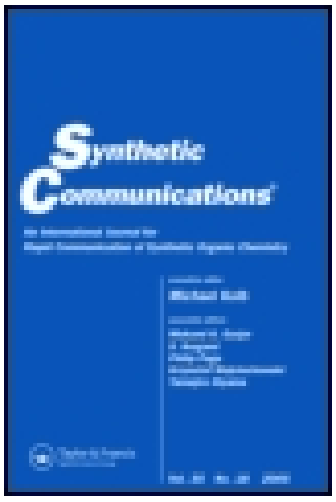

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Synthesis of [1,2,3]Triazolo[5,1-a]isoquinoline Derivatives via a Selective Cascade Cyclization Sequence of 1,2-bis(Phenylethynyl)benzene Derivatives

Shipeng Tao[a], Qinquan Hu[a], Huan Li[a], Shan Ma[a] & Yunfeng Chen[a]
[a] School of Chemical and Environmental Engineering, Wuhan Institute of Technology, Wuhan, P. R. China
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Synthesis of [1,2,3]triazolo[5,1-*a*]isoquinoline derivatives via a selective cascade cyclization sequence of 1,2-bis(phenylethynyl)benzene derivatives

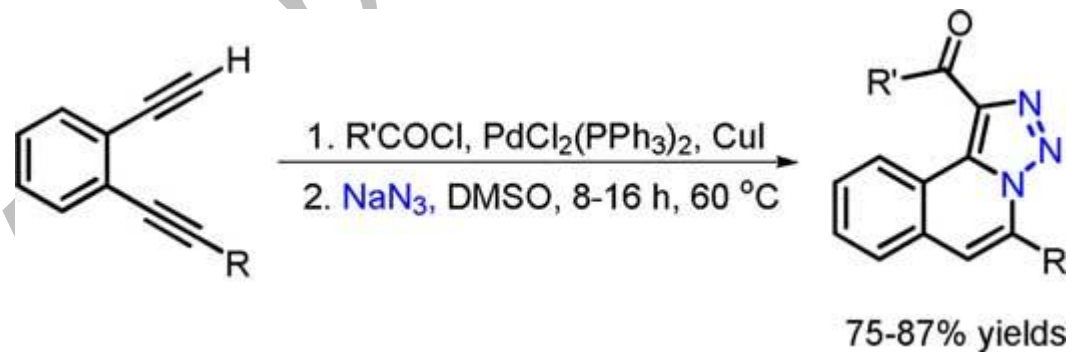
Shipeng Tao[1], Qinquan Hu[1], Huan Li[1], Shan Ma[1], Yunfeng Chen[1]

[1]School of Chemical and Environmental Engineering, Wuhan Institute of Technology, Wuhan, P. R. China

Address correspondence to Yunfeng Chen, E-mail: chyfch@hotmail.com

Abstract

A direct, concise, synthetic method for the generation of [1,2,3]triazolo[5,1-*a*]isoquinoline derivatives, using a selective cascade cyclization of unsymmetrical substituted 1,2-bis(phenylethynyl)benzene derivatives with NaN_3, has been developed. The reaction gave different substituted [1,2,3]triazolo[5,1-*a*]isoquinolines in moderate to good yields. It was found that the substituents on the alkynes were important for the selectivities of the cascade cyclization sequences.



KEYWORDS: [1,2,3]triazolo[*5*,1-*a*]isoquinoline, 1,2,3-triazole, cascade reaction, cyclization

