J. Chem. Research (S), 1999, 552–553†

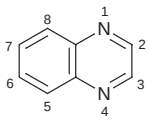
Novel 1,3-Dipolar Cycloaddition of Quinoxalinium *N*-Ylide to Alkene promoted by MnO_2: a New Approach to Synthesis of Pyrrolo[1,2-*a*]quinoxalines†

Jian Zhou,[a] Lande Zhang,[a] Yuefei Hu*[a,b] and Hongwen Hu[a,b]

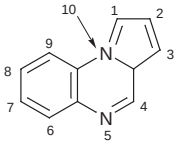
[a] *Department of Chemistry and* [b] *Coordination Chemistry Institute, Nanjing University, Nanjing 210093, People's Republic of China*

A novel approach to synthesize pyrrolo[1,2-*a*]quinoxalines was developed successfully by 1,3-dipolar cycloaddition of a quinoxalinium *N*-ylide to alkenes in the presence of MnO_2 under very convenient conditions and with moderate yields (40–52%).

Derivatives of pyrrolo[1,2-*a*]quinoxaline are heterocyclic compounds of increasing interest mainly for their biological activities in pharmaceutical and agrochemical researches.[1–5] Some of them have been synthetic target compounds in our agrochemical research project for a long time. However, most published procedures for the preparation of pyrrolo-[1,2-*a*]quinoxaline involve multi-step syntheses.[2,3,5–10] Some attractive procedures using cycloadditions of alkenes or alkynes are limited by inaccessible starting materials.[11–14]



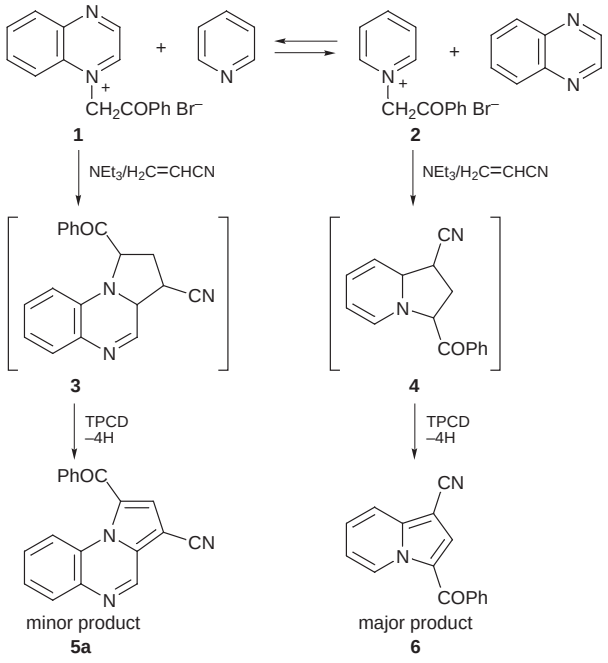
Quinoxaline



Pyrrolo[1,2-*a*]quinoxaline

1,3-Dipolar cycloaddition of heteroaromatic *N*-ylides to alkynes have been used widely for the preparation of various heterocyclic compounds.[15–17] Recently, we have reported a series of 1,3-dipolar cycloadditions of heteroaromatic *N*-ylides to alkenes, instead of alkynes, promoted by tetrakis(pyridine) cobalt(II) dichromate [$(py)_4Co(HCrO_4)_2$, TPCD] for the preparation of derivatives of indolizine under convenient conditions.[18–22] Surprisingly, these popular methods had never been used to synthesize derivatives of pyrrolo[1,2-*a*]quinoxaline. The main reason may be the very tedious preparation of quinoxalinium salts, the precursors of quinoxalinium *N*-ylides. For example, 1-phenacylquinoxalinium bromide **1** could be obtained in 28% yield by stirring a mixture of quinoxaline and 2-bromoacetophenone in chloroform at room temperature for 29 d.[23] By refluxing the same mixture in chloroform for 3 h only a black tar was obtained. When we attempted to warm the mixture at 60 °C without solvent a very vigorous polymerization occurred within 10 min. Finally, we found that the desired salt can be quickly obtained in 30% yield by first melting the mixture at 60 °C (about 5 min). Once the new solid appeared, ethyl acetate was added to quench the reaction to avoid the polymerization.

