## Notizen / Notes

# An Excellent Method for the Mild and Safe Oxidation of N-Heteroaromatic Compounds and Tertiary Amines

**Łukasz Kaczmarek*, Roman Balicki, and Paweł Nantka-Namirski**

Institute of Organic Chemistry, Polish Academy of Sciences,
Kasprzaka 44/52, 01-224 Warszawa, Poland

Received February 12, 1992

**Key Words:** *N*-Oxidation / Hydrogen peroxide / Urea / Phthalic anhydride

Selective, mild and safe *N*-oxidation of N-heteroaromatic compounds and tertiary amines affording high product yields was achieved by using the $H_2O_2$-urea/phthalic anhydride system.

N-Heteroaromatic oxides (such as pyridine or quinoline *N*-oxides) show a different behavior as compared to the corresponding unoxidized parent heteroaromatics or related quaternary ammonium salts in the reactions with electrophiles, nucleophiles or radicals and display interesting orientations and reactivities in substitution reactions. Since the oxygen atom may be removed by reduction or under the applied reaction conditions subsequent to the change in which its influence was exerted, the oxygen may be regarded as a temporary addition to the molecule, guiding reactions such as substitution or displacement[1].

The synthetic importance of aromatic *N*-oxides is reflected by a number of methods for their preparation. Most of these methods are based on direct *N*-oxidations with peracids, both applied as reagents [i.e. monoperphthalic[2], monopermaleic[3], perbenzoic[4] and the most popular *m*-chloroperbenzoic (MCPBA)[5] acid] and prepared *in situ* from 30–90% $H_2O_2$ and acetic[6] or trifluoroacetic[7] acid or their anhydrides[8,9].

The peracid reagents suffer from being relatively unstable and potentially explosive, and hence these compounds (including MCPBA) are now being replaced by the more stable and safe magnesium monoperphthalate (MMPP). However, MMPP is 5 times more expensive than MCPBA and the *N*-oxidation is carried out in acetic acid at 85 °C[10]. On the other hand, the most common *N*-oxidation, which consists in heating of the substrate with $H_2O_2$ in acetic or trifluoroacetic acid, has the drawback of being accompanied by side reactions, such as the oxidation of substituents[11] or fused benzene rings[12], nucleophilic substitution with a hydroxyl group[13] or hydrolysis of functional groups[14]. Moreover, the isolation the of products requires removal of the excess of the acid by distillation, which can result in a dangerous build-up of peroxides. Thus, the search for mild, safe and selective reagents for *N*-oxidation has been and still is the subject of active investigation. The new reagents, recently described in the literature, include 30% $H_2O_2$ with $NaHCO_3$ in a benzonitrile-methanol mixture at room temperature[15], sodium perborate in acetic acid[16] and $H_2O_2$ in the presence of phosphotungstic acid[17].

We report here on the high effectiveness of the readily accessible $H_2O_2$/urea adduct (UHP)[18]/phthalic anhydride system, which makes this safe and inexpensive reagent superior to other ones for the *N*-oxidation of N-heteroaromatics and tertiary amines. These compounds are smoothly converted to the corresponding *N*-oxides by stirring at room temperature a mixture of UHP, phthalic anhydride and the substrate in a chlorinated hydrocarbon (e.g. $CH_2Cl_2$), an alcohol (e.g. methanol) or in acetonitrile which, in some cases, appears to be the most suitable solvent (cf. Table 2, entries 6, 9, 11). The best results are obtained when 3.3–4.5 molar equivalents of UHP and 1.1–1.5 molar equivalents of phthalic anhydride are used. The products are easily isolated by alkalization with aqueous $K_2CO_3$ and subsequent extraction with chloroform or dichlormethane. On the other hand, if phthalic anhydride is replaced by acetic, benzoic or maleic anhydride, the yield of the reaction product is markedly lower (cf. Table 1, entries 1–3). However, when 30% $H_2O_2$ instead of UHP or the acid instead of the corresponding anhydride are used, no reaction occurs (cf. Table 1, entries 5 and 6).

