Novel and Efficient Synthesis of 2- and 4-N-Substituted Pyridine *N*-Oxides under Solvent-Free Conditions

Subramania Ranganathan,*[a] Y. B. R. D. Rajesh,[a] Isabella L. Karle*[b]

[a] Discovery Laboratory, Organic III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

[b] Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375-5341, USA
Fax +91(40)27160757; E-mail: ranga@iict.res.in

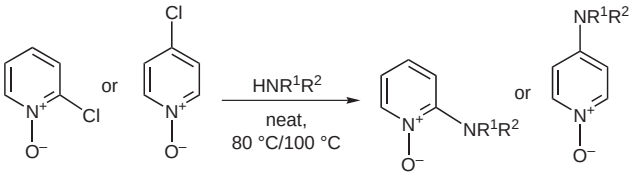
Received 28 December 2006

Abstract: Displacement of 2-or 4-chloropyridine *N*-oxides, with nitrogen nucleophiles, under solvent-free conditions offers a simple route to scarce N-substituted pyridine *N*-oxides.

Key words: chloropyridine *N*-oxides, nucleophilic substitution, amination, solvent-free conditions

We have reported recently[1] the enhancement of the solubility of silica in water by pyridine *N*-oxides having a nitrogen ligand, and the enhancement by these agents of the deposition of silica in rice plant. In order to widen the scope of the reaction, and to delineate the chemistry involved in the solubilization, we needed a range of 2- and 4-N-substituted pyridine *N*-oxides. An examination of the literature showed that only few such compounds have been reported and there lacked a general and reliable methodology for their synthesis. Since the early pioneering endeavors of Katritzky[2] and Ochiai,[3] little progress has been made.[4] These authors prepared 4-methylamino, 4-dimethylamino, 4-morpholino, 2-methylamino and 2-dimethylamino pyridine *N*-oxides by halogen displacement in water, under sealed tube conditions at approximately 140 °C for about 20 hours. Repetition by us showed that the workup is cumbersome, and once resulted in an explosion. The rate of displacement of chloropyridine *N*-oxides by piperidine, measured conductometrically follows the expected order 2 > 4 >> 3. Indeed, the rate of halogen displacement by piperidine in 3-chloropyridine *N*-oxide is too slow for kinetic assessment.[5] To test the intermediacy of pyridyne *N*-oxides,[6] chloropyridine *N*-oxides were subjected to treatment with KNH_2/NH_3 (–33 °C, 5 min). Whilst 2-chloropyridine *N*-oxides yielded a mixture of 2- and 3-amino compounds, suggesting incursion of pyridynes, the 3- and 4-chloro derivatives afforded only the 3- and 4-amino compound, respectively.[7,8]

After examination of several approaches, we found that simple heating of the 2-chloro[2b] and 4-chloro[3] pyridine *N*-oxide with 1.2 equivalents of the base at 80 °C (2-chloro) and 100 °C (4-chloro) for 0.5–2 hours, followed by column chromatography afforded the desired N-substituted pyridine *N*-oxides in good yields (Scheme 1). Since most of the compounds prepared are unreported they have been fully characterized. The results are summarized in Table 1 and Table 2.[9,13]



Scheme 1

Several compounds prepared in this work have the potential for further elaboration. From our vantage, compounds **8** and **10** (Table 1) have the potential for multidentate complexation. The crystal structure of these, reveal accumulation of water around the *N*-oxide.[10] Compounds **5** (Table 1), and **13** (Table 2) are suitable to craft reverse micellar systems harboring water pools[11] that may be useful for the study of the solubilization of silica in a hydrophobic environment.

Additionally, the ready availability of compounds described here has potential for diverse applications and hopefully will create a resurgence of interest in pyridine *N*-oxides.[12]

Acknowledgment

SR and Rajesh are grateful to the Department of Biotechnology, New Delhi, for financial assistance. We thank Dr. J. S. Yadav, director, IICT, Hyderabad, for his encouragement.

References and Notes

(1) Ranganathan, S.; Rao, Ch. C.; Vudayagiri, S. D.; Rajesh, Y. B. R. D.; Jagadeesh, B. *J. Chem. Sci.* **2004**, *116*, 169.

