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One-pot, two-step synthesis of 7-methylene-1,5-piperazine-fused 1,2,3-triazoles

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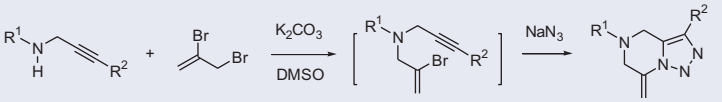
ABSTRACT

A facile, one-pot two-step synthesis of 7-methylene-1,5-piperazine-fused 1,2,3-triazole derivatives has been developed. The protocol employs an *N*-allylation of *N*-propargylated amines with 2,3-dibromopropene in the presence of K_2CO_3 in DMSO and a CuI-catalyzed [3 + 2] cycloaddition reaction of the synthetic *N*-(2-bromoallyl)-*N*-propargyl amines with sodium azide sequentially. Such a method provides methylene-substituted 1,2,3-triazole fused piperazines with some advantages such as simple operation, high efficiency and good product yield (80–91%) through readily available starting materials.

GRAPHICAL ABSTRACT



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[3 + 2] cycloaddition; 2,3-dibromopropene; 7-methylene-1,5-piperazine-fused 1,2,3-triazoles; N-propargylated amines; N-allylation; one-pot procedure

Introduction

1,2,3-Triazoles are a very important class of heterocyclic compounds, which are widely applied in pharmaceuticals, agrochemicals, dyes, corrosion inhibitors, biochemicals, polymers, and functional materials.[1,2] Since Sharpless[3a] and Meldel[3b] groups independently discovered the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, "click chemistry" has received growing interest in the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles. Following these pioneering works, many effective synthetic methods for achieving this ring system have been developed for different purposes.[4] At the same time, fused 1,2,3-triazoles have also attracted considerable interest due to their diverse array of pharmaceutical functionalities such as antitumor, antiproliferative, antivirus and glycosidase inhibitory activities.[5] Among the fused 1,2,3-triazoles family, 1,2,3-triazoles particularly condensed with heterocycles at the 1,5-positions exhibited significant biological activities.[6,7] For instance, 1,2,3-triazolo[1,5-*a*]quinoxaline has shown good affinity toward benzodiazepine and adenosine receptors.[6a,6b] Therefore,

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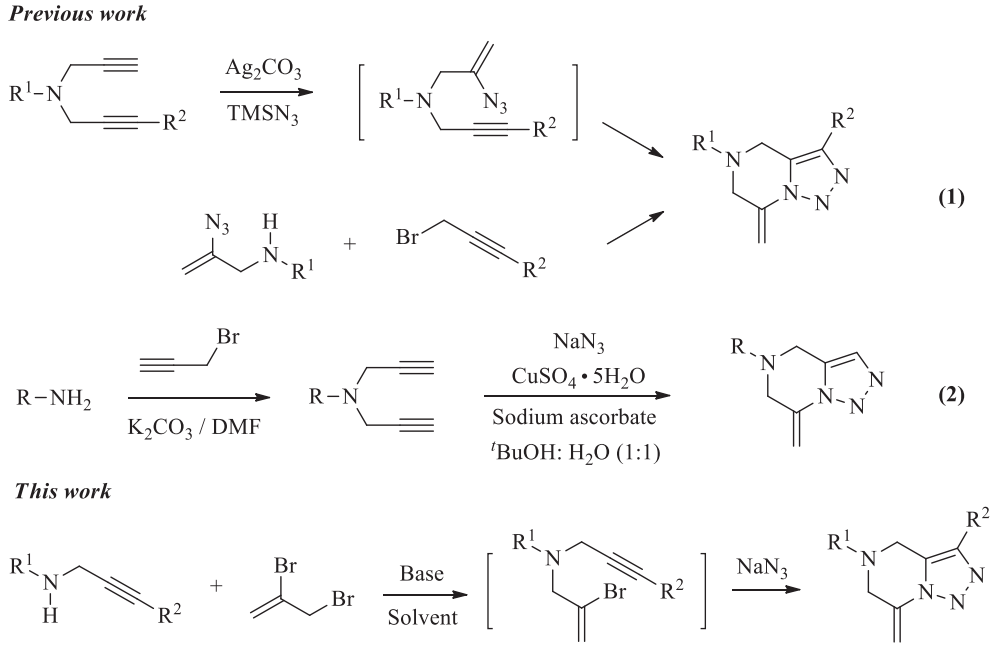
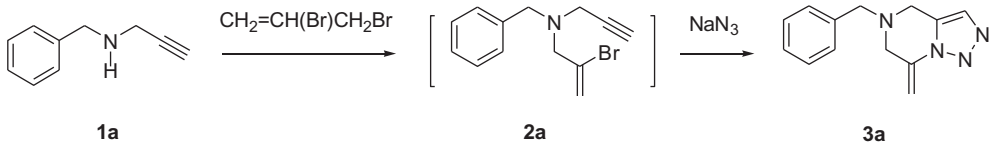


