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To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201601188

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601188

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Facile Synthesis of [1,2,3]Triazolo[5,1-*a*]isoquinolines via A Copper-Catalyzed Tandem Sonogashira Coupling/Cyclization Reaction

Mingzhu Fan, [a] Yi Liu, [a] Qinquan Hu, [a] Lihui Jia, [a] and Yunfeng Chen*[a]

Abstract: A highly efficient synthesis of [1,2,3]triazolo[5,1-*a*]isoquinoline derivatives was developed via a copper-catalyzed tandem Sonogashira coupling/regioselective 6-*endo* cyclization. This *NH*-triazole directed-annulation approach showed good functional group tolerance, and gave the corresponding N-fused heterocycles in good to excellent yields.

Introduction

Structurally novel fused heterocycles have drawn much attention due to their ubiquitous core structure together with potential biological and pharmaceutical activities[1]. Rapid and efficient construction of structurally diverse fused heterocycles from simple reactants remains a challenging task for synthetic organic chemists.[2] [1,2,3]triazolo[5,1-*a*]isoquinoline is an important class of fused heterocycles with wide applications in medicinal chemistry and material research.[3] In recent years, there have been relevant reports, such as, Kundu group[4] developed a condensation/[3+2] cycloaddition/6-*endo*-cyclization reaction sequence of 2-alkynylbenzaldehydes for synthesis of [1,2,3]triazolo[5,1-*a*]isoquinolines (Scheme 1a), but this strategy needs to separate (*E*)-1-(2-nitrovinyl)-2-(alkynyl)benzene intermediates, and the reactions cannot give 1-substituted products. Lately, Gulevskaya group[5] reinvestigated the cyclization of enediynes with NaN_3, they found that (*Z*)-hexa-3-en-1,5-diynes gave corresponding [1,2,3]triazolo[1,5-*a*]pyridines and [1,2,3]triazolo[5,1-*a*]isoquinolines (Scheme 1b), however, the reactions gave lower to moderate yields and lower regioselectivities for the substrates bearing two different alkyne-substituted groups. At the same time, we also developed a selective cascade cyclization sequence of 1,2-bis(phenylethynyl)benzene derivatives to afford 1-carbonyl substituted [1,2,3]triazolo[5,1-a]isoquinolines.[6]

Previously, we also developed a simple and efficient cascade process for the synthesis of 5-amino-[1,2,3]triazolo[5,1-*a*]isoquinoline derivatives by the condensation reaction between *NH*-triazole aryl halides and activated nitriles in the presence of Cu(I) catalyst and ligand.[7] We found this *NH*-triazole directed-annulation approach showed high reaction efficiency and wide substrate scope. Moreover, we developed a highly efficient one-pot *NH*-1,2,3-triazole synthetic strategy [8]. In continuation of our research for synthesis of new 1,2,3-triazole related heterocyclic compounds, herein we present a copper-catalyzed synthesis of various [1,2,3]triazolo[5,1-*a*]isoquinolines from *o*-bromo-aryl-*NH*-triazoles and terminal alkynes (Scheme 1c). This reaction proceeds in a mild condition and affords the products with high yields and reaction efficiency.

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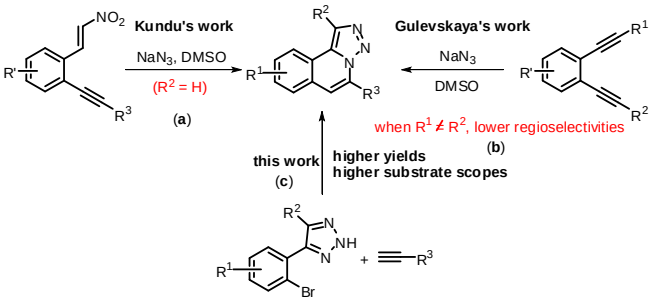
Scheme 1. Methods for synthesis of [1,2,3]triazolo[5,1-a]isoquinolines