(2) (a) Katritzky, A. R. *J. Chem. Soc.* **1956**, 2404. (b) Katritzky, A. R. *J. Chem. Soc.* **1957**, 191. (c) Katritzky, A. R.; Randall, E. W.; Sutton, L. E. *J. Chem. Soc.* **1957**, 1769. (d) Gardner, J. N.; Katritzky, A. R. *J. Chem. Soc.* **1957**, 4375. (e) Jones, R. A.; Katritzky, A. R. *J. Chem. Soc.* **1960**, 2937.

(3) Ochiai, E. *J. Org. Chem.* **1953**, *18*, 534.

(4) For similar procedures, see: (a) Essery, J. M.; Schofield, K. *J. Chem. Soc.* **1960**, 4953. (b) Taylor, E. C.; Driscoll, J. S. *J. Am. Chem. Soc.* **1960**, *82*, 3141. (c) Badger, G. M.; Rao, R. P. *Aust. J. Chem.* **1964**, *17*, 1399.

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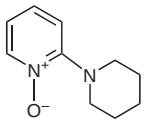
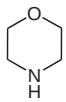
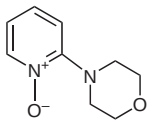
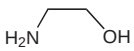
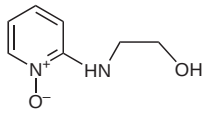
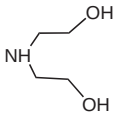
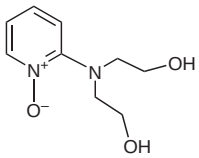
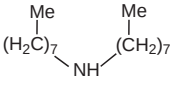
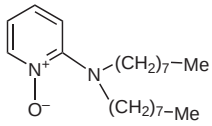
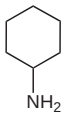
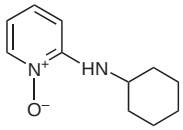
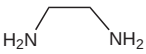
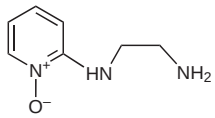
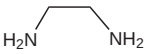
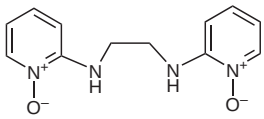
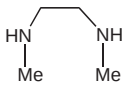
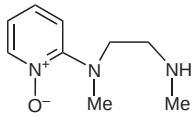
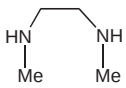
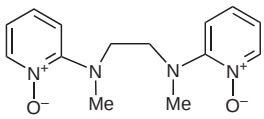
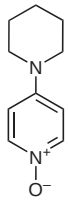
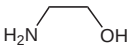
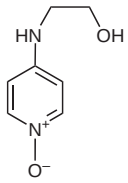
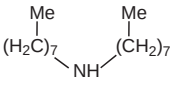
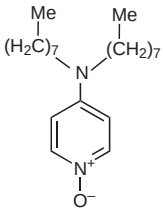
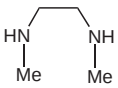
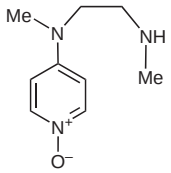
SYNLETT 2007, No. 8, pp 1215–1218
Advanced online publication: 18.04.2007
DOI: 10.1055/s-2007-977445; Art ID: D40006ST

Table 1 Synthesis of 2-N-Substituted Pyridine *N*-Oxides under Mild and Solvent-Free Conditions at 80 °C

Entry	Nucleophile	Pyridine *N*-oxide: nucleophile	Time (h)	Product	Yield (%)[a]
1		1.0:1.2	0.5	 **1**	89
2		1.0:1.2	0.5	 **2**	80
3		1.0:1.2	2.0	 **3**	84
4		1.0:1.2	0.5	 **4**	70
5		1.0:1.2	0.5	 **5**	60
6		1.0:1.2	1.0	 **6**	68
7		2.0:1.1	1.0	 **7**	60
8		2.0:1.1	1.0	 **8**	21
9		2.0:1.1	1.0	 **9**	52
10		2.0:1.1	1.0	 **10**	20

[a] Yields of isolated pure products.

