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ORIGINAL PAPER

Catalyst-free and selective oxidation of pyridine derivatives and tertiary amines to corresponding *N*-oxides with 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane

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Abstract The catalyst-free oxidation of various pyridine derivatives and tertiary amines to their corresponding *N*-oxides with 1,1,2,2-tetrahydroperoxy-1,2-diphenylethane as an efficient oxidant has been developed. The methodology proved to tolerate a number of functional groups. The reactions proceeded smoothly under solvent-free and mild conditions at room temperature. All the products were easily extracted from the reaction mixtures in excellent yields.

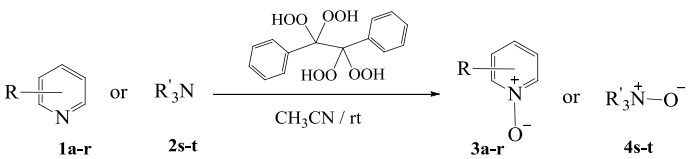
Graphical abstract The catalyst-free oxidation of various pyridine derivatives and tertiary amines to their corresponding *N*-oxides with 1,1,2,2-tetrahydroperoxy-1,2-diphenylethane as an efficient oxidant has been developed. The methodology proved to tolerate a number of functional groups. The reactions proceeded smoothly under solvent-free and mild conditions at room temperature. All the products were easily extracted from the reaction mixtures in excellent yields.

Keywords Oxidation · Pyridine-*N*-oxide · 1,2-Diphenyl-1,1,2,2-tetrahydroperoxyethane · Catalyst-free

Introduction

Heterocyclic *N*-oxides such as pyridine-*N*-oxide (PNO) and its derivatives represent an important class of compounds with ever-increasing importance owing to their usefulness as synthetic intermediates and biological value [1, 2]. Also, these compounds have been used as oxidants, auxiliary agents, protecting groups, and ligands in metal complexes and catalysts [3–7], and as useful reagents in radical decarboxylations [1, 2]. In addition, a wide variety of pyridine-*N*-oxides have been explored which exhibit anti-HIV activity [8–10]. A number of pyridine-*N*-oxides such as pyridine-*N*-oxide congener JPL-133 have been known as active inhibitors towards HIV-1 strains targeting HIV-1 reverse transcriptase (RT) and/or HIV-2 strains [8–11]. Also, other closely related pyridine-*N*-oxide derivatives are known which act against human cytomegalovirus.

The methods described in the literature for preparation of pyridine-*N*-oxides are usually accomplished employing peracids [12], such as peracetic acid, *m*-chloroperbenzoic acid (MCPBA) [13–16], magnesium monoperphthalate



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[17], esters of *N*-hydroxy-2-thiopyridone [18], HOF.CH_3N complex [19], or through cycloaddition reactions [20–23], and by ring transformation of isoxazoles [24].

Over the last few decades, several approaches to PNO have been developed using metal-based catalysts, aqueous hydrogen peroxide, and molecular oxygen as oxidants desirable to the chemical industry due to the minimized waste production associated with the stoichiometric reagents [25–30]. However, many of these catalysts are toxic and/or expensive which typically require special conditions to produce reasonable yields. Dioxiranes have been reported as versatile oxidizing agents to quantitatively and preferentially oxidize the aromatic azines such as pyridines and quinolines to the corresponding *N*-oxides [31–34].

Regarding the world-wide increasing concern on the environmental care, the scientists are encouraged to develop more eco-friendly processes which replace the hazardous catalysts and reagents with more benign and green solid catalysts. In the present research, we have developed a convenient and catalyst-free approach for the conversion of various pyridine derivatives and tertiary amines to their corresponding *N*-oxides using 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane as an effective and high potent green oxidant.

Experimental setup

Materials and instrumentation

Material and instruments

Chemicals were purchased from Merck chemical company and used without further purification. FT-IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets). The NMR spectra were recorded on 90 MHz JEOL FX 90Q, 200 MHz Varian and 400 MHz BRUKER spectrometers in $CDCl_3$ or DMSO-d6 solutions using TMS as internal standard. Melting points were determined in open capillary tubes with a Stuart SMP3 apparatus and were uncorrected.

