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

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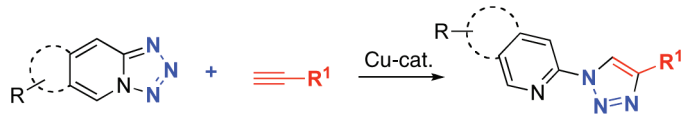
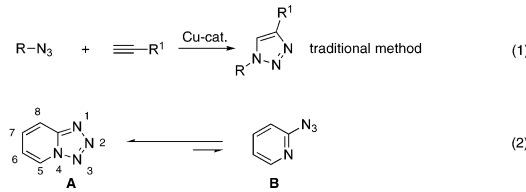
ABSTRACT



It has been shown that various pyrido-, quinolino-, pyrazino-, and quinoxalinotetrazoles can be used efficiently as azide components in 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] and antibacterial[2d] and antimicrobacterial activity.[2e]

Unarguably, 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 quinolinotriazoles is not straightforward because these azides exist in equilibrium between closed form (tetrazole **A**) and open form (azide **B**) (eq 2).[5]



(1)

(2)

Usually, the position of this equilibrium depends on several factors, such as the nature of substituents,[5] solvent,[6] and temperature.[5] Thus, it has been reported[7a] that a 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

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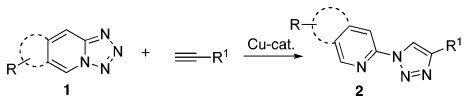
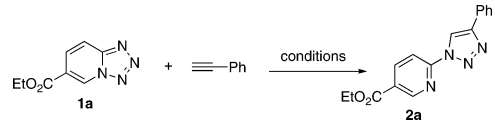
predominantly exist[7,8] in closed form **A**. It should be mentioned that pyridotetrazole has been employed in the preparation of organometallic complexes of late transition metals.[7a] Furthermore, there have been contradictory reports[9,10] on the employment of tetrazoles in the click reaction. For instance, it has been shown that pyridotetrazoles, existing in closed form, are inert toward click reaction under standard conditions.[9] However, there have been two reports[10a,b] in which single examples of successful click reaction of in situ generated pyridotetrazoles with alkynes were demonstrated. Moreover, when this manuscript was in preparation, a paper describing successful click reaction of purinotetrazole, which mainly exists in an 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 the employment of triazoles in click reaction,[9,10] we undertook an investigation aiming at the development of an efficient method using differently substituted tetrazoles in the synthesis of heterocyclic derivatives of 1,2,3-triazoles. Herein, we wish to report that various pyrido-, quinolino-, pyrazino-, and quinoxalinotetrazoles **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.

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.

With the 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 various 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 quinoxalinotetrazole (**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

(4) For original [3 + 2] cycloaddition, see: Huisgen, R. *Angew. Chem.* **1963**, *75*, 604. For selected recent reviews of click chemistry, see: (a) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (b) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51. (c) Nandivada, Jiang, H. X.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197. (d) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278. (e) Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4900. (f) Spiteri, C.; Moses, J. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 31. (g) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (h) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018. (i) Fukuzawa, S.-i.; Shimizu, E.; Kikuchi, S. *Synlett* **2007**, 2436. (j) Aucagne, V.; Berna, J.; Crowley, J. D.; Goldup, S. M.; Hanni, K. D.; Leigh, D. A.; Lusby, P. J.; Ronaldson, V. E.; Slawin, A. M. Z.; Viterisi, A.; Walker, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11950.

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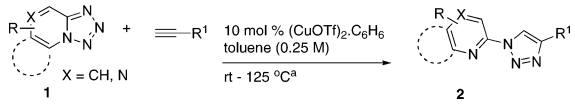
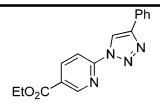
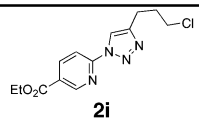
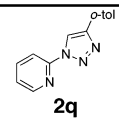
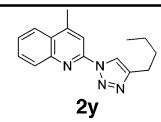
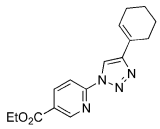
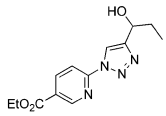
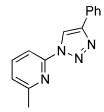
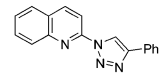
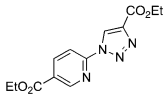
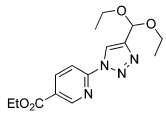
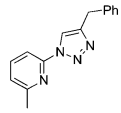
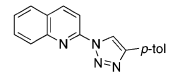
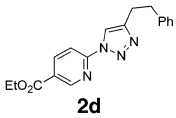
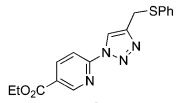
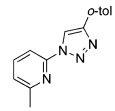
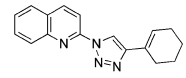
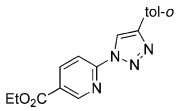
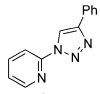
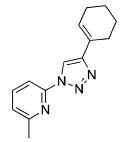
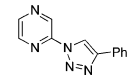
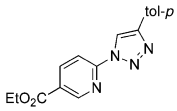
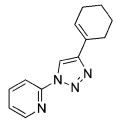
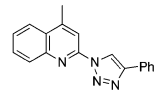
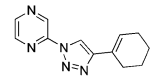
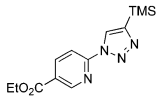
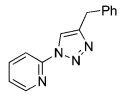
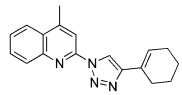
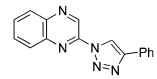
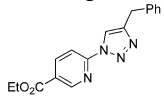
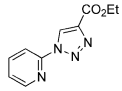
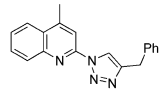
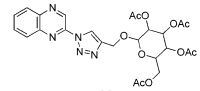
Table 2. Synthesis of Functionalized 1,4-Disubstituted Triazoles