INTRODUCTION

With the development of copper-catalyzed azide-alkyne "click" reaction, 1,2,3-triazoles became useful building blocks in medicinal, material, transition metal chemistry and others.[1-4] It was found that some compounds containing the 1,2,3-triazole ring system have shown a broad spectrum of biological activities including antifungal, antiviral, anti-allergic, anti-HIV, and antimicrobial activities.[5-8] By contrast with numbers of substituted 1,2,3-traizole compounds, 1,2,3-triazole-annulated polyheterocycles were scare. Even so, some of them have shown potential applications in various fields.[9-13] Recently, many approaches have been developed to synthesize 1,2,3-triazole- fused N-heterocycle.[14-18] However, most of the methods are mainly based on intramolecular azide-alkyne cycloaddition reactions (**Scheme 1a**).[19-24] In these methods, many efforts and steps need be done on the synthesis of precursors with azide and alkyne moieties in one molecule. There is a potential intermolecular 1,3-dipolar cyclization for these substrates, which will induce the formation of oligmers or polymers.

[1,2,3]triazolo[5,1-*a*]isoquinoline is a new kinds of 1,2,3-triazole fused heterocycle.[25-26] Previously, we have already developed a *NH*-1,2,3-triazoles post-annulation strategy for the synthesis of 5-NH_2-[1,2,3]triazolo[5,1-*a*]isoquinolines with high effectiveness.[27] Another direct method to construct [1,2,3]triazolo[5,1-*a*]isoquinoline core structure is intermolecular cascade cyclization of enediynes with NaN_3. Recently, Gulevskaya group reinvestigated the cyclization reactions of enediynes with NaN_3.[28] They found

(Z)-hexa-3-en-1,5-diynes gave corresponding [1,2,3]triazolo[1,5-*a*]pyridines and other fused heterocycles rather than 1-aryl-*1H*-benzotriazoles (**Scheme 1b**). [29] However, these reactions need high reaction temperature and long reaction time, the yields and selectivities were not very high. Inspired by this, we introduced a carbonyl group to 1,5-diynes which could activate the alkyne towards "N_3" attack, which maybe lower the reaction temperature and improve the selectivity of cyclization (**Scheme 1c**). Herein, we report a selective cascade cyclization reaction of 1,2-diethynylbenzene derivatives with NaN_3 for the synthesis of [1,2,3]triazolo[5,1-*a*]isoquinoline compounds.

RESULT AND DISCUSSION

There were two reaction sequences for the cascade cyclization reactions of unsymmetric 1,2- bis(phenylethynyl)benzene derivatives and NaN_3. According to the calculated results,[28] the rate-determining step of cascade cyclization of enediynes with NaN_3 was the [3+2] cyclization reaction, so the reaction sequence could be adjusted by the reactivity of the alkyne towards NaN_3. In general, the cyclization reactions of more electron-deficient alkynes with NaN_3 were easier than electron-rich alkynes.[30] Firstly, we tested the 1,2-bis(phenylethynyl)benzene derivative **2** in which one *p*-OMe phenyl group was installed on one of the alkyne moiety. When it reacted with NaN_3 (**Scheme 2a**), the obtained products were mixtures, which cannot be separated by simple silica column chromatography. The ^{1}H NMR spectrum of products showed the ratio of two isomers was about 3:5 (see supporting information). Interestingly, we have also obtained the crystal

structures of the products, which showed the cocrystallization of two isomers (**3** and **4**, 1:1) (**Figure 1a**). We proposed that the substituent effect was not obvious under high reaction temperature, and attempts to reduce the reaction temperature (140 ℃) gave the same ratio of the isomers and lower conversion.

Then we investigated the cyclization reactions of other different kind of substituted unsymmetrical 1,2-bis(phenylethynyl)benzene derivatives with NaN_3. It's gratifying that the enediyne **5** reacting with NaN_3 gave the **6** as the major product (**Scheme 2b**) and the yield was up to 64%. The structure was also characterized by single-crystal X-ray diffraction (**Figure 1b**), in this case, the first cyclization step happened in the two aromatic substituted alkyne, then N-attack cyclization happened in another alkyne moiety. And we also checked other alkyl substituted diynes (**Scheme 3**), intermediates **7** and **8** could give the major products **9** and **10** in 60% and 57% yields (for two steps). Interestingly, the diyne **11** gave the product **13** in which the 2-hydroxypropyl group was cleaved, while intermediate diyne **12** in which 2-hydroxypropyl protecting group was first removed by potassium hydroxide gave other mixtures under the same condition, so the 2-hydroxypropyl group should be cleaved after the cascade cyclization. Although the cyclization reaction of aromatic and alkyl substituted 1,2-bis(phenylethynyl)benzene derivatives with NaN_3 gave corresponding products via selective cyclization, it was regretful that these reactions also need high temperature and