The *N*-oxidation reported here does not affect most other functional groups, such as alkyl, halogen, alkoxycarbonyl, acetyl, carbamoyl, hydroximinomethyl, alkoxyl and acetamidoyl as well as a fused benzene ring. However, a partial hydrolysis of the cyano group and oxidation of the amino group are observed.

In conclusion, the simplicity, selectivity, efficiency, safeness, and mildness of the reaction in connection with the low cost of reagents and easy isolation of products render the present method a preferable alternative to existing procedures for the conversion of N-heteroaromatics and tertiary amines to their *N*-oxides.

## Experimental

*General Procedure*: UHP (2.1 g, i.e. the equivalent of 11 mmol of $H_2O_2$) and the corresponding anhydride (11 mmol) in the respective

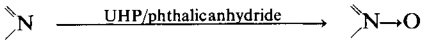
Table 1. *N*-Oxidation of 4-*tert*-butylpyridine with the different reagent systems

$$\text{4-}\textit{tert}\text{-butylpyridine} \xrightarrow{[O]} \text{4-}\textit{tert}\text{-butylpyridine } \textit{N}\text{-oxide}$$

| Entry[a] | Reagent system | Solvent | Time [h] | Yield[b] [g] (%) |
|---|---|---|---|---|
| 1 | acetic anhydride/UHP | $CH_2Cl_2$ | 24 | 1.00 (66) |
| 2 | benzoic anhydride/UHP | $CH_2Cl_2$ | 1 | 0.76 (50) |
| 3 | maleic anhydride/UHP | $CH_2Cl_2$ | 1 | 0.91 (60) |
| 4 | phthalic anhydride/UHP | $CH_2Cl_2$ | 1 | 1.40 (93) |
| 5 | phthalic anhydride/30% $H_2O_2$ | $CH_2Cl_2$ | 24 | – (0) |
| 6 | benzoic acid/UHP | $CH_2Cl_2$ | 24 | – (0) |
| 7 | phthalic anhydride/UHP | $CH_3OH$ | 2 | 1.42 (94) |

[a] In all cases 10 mmol (1.35 g) of starting material is used. – [b] Yields of isolated products.

Table 2. Oxidation of N-heteroaromatics and tertiary amines with the UHP/phthalic anhydride system



