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1,3-DIPOLAR CYCLOADDITION OF PYRIDYNES AND AZIDES: CONCISE SYNTHESIS OF TRIAZOLOPYRIDINES

Nozomi Saito,[1],* Ken-ichi Nakamura,[1] and Yoshihiro Sato[1,2],*

[1]Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan: and [2]ACT-C, Japan Science and Technology Agency (JST), Sapporo 060-0812, Japan. E-mail: biyo@pharm.hokudai.ac.jp

This paper is dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

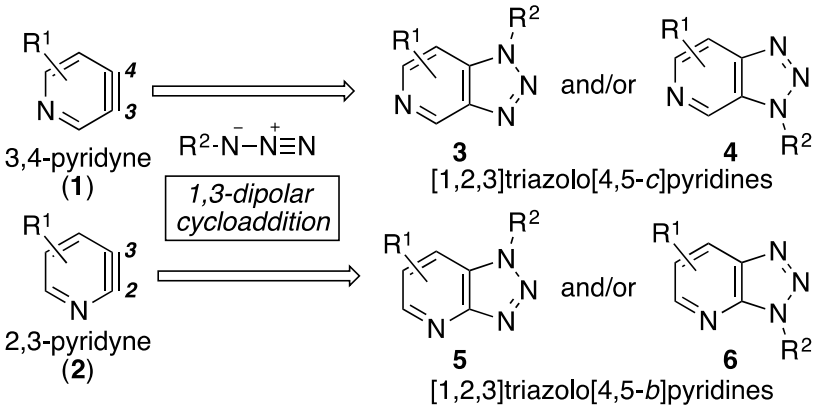
Abstract – 1,3-Dipolar cycloaddition of pyridynes and organic azides was investigated. Thus, 3,4-pyridynes and 2,3-pyridynes were reacted with various organic azides under mild conditions to afford the corresponding [1,2,3]triazolo[4,5-*c*]pyridines and [1,2,3]triazolo[4,5-*b*]pyridines, respectively. In the case of the reaction of 3,4-pyridyne, it was also found that a substituent on the pyridine ring affected the regioselectivity of the cycloaddition.

Benzyne has been recognized as a unique synthon in organic synthesis, and numerous examples of transformations of benzyne into useful organic compounds have been demonstrated.[1] Pyridynes, nitrogen-containing analogs of benzyne, are also attractive synthetic units for the synthesis of poly-substituted pyridine derivatives.[2] However, in contrast to extensive studies on benzyne chemistry, synthetic utilization of pyridynes has been limited. Therefore, the development of a new method for transformation of pyridyne remains a frontier in recent organic synthesis. In this context, we have reported synthesis of isoquinoline derivatives through nickel-catalyzed [2+2+2] cycloaddition of 3,4-pyridines and diynes, in which the triple bond in 3,4-pyridyne was utilized as a reactive alkyne.[3] Furthermore, we also demonstrated a new synthetic approach to pyridodiazepines, pyridodiazocines and pyridooxazepines via addition of cyclic ureas or *N*-methyloxazolidinone to 2,3- or 3,4-pyridynes.[4]

1,3-Dipolar cycloaddition of azides and alkynes has been established as a powerful and efficient methodology for the synthesis of triazole derivatives in modern organic chemistry.[5] Benzyne could also be employed as a 1,3-dipolarophile to give benzotriazole derivatives, and a number of examples of benzotriazole synthesis by this reaction have been reported.[6] On the other hand, there are only a few

examples of 1,3-dipolar cycloaddition of pyridyne, and there has been no examples in which azide was used as a 1,3-dipolar reagent.[7]

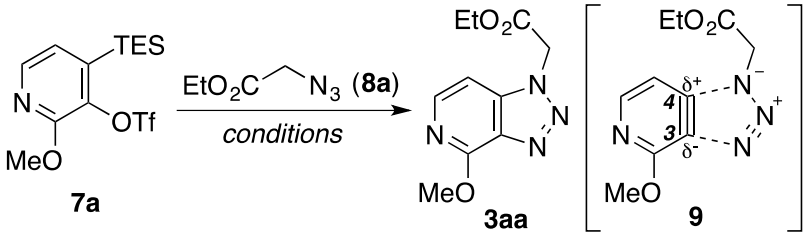
Based on the above background, we envisaged that if the 1,3-dipolar cycloaddition of 3,4-pyridyne (**1**) and 2,3-pyridyne (**2**) proceeds in a manner similar to that of the reaction of benzyne, [1,2,3]triazolo[4,5-*c*]pyridines (**3** and **4)** and [1,2,3]triazolo[4,5-*b*]pyridines (**5** and **6**), whose frameworks are often found in some biologically active compounds as well as functional materials,[8] would be produced, respectively (Scheme 1).