long reaction time, and much excess NaN_3 were needed to improve the conversion, furthermore, the yields were not very high.

The electron-withdrawing group substituted alkynes were more active towards Nu attack under mild conditions, such as the carbonyl group activated alkynes could be easy attacked by "N_3" to form 1,2,3-triazoles.[31-35] Inspired by this, the carbonyl groups substituted 1,2-diethynylbenzene derivatives were synthesized by the Sonogashira reactions of the acyl chloride with terminal alkynes.[36,37] Satisfactorily, their cascade cyclization reactions with NaN_3 could be conducted at 60 ℃, and different substituens all gave the products in high total yields (two steps). The results were shown in **Table 1**, and the product **15a** was identified by X-ray crystal structure analysis (**Figure 2**). 2-hydroxypropyl substituted alkynes gave the deprotected products (**15e** and **15f**) under this condition. It was revealed that the cascade cyclization sequences were conducted by the designed method, the first cycloaddition happened in the carbonyl activated alkyne, which was the rate-determining step, and then *6-endo-dig* cyclization step happened quickly, overall, the cascade reaction showed high selectivity.

In conclusion, we developed a method for the synthesis of the [1,2,3]triazolo[5,1-*a*]isoquinoline derivatives by the treatment of the substituted 1,2-diethynylbenzene derivatives with NaN_3 in DMSO. It was found that the regioselectivities of the reactions were decided by two substituents in the alkynes of

1,2-diethynylbenzenes. For the acyl-substituted 1,2-diethynylbenzenes, the cascade cyclizations with NaN_3 could happen under mild conditions and give the corresponding products in high yields. Further investigation for the application of this strategy in the synthesis of other N-heterocycle and the properties of the [1,2,3]triazolo[5,1-*a*] isoquinoline derivatives are underway.

EXPERIMENTAL

General Methods and materials: All of the reactions were carried out in 25 mL round-bottom flasks with air condensers. Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 600 MHz and 400 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (TMS) (0.00 ppm) or $CDCl_3$ (7.26 ppm) for ^{1}H, $CDCl_3$ (77.0 ppm) for ^{13}C and d^6-DMSO (2.5 ppm) for ^{1}H, (39.5 ppm) for ^{13}C. Flash column chromatography was performed on 200-300 mesh silica gel. Analytical thin layer chromatography was performed with precoated glass baked plates (250 μ) and visualized by fluorescence. MS were measured on a Bruker Apex IV FTMS spectrometer. Melting points were measured on a melting point tester RY-1G apparatus and uncorrected. All the products had passed the infrared detector.

Typical Procedure For Preparation Of [1,2,3]Triazolo[5,1-*A*]Isoquinoline Derivatives (15a-F)

1-ethynyl-2-(phenylethynyl)benzene (202 mg, 1 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.1 mmol) were added to a pear-shaped Schlenk tube charged with a magnetic stirrer. The tube was evacuated and backfilled with argon and then degassed Et_3N and THF (6 mL, V/V, 1:1) was introduced, then the 2-chlorobenzoyl chloride (262 mg, 1.5 mmol) was introduced. The mixtures were heating at 60℃ for 2 hours. Then the reaction mixture cooled to room temperature, next filtrated with short flash column chromatography (silica gel), and eluted with EtOAc. The combined solution was removed the solvent under reduced pressure to give an oil, which redissolved in DMSO (5 mL) without further purification, and then NaN_3 (98 mg, 1.5 mmol) was added. The mixture was heated at 60 ℃. The reaction was monitored by TLC. After the completion of the reaction, the mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and dried with anhydrous Na_2SO_4. Concentration under reduced pressure and purification of the residue by flash chromatography on silica gel gave **15a** as white solid (82% yield for two steps).

