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

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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 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 pyridoazepines via addition of cyclic ureas or N-methylloxazolidinone 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 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](image)

**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, 1H-[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.
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>
<thead>
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<th>run</th>
<th>azide</th>
<th>product (%)</th>
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<tr>
<td>1</td>
<td>8b (R^3 = R^4 = H)</td>
<td>3ab: 70</td>
</tr>
<tr>
<td>2</td>
<td>8c (R^3 = R^4 = Me)</td>
<td>3ac: 71</td>
</tr>
<tr>
<td>3</td>
<td>8d (R^3 = H, R^4 = OMe)</td>
<td>3ad: 80</td>
</tr>
<tr>
<td>4</td>
<td>8e (R^3 = H, R^4 = Cl)</td>
<td>3ae: 63</td>
</tr>
<tr>
<td>5</td>
<td>8f (R^3 = H, R^4 = CO_2Et)</td>
<td>3af: 59</td>
</tr>
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</table>

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 1H-[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 8aa afforded 3H-[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 1H-[1,2,3]triazolo[4,5-c]pyridine derivatives were unambiguously determined by X-ray crystallographic analysis of compound 3ah (Figure 1).10

![Figure 1. X-Ray structure of 3ah](image)

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 3H-[1,2,3]triazolo[4,5-b]pyridine derivatives 6 in low to moderate yields.
The structures of the $3H$-[1,2,3]triazolo[4,5-c]pyridine derivatives were also determined by X-ray crystallographic analysis of $6bc$ (Figure 2).$^{10}$

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.

ACKNOWLEDGEMENTS
This work was partly supported by a Grant-in-Aid for Young Scientists (B) (No. 24790002) and a Grant-in-Aid for Scientific Research (B) (No. 23390001) from JSPS and by a Grant-in-Aid for Scientific Research on Innovative Areas “Molecular Activation Directed toward Straightforward Synthesis” (Nos. 23105501 and 25105701) from MEXT, Japan. N.S. acknowledges Takeda Science Foundation for financial support.

REFERENCES AND NOTES


7. For 1,3-dipolar cycloaddition of pyridynes and pydiazine N-oxide, see: J. Kurita, N. Kakusawa, S. Yasuike, and T. Tsuchiya, *Heterocycles*, 1990, 31, 1937; For 1,3-dipolar cycloaddition of pyridynes and isoquinolinium-2-yl amide, see: L. Jiang, X. Yu, B. Fang and J. Wu, *Org. Biomol. Chem.*, 2012, 10, 8102; For 1,3-dipolar cycloaddition of pyridynes and nitrones, see: Ref 2l.


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. 2l.

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 (113.2mg, 0.305 mmol) in MeCN (3.0 mL) were successively added 8a (0.33 L, 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 CH2Cl2/hexane); IR (film, CHCl3) 2989, 1738, 1600, 1492, 1233 cm⁻¹; ¹H NMR (500 MHz, CDCl3)  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); ¹³C NMR (125 MHz, CDCl3) δ  165.8, 156.4, 143.1, 139.5, 132.7, 98.9, 62.3, 53.9, 49.0, 13.8.

For spectral data of the products (Table 2, runs 4 and 5). For 3ea: ¹H NMR (500 MHz, CDCl3) 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, CDCl3) 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, CDCl3) 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, CDCl3) 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).