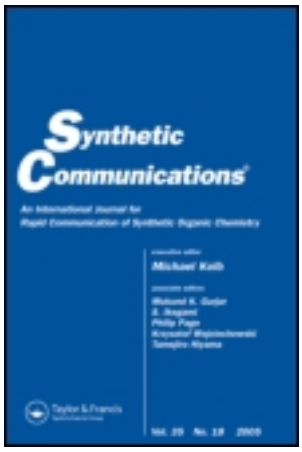

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A Simple and Efficient Method for the Preparation of Heterocyclic N-Oxide

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ABSTRACT

Pyridine, 2-methylpyridine, 3-methylpyridine, 4-methylpyridine, 2,4-dimethylpyridine, 2,6-dimethylpyridine, quinoline, isoquinoline and 2-chloropyridine are readily oxidized to their N-oxides with a solution of trichloroisocyanuric acid, acetic acid, sodium acetate and water in acetonitrile and methylene dichloride in 78%–90% yields.

Key Words: Heterocyclic N-oxide; Oxidation; Acetonitrile; Methylene dichloride; Trichloroisocyanuric acid.

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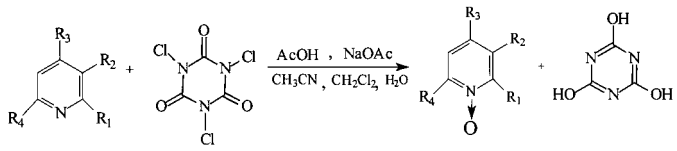
Pyridine-N-oxide is a useful building block in organic synthesis.[1–3] Pyridine or other heterocyclic nitrogen compounds can be converted into pyridine-N-oxide or other heterocyclic N-oxides using various oxidizing agents,[4–10] which including peracetic acid,[4] $HOF \cdot CH_3CN$,[5] m-chloroperbenzoic acid,[6] sodium perborate in acetic acid[7] and H_2O_2-catalyzed by a Mn-porphyrin.[8] Trichloroisocyanuric acid [1,3,5-trichloro-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione] has been a useful reagent in organic synthesis,[11] it has been used to oxidized secondary alcohol to ketones,[12] sulfides to sulfoxide[13] in good yields. We have now found that trichloroisocyanuric acid [1,3,5-trichloro-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione] (**2**) is very efficient, highly selective reagent for oxidation of pyridine or other heterocyclic nitrogen compounds, which can be converted into pyridine-N-oxide or other heterocyclic N-oxides.

A solution of pyridine or other heterocyclic nitrogen compounds **1**, acetic acid, sodium acetate, water and trichloroisocyanuric acid **2** in acetonitrile and methylene dichloride underwent oxidation to produce the corresponding pyridine-N-oxide or other heterocyclic N-oxides **3** along with cyanuric acid **4** and hydrogen chloride. Yields are good to excellent (Sch. 1 and Table 1).

Although acetonitrile generally worked well, in some instances other solvents such as methelene dichloride were more suitable due to that some heterocyclic nitrogen compounds have relative poor solubility in acetonitrile. To enhance the rate of oxidation a trace of water was added to the heterocyclic nitrogen compounds reaction mixture. In absolute anhydrous condition the reaction hardly proceed under similar conditions. But excessive water will reduce the rate of oxidation and give poor yields. Since hydrogen chloride is produced in the reaction and it can then react with **2** to form chlorine,[14]



1 **2** **3** **4**

1a, 3a: R_1, R_2, R_3, R_4 = H; **1b, 3b:** R_1 = CH_3, R_2, R_3, R_4 = H;
1c, 3c: R_2 = CH_3, R_1, R_3, R_4 = H; **1d, 3d:** R_3 = CH_3, R_1, R_2, R_4 = H;
1e, 3e: R_1, R_3 = CH_3, R_2, R_4 = H; **1f, 3f:** R_1, R_4 = CH_3, R_2, R_3 = H;
1g, 3g: R_1R_2 = -CH=CH-CH=CH-, R_3, R_4 = H;
1h, 3h: R_1, R_4 = H, R_2R_3 = -CH=CH-CH=CH-;
1i, 3i: R_1 = Cl, R_2, R_3, R_4 = H

Scheme 1.

