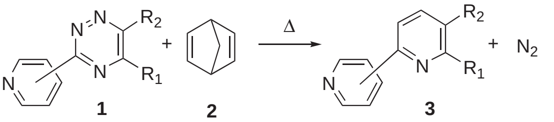
Synthesis of 2-Pyridylpyridines via Aza-Diels–Alder Reactions between 3-Pyridyl-1,2,4-triazines and Some Vinyl Alkanoates

Taichi Shintou, Fumiaki Ikeuchi, Hirokazu Kuwabara, Ken Umihara, and Isamu Itoh*
Synthetic Chemistry Research Laboratory, Sankio Chemical Co., Ltd., 5-2-3 Higashiyahata, Hiratsuka 254-0016

(Received February 17, 2005; CL-050215)

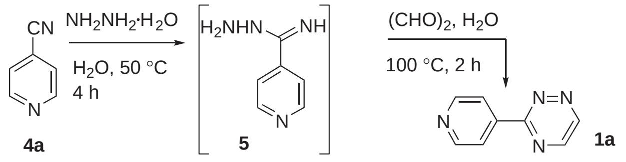
New synthetic procedure for 2,ω-bipyridines involving aza-Diels–Alder reaction between 3-(ω-pyridyl)-1,2,4-triazine and vinyl octanoate or decanoate as a dienophile is described.

In the course of synthetic studies on 2-pyridylpyridine derivatives, which have been well known as fundamental building blocks of some potent drugs,[1–3] Sauer *et al.*[4] reported the aza-Diels–Alder reaction of 3-(ω-pyridyl)-1,2,4-triazine **1** and 2,5-norbornadiene (**2**) as an attractive synthetic procedure of substituted 2,ω-bipyridines **3** in an excellent yield (Eq 1). Their procedure, however, contains two serious problems: i) when ω-cyanopyridine was treated in order with HCl in EtOH at 0 °C to rt, with hydrazine•HCl salt and Et_3N, and then with $(CHO)_2$ at −70 °C, **1** was afforded in only 10% overall yield;[5] ii) **2** as a dienophile requiring 10 equiv. is highly expensive and seems to be unsuitable for an industrial application. Accordingly, a synthetic process of various 2-pyridylpyridine derivatives via 1,2,4-triazines using highly reactive $(CHO)_2$ is so difficult that there have been no reports on the process. We describe herein a general procedure developed by detailed improvement and extension of the known method.[4,5]



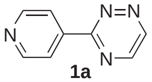
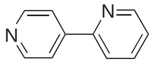
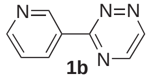
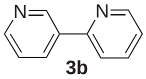
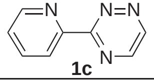
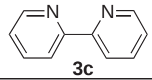
(1)

At first, we established preparation of 3-(4′-pyridyl)-1,2,4-triazine (**1a**) by a modification of the Lee procedure[5] (Scheme 1). 4-Cyanopyridine (**4a** 1 equiv.) was reacted with $NH_2NH_2{\cdot}H_2O$ (1 equiv.) in H_2O at 50 °C for 4 h to give 3-(4′-pyridyl)amidrazone (**5**), which, without purification, was treated with 40% aq $(CHO)_2$ in H_2O at 100 °C for 2 h providing **1a** in 85% overall yield.[6] The aza-Diels–Alder reaction of **1a** (1 equiv.) and **2** (10 equiv.) in xylene for 4 h under reflux provided 2,4′-bipyridine (**3a**) in 80.0% yield. The representative synthetic results of the related 2-pyridylpyridines were revealed in Table 1.[6]



Scheme 1. Efficient preparation of 3-(4′-pyridyl)-1,2,4-triazine (**1a**).

