Tetrahedron Letters 49 (2008) 6933–6935

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A safe, convenient and efficient method for the preparation of heterocyclic N-oxides using urea·hydrogen peroxide

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ARTICLE INFO

Article history:
Received 23 June 2008
Revised 16 September 2008
Accepted 22 September 2008
Available online 25 September 2008

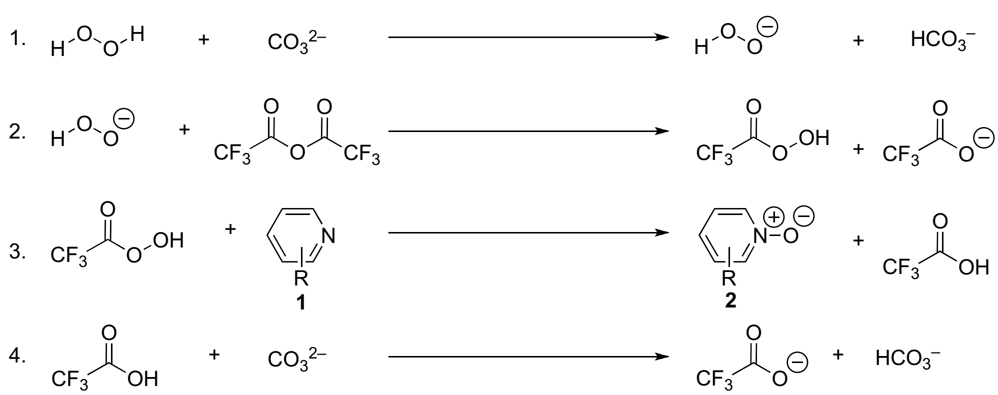
Keywords:
N-Oxide
Urea·hydrogen peroxide
Trifluoroperacetic acid
Pyrimidine
Pyridine
Quinoline

ABSTRACT

A novel, convenient, and high-yielding method has been developed for the preparation of heterocyclic N-oxides. The reaction uses the urea·hydrogen peroxide addition complex as a peroxide source for the in situ generation of trifluoroperacetic acid. The advantages of this method are easy handling of a stable, solid oxidant; high yields and simple removal of excess reagents and by-products.

N-Oxides have important roles in organic synthesis, a recent example being their use as a surrogate for heterocyclic boronic acids in a Pd-catalyzed cross-coupling reaction.[1] A wide variety of N-oxidation reagents and conditions has been reported, for example, acetic acid and hydrogen peroxide ($AcOH/H_2O_2$),[2] *m*-chloroperbenzoic acid (*m*CPBA),[3] monoperoxyphthalic acid,[4] dioxirane[5] and Caro's acid (H_2SO_5).[6] Some methods also employ transition metal catalysts.[7] All of these routes are beset by limitations of incomplete reaction, contaminating by-products and high cost, in addition to awkward purifications or handling of hazardous liquid oxidizing agents.

Trifluoroperacetic acid (TFPA) is a powerful and effective oxidant due to the influence of the three electronegative fluorine atoms. It is typically generated from high-concentration (60–90%)



Scheme 1. Mechanism for the N-oxidation of heterocyclic compounds with UHP and TFAA.

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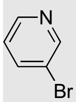
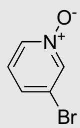
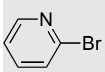
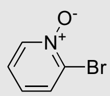
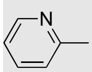
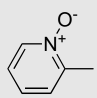
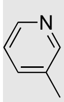
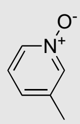
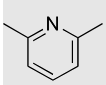
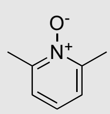
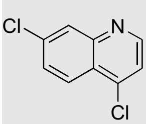
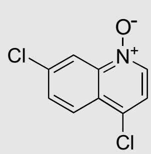
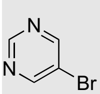
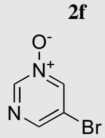
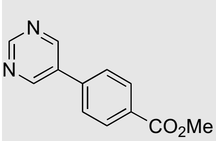
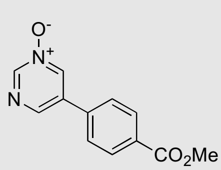
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.124

aqueous hydrogen peroxide,[8] which is unstable, hazardous to transport and requires specialist handling. Herein, we report an adaptation of a Baeyer–Villiger oxidation procedure[9] to the preparation of heterocyclic N-oxides. Urea·hydrogen peroxide (UHP), an odourless, white solid which contains 35% of H_2O_2, acts as hydrogen peroxide source for the in situ generation of trifluoroperacetic acid in the presence of trifluoroacetic anhydride (TFAA). The process is outlined in Scheme 1. A significant advantage of this method over the alternative reagents cited above is that all the reagents and by-products are freely soluble in water. This means they can be separated from the desired reaction products by partition between water and an organic solvent such as dichloromethane.

