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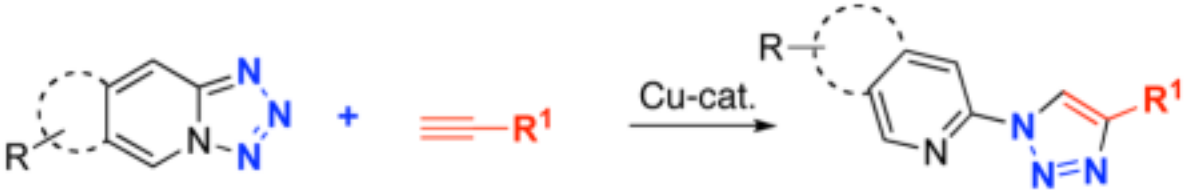
Fused Tetrazoles as Azide Surrogates in Click Reaction: Efficient Synthesis of N-Heterocycle-substituted 1,2,3-Triazoles

Buddhadeb Chattopadhyay, **Claudia I. Rivera Vera**, **Stepan Chuprakov**, and **Vladimir Gevorgyan***
Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

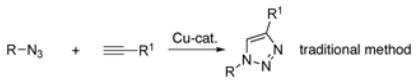
Abstract



It has been shown that various pyrido-, quinolino-, pyrazino- and qunoxalinotetrazoles can efficienly be used as azide components in the Cu-catalyzed click reaction with alkynes. This method allows for efficient synthesis of a wide variety of N-heterocyclic derivatives of 1,2,3-triazoles.

1,2,3-Triazoles are biologically important units.[1] Pyridotriazoles and quinolinotriazoles are particularly interesting as they exhibit a wide range of biological properties, including control of arthropod pests,[2a] substance-related disorders,[2b] ATP-competetive inhibition of vascular endothelial growth factor receptors I and II,[2c] antibacterial,[2d] and antimicrobacterial activity.[2e]

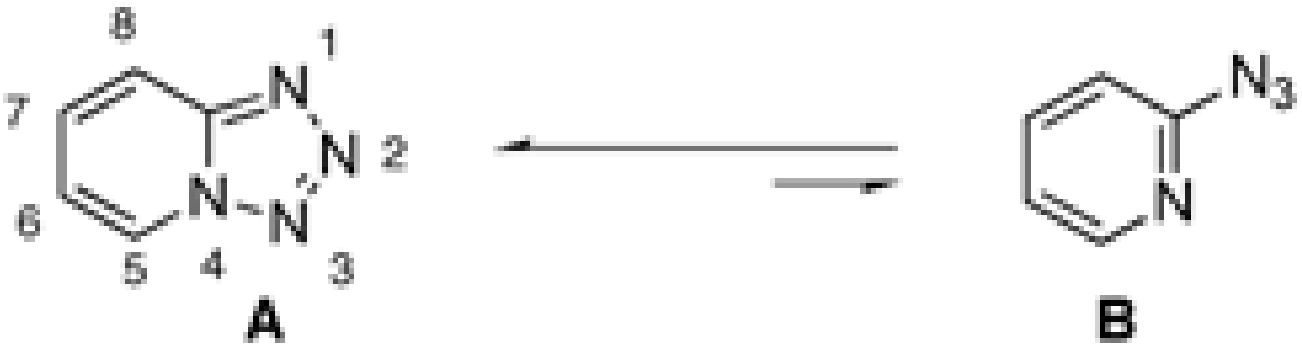
Unarguably, the Cu-catalyzed click chemistry[3] of azide with alkyne is the most efficient way to assemble the 1,2,3-triazole ring[4] (eq. 1). However, preparation of pyrido- and quinolino-triazoles is not straightforward since these azides exist in equlibrium between closed form (tetrazole **A**) and open form (azide **B**) (eq. 2).[5]



(1)

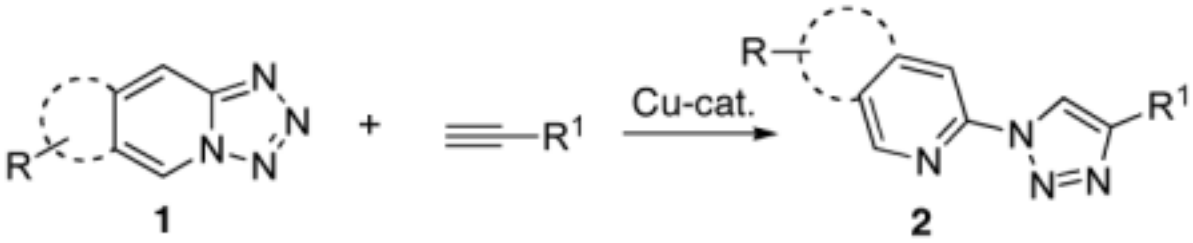
vlad@uic.edu.