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Table 1. Synthesis of compounds **3a–i**.

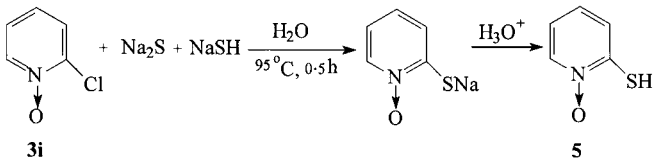
Product	R_1	R_2	R_3	R_4	Yield (%)[a]
3a	H	H	H	H	81
3a[b]	H	H	H	H	61
3b	CH_3	H	H	H	84
3c	H	CH_3	H	H	82
3d	H	H	CH_3	H	89
3e	CH_3	H	CH_3	H	78
3f	CH_3	H	H	CH_3	80
3g	–CH=CH–CH=CH–		H	H	90
3h	H	–CH=CH–CH=CH–		H	79
3i	Cl	H	H	H	80

[a]Isolated yield.
[b]Without sodium acetate–acetic acid buffer media.

sodium acetate–acetic acid buffer media is used. Without sodium acetate and acetic acid in the reaction mixture the products **3** were produced in only 50–60% yields along with a few byproducts.

Heterocyclic N-oxides **3** have recently emerged as valuable reagents for organic synthesis. For example, 2-chloropyridine-N-oxide **3i** was transformed into 2-mercaptopyridine-N-oxide **5** in 94% yield by treatment with sodium sulfide and sodium hydrosulfide in aqueous solution (Sch. 2). 2-Mercaptopyridine-N-oxide **5** and its alkali metal salts were used for the preservation animal skins and leather.[17]

In conclusion, the oxidation reaction of nitrogen containing heterocycles with compound **2** provides a direct route to the N-oxides. The method has some attractive advantages such as cheap, safe and stable source of starting materials, high yields, mild reaction conditions, simple procedure and shorter reaction time.



3i **5**

Scheme 2.

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EXPERIMENTAL

^{1}H NMR spectra were recorded on AVANVE-300 spectrometer with TMS as internal standard. IR spectra were determined on VECTOR-55 instrument. Silica gel 60 GF254 was used for analytical and preparative TLC. All products were characterized by comparison with authentic samples using IR, ^{1}H NMR and m.p.

General Procedure for the Synthesis of 3a–i

In a 25 mL two-neck flask were placed 2 mmol of the heterocyclic nitrogen compounds **1**, 2 mmol of acetic acid, 3 mmol of sodium acetate, 2 mL of acetonitrile, 2 mL of methylene chloride, 0.1 mL of water. The mixture in flask was allowed to stir for 5 min before the addition of the solution of **2** was started. The solution of **2** (1.5 mmol) in 1.5 mL of acetonitrile was added dropwise through a syringe. After a few minutes, the reaction temperature began to rise. The addition took a total of 15 min and that was followed by an additional 2 h of stirring at 40°C. Excess **2** was destroyed by the slow addition of saturated $NaHSO_3$ solution. During this process, wet iodide-starch test paper was used to periodically test for the presence of oxidizing power. The precipitate of cyanuric acid **4** was removed by filtration and washed with diethyl ether. Most of the solvent was removed from the filtrate with a rotary evaporator and the residue was diluted with 20 mL of diethyl ether. The ether solution was washed with saturated NaCl solution (2 × 3 mL) and dried over $MgSO_4$. After filtration and concentration, the crude product was purified by preparative TLC on silica gel and eluted with hexane and ethyl acetate (3/1).

3a. A white solid. m.p. 63–65°C (lit.:[15] 61–65°C). ^{1}H NMR: $\delta = 8.18$ (d, $J = 7.2$ Hz, 2H), 7.62 (d, $J = 7.34$ Hz, 1H), 7.42 (dd, $J = 7.2$ Hz, 7.34 Hz, 2H); IR (ν_{max}, KBr) 3050, 1625, 1480, 1455, 1045, 1020 cm^{-1}.