(2-chlorophenyl)(5-phenyl-[1,2,3]triazolo[5,1-a]isoquinolin-1-yl)methanone (**15a**). IR(KBr): ν_{max}= 1656, 1521, 1064, 941, 858cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 9.94 (d, *J* = 3.0 Hz, 1H), 7.88-7.95 (m, 3H), 7.80-7.82 (m, 2H), 7.59-7.62 (m, 1H), 7.52 (s, 3H), 7.41-7.50 (m, 3H), 7.24-7.40 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.7, 139.9, 139.8, 136.0, 134.8, 131.72, 131.67, 131.6, 131.3, 131.1, 130.1, 123.0, 129.8,

129.7, 128.9, 128.5, 128.3, 127.3, 126.4, 122.3, 118.0 ppm; ESI-MS(m/z): 383.1[$C_{23}H_{14}{}^{35}ClN_3O]^+$, 385.1[$C_{23}H_{14}{}^{37}ClN_3O]^+$ (3:1); HRMS(ESI): calcd.[$C_{23}H_{14}ClN_3O+H]^+$: 384.0898, found: 384.0902.

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SUPPORTING INFORMATION

Full experimental detail, ^1H and ^{13}C NMR spectra and X-ray data for this article can be accessed on the publisher's website. Please make the words "publisher's website" a live DOI link.

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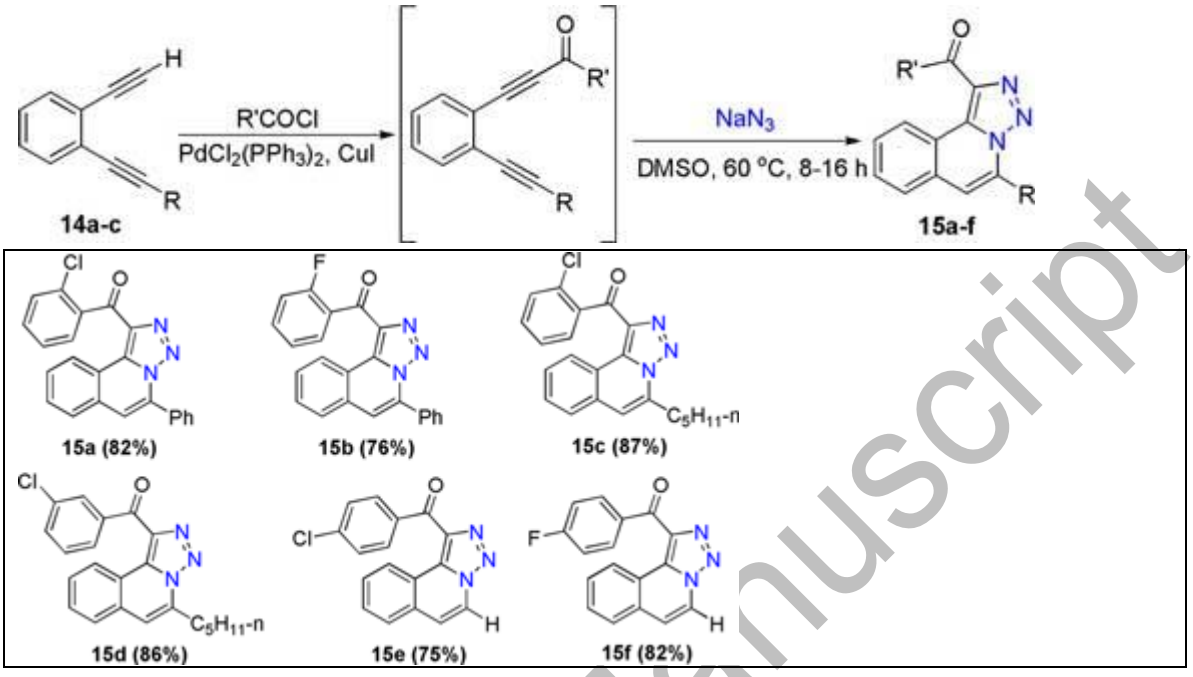
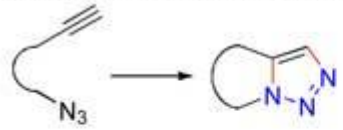
Table 1.