Scheme 1. Plan for the synthesis of triazolopyridines via 1,3-dipolar cycloaddition of pyridynes and organic azides

To examine the feasibility of the above plan, we set out to investigate the reaction of ethyl azidoacetate (**8a**) and 2-methoxy-3,4-pyridyne precursor **7** since the reaction of 2-methoxy-3,4-pyridyne and cyclic ureas showed good reactivity and regioselectivity as previously reported.[4] First, the reaction of the precursor **7a** and **8a** was carried out in the presence of KF as a fluoride source and 18-crown-6 in THF (Table 1, run 1). As a result, 1*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivative **3aa** was produced in 38% yield as a single regioisomer. This result indicated that the C-N bond formation regioselectively occurred between the nitrogen atom with a negative charge and the carbon atom at the 4-position in the pyridine ring depicted as **9**.[9] After several screenings of fluoride sources and solvents, it was found that the use of CsF in MeCN gave a good result (run 4). As the amount of azide **8a** was increased, the yield of **3aa** improved, and finally the reaction of **7a** and 10 equivalents of **8a** afforded **3aa** in 77% yield (run 7). In the reactions that the desired product was obtained in low or moderate yield (runs 1-4), some polymeric by-products of pyridyne were observed. Pyridyne species are known to be highly reactive while the reactivity of azide **8a** seemed to be low, which would result in formation of the undesired polymerization of pyridyne rather than the coupling of pyridyne and azide in the case of the reaction using small amounts of azide.

Table 1. Optimization of Reaction Conditions[a]

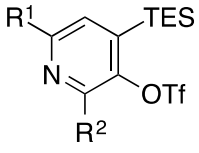
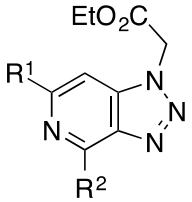
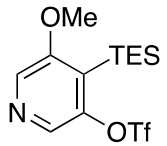
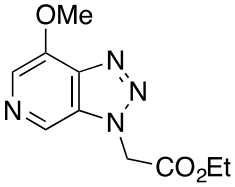
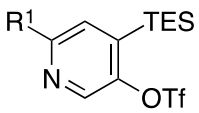
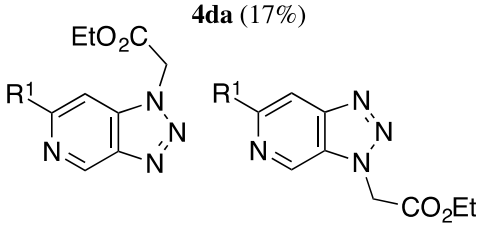


run	fluoride source	solvent	**8a** (equiv)	time (h)	yield (%)
1	KF / 18-crown-6	THF	1.5	24	38
2	TMAF	THF	1.5	24	25
3	CsF	THF	1.5	1	43
4	CsF	MeCN	1.5	2	47
5	CsF	MeCN	3	3	59
6	CsF	MeCN	5	3	69
7	CsF	MeCN	10	3	77

[a] The reaction was carried out in the presence of 2 equivalents of fluoride source at room temperature.