Supporting Information Available: Experimental procedures and characterization of new compounds.



(2)

Usually, the position of this equilibrium depends on several factors, such as nature of substituents,[5] solvent[6] and temperature.[5] Thus, it has been reported[7a] that NO_2 group at the C-6 position of tetrazole favors the open form (azide **B**). On the contrary, tetrazoles with NO_2, COOH, and Cl groups at the C-8 position, and unsubstituted tetrazole predominantly exist[7,8] in closed form **A**. It should be mentioned that pyridotetrazole has been employed in the preparation of organometallic complexes of late transition metals.[7a] Furthermore, there have been contradictory reports[9,10] on the employment of tetrazoles in the click reaction. For instance, it has been shown that pyridotetrazoles, existing in closed form, are inert toward click reaction under standard conditions.[9] By other hand, there have been two reports10a,b in which single examples of successful click reaction of generated *in situ* pyridotetrazoles with alkynes were demonstrated. Moreover, when this manuscript was under preparation, a paper describing successful click reaction of purinotetrazole, which mainly exists in open form, has appeared. [10c] Accordingly, motivated by the high biological importance of pyridyl- and quinolinyl-containing triazoles[2] and intrigued by the contradictory results on employment of triazoles in click reaction,[9,10] we undertook investigation aming at the development of efficient method for employment of differently substituted tetrazoles in synthesis of heterocyclic derivatives of 1,2,3-triazoles. Herein, we wish to report that various pyrido- quinolino-, pyrazino- and qunoxalinotetrazoles **1** can efficiently be employed in click reaction with alkynes to give the corresponding heterocyclic derivatives of 1,2,3-triazoles **2** (eq. 3).



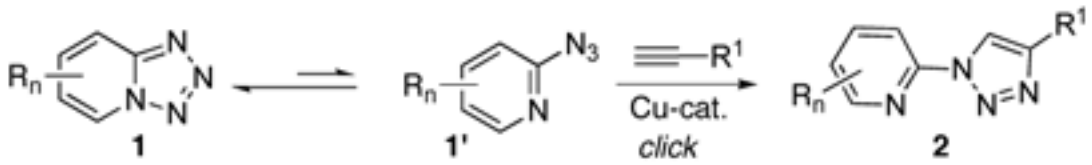
(3)

We first examined the reaction of tetrazole **1a** with phenyl acetylene employing the most popular[3b] click chemistry conditions (Table 1, entry 1). However, no formation of desired product **2a** was observed. Employment of other copper salts was more effective. Thus, when the reaction was performed in the presence of 10 mol% CuI,[4a] it afforded the product **2a** in 10% yield (entry 2). Use of $Cu(OTf)_2$[4i] gave 5% of product (entry 3). A substantial improvement of the yield (52%) has been achieved with $(CuOTf)_2 \cdot C_6H_6$[4j] (entry 4).

Gratifyingly, analogous reaction at room temperature gave 81% of **2a** (entry 5). THF was equally efficient as toluene in the reaction (entry 6). Switching to other solvents (entries 7 and 8) was not beneficial for this reaction.

With the best-optimized conditions in hand, we tested the generality of the click reaction of tetrazoles (Table 2). To our delight, these newly developed conditions appeared to be very general for a spectrum of N-fused tetrazoles giving an easy access to 1,4-triazoles **2**. Thus, reaction of ester-containing pyridotetrazole (**1a**) with varios alkynes proceeded smoothly at room temperature to produce differently substituted pyridyl-containing triazoles in good to excellent yields (entries 1–12). Reactions of unsubstituted (**1b**) and C-5 methyl-substituted (**1c**) tetrazoles were efficient at elevated temperatures (entries 13–21). It was also found that various N-fused heterocyclic tetrazoles, such as quinolinotetrazoles (**1d**, entries 22–28), pyrazinotetrazole (**1e**, entry 29 and 30) and qunoxalinotetrazole (**1f**, entries 31 and 32) successfully underwent click reaction to give the corresponding N-heterocycle-substituted 1,4-triazoles **2** in good yields. These reaction conditions appeared to be very general with respect to the alkyne component, as alkynes possessing various alkyl, aryl, alkenyl, benzyl, homobenzyl, ester, trimethylsilyl, alkyl chloride, secondary alcohol, acetal, thiophenyl, and even sugar groups provided good to high yields of triazoles **2**.