Scheme 1. Synthetic routes to 7-methylene-1,5-piperazine-fused 1,2,3-triazoles.

searching convenient access to the fused 1,2,3-triazoles derivatives is highly appealing work. In recent years, several synthetic routes to 1,2,3-triazoles fused at the 1,5-positions with a piperazine framework have been described by alkyne-azide intramolecular "click" reaction from different starting materials such as α-amino acid, primary amine and sulfamidate derivatives.[8–17] Among them, Ning et al.,[15] have explored that the tandem hydroazidation/alkyne-azide cycloaddition of diynes with TMS-N_3 under Ag_2CO_3 catalysis to the methylene-substituted triazolo[1,5-*a*]pyrazines (Scheme 1, Eq. (1)). The formation of several analogous 1,5-fused-1,2,3-triazole compounds by click reaction of vinyl azides and propargyl bromides have also been investigated in this study. In addition, 1,3-dipolar cycloaddition followed by intramolecular 6-exodig cycloaddition of diprop-2-ynylamines was used to construct the similar products (Scheme 1, Eq. (2)).[16] These methods provided easy access to the desired fused 1,2,3-triazoles, but it needs more toxic and expensive reagents, as well as vinyl azides, which are not easy to obtain. As far as we know, there are few reports on triazolo [1,5-*a*] pyrazine derivatives containing functional methylene groups. Herein, we report a one-pot, two-step procedure for the construction of 7-methylene-1,5-piperazine-fused 1,2,3-triazoles by sequent *N*-allylation and click reaction from *N*-propargylated amines, 2,3-dibromopropene and NaN_3, as shown in Scheme 1.

In order to find the most suitable one-pot reaction conditions, *N*-propargyl benzylamine (**1a**), 2,3-dibromopropene and NaN_3 were chosen as model substrates for the preparation of 5-benzyl-7-methylene-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine (**3a**). For this purpose, the formation of *N*-(2-bromoallyl)-*N*-propargyl benzylamine (**2a**), the key step in the proposed route were firstly explored (Scheme 2), and the corresponding experimental results were outlined in Table 1. As highlighted in Table 1, the nature of the base played a crucial role in this process, exemplified by the observation



Scheme 2. Formation of 1,5-piperazine-fused 1,2,3-triazole derivative (**3a**).

Table 1. Screening of reaction conditions in the synthesis of **2a**[a].

Entry	Base	Solvent	Temperature (°C)	Time (h)	Yield of **2a** (%) [b]
1	Et_3N	CH_3CN	r.t.	6	0
2	DBU	CH_3CN	r.t	6	0
3	Cs_2CO_3	CH_3CN	r.t	6	70
4	K_2CO_3	CH_3CN	r.t	6	75
5	K_2CO_3	DCE	r.t	6	0
6	K_2CO_3	Toluene	r.t	6	0
7	K_2CO_3	EtOH	r.t	6	51
8	K_2CO_3	Dioxane	r.t	6	42
9	K_2CO_3	DMF	r.t	6	80
10	K_2CO_3	DMSO	r.t	6	85
11	K_2CO_3	DMSO	80	5	90
12	K_2CO_3	DMSO	80	5	90[c]