Caution Although we did not encounter any problem with 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane and other hydroperoxides, it is potentially explosive and should be handled with precautions; all reactions should be carried out behind a safety shield inside a fume hood and transition metal salts or heating should be avoided.

Typical preparation of 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane

Following our previously reported procedure [40], this compound was prepared from $SbCl_3$-catalyzed reaction of benzil with 30 % aqueous H_2O_2 as described below (Scheme 1).

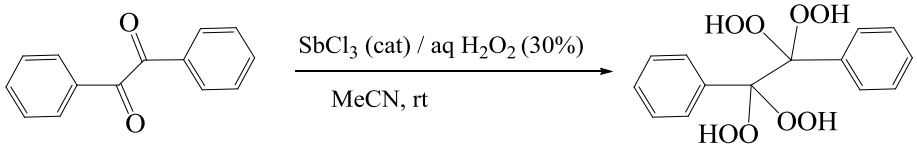
To a stirred solution of benzil (210 mg, 1 mmol) in CH_3CN (5 mL) was added $SbCl_3$ (23 mg, 0.1 mmol) and the resulting mixture was stirred for 5 min at room temperature. Then, aqueous 30 % H_2O_2 (5 mmol) was added to the reaction mixture and let to stir for 24 h at room temperature. After completion of the reaction as monitored by TLC, water (5 mL) was added and the product was extracted with EtOAc (3 × 5 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica-packed column chromatography (hexane–EtOAc) to afford pure product in 97 % yield (300 mg); mp 97–100 °C. Similarly, other *gem*-dihydroperoxides examined in Table 2 for comparison were prepared following the same procedure.

Typical procedure for oxidation of pyridines and tertiary amines to corresponding *N*-oxides

To a solution of pyridine derivative **1** or tertiary amine **2** (1 mmol) in acetonitrile (5 mL) was added 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane (1 g, 3 mmol). The resulting mixture was stirred at room temperature for an appropriate time (Table 2). After completion of the reaction as monitored by TLC, the reaction mixture was diluted with toluene (10 mL) and water (6 mL). The aqueous layer which contained the product was separated from the organic layer and evaporated under reduced pressure to leave the product. The products were characterized on the basis of their melting points, elemental analysis and IR, ^1H NMR and ^{13}C NMR spectral analysis.

Results and discussion

In continuation of our ongoing research on the synthesis of various hydroperoxides [35–40], and their applications as high potent oxidants for various organic transformations [41–48], we were encouraged to investigate the hitherto unexplored oxidative potential of 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane for oxidative conversion of pyridines



Scheme 1 $SbCl_3$-catalyzed synthesis of 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane

Scheme 2 Oxidation of pyridine derivatives and tertiary amines to corresponding *N*-oxides with 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane

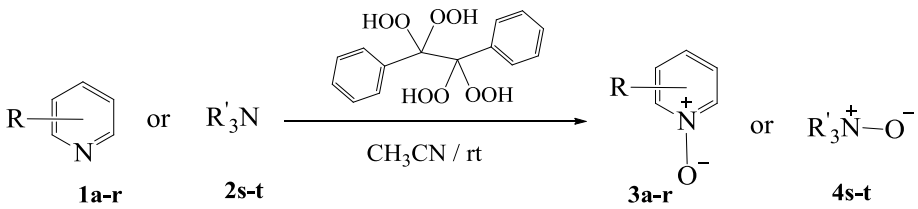


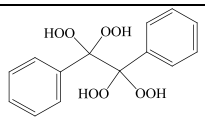
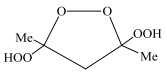
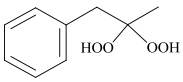
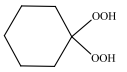
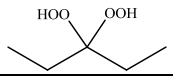
Table 1 Screening the conditions of the model oxidation of pyridine 1a to pyridine-*N*-oxide 3a with 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane