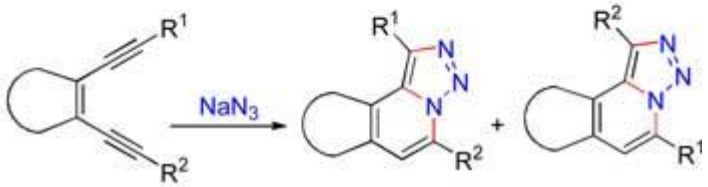


Scheme 1. Strategies for the synthesis of fused 1,2,3-triazole heterocycles.

(a) intramolecular cyclization strategy

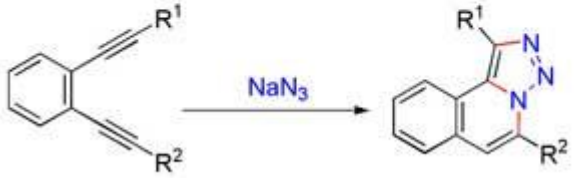


(b) intermolecular cascade cyclization strategy



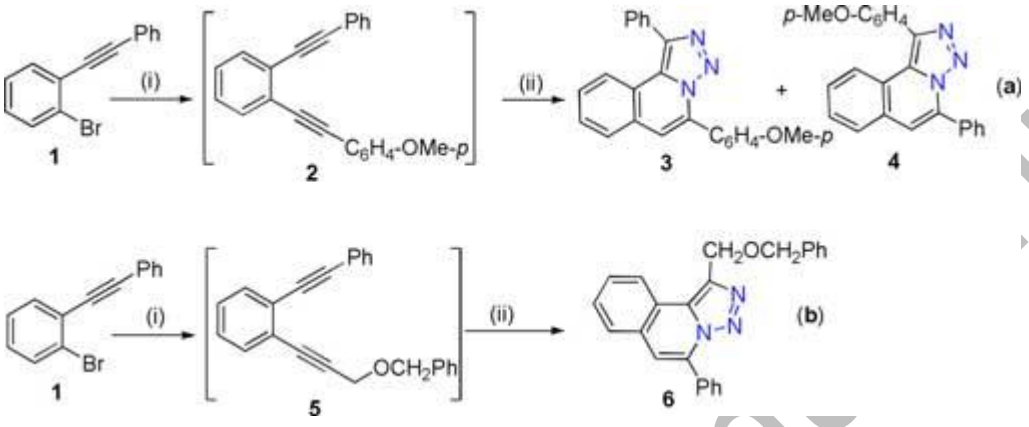
Conditions: DMF; 80-100 ^{o}C; 12 h to 10 days; yields:17% to 85% (combined) ; ratios: < 3:1 when $R^1 \neq R^2$.

(c) this work



R^1 = Ar, R^2 = alkyl; R^1 = COR, R^2 = Ar or alkyl

Scheme 2. *Reagent and conditions*: (i) 1-ethynyl-4-methoxybenzene or ((prop-2-ynyloxy) methyl)benzene (1.2 eq), $PdCl_2(PPh_3)_2$ (0.05 eq), CuI (0.06 eq), Et_3N/THF(0.5 M, V/V, 1:1), 80 ℃; (ii) NaN_3(3-5 eq), DMSO, 160 ℃, 48 h.