[a]Reaction conditions: **1a** (1.0 mmol), 2,3-dibromopropene (1.0 mmol), base (1.0 mmol) and solvent (10 mL). [b]Isolated yield. [c]K_2CO_3 (1.5 mmol) was used.

that **2a** was not formed when triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were employed (Table 1, entry 1 and 2). In contrast, inorganic bases such as cesium carbonate and potassium carbonate could promote effectively the formation of **2a** in 70% and 75% yields (Table 1, entry 3 and 4), respectively. A screen of solvents showed that the desired product **2a** was not generated when the reaction was carried out in 1,2-dichloroethane (DCE) or toluene (Table 1, entry 5 and 6), and **2a** was formed in low yields when ethanol and dioxane were used as solvents (Table 1, entry 7 and 8).

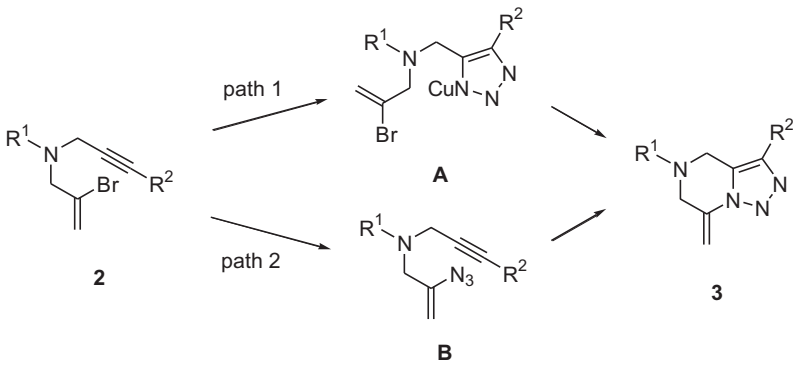
After a series of optimization, it was found that acetonitrile, *N,N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO) could be used in this transformation, and DMSO seemed to be the most suitable solvent for this transformation in comparison with others. Moreover, increasing the reaction temperature to 80 °C in DMSO could not only increase the yield of **2a** but also shorten the reaction time (Table 1, entry 11). Further screening showed that increasing the amount of k_2CO_3 to 1.5 equivalent did not result in an improved yield of **2a** (Table 1, entry 12).

With **2a** in hand, without isolating this compound, the reaction mixture was subjected to intramolecular cycloaddition. After further study on the [3 + 2] cycloaddition with some copper (I) catalysts such as CuCl, CuBr and CuI, it was found that the expected triazole derivative **3a**, as only product was obtained in 86% yield in the presence of CuI (10 mol %) and K_2CO_3 at 65 °C for 5 h, whereas the possible isomers of **3a**, 5-benzyl-7-methyl-4,5-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazine was not observed. Changing CuI loading from 10 mol % to 20 mol % did not alter the yield of **3a**, while using 10 mol % CuCl or CuBr gave 42% and 68% yields, respectively. In another experiment, the same reaction was tested through thermal cycloaddition (90 °C, 5 h), **3a** was formed in 75% yield with **2a** being isolated, and no better results were obtained at an elevated temperature of 120 °C or prolonging the reaction time.

Table 2. Preparation of compounds (**3a–3m**) *via* one-pot two-step reaction.[a]

Entry	R^1 (1)	R^2	Products (3)	Yield (%)[b]
1	$C_6H_5CH_2$ (**1a**)	H	**3a**	86
2	$C_6H_5CH_2$ (**1a**)	C_6H_5	**3b**	81
3	$C_6H_5CH_2$ (**1a**)	4-ClC_6H_4	**3c**	80
4	$C_6H_5CH_2$ (**1a**)	4-$CH_3C_6H_4$	**3d**	82
5	$C_6H_5CH_2$ (**1a**)	CH_3	**3e**	89
6	4-$CH_3OC_6H_4CH_2$ (**1b**)	H	**3f**	88
7	4-$CH_3C_6H_4CH_2$ (**1c**)	H	**3g**	86
8	2-$ClC_6H_4CH_2$ (**1d**)	H	**3h**	81
9	3-$BrC_6H_4CH_2$ (**1e**)	H	**3i**	83
10	C_6H_5 (**1f**)	H	**3j**	88
11	4-$CH_3OC_6H_4$ (**1g**)	H	**3k**	92
12	4-$CH_3C_6H_4$ (**1h**)	H	**3l**	91
13	4-ClC_6H_4 (**1i**)	H	**3m**	82

[a]Reaction conditions: **1** (1.0 mmol), 2,3-dibromopropene (1.0 mmol), K_2CO_3 (1.0 mmol) and solvent (6 mL). [b]Isolated yield.