3b. A white solid. m.p. 48–50°C (lit.:[18] 48–50°C). ^{1}H NMR: $\delta = 8.44$ (d, $J = 5.67$ Hz, 1H), 8.30 (m, 1H), 7.71 (m, 2H), 2.64 (s, 3H); IR (ν_{max}, KBr) 3041, 1618, 1398, 1046 cm^{-1}.

3c.[19] Oil. ^{1}H NMR: $\delta = 8.11$ (s, 1H), 8.04 (d, $J = 7.34$ Hz, 1H), 7.26 (dd, $J = 7.3$ Hz, $J = 7.34$ Hz, 1H), 7.18 (d, $J = 7.34$ Hz, 1H), 2.23 (s, 3H); IR (ν_{max}, film) 3050, 1615, 1455, 1055, 1010 cm^{-1}.

3d. A white solid, mp: 183–185°C (lit.:[18] 182–185°C). ^{1}H NMR: $\delta = 8.47$ (d, $J = 6.09$ Hz, 2H), 7.76 (d, $J = 6.09$ Hz, 2H), 2.54 (s, 3H); IR (ν_{max}, KBr) 3045, 1643, 1612, 1510, 1449, 1383, 1030 cm^{-1}.

3e.[20] A white solid, m.p. 290–292°C (dec). ^{1}H NMR: $\delta = 8.15$ (s, 1H), 7.29 (m, 2H), 2.45 (s, 3H), 2.33 (s, 3H); IR (ν_{max}, KBr) 3054, 1634, 1406, 1054, 806 cm^{-1}.

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3f.[18] A white solid, m.p. 52–55°C. ^{1}H NMR: $\delta = 8.17$ (t, $J = 7{,}90$, 1H), 7.52 (d, $J = 7.90$ Hz, 2H), 2.62 (s, 6H); IR (ν_{max}, KBr) 3027, 1719, 1462, 1397, 1052, 779 cm^{-1}.

3g. A white solid, mp: 58–60°C (lit.:[9] 59–61°C). ^{1}H NMR: $\delta = 8.76$ (d, $J = 4.89$ Hz, 1H), 8.57 (d, $J = 8.4$ Hz, 1H), 7.84 (m, 3H), 7.62 (m, 2H); IR (ν_{max}, KBr) 3046, 1637, 1596, 1502, 1056, 812 cm^{-1}.

3h. A white solid, m.p. 135–136°C (lit.:[16] 137°C). ^{1}H NMR: $\delta = 8.41$(s, 1H), 8.24 (d, $J = 8.3$ Hz, 1H), 7.42 (m, 3H), 7.53 (m, 2H); IR (ν_{max}, KBr): 3030, 1630, 1500, 1045 cm^{-1}.

3i. A white solid, m.p. 140–142°C (lit.:[20] 140–142°C). ^{1}H NMR: $\delta = 8.04$ (d, $J = 8.0$ Hz, 1H), 7.56 (m, 2H), 7.40 (m, 1H); IR (ν_{max}, KBr): 3085, 3020, 1590, 1495, 1440, 1205, 1100 cm^{-1}.

The Synthesis of 2-Chloropyridine 5

In a 25 mL two-neck flask wase placed a solution of **3j** (2 mmol) and 1.5 mL of water. The mixture in flask was allowed to heated to 95°C before the addition an aqueous solution containing 1.5 mL of water, 1.5 mmol of sodium sulfide and 2.2 mmol of sodium hydrosulfide was started. After the addition was completed, the reaction mixture was heated at 95°C for an additional 30 min. The reaction mixture was poured into water (5 mL), neutralized with 1 M HCl and extracted with methylene chloride (3 × 5 mL). The combined organic layer was washed with brine (2 × 3 mL) and dried over $MgSO_4$. After filtration and concentration, the crude product was purified by preparative TLC on silica gel and eluted with hexane and ethyl acetate (4/1) to give **5** in 94% yield.

5. A white solid, mp: 71–72°C (lit.:[20] 70–72°C). ^{1}H NMR: $\delta = 8.50$ (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.40 (m, 1H), 7.12 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H); IR (ν_{max}, KBr): 3100, 1600, 1570, 1130, 810, 750 cm^{-1}.

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