no.	product	yield [%][b]	no.	product	yield [%][b]	no.	product	yield [%][b]	no.	product	yield [%][b]
1[c]	 **2a**	81	9[c]	 **2i**	64	17[d]	 **2q**	37	25[e]	 **2y**	68
2[c]	 **2b**	88	10[c]	 **2j**	84	18[d]	 **2r**	74	26[e]	 **2z**	62
3[c]	 **2c**	70	11[c]	 **2k**	50	19[d]	 **2s**	88	27[e]	 **2aa**	63
4[c]	 **2d**	63	12[c]	 **2l**	53	20[d]	 **2t**	81	28[e]	 **2bb**	54
5[c]	 **2e**	60	13[d]	 **2m**	62	21[d]	 **2u**	81	29[d]	 **2cc**	51
6[c]	 **2f**	65	14[d]	 **2n**	66	22[e]	 **2v**	88	30[d]	 **2dd**	57
7[c]	 **2g**	86[l]	15[d]	 **2o**	67	23[e]	 **2w**	62	31[d]	 **2ee**	73
8[c]	 **2h**	72	16[d]	 **2p**	58	24[e]	 **2x**	77	32[d]	 **2ff**	66

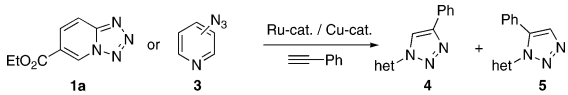
[a] See Supporting Information for details. [b] Isolated yield. [c] Reactions performed at room temperature. [d] Reactions performed at 100 °C. [e] Reactions performed at 125 °C.

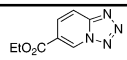
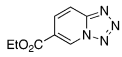
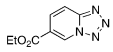
possibility of employment of N-fused tetrazoles in the Ru-catalyzed[11] synthesis of 1,5-triazoles **5** (Table 3). However, when **1a** was treated with phenyl acetylene in the presence of 5 mol % $RuCpCl(PPh_3)_2$ at 110 °C for 24 h in dioxane (entry 1), no desired product was formed. Employment of more active catalyst $[RuCp^*Cl(PPh_3)_2]$[11] also gave no reaction (entry 2). Probably, the azide-coordinated Ru-catalyst, in contrast to the Cu-catalyst (entry 3), is deactivated by 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 an 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

(11) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.

(12) For lower reactivity of 2-pyridyl diazocompounds in Rh-catalyzed transformations, see: Davies, H. M. L.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595.

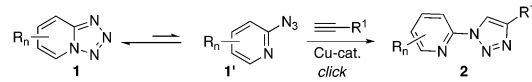
Table 3. Toward the Synthesis of 1,5-Disubstituted Triazoles[a]



no.	substrate	catalyst	4	5
1		$RuCpCl(PPh_3)_2$	-	-
2		$RuCp^*Cl(PPh_3)_2$	-	-
3		$(CuOTf)_2C_6H_6$	81%	-
4		$RuCp^*Cl(PPh_3)_2$	23%	36%[b]
5		$(CuOTf)_2C_6H_6$	91%	-
6		$RuCp^*Cl(PPh_3)_2$	3%	56%
7		$(CuOTf)_2C_6H_6$	87%	-

[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).

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 quinoxalinotetrazoles, 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 because of deactivation of the Ru-catalyst, pyridotetrazoles cannot be used as azide precursors in the synthesis of 1,5-disubstituted triazoles.

Acknowledgment. The support of the NIH (GM-6444) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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