| Entry | Substrate[a,b] | Product[c,d]<br>m.p. [°C] | Solvent | Time [h] | Yield[e] [g] (%) |
|---|---|---|---|---|---|
| 1 | 2-picoline | *N*-oxide<br>– | $CH_2Cl_2$ | 1 | 1.04 (95) |
| 2 | 2,2′-bipyridyl[f] | di-*N*-oxide<br>above 300 | $CH_2Cl_2$ | 24 | 0.92 (98) |
| 3 | 4,4′-bipyridyl[f] | di-*N*-oxide<br>above 300 | $CH_2Cl_2$ | 24 | 0.75 (80) |
| 4 | quinoline | *N*-oxide hydrate<br>60–62 | $CH_2Cl_2$ | 2 | 1.40 (86) |
| 5 | phenazine[f] | di-*N*-oxide<br>204 (dec.) | $CH_2Cl_2$ | 24 | 0.30 (28) |
| 6 | phenazine[f] | di-*N*-oxide | $CH_3CN$ | 24 | 0.85 (80) |
| 7 | furo[3,2-*b*:4,5-*b*′]-bipyridine[f,19] | di-*N*-oxide<br>219–222 | $CH_2Cl_2$ | 12 | 0.80 (79) |
| 8 | 2-chloropyridine | *N*-oxide<br>59–60 | $CH_2Cl_2$ | 24 | 0.15 (12) |
| 9 | 2-chloropyridine | *N*-oxide | $CH_3CN$ | 3 | 1.19 (92) |
| 10 | 3,5-dibromopyridine | *N*-oxide<br>143–144 | $CH_2Cl_2$ | 24 | 1.04 (41) |
| 11 | 3,5-dibromopyridine | *N*-oxide | $CH_3CN$ | 2 | 2.43 (96) |
| 12 | ethyl isonicotinate | *N*-oxide<br>68–70 | $CH_2Cl_2$ | 4 | 1.50 (90) |
| 13 | methyl nicotinate | *N*-oxide<br>97–98 | $CH_2Cl_2$ | 4 | 1.50 (98) |
| 14 | nicotinamide | *N*-oxide[g]<br>287–288 | $CH_2Cl_2$ | 3 | 1.10 (80) |
| 15 | 4-acetylpyridine | *N*-oxide<br>134–136 | $CH_2Cl_2$ | 4 | 1.30 (95) |
| 16 | 2-methoxypyridine | *N*-oxide<br>– | $CH_2Cl_2$ | 24 | 0.60 (48) |
| 17 | 3-acetamidopyridine | *N*-oxide<br>215–216 | $CH_2Cl_2$ | 2 | 1.15 (76) |
| 18 | picolinaldehyde oxime | *N*-oxide<br>230–235 | $CH_2Cl_2$ | 6 | 1.00 (72) |
| 19 | 4-cyanopyridine | *N*-oxide[h] | $CH_2Cl_2$ | 4 | 0.25 (21) |
| 20 | 3-aminopyridine | – | $CH_2Cl_2$ | 2 | – |
| 21 | *N*,*N*-diethylaniline | *N*-oxide<br>– | $CH_2Cl_2$ | 1 | 1.62 (98) |
| 22 | triethylamine | *N*-oxide<br>above 40 | $CH_2Cl_2$ | 1 | 0.98 (84) |

[a] Commercial material unless otherwise specified. – [b] 10 mmol unless otherwise specified. – [c] Purified by crystallization or column chromatography (entries 1, 5, 6 and 16). – [d] Confirmed by comparison of TLC, m.p. and IR with those of authentic samples or literature data. – [e] Yields of isolated products. – [f] 5 mmol. – [g] Isolated by filtration. – [h] Isonicotinamide *N*-oxide is also formed.

solvent (25 ml) are stirred at room temperature for 15 min. Then the substrate (10 mmol if 1 nitrogen atom is present in the molecule or 5 mmol if 2 nitrogen atoms are present) is added and the mixture is stirred at room temperature until the starting material is consumed (TLC control). The mixture is neutralized with saturated aqueous $K_2CO_3$ and extracted continuously with $CHCl_3$. The extract is dried, the solvent evaporated and the residue purified.

The results are listed in Tables 1 and 2.

[1] E. Ochiai, *Aromatic Amine Oxides*, Elsevier, Amsterdam, **1967**.

[2] B. Bobrański, L. Kochańska, A. Kowalewska, *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 2385–2388.

[3] M. A. Weiner, *J. Organomet. Chem.* **1970**, *23*, C20–C22.

[4] J. Meisenheimer, *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 1848–1853.

[5] O. E. Edwards, D. C. Gillespie, *Tetrahedron Lett.* **1966**, 4867–4870.

[6] E. Ochiai, Z. Sai, *Yakugaku Zasshi* **1945**, *65A*, 73–74 [*Chem. Abstr.* **1951**, *45*, 8526].

[7] G. E. Chivers, H. Suschitzky, *J. Chem. Soc. Chem. Commun.* **1971**, 28–29.

[8] K. Takabe, T. Yamada, T. Katagiri, *Chem. Lett.* **1982**, 1987–1988.

[9] V. Tortorella, *J. Chem. Soc., Chem. Commun.* **1966**, 308–309.

[10] P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney, N. Thompson, *Synthesis* **1987**, 1015–1017.