Following the published procedure, a mixture of 1-phenacylquinoxalinium bromide **1**, acrylonitrile **7a**, triethylamine and TPCD in DMF was heated at 80–90 °C for 5 h. After work-up, two solid products were obtained. Unfortunately, the expected product, 1-benzoyl-3-cyano-pyrrolo[1,2-*a*]quinoxaline **5a**, was obtained in 9% yield only. The major product was separated in 59% yield with melting point 128–129 °C and its structure assigned as 3-benzoyl-1-cyanoindolizine **6** (lit.[19] mp 128–130 °C) by IR, ^{1}H NMR and MS. Obviously it is a 1,3-dipolar cycloadduct from the reaction of *N*-phenacylpyridinium bromide **2** with acrylonitrile **7a**. It was believed that the salt **2** was formed by the exchange between 1-phenacylquinoxalinium bromide **1** and pyridine, which came from TPCD, because pyridine is a stronger nucleophile than quinoxaline (Scheme 1).



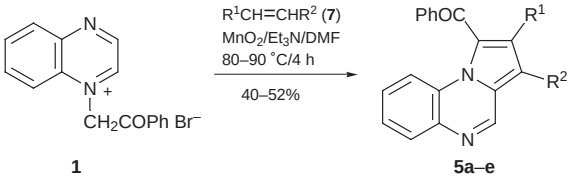
Scheme 1

In our previous papers, 1,3-dipolar cycloadditions of heteroaromatic *N*-ylides to alkenes promoted by TPCD involved a one-pot reaction combined with a 1,3-dipolar cycloaddition and a dehydrogenating aromatization. For this reason, use of a dehydrogenating reagent in the procedure is essential to meet the requirement of the mechanism. To avoid producing the by-product 3-benzoyl-1-cyano-indolizine **6**, MnO_2 was recommended to replace TPCD as a dehydrogenating reagent. As was expected, when MnO_2 was used in the above reaction, compound **5a** was obtained smoothly in 48% yield as a sole product. By the same procedure, pyrrolo[1,2-*a*]quinoxalines **5b**–**5e** were prepared respectively from corresponding methyl acrylate **7b**, methyl vinyl ketone **7c**, diethyl fumarate **7d** and

* To receive any correspondence (*e-mail*: pyorg@netra.nju.edu.cn).

† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

N-phenylmaleimide **7e** in moderate yields (40–52%) (Scheme 2).



1 **5a–e**

5,7	R^1	R^2	Yields (%)
a	H	CN	48
b	H	CO_2Me	49
c	H	COMe	52
d	CO_2Et	CO_2Et	48
e	–CO(NPh)CO–		40

Scheme 2

In conclusion, MnO_2 has proved to be a satisfactory substitute for TPCD in 1,3-dipolar cycloaddition of 1-phenacylquinoxalinium *N*-ylide **1** with alkenes **7a–7e**) and a one-pot procedure was developed successfully to prepare derivatives of pyrrolo[1,2-*a*]quinoxaline **5a–5e** in moderate yields (40–52%) under mild conditions.

Experimental

All melting points were determined on a Yanaco apparatus and are uncorrected. The IR spectra were recorded on a Nicolet FT-IR SDX spectrometer with KBr pellets, ^{1}H NMR spectra on a Bruker ACF-300 spectrometer with TMS as internal reference and MS spectra on a ZAB-HS mass spectrometer at 70 eV. The elemental analyses were performed on a Perkin-Elmer 240C instrument.

1-*Phenacylquinoxalinium Bromide* **1**.—A stirred solid mixture of quinoxaline (1.3 g, 10 mmol) and 2-bromoacetophenone (2.0 g, 10 mmol) was warmed at 60 °C to melt. Once the new solid had appeared (about 5 min), ethyl acetate (2.0 mL) was added to quench the reaction and the suspension produced was stirred for 5 min at room temperature. The brown crystals were collected by filtration and rinsed with a small amount of ethyl acetate to give 0.96 g (30%) of crude salt **1**, mp 187–191 °C; ν_{max}/cm^{-1} 1679, 1592, 1512, 1335, 1221, 990, 762. It was used in the next step directly without any further purification.

General Procedure for Preparation of Pyrrolo[1,2-a]*quinoxalines* **5**.—A suspension of 1-phenacylquinoxalinium bromide **1** (10 mmol), alkene **7** (50 mmol), MnO_2 (80 mmol) and Et_3N (20 mmol) in DMF (50 mL) was stirred at 80–90 °C for 4 h (monitored by TLC). After the mixture was cooled to room temperature, the solid was filtered off and the filtrate poured into water (100 mL). The crude product was collected by filtration and purified by chromatography [silica gel, 20% ethyl acetate in light petroleum (bp 60–90 °C)] to give pure compound **5**, which can be recrystallized from acetone–light petroleum.

