the reaction conditions (Table 1). We were pleased to find that product **2a** was obtained in 67% yield in the presence of NaN_3 (2 equiv.) and CuO (1 equiv.) in DMF at 100 °C for 24 h (Table 1, entry 1). To improve the reaction efficiency, we first examined the influence of various copper catalysts, but only a trace amount of the desired product was detected (Table 1, entries 2–4). Subsequently, different solvents such as DMSO, dimethylacetamide (DMA), and THF were investigated, but they were less efficient than DMF (Table 1, entries 5–7). The effect of the reaction temperature was also tested, and 110 °C was found to be the most effective. Although the yield decreased at lower temperatures (80 °C), no improvement was achieved upon conducting the reaction at higher temperatures (130 °C)

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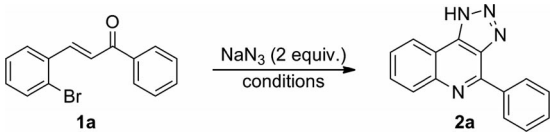
(Table 1, entries 8–10). Gratifyingly, the yield was enhanced to 82% if 2 equiv. of CuO was added (Table 1, entries 11 and 12). Additionally, there was no clear change in the yield of the product if 3 equiv. of NaN_3 was employed (Table 1, entry 13). Thus, the best result was obtained by stirring a mixture of **1a** (1.0 equiv.), NaN_3 (2.0 equiv.), and CuO (2.0 equiv.) in DMF at 110 °C for 24 h.

Table 1. Optimization of the reaction conditions.[a]

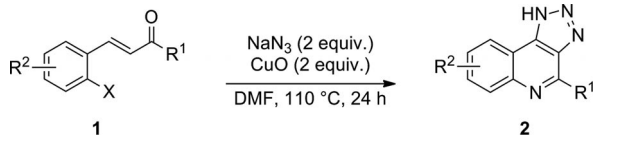


Entry	Catalyst	Equiv.	T [°C]	Solvent	Yield [%][b]
1	CuO	1	100	DMF	67
2	$Cu(OAc)_2$	1	100	DMF	trace
3	$Cu(OTf)_2$	1	100	DMF	trace
4	CuBr	1	100	DMF	trace
5	CuO	1	100	DMSO	65
6	CuO	1	100	DMA	trace
7	CuO	1	100	THF	0
8	CuO	1	80	DMF	59
9	CuO	1	110	DMF	77
10	CuO	1	130	DMF	76
11	CuO	0.1	110	DMF	48
12	CuO	2	110	DMF	82
13	CuO	2	110	DMF	80[c]

[a] Conditions: **1a** (0.20 mmol), NaN_3 (0.40 mmol), solvent (2 mL), 24 h. [b] Yield of isolated product after column chromatography. [c] With NaN_3 (0.60 mmol).

To demonstrate the efficiency and generality of this reaction, a wide range of (*E*)-3-(2-haloaryl)-1-arylprop-2-en-1-ones were examined under the optimized reaction conditions (Table 2). Generally, 1-(2-bromoaryl)enones with various R^1 and/or R^2 substituents were compatible with the reaction conditions, and the desired products were afforded in moderate to good yields. The structure of **2c** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1). Substrates in which R^1 = NH_2 or OH were not compatible with this reaction, and these substrates afforded the desired product in only low yield or not at all (Table 2, entries 4 and 5). Notably, halogen substituents, especially Br and I, were also well tolerated, and these derivatives can undergo further coupling reactions for the synthesis of more complex molecules (Table 2, entries 6–9, 17, 18). Upon reaction of 1-(2-bromoaryl)enones **1** with R^1 = 3-NO_2, only 43% yield of the desired product was obtained (Table 2, entry 11). Substrates with more bulky R^1 substituents were also efficiently transformed and delivered the desired products in satisfactory yields (Table 2, entries 12–14). Aliphatic R^1 substituents, such as isopropyl and ethyl, were not suitable for this reaction (Table 2, entry 15). Furthermore, the substrate in which R^2 = 4-F delivered a relatively low yield of the product, probably as a result of a strong electron-withdrawing effect. Unfortunately, upon replacing the halide X by F or Cl, the reaction failed to give the desired product (Table 2, entry 19).