Table 2 Synthesis of 4-N-Substituted Pyridine *N*-Oxides under Mild and Solvent-Free Conditions at 100 °C

Entry	Nucleophile	Pyridine *N*-oxide: nucleophile	Time (h)	Product	Yield (%)[a]
1		1.0:1.2	1.0	 **11**	70
2		1.0:1.2	1.0	 **12**	63
3		1.0:1.2	1.0	 **13**	55
4		2.0:1.1	2.0	 **14**	56

[a] Yields of isolated pure products.

(6) Chloropyridine *N*-oxides on treatment with KNH_2/NH_3 can undergo either elimination to pyridyne *N*-oxides (dehydropyridine *N*-oxides) or direct substitution. In the former case, elements of ammonia can be accepted at either of the locations to give a mixture of amino pyridine *N*-oxides.

(7) Kato, T.; Niitsuma, T.; Kusaka, N. *Yakugaku Zasshi* **1964**, *84*, 432; *Chem. Abstr.* **1964**, *61*, 4171d.

(8) The chemistry and applications of pyridine *N*-oxides is receiving increasing attention due to their usefulness as synthetic intermediates in biologically important compounds, protecting groups, auxiliary agents, oxidizing agents, templates for metal complexation and in the design of catalysts. See: (a) Youssif, S. *ARKIVOC* **2001**, *(i)*, 242. (b) Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, **1991**. (c) Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocyclic N-Oxides*; Academic Press: New York, **1971**.

(9) As predicted by the order of reactivity (cf. ref. 5) nucleophilic displacement was very efficient with 2-chloropyridine *N*-oxides. On the other hand those with 4-chloropyridine *N*-oxides was sluggish and failed in some cases.

(10) Karle, I. L.; Rajesh, Y. B. R. D.; Ranganathan, S. *unpublished results*.

(11) Ranganthan, D.; Singh, G. P.; Ranganathan, S. *J. Am. Chem. Soc.* **1989**, *111*, 1144.

(12) The effect of all the compounds reported on the enhancement of the solubility of silica in water will be examined.

(13) **General Procedure for the Preparation of 2- and 4-N-Substituted Pyridine *N*-Oxides**
A mixture of 2- or 4-chloro pyridine *N*-oxide (3 mmol) and amine (3.6 mmol) was heated at 80 °C for the 2-chloro compounds, and at 100 °C for the 4-chloro compounds for time periods indicated in Table 1 and Table 2. Pure products were secured by chromatography on a column of silica gel and elution with $CHCl_3$–MeOH.
Most compounds reported are novel and the remaining lack modern data. Therefore data for their characterization are presented below.
Spectral Data
Compound **1**: mp 120–124 °C (dark brown plates). IR (KBr): 1242, 773 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.61–1.68 (m, 2 H), 1.75–1.82 (m, 4 H), 3.30–3.34 (m, 4 H), 6.79–6.86 (m, 2 H), 7.18 (app t, 1 H, *J* = 8.5 Hz), 8.19 (d, 1 H, *J* = 7.7 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.0, 25.2, 48.7, 114.8, 117.0, 126.8, 140.3, 155.0. MS (EI): *m*/*z* = 178 [M^+]. HRMS: *m*/*z* calcd for $C_{10}H_{14}N_2O$: 178.1106; found: 178.1026.

Compound **2**: mp 143–146 °C (colorless crystals). IR (KBr): 2867, 2819, 1599, 1491, 1240, 1110, 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.40–3.43 (m, 4 H), 3.91–3.95 (m, 4 H), 6.83–6.93 (m, 2 H), 7.21–7.26 (m, 1 H), 8.20 (d, 1 H, *J* = 7.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 48.0, 66.6, 114.5, 118.2, 127.4, 140.6, 154.1. MS (EI): *m*/*z* = 180 [M^+]. HRMS: *m*/*z* calcd for $C_9H_{12}N_2O_2$: 180.0899; found: 180.0877.