Scheme 3. The cascade cyclization of 1,2-bis(phenylethynyl)benzene with NaN_3

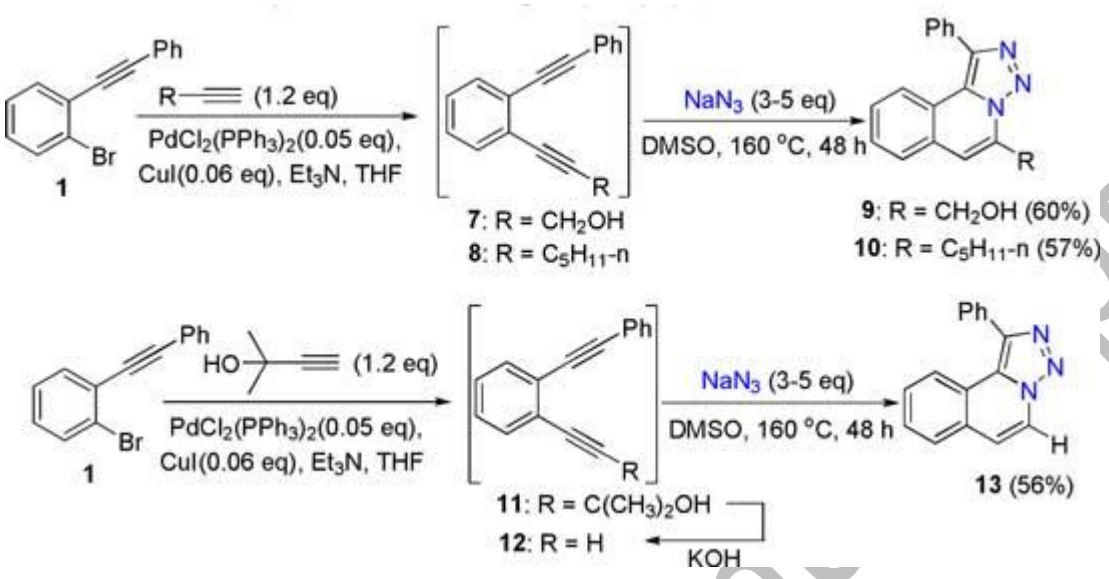
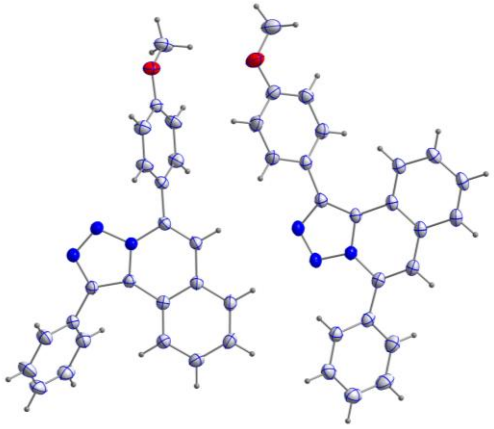
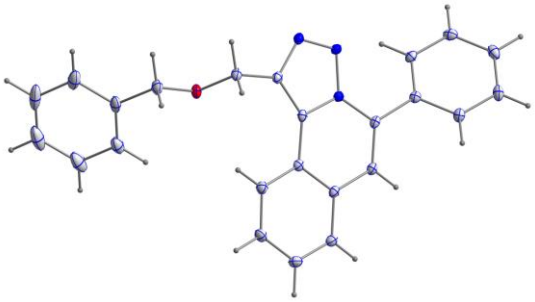


Figure 1. The crystal structures of compound **3** and **4** (cocrystallization) and **6** (ellipsoids at 30% of probability).



(**a**)



(**b**)

Figure 2. The crystal structure of compound **15a** (ellipsoids at 30% of probability).