Table 2. Substrate scope of the (*E*)-3-(2-haloaryl)-1-arylprop-2-en-1-ones.[a]



Entry	R^1	R^2	X	Product	Yield [%][b]
1	C_6H_5	H	Br	**2a**	82
2	4-$CH_3C_6H_4$	H	Br	**2b**	73
3	4-$OCH_3C_6H_4$	H	Br	**2c**	72
4	4-$NH_2C_6H_4$	H	Br	**2d**	32
5	4-OHC_6H_4	H	Br	**2e**	0
6	4-FC_6H_4	H	Br	**2f**	73
7	4-ClC_6H_4	H	Br	**2g**	85
8	4-BrC_6H_4	H	Br	**2h**	60
9	4-IC_6H_4	H	Br	**2i**	61
10	4-$NO_2C_6H_4$	H	Br	**2j**	76
11	3-$NO_2C_6H_4$	H	Br	**2k**	43
12	4-PhC_6H_4	H	Br	**2l**	55
13	naphthyl	H	Br	**2m**	75
14	6-methoxynaphthyl	H	Br	**2n**	68
15	isopropyl/ethyl	H	Br	**2o**	0
16	4-$CH_3C_6H_4$	5-OCH_3	Br	**2p**	74
17	4-$CH_3C_6H_4$	4-F	Br	**2q**	36
18	4-$CH_3C_6H_4$	4-Cl	Br	**2r**	77
19	C_6H_5	H	Cl/F	**2a**	0

[a] Conditions: **1** (0.20 mmol), NaN_3 (0.40 mmol), CuO (0.40 mmol), DMF (2 mL), 24 h, 110 °C. [b] Yield of isolated product after column chromatography.

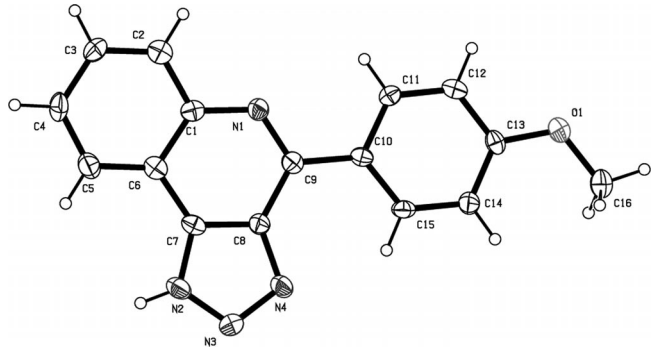


Figure 1. X-ray crystal structure of **2c**.

Conclusions

In conclusion, we have successfully demonstrated a facile and efficient protocol for the synthesis of 4-substituted-1*H*-[1,2,3]triazolo[4,5-*c*]quinolines in moderate to good yields. This protocol allowed the formation of two heterocyclic rings in a one-pot reaction through the CuO-promoted tandem cyclization of readily available (*E*)-3-(2-bromoaryl)-1-arylprop-2-en-1-ones with sodium azide. It will be a useful strategy for the construction of novel and valuable N-heterocyclic compounds in organic and medicinal chemistry.

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Experimental Section

Typical Procedure for the Preparation of 4-Substituted-1*H*-[1,2,3]triazolo[4,5-*c*]quinolines 2: (*E*)-3-(2-bromoaryl)-1-arylprop-2-en-1-one **1** (0.20 mmol), sodium azide (0.40 mmol, 26 mg), CuO (0.40 mmol, 32 mg), and DMF (2 mL) were added to a flask with a magnetic stirring bar. The resulting mixture was stirred at 110 °C for 24 h. After cooling to room temperature, water (20 mL) was added to the mixture, and the organic material was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (2 × 5 mL), dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was subjected to flash column chromatography (petroleum ether/EtOAc, 2:1) to give product **2**.

Supporting Information (see footnote on the first page of this article): Synthesis and characterization data and copies of the ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgments

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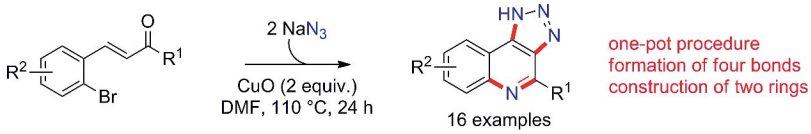

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