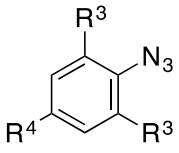
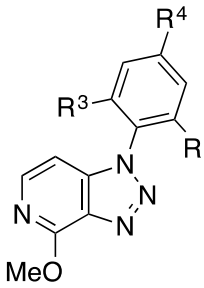
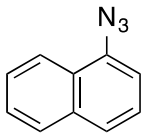
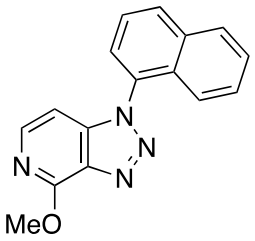
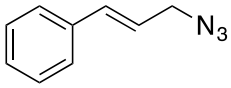
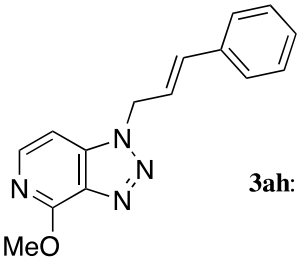
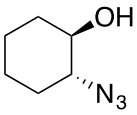
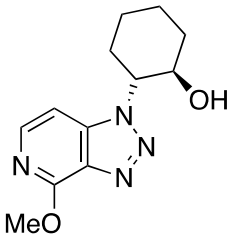
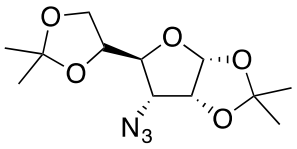
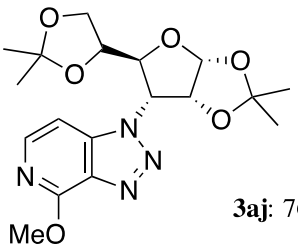
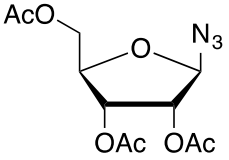
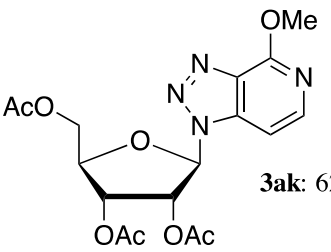
With optimal conditions in hand, we set out to conduct scope and limitation studies of the 1,3-dipolar cycloaddition. First, we investigated the reactions of various 3,4-pyridynes and ethyl azidoacetate (**8a**) (Table 2). The reaction of 3,4-pyridyne **7b** having an *N*,*N*-diethylcarbamoyl group at the 2-position and

Table 2. Reactions of Various 3,4-Pyridynes and Ethyl Azidoacetate (**8**)[a]

run	pyridyne precursors	product	
			
1	**7b** (R^1 = H, R^2 = $CONEt_2$)	**3ba** (36%)	
2	**7c** (R^1 = R^2 = OMe)	**3ca** (78%)	
3	 **7d**	 **4da** (17%)	
			
4	**7e** (R^1 = H)	**3ea** (19%)	**4ea** (10%)
5	**7f** (R^1 = OMe)	**3fa** (37%)	**4fa** (23%)

[a]reaction conditions: **8a** (10 equiv), CsF (2.0 equiv), MeCN, room temperature, reaction time: 3 h (runs 1, 2, 4, and 5), 5 h (run 3)

Table 3. Reactions of 2-Methoxy-3,4-pyridyne and Various Azides[a]

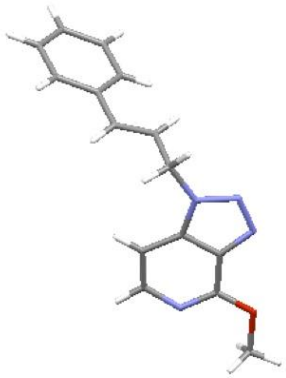
run	azide	product (%)
1	 **8b** (R^3 = R^4 = H)	 **3ab**: 70
2	**8c** (R^3 = R^4 = Me)	**3ac**: 71
3	**8d** (R^3 = H, R^4 = OMe)	**3ad**: 80
4	**8e** (R^3 = H, R^4 = Cl)	**3ae**: 63
5	**8f** (R^3 = H, R^4 = CO_2Et)	**3af**: 59
6	 **8g**	 **3ag**: 70
7	 **8h**	 **3ah**: 63
8	 **8i**	 **3ai**: 62
9	 **8j**	 **3aj**: 76
10	 **8k**	 **3ak**: 62

[a]reaction conditions: **8** (10 equiv), CsF (2.0 equiv), MeCN, room temperature, reaction time: 6 h (runs 1-5 and 7), 3 h (runs 6 and 8-10).

8a also gave 1*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivative **3ba** in moderate yield, though the regioselectivity was still high (run 1). 2,6-Dimethoxy-3,4-pyridyne **7c** reacted with **8a** to give the coupling product in 78% yield (run 2). The reaction of 5-methoxy-3,4-pyridyne **7d** and azide **8a** afforded 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivative **4da** in 17% yield as a single regioisomer (run 3). On the other hand, no regioselectivity was observed in the reaction of simple 3,4-pyridyne **7e** or 6-methoxy-3,4-pyridyne **7f**, and both regioisomers **3ea** and **4ea** or **3fa** and **4fa** were obtained in moderate yields, respectively (runs 4 and 5).