Results and Discussion

The 4-(2-bromophenyl)-2H-1,2,3-triazole and phenylacetylene were selected for the reaction condition screening. The results are summarized in **Table 1**. Initially we proposed that the Sonogashira coupling[9] /regioselective 6-*endo* cyclization tandem sequence[10] of *o*-bromo-aryl-*NH*-triazoles with terminal alkynes would occur smoothly with Pd catalyst (**Table 1**, entry 1) under argon atmosphere to give triazolo isoquinoline derivatives. Firstly, the reaction was carried out using $PdCl_2(PPh_3)_2$ together with CuI as catalyst, K_2CO_3 as base and DMSO as solvent at 110 °C, the corresponding product **3a** was obtained with 88% isolated yield. Encouraged by some copper catalyzed directed C-H or C-X activation[11], we assumed whether Cu(I) could catalyze this reaction solely. Indeed, this reaction could happen without Pd catalyst, CuI alone could promote this reaction, the yield was up to 90% when 10% CuI was used, other Cu(I) salts were inferior to CuI (**Table 1**, entries 4 and 5). Moreover, other catalysts were also tested. It revealed that Cu(II) salts, such as $CuCl_2$, $CuSO_4$, $Cu(OAc)_2$ could also promote this reaction (**Table 1**, entries 6-8), but the results were not better than CuI. When the reaction proceeded in air, the yield decreased to 25%, however, if the amount of $Cu(OAc)_2$ was added to 50%, **3a** was obtained with 88% isolated yield. It is noteworthy that the Glaser coupling[12] product was found when Cu(II) was used as catalyst, we proposed that the Cu(II) species was converted to Cu(I) species during the process of Glaser coupling, which promoted the Sonogashira coupling reaction in this reaction system. Considering the cost and efficiency of the reaction, the Cu(I) could be better choice for this reaction. Further lowered the reaction temperature to 80 °C, the yield of **3a** could decrease to 45% (**Table 1**, entry 11). Switching solvents from DMSO to DMF afforded **3a** in diminished yield (**Table 1**, entry 12). The subsequent screening of different bases (**Table 1**, entries 13-15) gave **3a** in 60% yield when NaOAc was used as base (**Table 1**, entry 15), while K_3PO_4 and Cs_2CO_3 didn't give better results. Attempting to introduce ligand gave the unsatisfactory result, 1,10-phenanthroline (phen) couldn't promote the efficiency of CuI, which gave the same result as ligand-free condition (**Table 1**, entries 2 and 16).

As CuI/K_2CO_3/DMSO was identified as a suitable catalyst system, the synthesis of various [1,2,3]triazolo[5,1-a]isoquinolines with different substituents was explored, the *o*-

Table 1. The optimization of the reaction condition[a]