After developing the “tetrazole-clicking” approach for the synthesis of 1,4-triazoles, we next examined the possibility of employment of N-fused tetrazoles in the Ru-catalyzed[11] synthesis of 1,5-triazoles **5** (Table 3). However, when **1a** was treated with phenyl acetylene in the presence of 5 mol% $RuCpCl(PPh_3)_2$ at 110°C for 24h in dioxane (entry 1), no desired product was formed. Employment of more active catalyst $[RuCp^*Cl(PPh_3)_2]11$ gave no reaction, as well (entry 2). Probably, the azide-coordinated Ru-catalyst, in contrast to the Cu-catalyst (entry 3), is deactivated by the chelation with the nitrogen atom of the pyridine ring.[12] To test this hypothesis, we performed reactions of 3-azido- and 4-azido- pyridines with this Ru(II) catalyst where no such type of chelation is possible. Indeed, it was found that 3-azidopyridine smoothly underwent cycloaddition reaction with phenyl acetylene (Table 3, entry 4) with $RuCp^*Cl(PPh_3)_2$ providing inseparable mixture of 1,4-triazole and 1,5-triazole in 59% yield (1:1.5). Reaction of 4-azidopyridine gave 1,5-triazole as the major product (Table 3, entry 6). Expectedly, employment of Cu-catalysis for click reaction of 3-azido- and 4-azido- pyridines proceeded uneventfully providing 1,4-disubstituted triazoles in excellent yields (entries 5 and 7). Thus, it became evident that under the Ru-catalysis tested, pyridotetrazoles could not be used as precursors for 1,5-disubstituted triazoles.



(4)

In summary, it has been shown that pyrido-, quinilino-, pyrazino-, and qunoxalinotetrazoles, which exist in open/close form equilibrium (between **1** and **1′**, eq. 4) can be employed as azide surrogates in the Cu-catalyzed click reaction. This reaction is efficient with a wide variety of alkynes to produce N-heterocyclic derivatives of 1,4-disubstituted triazoles **2**. It has also been found that, probably due to deactivation of Ru-catalyst, pyridotetrazoles cannot be used as azide precursors in the synthesis of 1,5-disubstituted triazoles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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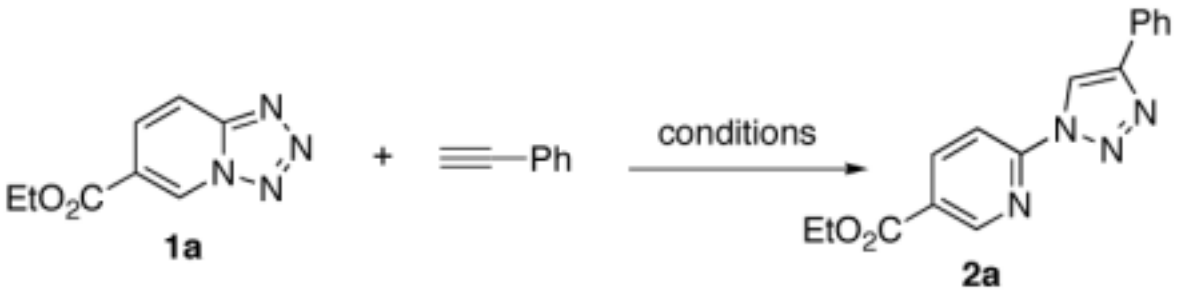
Table 1

Optimization of click reaction of tetrazoles.



no.	catalyst 10 mol %	solvent 0.25 M	*t* [°C]	time [h]	yield[a] [%]
1	$CuSO_4 \cdot 5H_2O$, Na-ascorbate	DCM:H_2O (1:1)	60	24	0
2	CuI	toluene	100	24	10
3	$Cu(OTf)_2$	toluene	100	24	5
4	$(CuOTf)_2 \cdot C_6H_6$	toluene	100	2	52[b]
5	**$(CuOTf)_2 \cdot C_6H_6$**	**toluene**	**rt**	**7**	**81**
6	$(CuOTf)_2 \cdot C_6H_6$	THF	60	12	76
7	$(CuOTf)_2 \cdot C_6H_6$	DCE	100	24	0
8	$(CuOTf)_2 \cdot C_6H_6$	1,4-dioxane	100	24	0

[a] Isolated yields.