Table 1. The preparation of 2-pyridylpyridines via the aza-Diels–Alder reaction of 3-(ω-pyridyl)-1,2,4-triazine **1** and 2,5-norbornadiene (**2**)[a]

Run	Triazine **1**[b]	Product **3**[c]	Yield/%	Purity/%
1	 **1a**	 **3a**	80.0	99.2
2	 **1b**	 **3b**	85.3	98.9
3	 **1c**	 **3c**	88.2	99.3

[a]The thermal reaction was carried out with **1** (1 equiv.) and **2** (10 equiv.) in xylene at 90 to 120 °C for 3 to 5 h. [b]The starting triazine **1** was prepared from the readily available cyanopyridine. The pyridine (1 equiv.) was treated with $NH_2NH_2{\cdot}H_2O$ in H_2O at 30 to 70 °C for 2 to 5 h to give the amidrazone, which was reacted with 40% aq $(CHO)_2$ (1 equiv.) in H_2O at 60 to 100 °C for 1 to 2 h leading to formation of **1**. [c]The structure of the product was identified by IR, NMR, and MS. [d]Yield based on the starting triazine **1**. [e]The respective purities were determined by HPLC analysis.

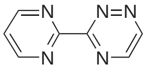
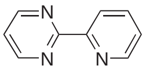
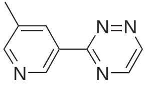
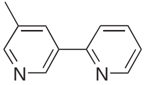
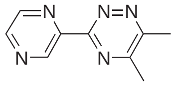
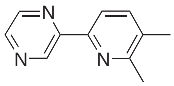
Table 2. The preparation of 2,4′-Pyridylpyridine (**3a**) via aza-Diels–Alder reaction of 3-(4′-pyridyl)-1,2,4-triazine (**1a**) and vinyl alkanoates **6** (CH2=CH–OCOR)[a]

Run	Dienophile **6**	Reaction temp/°C	Reaction time/h	Yield/% of **3a**[b]	Purity/% of **3a**[c]
1	**6a**, R = Me	110	>72	9.2	—
2	**6b**, R = CH_2Me	127	>72	15.2	—
3	**6c**, R = CMe_3	160	48	87.8	98.8
4	**6d**, R = $(CH_2)_2Me$	162	42	88.6	98.5
5	**6e**, R = $(CH_2)_3Me$	166	48	87.8	98.8
6	**6f**, R = $(CH_2)_4Me$	180	16	90.4	99.2
7[d]	**6g**, R = $(CH_2)_6Me$	205	3	91.4	99.2
8[d]	**6h**, R = $(CH_2)_8Me$	210	2	90.7	99.3
9	**6i**, R = C_6H_5	200	6	88.9	98.9

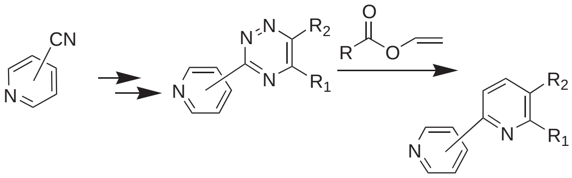
[a]The representative reaction was as follows; the mixture of **1a** (1 equiv.) and vinyl decanoate **6h** (2 equiv.) in diisopropylbenzene was heated at 210 °C for 2 h, diluted with toluene, and washed with 1 M HCl. The aq layer was basified with 9 M NaOH and extracted with toluene to give **3a** as crystals in 90.7% yield (Run 8). The structure of **3a** was identified by IR, NMR, and MS. [b]Yield based on the starting triazine **1**. [c]The respective purities were determined by HPLC analysis. [d]The melting point of **3a** was 60.6–61.4 °C. (reference: P. Kraumholz, *J. Am. Chem. Soc.*, **73**, 4449 (1951). 61.1–61.5 °C.)