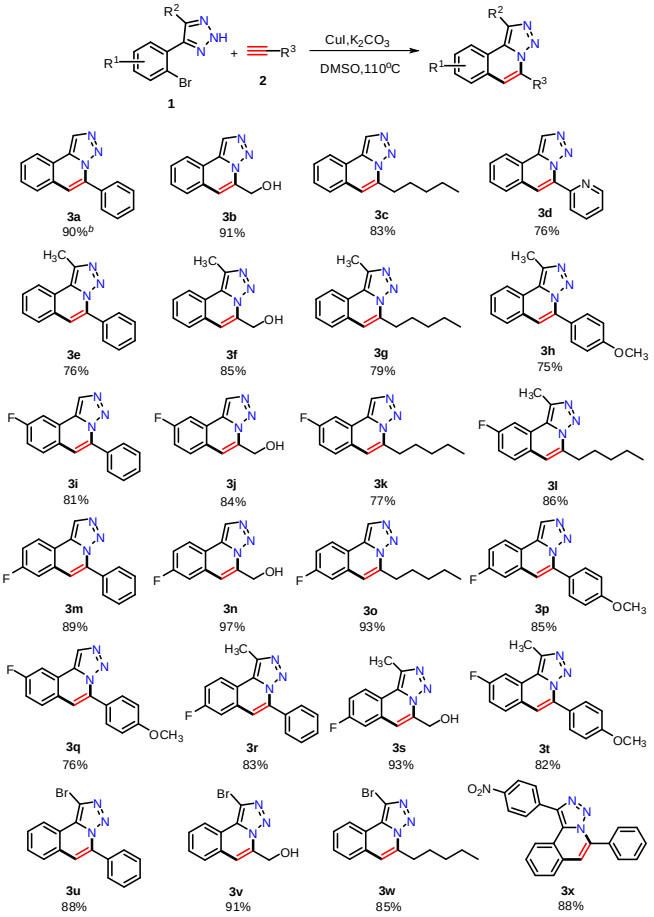
1a 2a 3a

Entry	Cat	Amount	Base	T (°C)	Solvent	Yield (%)[b]
1	$PdCl_2(PPh_3)_2$ /CuI	5%/6%	K_2CO_3	110	DMSO	88
2	CuI	5%	K_2CO_3	110	DMSO	57
3	**CuI**	**10%**	**K_2CO_3**	**110**	**DMSO**	**90**
4	CuCl	10%	K_2CO_3	110	DMSO	76
5	CuBr	10%	K_2CO_3	110	DMSO	81
6	$Cu(OAc)_2$	10%	K_2CO_3	110	DMSO	72
7	$CuSO_4$	10%	K_2CO_3	110	DMSO	70
8	$CuCl_2$	10%	K_2CO_3	110	DMSO	28
9[c]	$Cu(OAc)_2$	10%	K_2CO_3	110	DMSO	25
10[c]	$Cu(OAc)_2$	50%	K_2CO_3	110	DMSO	88
11	CuI	10%	K_2CO_3	80	DMSO	45
12	CuI	10%	K_2CO_3	110	DMF	78
13	CuI	10%	K_3PO_4	110	DMSO	<10
14	CuI	10%	Cs_2CO_3	110	DMSO	<10
15	CuI	10%	NaOAc	110	DMSO	60
16	CuI/phen	5%/6%	K_2CO_3	110	DMSO	56

[a] Reaction condition: 4-(2-bromophenyl)-2H-1,2,3-triazole (**1a**) (100 mg, 1 mmol), phenylacetylene (68.4 mg, 1.5 mmol), CuI (4.2 mg, 0.1 mmol), K_2CO_3 (123.4 mg, 2 mmol), DMSO (6 mL), 5-6 h, under argon atmosphere; [b] isolated yields; [c] in air.

bromo-aryl-*NH*-triazoles could be easily obtained by our one- in the aryl ring, it revealed that *NH*-triazole directed Sonogashira coupling could overcome the electron effect of the aryl ring. Good substitute group tolerance at the triazole C-5 position was observed, the R^2 in the triazole ring can be H, alky
pot synthetic strategy.[8] As shown in Scheme 2, it seemed that there was no obvious substituent effect observed for the R^1 l (**Me**), aryl groups and Br atom. It had been observed that when the R^2-H in the triazole ring was replaced to Me, it gave a slightly reduced isolated yield, such as **3a** and **3e**, **3b** and **3f**. Although there were two Br atoms in the substrates, the Br atom at the triazole C-5 position didn't affect the cascade reaction (**3u**, **3v** and **3w**), the desired aryl-Br Sonogashira coupling was obtained exclusively (over the triazole-Br Sonogashira coupling), which exhibited the directing effect of the triazole during the reaction process. From this point of view, the reaction mechanism could involve a Cu-catalyzed *NH*-triazole-directed Sonogashira coupling and a subsequent 6-*endo*-dig cyclization reaction. By contrast with Kundu's strategy[5], using 2-alkynylbenzaldehydes as starting materials could not give R^2-substituted (such as Br, aryl(**3x**)) products, so our *NH*-triazole directed-annulation approach should be a good compensate, which showed better diversity of the products. Further, different terminal alkynes, such as aryl- and alkyl-acetylenes were also suitable reaction partners for this cascade reaction. The electron-donating group OMe, gave a slightly reduced isolated yield. Gratifyingly, 3-hydroxy-1-propyne and 2-pyridylacetylene were also tolerated in this reaction, and 3-hydroxy-1-propyne gave the corresponding products in better yields (**3b**, **3f**, **3j**, **3n**, **3s** and **3v**).

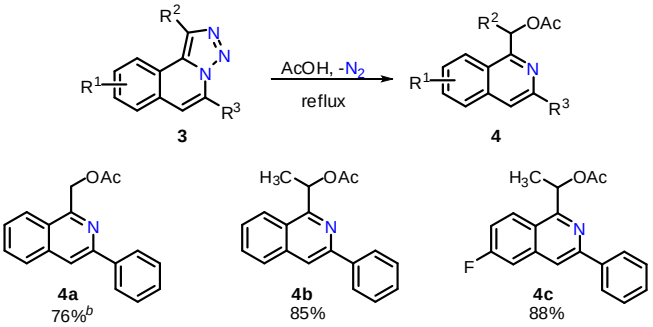
Scheme 2. Reaction substrate scope



[a]Reaction conditions: *o*-bromo-aryl-triazoles (**1**) (1 mmol), terminal alkynes (**2**) (1.2-1.5 mmol), CuI (0.1 mmol), K_2CO_3 (2 mmol), DMSO (6 mL), 5-6 h, under argon atmosphere. [b] Isolated yield.