1-*Benzoyl*-3-*cyanopyrrolo*[1,2-a]*quinoxaline* **5a**.—This compound was obtained as yellowish needles, mp 201–203 °C (Found: C, 76.75; H, 4.03; N, 14.28. $C_{19}H_{11}N_3O$ requires C, 76.76; H, 3.73; N, 14.13%); ν_{max}/cm^{-1} 2225, 1650, 1550, 1456, 1256, 1156, 943, 756; δ_H 9.22 (1H, s, C4-H), 8.18 (1H, d, *J* 8.3, C9-H), 8.10 (1H, d, *J* 8.5, C6-H), 8.05 (2H, d, *J* 7.6, ArH), 7.74 (1H, t, *J* 7.4, ArH), 7.67 (1H, t, *J* 7.6 Hz, ArH), 7.63–7.58 (3H, m, ArH), 7.47 (1H, s, C2-H); *m/z* (%) 297 (M$^+$, 100), 271 (2), 220 (28), 192 (8), 105 (63), 77 (65).

Methyl 1-*benzoylpyrrolo*[1,2-a]*quinoxaline*-3-*carboxylate* **5b**.—This compound was obtained as yellow crystals, mp 177–179 °C (Found: C, 72.80; H, 4.45; N, 8.47. $C_{20}H_{14}N_2O_3$ requires C, 72.72; H, 4.27; N, 8.48%); ν_{max}/cm^{-1} 3058, 2945, 1708, 1644, 1595, 1553, 1258, 1089, 920, 752. δ_H 9.75 (1H, s, C4-H), 8.13 (1H, d, *J* 8.5, C9-H), 8.09–8.06 (3H, m, ArH), 7.69 (1H, t, *J* 7.3 Hz, ArH), 7.63 (1H, s, C2-H), 7.62–7.54 (4H, m, ArH), 3.95 (3H, s, OCH_3); *m/z* (%) 330 (M$^+$, 20), 299 (6), 271 (5), 253 (7), 130 (100), 122 (30), 105 (66), 77 (54).

3-*Acetyl*-1-*benzoylpyrrolo*[1,2-a]*quinoxaline* **5c**.—This compound was obtained as yellow crystals, mp 183–185 °C (Found: C, 76.18; H, 4.98; N, 9.01. $C_{10}H_7NO$ requires C, 76.42; H, 4.49; N, 8.91%); ν_{max}/cm^{-1} 1666, 1631, 1588, 1546, 1265, 970, 913, 759; δ_H 9.93 (1H, s, C4-H), 8.17 (1H, d, *J* 8.1, C9-H), 8.10–8.06 (3H, m, ArH), 7.73 (1H, t, *J* 7.3 Hz, ArH), 7.64–7.53 (4H, m, ArH), 7.53 (1H, s, C2-H), 2.58 (3H, s, CH_3); *m/z* (%) 314 (M$^+$, 61), 299 (100), 271 (8), 237 (6), 105 (31), 77 (36).

Diethyl 1-*benzoylpyrrolo*[1,2-a]*quinoxaline*-2,3-*dicarboxylate* **5d**.—This compound was obtained as yellow needles, mp 142–144 °C (Found: C, 69.30; H, 4.62; N, 6.89. $C_{24}H_{20}N_2O_5$ requires C, 69.22; H, 4.84; N, 6.73%); ν_{max}/cm^{-1} 2988, 1715, 1652, 1595, 1251, 977, 871, 752; δ_H 9.63 (1H, s, C4-H), 8.10 (1H, d, *J* 8.0, C9-H), 7.96 (2H, d, *J* 7.5, ArH), 7.68–7.63 (2H, m, ArH), 7.56–7.49 (3H, m, ArH), 7.42 (1H, t, *J* 7.7, ArH), 4.44 (2H, q, *J* 7.0, OCH_2), 3.93 (2H, q, *J* 7.0, OCH_2), 1.41 (3H, t, *J* 7.0, CH_3), 1.03 (3H, t, *J* 7.0 Hz, CH_3); *m/z* (%) 416 (M$^+$, 100), 371 (20), 343 (7), 299 (26), 105 (44), 77 (36).