[11] R. Adams, S. Miyano, *J. Am. Chem. Soc.* **1954**, *76*, 3168–3171.

[12] M. M. Robinson, B. L. Robinson, *J. Am. Chem. Soc.* **1958**, *80*, 3446–3449.

[13] E. Ochiai, Ch. Kaneko, I. Shimada, Y. Murata, T. Kosuge, S. Miyashita, Ch. Kawasaki, *Chem. Pharm. Bull. (Tokyo)* **1960**, *8*, 126–130.

[14] M. L. Peterson, *J. Org. Chem.* **1960**, *25*, 565–569.

[15] A. R. Katritzky, D. Rasala, F. Brito-Palme, *J. Chem. Res. (S)* **1988**, 42–43.

[16] A. McKillop, D. Kemp, *Tetrahedron* **1989**, *45*, 3299–3306.

[17] C. J. Cabre, C. A. Palomo, *Afinidad* **1988**, *45*, 511–515 [*Chem. Abstr.* **1989**, *111*, 77817].

[18] C. Lu, E. W. Hughes, P. A. Giguére, *J. Am. Chem. Soc.* **1941**, *63*, 1507–1513.

[19] Ł. Kaczmarek, *Pol. J. Chem.* **1985**, *59*, 1141–1148.

[71/92]

## CAS Registry Numbers

2-picoline: 109-06-8 / 2,2′-bipyridyl: 366-18-7 / 4,4′-bipyridyl: 553-26-4 / quinoline: 91-22-5 / phenazine: 92-82-0 / furo[3,2-*b*:4,5-*b*′]bipyridine: 101303-29-1 / 2-chloropyridine: 109-09-1 / 3,5-dibromopyridine: 625-92-3 / ethyl isonicotinate: 1570-45-2 / methyl nicotinate: 93-60-7 / nicotinamide: 98-92-0 / 4-acetylpyridine: 1122-54-9 / 2-methoxypyridine: 1628-89-3 / 3-acetamidopyridine: 5867-45-8 / picolinaldehyde oxime: 873-69-8 / 4-cyanopyridine: 100-48-1 / 3-aminopyridine: 462-08-8 / *N*,*N*-diethylaniline: 91-66-7 / triethylamine: 121-44-8 / 2-picoline *N*-oxide: 931-19-1 / 2,2′-bipyridyl di-*N*-oxide: 2935-74-2 / 4,4′-bipyridyl di-*N*-oxide: 24573-15-7 / quinoline *N*-oxide: 1613-37-2 / phenazine di-*N*-oxide: 303-83-3 / furo[3,2-*b*:4,5-*b*′]bipyridine di-*N*-oxide: 141271-94-5 / 2-chloropyridine *N*-oxide: 2402-95-1 / 3,5-dibromopyridine *N*-oxide: 2402-99-5 / ethyl isonicotinate *N*-oxide: 14906-37-7 / methyl nicotinate *N*-oxide: 15905-18-7 / nicotinamide *N*-oxide: 1986-81-8 / 4-acetylpyridine *N*-oxide: 2402-96-2 / 2-methoxypyridine *N*-oxide: 20773-98-2 / 3-acetamidopyridine *N*-oxide: 15010-23-8 / picolinaldehyde oxime *N*-oxide: 698-21-5 / 4-cyanopyridine *N*-oxide: 14906-59-3 / *N*,*N*-diethylaniline *N*-oxide: 826-42-6 / triethylamine *N*-oxide: 2687-45-8 / 4-*tert*-butylpyridine *N*-oxide: 3978-81-2 / 4-*tert*-butylpyridine *N*-oxide: 23569-17-7 / urea hydrogen peroxide: 124-43-6 / phthalic anhydride: 85-44-9 / hydrogen peroxide: 7722-84-1 / urea: 57-13-6 / acetic anhydride: 108-24-7 / benzoic anhydride: 93-97-0 / maleic anhydride: 108-31-6