With the [1,2,3]triazolo[5,1-a]isoquinolines in hand, we then explored the application of these fused heterocycles, simple treatment of the [1,2,3]triazolo[5,1-a]isoquinolines with AcOH in reflux condition, the corresponding denitrogenative ring-opening[13] isoquinoline products were obtained with good yields (Scheme 3), which applied a new strategy for synthesis of this biological important products.[14]

Scheme 3. Denitrogenative ring-opening reactions of [1,2,3]triazolo[5,1-a]isoquinolines



[a]Reaction conditions: [1,2,3]triazolo[5,1-*a*]isoquino- lines (**3**) (1 mmol), AcOH (5 mL), reflux, overnight. [b] Isolated yield.

Conclusions

In conclusion, a simple and efficient Cu(I) catalyzed tandem Sonogashira coupling/regioselectve 6-*endo* cyclization reaction has been developed. This *NH*-triazole directed-annulation approach showed good functional tolerances and easily avaiable raw materials, which led to the diverse [1,2,3]triazolo-[5,1-*a*]isoquinoline derivatives in good to excellent yields. Further studies about the directed-annulation approach for synthesis of other fused heterocycles and the applications of this transformation are ongoing in our laboratory.

Experimental Section

Typical procedure for the synthesis of **3a**
The mixture of 4-(2-bromophenyl)-2H-1,2,3-triazole (**1a**) (100 mg, 1 mmol), phenylacetylene (68.4 mg, 1.5 mmol), CuI (4.2 mg, 0.1 mmol), and K_2CO_3 (123.4 mg, 2 mmol), were stirred in 6 mL DMSO at 110 ^oC under argon atmosphere. After 5-6 h (as monitored by TLC), the solution was poured into water, and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The resulting mixture was chromatographed on silica gel by eluting with ethyl acetate/ petroleum ether to afford 98 mg (90%) of **3a** as white solid.

Typical procedure for the synthesis of **4a**
5-phenyl-[1,2,3]triazolo[5,1-*a*]isoquinoline (**3a**) (200 mg, 1 mmol), was stirred in 5 mL AcOH for refluxing overnight (as monitored by TLC), the solution was poured into water, then neutralized by aqueous Na_2CO_3, then extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The resulting mixture was chromatographed on silica gel by eluting with ethyl acetate/petroleum ether to afford 171.9 mg (76%) of **4a** as colorless oil.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (21002076, 21101123 and 21441007), Key Projects of Hubei Provincial Department of Education (D20151502), and the Scientific Research Foundation for the Returned Overseas Chinese Scholars for financial support.

Keywords: copper-catalyzed • Sonogashira coupling • tandem reaction • [1,2,3]triazolo[5,1-*a*]isoquinoline • N-fused heterocycles

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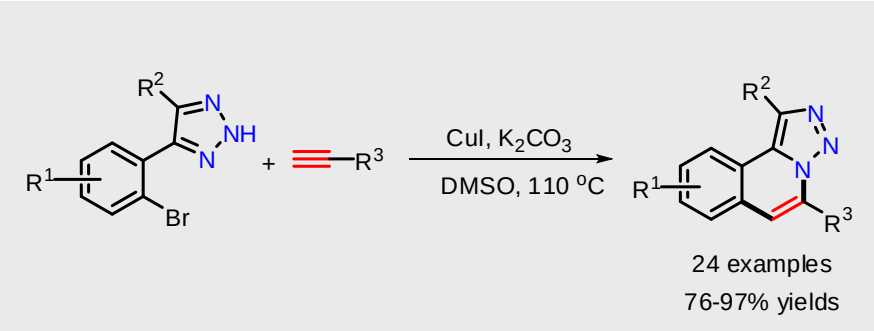

Key Topic*

*Mingzhu Fan,[a] Yi Liu,[a] Qinquan Hu,[a] Lihui Jia,[a] and Yunfeng Chen[a]**

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Facile Synthesis of [1,2,3]Triazolo[5,1-*a*]isoquinolines via A Copper-Catalyzed Tandem Sonogashira Coupling/Cyclization Reaction

A highly efficient synthesis of [1,2,3]triazolo[5,1-*a*]isoquinoline derivatives was developed via a copper-catalyzed tandem Sonogashira coupling/regioselective 6-*endo* cyclization. This *NH*-triazole directed-annulation approach showed good functional group tolerance, and gave the corresponding N-fused heterocycles in good to excellent yields.

*Copper-catalyzed, Sonogashira coupling, tandem reaction, [1,2,3]triazolo[5,1-*a*]isoquinoline, N-fused heterocycles