The influence of solvent on the success of the conversion was paramount. The reaction involves polar and ionic species that are insoluble in low-polarity organic solvents, and also intermediates that are sensitive to water or alcohols. Chloroform and 1,4-dioxane (polarity index 4.1 and 4.8, respectively)[10] were found to possess suitable physical and chemical properties—stability, solubility of reagents and boiling point. The yields of N-oxidation are shown

Table 1
N-Oxidation of heterocyclic compounds

Substrate	Product	Yield[a] (%)	
		$CHCl_3$ solvent	Dioxane solvent
 **1a**	 **2a**	93 (90)	100 (97)
 **1b**	 **2b**	97 (93)	100 (97)
 **1c**	 **2c**	100 (96)	100 (96)
 **1d**	 **2d**	100 (94)	100 (95)
 **1e**	 **2e**	100 (96)	100 (95)
 **1f**	 **2f**	95 (86)	98 (88)
 **1g**	 **2g**	100 (95)	100 (96)
 **1h**	 **2h**	90 (81)	No reaction

[a] Conversion determined by ^{1}H NMR; isolated yields are shown in parentheses.

in Table 1.[11,12] It is apparent that 1,4-dioxane generally increased the yield of the N-oxide, although pyrimidine **1h** was not oxidized at all. The reason for this remains unclear.

The generality of the method is demonstrated by the range of pyridine, quinoline and pyrimidine substrates converted (Table 1). For heterocyclic compounds poorly oxidized by *m*CPBA and other reagents because of electronic and steric hindrance, significantly improved yields were achieved. For example, the yield of 5-bromopyrimidine-N-oxide **2g** with *m*CPBA is just 29%[13] and reported yields of quinoline-N-oxide **2f** are, respectively, 35% or 50% when using H_2O_2/Ti-MCM-41[14] or $RuCl_3$/bromamine-T.[15] Even for severely hindered biarylpyrimidines and pyridines, improved conversion rates were achieved over alternative reagents, and the straightforward purification rendered these preparatively valuable procedures.

In summary, an improved, safe and convenient method has been developed for N-oxidation. In most cases, very high conversion rates were achieved; even so, a major advantage of this method is that the products are easy to isolate, so the reaction is useful even for sterically compromised substrates that are usually difficult to oxidize.

Acknowledgement

This work was supported, in part, by a project grant from the Association for International Cancer Research, St. Andrews, UK.

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11. *General method for* **2a**. In a typical procedure, K_2CO_3 (20 mmol) and UHP (10 mmol) were stirred in dry 1,4-dioxane or $CHCl_3$ (100 ml) for 1 h, then TFAA (10 mmol) was added dropwise below 12 °C. The mixture was allowed to reach rt, the heterocyclic compound (1 mmol) added and the mixture stirred overnight at 50 °C (1,4-dioxane, if used, was then removed by evaporation and replaced with DCM). The mixture was washed with water (50 ml), the organic layer dried over $MgSO_4$ and the solvent removed by evaporation to produce a yellow oil, 0.179 g (97%) shown to be a single compound by high-field NMR. ^{1}H NMR (600.17 MHz, $CDCl_3$), 8.34 (s, 1H), 8.13 (d, *J* = 5.5 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.15 (m, 1H). ^{13}C NMR (150.91 MHz, $CDCl_3$) 140.98, 138.1, 128.8, 126.1, 120.6. MS (ES+): *m*/*z* 176/174 (100%) $(M+H)^+$, 124 (55%), 42 (25%).
12. N-Oxide **2h** was prepared following the general method using chloroform as solvent and purified by column chromatography (silica gel, chloroform/methanol 95:5) to give 0.186 g (81%) as a white solid, mp 165–166 °C. ^{1}H NMR (600.17 MHz, $CDCl_3$), 8.98 (s, 1H), 8.59 (s, 1H), 8.45 (s, 1H), 8.19 (d, *J* = 7.4 Hz, 2H), 7.62 (d, *J* = 7.4 Hz, 2H), 3.95 (s, 3H). ^{13}C NMR (150.91 MHz, $CDCl_3$) 166.0, 148.6, 142.1, 141.9, 136.0, 134.9, 132.0, 131.0, 127.3, 52.6. MS (ES+): *m*/*z* 231 (100%) $(M+H)^+$, 214 (50%), 183 (60%), 162 (60%); IR (KBr): 3350 (O–H), 3050m (Ar, C–H), 2950m, 1725s (C=O), 1275s (C–O) cm^{-1}. CHN: found: C, 62.40; H, 4.51; N, 11.79. $C_{12}H_{10}N_2O_3$ requires: C, 62.60; H, 4.38; N, 12.17.
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