Compound **3**: thick brown liquid. IR (Neat): 3348, 2932, 1627, 1195 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.38–3.43 (m, 2 H), 3.90–3.93 (m, 2 H), 6.55–6.63 (m, 2 H), 7.21–7.27 (m, 1 H), 7.57 (br, 1 H), 8.05 (d, 1 H, *J* = 7.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 45.5, 60.5, 106.7, 111.3, 130.2, 137.3, 150.6. MS (EI): *m*/*z* = 154 [M^+]. HRMS: *m*/*z* calcd for $C_7H_{10}N_2O_2$: 154.0742; found: 154.0744.

Compound **4**: pale brown liquid. IR (neat): 3365, 1506, 1202 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.60–3.65 (m, 4 H), 3.71–3.75 (m, 4 H), 6.88 (app t, 1 H, *J* = 7.0 Hz), 7.10 (d, 1 H, *J* = 10.1 Hz), 7.31 (app t, 1 H, *J* = 8.5 Hz), 8.14 (d, 1 H, *J* = 7.9 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 52.0, 58.5, 116.7, 117.5, 129.5, 139.7, 152.8. MS (EI): *m*/*z* = 198 [M^+]. HRMS: *m*/*z* calcd for $C_9H_{14}N_2O_3$: 198.1004; found: 198.1104.

Compound **5**: quasi-crystalline brown thick liquid. IR (neat): 2926, 2855, 1241 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$,): δ = 0.84–0.88 (m, 6 H), 1.24 (br, 20 H), 1.52 (br, 4 H), 3.38–3.43 (m, 4 H), 6.74–6.84 (m, 2 H), 7.14 (app t, 1 H, *J* = 8.7 Hz), 8.14 (d, 1 H, *J* = 7.8 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.0, 22.4, 26.8, 27.5, 29.0, 29.2, 31.7, 50.5, 116.2, 116.3, 127.8, 140.9, 153.6. MS (EI): *m*/*z* = 334 [M^+]. HRMS: *m*/*z* calcd for $C_{21}H_{38}N_2O$: 334.2984; found: 334.2969.

Compound **6**: pale yellow liquid. IR (neat): 2931, 2854, 1622, 1571, 1525, 1196, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.45 (m, 6 H), 1.76–1.83 (m, 2 H), 2.00–2.04 (m, 2 H), 3.27–3.38 (m, 1 H), 6.47–6.60 (m, 2 H), 6.80 (br, 1 H), 7.20 (app t, 1 H, *J* = 8.3 Hz), 8.11 (d, 1 H, *J* = 7.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.6, 25.2, 32.6, 50.5, 105.9, 110.5, 128.2, 137.2, 149.3. MS (EI): *m*/*z* = 193 [M^+ + 1]. HRMS: *m*/*z* calcd for $C_{11}H_{16}N_2O$: 192.1263; found: 192.1164.

Compound **7**: mp 180–182 °C (dark brown plates). IR (KBr): 3423, 3234, 1628, 1575, 1198 cm^{-1}. ^1H NMR (200 MHz, D_2O): δ = 3.23–3.29 (m, 2 H), 3.68–3.74 (m, 2 H), 6.81 (app t, 1 H, *J* = 6.8 Hz), 6.95 (d, 1 H, *J* = 8.6 Hz), 7.55 (app t, 1 H, *J* = 7.8 Hz), 8.02 (d, 1 H, *J* = 6.6 Hz). ^{13}C NMR (75.47 MHz, D_2O): δ = 38.3, 39.0, 108.1, 113.3, 133.7, 137.6, 149.7. MS (EI): *m*/*z* = 153 [M^+]. HRMS: *m*/*z* calcd for $C_7H_{11}N_3O$: 153.0902; found: 153.0899.

Compound **8**: mp 242–244 °C (pale brown rods). IR (KBr): 3337, 1626, 1578, 1528, 1188, 767 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ = 3.73 (s, 4 H), 6.73 (app t, 2 H, *J* = 7.2 Hz), 6.97 (d, 2 H, *J* = 7.2 Hz), 7.45 (app t, 2 H, *J* = 8.4 Hz), 8.02 (d, 2 H, *J* = 6.6 Hz). ^{13}C NMR (75.47 MHz, D_2O): δ = 41.2, 107.9, 112.3, 133.2, 137.3, 150.0. MS (EI): *m*/*z* = 246 [M^+]. HRMS: *m*/*z* calcd for $C_{12}H_{14}N_4O_2$: 246.1116; found: 246.1105.