Next, 1,3-dipolar cycloaddition of 2-methoxy-3,4-pyridyne and various organic azides was examined (Table 3). The reaction of **7a** and aromatic azides **8b-8g** in the presence of CsF proceeded smoothly to give the corresponding [1,2,3]triazolo[4,5-*c*]pyridines **3ab-3ag** in good yields (runs 1-6). Cinnamyl azide (**8h**) was reacted with 2-methoxy-3,4-pyridyne to give triazolopyridine derivative **3ah** in 63% yield (run 7). The hydroxy group of azide **8i** was tolerated under the reaction conditions, giving the corresponding coupling product **3ai** in 63% yield (run 8). Sugar-derived azides **8j** and **8k** were also applicable to the cycloaddition with 2-methoxy-3,4-pyridyne to afford poly-functionalized triazolopyridines **3aj** and **3ak**, respectively, in good yields (runs 9 and 10).

The structures of the 1*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivatives were unambiguously determined by X-ray crystallographic analysis of compound **3ah** (Figure 1).[10]

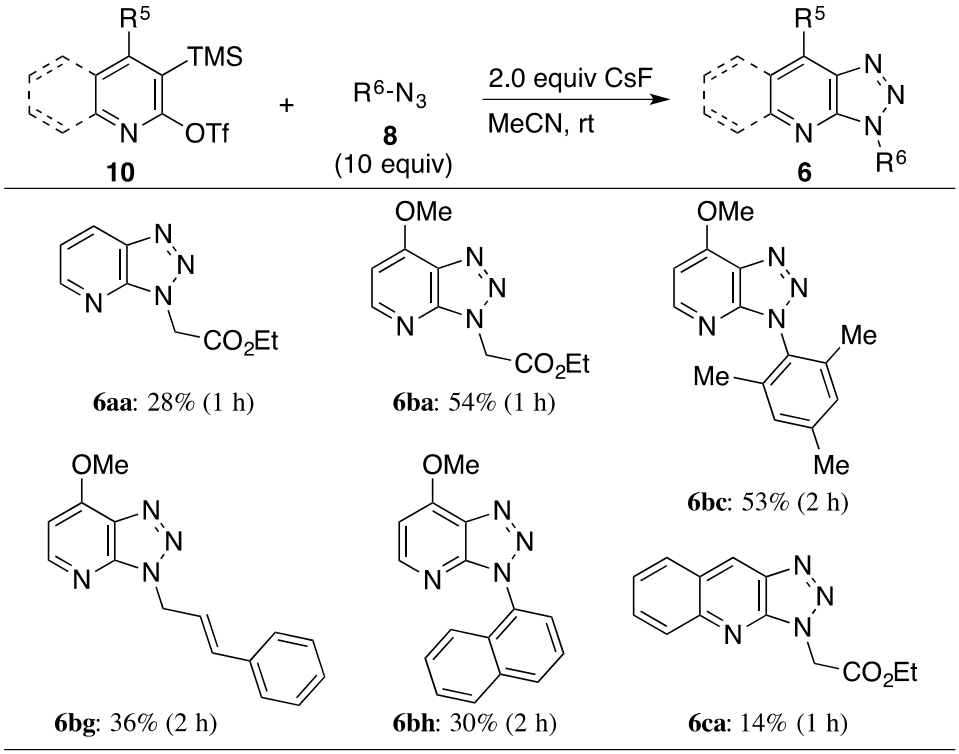


Crystal System	monoclinic
Space Group	$P2_1/c$ (#14)
Lattice Parameters	a = 14.492(4) Å
	b = 7.317(4) Å
	c = 12.695(4) Å
	β = 95.07(2)°
	V = 1341.0(8) Å^3
R	0.0438
wR2	0.1530
GOF	1.022

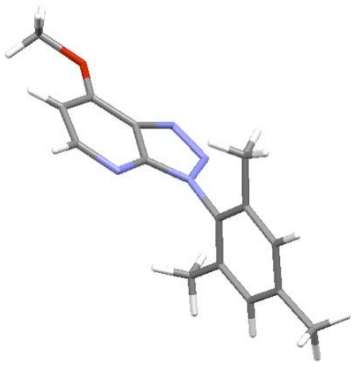
Figure 1. X-Ray structure of **3ah**

We turned our attention to the cycloaddition of 2,3-pyridynes and organic azides (Table 4). In all cases, the reaction of **10** and **8** proceeded in a highly regioselective manner to give the corresponding 3*H*-[1,2,3]triazolo[4,5-*b*]pyridine derivatives **6** in low to moderate yields.