As the solution of the next problem, we searched another more effective dienophiles in place of **2**, which is rather toxic to human being, highly costs, and requires 10 equiv. amount for completion of the reaction. Eventually, we found that, when vinyl acetate **6a** was used as a dienophile, the aza-Diels–Alder reaction proceeded rather slowly (>72 h) but to give the desired **3a** though in 9.2% yield (Table 2, Run 1).[7] Accordingly, we

Table 3. The preparation of 2-pyridylpyridines via aza-Diels–Alder reaction of 3-(ω-pyridyl)-1,2,4-triazine **1** and vinyl decanoate **6h**

Run	Triazine **1**	Product **3**	Yield/%	Purity/%
1	**1b**	**3b**	89.8	99.1
2	**1c**	**3c**	93.3	99.5
3			88.7	99.0
4			89.4	99.3
5			90.8	98.9

examined to use various related vinyl alkanoates **6**. The results are summarized in Table 2. The yield of **3a** depends on a reaction temperature and amounted to 91.4% or 90.7% yield with a high purity (>99.2% from HPLC) in the case of vinyl octanoate **6g** or decanoate **6h** (Runs 7 and 8). Accordingly, some other triazines were treated with **6h** and the results were summarized in Table 3. The yields were more than 89% with excellent purity in all triazines.



(2)

Thus, we developed the new efficient procedure for the synthesis of various 2,ω-bipyridine derivatives (Eq 2). The process consists of the preparatory step of 3-(ω-pyridyl)-1,2,4-triazine **1** from ω-cyanopyridine **4** in H_2O and the synthetic step of 2,ω-pyridylpyridine **3** by the aza-Diels–Alder reaction from the 1,2,4-triazine **1** and vinyl octanoate **6g** or decanoate **6h** as a dienophile.[8,9] It should be emphasized that the new method is quite suitable for an industrial production for supply of valuable 2,ω-bipyridine derivatives as versatile technical synthetic intermediates.

References

1 D. R. Sidler, R. D. Larsen, M. Chartrain, N. Ikemoto, C. M. Roberge, C. S. Taylor, W. Li, and G. F. Bills, WO 99/07695 (1999).

2 K. Kamei, N. Maeda, and T. Tatsuoka, WO 99/03847 (1999).

3 D. Cui, M. R. Davis, M. Dunn, B. E. Evans, H. P. Kari, B. Lagu, D. Nagarathnam, K. P. Vyas, and K. Zhang, U. S. Patent 6,274,585 B1 (2001).

4 G. R. Pabst and J. Sauer, *Tetrahedron Lett.*, **39**, 6687 (1998); G. R. Pabst, K. Schmid, and J. Sauer, *Tetrahedron Lett.*, **39**, 6691 (1998); G. R. Pabst and J. Sauer, *Tetrahedron Lett.*, **39**, 8817 (1998); O. C. Pfuller and J. Sauer, *Tetrahedron Lett.*, **39**, 8821 (1998); G. R. Pabst, O. C. Pfuller, and J. Sauer, *Tetrahedron Lett.*, **39**, 8825 (1998); J. Sauer, D. K. Heldmann, and G. R. Pabst, *Eur. J. Org. Chem.*, **1993**, 313.

5 J.-K. Lee, S.-N. Kim, and S.-G. Lee, *J. Korean Chem. Soc.*, **39**, 755 (1995).

6 F. Ikeuchi, T. Shintou, and H. Suda, WO 00/76975 (2000).

7 T. Shintou and F. Ikeuchi, Jpn. Patent 2001-158773 A (2001).

8 For a sole precedent of aza-Diels–Alder reaction using vinyl acetate **6a** as a dienophile: W. Dittmar, J. Sauer, and A. Steigel, *Tetrahedron Lett.*, **59**, 5171 (1969).

9 Review of preparation of pyridine derivatives by using triazines via aza-Diels–Alder reaction: D. L. Boger and S. M. Weinreb, "Hetero Diels-Alder Methodology in Organic Synthesis," Academic Press, New York (1987), pp 323–335; "Comprehensive Organic Synthesis," ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 5, Chap. 4.3.5.

Published on the web (Advance View) May 21, 2005; DOI 10.1246/cl.2005.836