Compound **9**: pale brown liquid. IR (neat): 3420, 1365 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.79–2.84 (m, 3 H), 3.07 (s, 3 H), 3.33–3.40 (m, 2 H), 3.61–3.67 (m, 2 H), 6.96–7.05 (m, 2 H), 7.42 (app t, 1 H, *J* = 8.7 Hz), 8.11 (d, 1 H, *J* = 7.6 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 34.4, 37.9, 46.3, 47.9, 115.7, 117.9, 130.3, 139.7, 153.5. MS (EI): *m*/*z* = 181 [M^+]. HRMS: *m*/*z* calcd for $C_9H_{15}N_3O$: 181.1215; found: 181.1215.

Compound **10**: mp 192–194 °C (pale brown rods). IR (KBr): 3369, 3257, 1615, 1516, 1186, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.04 (s, 6 H), 3.89 (s, 4 H), 6.76 (app t, 2 H, *J* = 6.8 Hz), 6.82 (d, 2 H, *J* = 8.5 Hz), 7.16 (app t, 2 H, *J* = 8.7 Hz), 8.09 (d, 2 H, *J* = 7.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 39.2, 49.9, 114.6, 116.3, 127.4, 140.3, 154.4. MS (EI): *m*/*z* = 274 [M^+]. HRMS: *m*/*z* calcd for $C_{14}H_{18}N_4O_2$: 274.1429; found: 274.1419.

Compound **11**: pale brown liquid. IR (neat): 2947, 1637 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.70–1.73 (m, 6 H), 3.47–3.50 (m, 4 H), 6.82 (d, 2 H, *J* = 7.8 Hz), 8.09 (d, 2 H, *J* = 8.0 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 23.9, 25.0, 47.7, 108.9, 139.3, 150.7. MS (ESI): *m*/*z* = 179 [M^+ + 1]. HRMS: *m*/*z* calcd for $C_{10}H_{14}N_2O$: 178.1106; found: 178.1091.

Compound **12**: thick brown liquid. IR (neat): 3278, 1642, 1539, 1061 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ = 3.36–3.40 (m, 2 H), 3.75–3.81 (m, 2 H), 6.74 (d, 2 H, *J* = 7.4 Hz), 7.87 (d, 2 H, *J* = 7.4 Hz). ^{13}C NMR (75.47 MHz, D_2O): δ = 44.7, 59.6, 108.4, 139.0, 152.5. MS (EI): *m*/*z* = 155 [M^+ + 1]. HRMS: *m*/*z* calcd for $C_7H_{10}N_2O_2$: 154.0742; found: 154.0644.

Compound **13**: quasi-crystalline thick brown liquid. IR (neat): 2927, 2855, 1466 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.87–0.92 (m, 6 H), 1.29 (br, 20 H), 1.52 (br, 4 H), 2.57–2.64 (m, 4 H), 7.27 (d, 2 H, *J* = 7.9 Hz), 8.15 (d, 2 H, *J* = 7.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 22.5, 25.9, 26.8, 29.0, 29.1, 31.6, 47.7, 126.7, 140.3, 157.6. MS (ESI): *m*/*z* = 335 [M^+ + 1]. HRMS: *m*/*z* calcd for $C_{21}H_{38}N_2O$: 334.2984; found: 334.2964.

Compound **14**: pale brown liquid. IR (neat): 3401, 3047, 1643, 1551, 1339, 1218, 815 cm^{-1}. ^1H NMR (200 MHz, D_2O): δ = 2.78 (br, 3 H), 3.24 (s, 3 H), 3.33–3.49 (m, 2 H), 3.91–4.01 (m, 2 H), 7.03 (d, 2 H, *J* = 7.3 Hz), 8.15 (d, 2 H, *J* = 7.3 Hz). ^{13}C NMR (50 MHz, D_2O): δ = 35.8, 40.8, 47.8, 50.3, 109.9, 141.6, 160.2. MS (ESI): *m*/*z* = 182 [M^+ + 1]. HRMS: *m*/*z* calcd for $C_9H_{15}N_3O$: 181.1215; found: 181.1225.