Scheme 3. Plausible reaction mechanism.

Finally, the optimized reaction conditions were extended to a variety of *N*-propargylated amines (**1a–1i**), derived from benzyl amines and primary aromatic amines, and the results were summarized in Table 2. As observed from Table 2, for all substrates, the reaction could proceed smoothly and the corresponding 7-methylene-1,5-piperazine-fused 1,2,3-triazoles (**3a–3m**) were obtained in good yields. No significant difference in reactivity was found for the examined benzyl amines, including those containing 2-chloro, 3-bromo, 4-methyl, and 4-methoxy groups (Table 2, entries 1–9). It is noteworthy higher yields were obtained when R^2 was methyl group rather than an aryl group (Table 2, entries 2–5). Furthermore, a variety of arylamines substituted by 4-methyl, 4-methoxy, 4-chloro on the benzene ring were also converted effectively to the corresponding products (Table 2, entries 10–13).

On the basis of the above experimental results and the literature reports on the copper(I)-catalyzed azide-alkyne click reactions,[18a,18b] two plausible mechanistic paths (**1** or **2**) could be considered for the formation of products **3,** as shown in Scheme 3. Path **1** involves an initial formation of 1,2,3-triazole copper-intermediate **A**, followed by intramolecular Ullmann-type coupling to give 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazines (**3**). Path **2** takes place a copper-catalyzed Ullmann-type coupling to form intermediate **B** firstly, and subsequent intramolecular azide-alkyne cycloaddition produces the final product **3**.

In summary, we have developed a simple and efficient, one-pot, two-step reaction for the synthesis of 7-methylene-1,5-piperazine-fused 1,2,3-triazole derivatives from readily available starting materials under mild conditions. Considering the potential broad bioactivities in such fused bicyclic structures, this method might be practically useful. Further investigation concerning the scope and synthetic application of the present functional fused 1,2,3-triazoles is ongoing in our laboratory.

Experimental

N-Propargylated amines (**1a–1i**) were prepared in good yields by the reaction of primary amines with propargyl bromides in the presence of anhydrous potassium carbonate in DMF. The other reagents and solvents were purchased from commercial suppliers and were used without further purifications. The reaction progress was detected by thin layer chromatography (TLC) on GF254 silica gel analytical aluminum plates, and the products were visualized by UV spectrophotometer. Column chromatography was performed using silica gel 60 (250–400 mesh) with petroleum ether/ethyl acetate as eluent. Melting points were measured with a Beijing-Taike X-4 apparatus without corrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated $CDCl_3$ on an Avance-Bruker 400 MHz NMR spectrometer, operating at 400 and 100 MHz, respectively. FTIR analyses were performed with a Perkin-Elmer SP One FTIR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 Elemental Analyzer.

General procedure for the preparation of 7-methylene-1,5-piperizine-fused 1,2,3-triazoles

A mixture of *N*-propargylated amine (1.0 mmol), K_2CO_3 (1.0 mmol) and 2,3-dibromopropene (1.0 mmol) in DMSO (6 mL) was stirred at 90 °C for 5–6 h until the reaction was completed (determined by TLC). After cooling to room temperature, CuI (19 mg, 0.1 mmol) was added to the mixture, and the mixture was then stirred at 65 °C for 5–6 h (TLC monitoring). After completion, water (15 mL) was added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was loaded onto a column and purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 10:1) to afford the final product.

Characterization data of all target compounds, copies of ^{1}H NMR and ^{13}C NMR spectra of new compounds. This material can be found via the "Supplementary Content".

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