[b] Some decomposition products were found.

product	yield [%][b]	no.	yield [%][b]
2y	68	25[e]	37

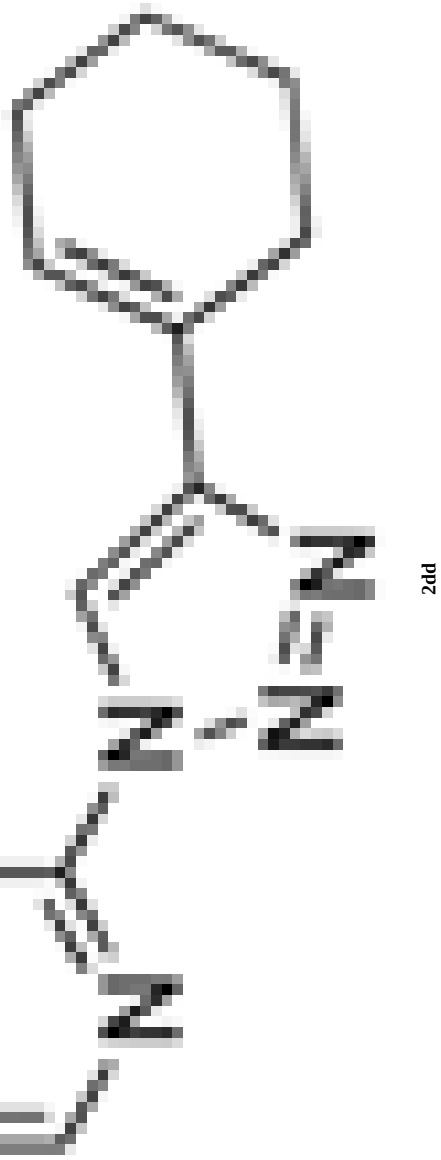
no.	product	yield [%][b]
26[e]	2z	62

no.	product	yield [%][b]
26[e]		74

product	yield [%][b]	no.	yield [%][b]
2aa	63	*27*[e]	88

product	yield [%][b]	no.	yield [%][b]
2bb	54	28[e]	81

no.	product	yield [%][b]
29[d]		81
2cc		51

product	yield [%][b]	no.	yield [%][b]	product
 2dd	57	30[d]	88	

product	yield [%][b]	no.	yield [%][b]
2ee	73	31[d]	62

yield [%][b]	no.	yield [%][b]	product
77	32[d]	66	2ff

[a] See Supporting Information for details.

[b] Isolated yield.

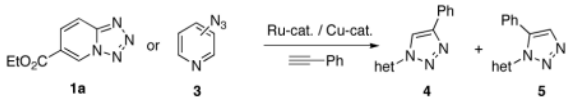
[c] Reactions performed at room temperature.

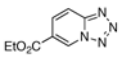
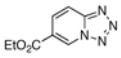
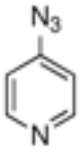
[d] Reactions performed at 100°C.

[e] Reactions performed at 125°C.

Table 3

Toward synthesis of 1,5-disubstituted triazoles.[a]



no.	substrate	catalyst	4
1		$RuCpCl(PPh_3)_2$	-
2		$RuCp^*Cl(PPh_3)_2$	-
3		$(CuOTf)_2C_6H_6$	8
4		$RuCp^*Cl(PPh_3)_2$	2
5		$(CuOTf)_2C_6H_6$	9
6		$RuCp^*Cl(PPh_3)_2$	3
7		$(CuOTf)_2C_6H_6$	8

[a] Isolated yield. Reaction conditions: 5 mol % catalyst, 1,4-dioxane 0.25 M, 110°C (entries 1, 2, 4 and 6); 10 mol % catalyst, PhMe 0.25 M, 100°C (entries 3, 5 and 7).

[b] Inseparable mixture of **4** and **5** (1:1.5).