Table 4. Reactions of 2,3-Pyridynes and Various Azides



The structures of the 3*H*-[1,2,3]triazolo[4,5-*c*]pyridine derivatives were also determined by X-ray crystallographic analysis of **6bc** (Figure 2).[10]



Crystal System	monoclinic
Space Group	$P2_1/a$ (#14)
Lattice Parameters	a = 11.880(2) Å
	b = 7.582(4) Å
	c = 15.300(3) Å
	β = 91.68(2)°
	V = 1377.5(7) Å^3
R	0.0524
wR2	0.1364
GOF	1.039

Figure 2. X-Ray structure of **6bc**

In summary, we succeeded in developing a new method for the synthesis of triazolopyridine derivatives via 1,3-dipolar cycloaddition of pyridynes and azides.[11,12] It was also found that the regioselectivity of the cycloaddition was affected by the substituents on the pyridine ring. Further studies including evaluation of biological activities of triazolopyridines prepared by this protocol are in progress.

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8. a) G. Jones and D. R. Sliskovic, 'Advances in Heterocyclic Chemistry', Vol. 34, ed. by A. R. Katritzky, Academic Press, Inc., London, 1983, pp. 79-143 and references cited therein; b) G. Jones, 'Advances in Heterocyclic Chemistry', Vol. 83, ed. by A. R. Katritzky, Academic Press, Inc., London, 2002, pp. 1-70 and references cited therein; c) G. Jones and B. Abarca, 'Advances in Heterocyclic Chemistry', Vol. 100, ed. by A. R. Katritzky, Academic Press, Inc., London, 2010, pp. 195-252 and references cited therein.
9. The same regioslectivity was observed in 1,3-dipolar cycloaddition of 2-sulfonyloxy-3,4-pyridyne and nitrone. This selectivity is rationalized by the high electrophilicity of the distorted positive carbon atom at the 4-position in the pyridine ring. See, Ref. 2*l*.
10. Crystallographic data for **3ah** and **6bc** have been deposited at the Cambridge Crystallographic Data Center (CCDC 944762 for **3ah** and CCDC 945153 for **6bc**). The regiochemistry of other [1,2,3]triazolo[4,5-*c*]pyridines **3aa-3fa, 3ab**, and **3ad-3ak** was assumed to be the same configuration as that of **3ah** from analogy with other spectral data of **3ah**. The structure of other [1,2,3]triazolo[4,5-*b*]pyridines **6aa**, **6ba**, **6bg**, **6bh**, and **6ca** was also deduced by the analogy to that of **6bc**.
11. Typical Experimental Procedure (Table 1, run 7). To a solution of **7a** (113.2 mg, 0.305 mmol) in

MeCN (3.0 mL) were successively added **8a** (0.33 mL, 3.00 mmol) and CsF (96.5 mg, 0.635 mmol), and the resulting mixture was stirred at room temperature for 3 h. After the mixture was filtered through silica gel pad, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/1) to give **3aa** (55.1 mg, 77%) as a colorless solid. mp 148-150 °C (recrystallized from CH_2Cl_2/hexane); IR (film, $CHCl_3$) 2989, 1738, 1600, 1492, 1233 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 6.0 Hz, 1 H), 6.94 (d, *J* = 6.0 Hz, 1 H), 5.34 (s, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.12 (s, 3 H), 1.18 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 156.4, 143.1, 139.5, 132.7, 98.9, 62.3, 53.9, 49.0, 13.8.

12. For spectral data of the products (Table 2, runs 4 and 5). For **3ea**: ^1H NMR (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.60 (d, *J* = 6.0 Hz, 1 H), 7.44 (d, *J* = 6.0 Hz, 1 H), 5.44 (s, 2 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 1.28 (t, *J* = 7.2 Hz, 3 H). For **4ea**: ^1H NMR (500 MHz, $CDCl_3$) δ 9.09 (s, 1 H), 8.57 (d, J = 5.5 Hz, 1 H), 7.98 (d, *J* = 5.5 Hz, 1 H), 5.44 (s, 2 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H). For **3fa**: ^1H NMR (500 MHz, $CDCl_3$) δ 9.06 (s, 1H), 6.62 (s, 1 H), 5.31 (s, 2 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 4.01 (s, 3 H) 1.26 (t, *J* = 7.2 Hz, 3 H). For **4fa**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1 H), 7.25 (s, 1 H), 5.31 (s, 2 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 4.00 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3 H).