N-*Phenyl* 1-*benzoylpyrrolo*[1,2-a]*quinoxaline*-2,3-*dicarboximide* **5e**.—This compound was obtained as reddish needles, mp 142–144 °C (Found: C, 74.56; H, 3.66; N, 10.21. $C_{26}H_{15}N_3O_3$ requires C, 74.81; H, 3.62; N, 10.07%); ν_{max}/cm^{-1} 1742, 1720, 1650, 1595, 1560, 1342, 1270, 980, 750; δ_H 9.36 (1H, s, C4-H), 8.18 (1H, d, *J* 8.2, C9-H), 8.15 (2H, d, *J* 7.8, ArH), 7.82 (1H, d, *J* 8.5, ArH), 7.74 (1H, t, *J* 7.3, ArH), 7.66 (1H, t, *J* 7.6, ArH), 7.60–7.55 (3H, m, ArH), 7.45 (2H, d, *J* 7.8 Hz, ArH), 7.37–7.35 (3H, m, ArH); *m/z* (%) 417 (M$^+$, 100), 105 (1), 77 (1).

We are grateful to the Science Foundation of China for financial support.

Received, 16th March 1999; Accepted, 24th May 1999
Paper E/9/02053E

References

1 R. F. Neale, S. L. Fallon, W. C. Boyar, J. W. F. Wasley, L. L. Martin, G. A. Stone, B. S. Glaeser and C. M. Sinton, *Eur. J. Pharmacol.*, 1987, **136**, 1.
2 I. Maeba, T. Takeuchi, T. Iijima and H. Furukawa, *J. Org. Chem.*, 1988, **53**, 1401.
3 I. Maeba, K. Kitaori, Y. Itaya and C. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1990, 67.
4 J. E. Macor, C. A. Burkhart, J. H. Heym, J. L. Ives, L. A. Lebel, M. E. Newman, J. A. Nielsen, K. Kyan, D. W. Schulz, L. K. Torgersen and B. Kenneth Koe, *J. Med. Chem.*, 1990, **33**, 2087.
5 G. Campiani, V. Nacci, F. Corelli and M. Anzini, *Synth. Commun.*, 1991, **21**, 1567.
6 E. C. Taylor and E. S. Hand, *J. Am. Chem. Soc.*, 1963, **85**, 770.
7 E. C. Taylor and G W. H. Cheeseman, *J. Am. Chem. Soc.*, 1964, **86**, 1830.
8 G. W. H. Cheeseman and B. Tuck, *J. Chem. Soc.*, 1965, 3678.
9 C. H. Weidner, F. M. Michaels, D. J. Beltman and C. J. Montgomery, *J. Org. Chem.*, 1991, **56**, 5594.
10 D. Korakas, A. Kimbaris and G. Varvounis, *Tetrahedron*, 1996, **52**, 10751.
11 G. Capozzi, R. Ottana, G. Romeo, G. Sindina, N. Uccella and G. Valle, *J. Chem. Res. (S)*, 1986, 234.
12 H. Suschitzky, B. J. Wakefield and R. A. Whitter, *J. Chem. Soc., Perkin Trans. 1*, 1975, 2409.
13 H. S. Kim, Y. Kurasawa, C. Yoshii, M. Masuyama, A. Takada and Y. Okamoto, *J. Heterocycl. Chem.*, 1990, **27**, 1115.
14 Y. Kurasawa, R. Katoh, F. Mori, M. Fukuchi, M. Okamoto, A. Takada, H. S. Kim and Y Okamoto, *J. Heterocycl. Chem.*, 1992, **29**, 1009.
15 N. S. Prostakov and O. B. Batibaev, *Russ. Chem. Rev.*, 1975, **44**, 748.
16 T. Uchida and K. Matsumoto, *Synthesis*, 1976, 209.
17 W. Flitsch, in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katrizky and C. W. Rees, Pergamon, Oxford, 1984, vol. 4, p. 476.
18 Y. Hu, X. Wei and H. Hu, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, New York, 1995, vol. 7, p. 4780.
19 X. Wei, Y. Hu, T. Li and H. Hu, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2487.
20 J. Zhou, Y. Hu and H. Hu, *Synth., Commun.*, 1998, **28**, 3397.
21 J. Zhou, Y. Hu and H. Hu, *Synthesis*, 1999, 166.
22 J. Zhou, Y. Hu and H. Hu, *J. Chem. Res. (S)*, 1999, 136.
23 W. K. Easley and C. T. Bahner, *J. Am. Chem. Soc.*, 1950, **72**, 3803.