Entry	Solvent	Oxidant (mmol)	Time (min)	Yield (%)[a]
1	*n*-Hexane	3	120	25
2	Et_2O	3	120	45
3	EtOAc	3	60	65
4	CH_3CN	3	3	98
5	CH_3CN	4	8	95
6	CH_3CN	2	15	65

Conditions: pyridine (1 mmol), solvent (5 mL), r.t

[a] Isolated yield

Table 2 Comparison of oxidative activity of 1,2 diphenyl-1,1,2,2-tetrahydroperoxyethane with some various gem-dihydroperoxides in the oxidation of pyridine to pyridine *N*-oxide

Entry	Oxidant	Time (min)	Yield (%)
1		3	98
2		120	42
3		180	30
3		240	trace
4		240	10

[a] Conditions: pyridine (1 mmol), oxidant (3 mmol), CH3CN (5 mL), r.t

and tertiary amines into their corresponding *N*-oxides. As shown in Scheme 1, various substituted pyridines **1** and tertiary amines **2** were reacted with 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane as an efficient oxidant. The reactions proceeded smoothly in acetonitrile at room temperature to afford the corresponding *N*-oxides **3** and **4**, respectively, in excellent yields (Scheme 2).

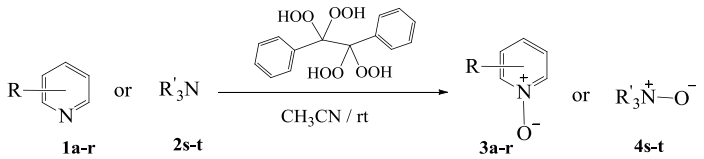
To screen the reaction parameters, we preliminarily reacted pyridine **1a** with 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane at room temperature as the model reaction. The effects of solvent and the oxidant loading on the reaction were screened using different solvents such as *n*-hexane, Et_2O, EtOAc, CH_3CN, with different amounts of the oxidant (Table 1). As seen in Table 1, we discovered that the best result in terms of the yield (98 %) and reaction time (3 min) were obtained when CH_3CN was used as the solvent of choice with using three equimolar amount of the oxidant (entry 4). We also noticed that, using higher and lower oxidant loadings resulted in reduced yields and higher reaction times (entries 5 and 6).

Moreover, a comparison for the efficiency of the oxidative activity of 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane in oxidation of pyridine with several other previously reported *gem*-dihydroperoxides [40, 43], under optimized conditions is presented. The results summarized in Table 2 show that 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane is superior in terms of yield, reaction time and easy extraction of the pyridine oxide from the reaction mixture by water due to its high solubility in water, whereas the remaining oxidant and the reproduced benzil in the reaction mixture both remained insoluble in water.

To establish the generality of the reaction, a series of pyridine derivatives **1a–r** and tertiary amine **2s–t** bearing different substituent groups were reacted with the oxidant 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane under the optimized conditions and the results are summarized in Table 3. In general, the reactions proceeded almost rapidly and smoothly to furnish the respective *N*-oxides **3a–q** and **4t** products in excellent and comparable yields (98–78 %) irrespective of the nature of the substituent groups on the aromatic ring. However, 2-benzoylpyridine **1j** and 3-benzoylpyridine **1k** exhibited no reactivity in this reaction which remained almost intact after a long reaction time (entries **j** and **k**). It is interesting to note that, in 2,2′-bipyridine (entry **n**), 4,4′-bipyridine (entry **o**) and 2,4,6-trimethylpyrimidine (entry **r**), the ring nitrogen atoms were both converted to *N*-oxides in this reaction.

On the basis of the formation of benzil and hydrogen peroxide which were detected in the course of the reaction, a plausible reaction mechanism proposed to explain the oxidation of pyridine derivatives and tertiary amines with 1,2-diphenyl-1,1,2,2-tetrahydroxyethane is depicted in Scheme 3. The reaction is likely initiated by nucleophilic attack of the pyridine nitrogen atom on the peroxidic oxygen of the oxidant to produce the intermediate **I** which

Table 3 Catalyst-free oxidation of pyridine derivatives and tertiary amines to corresponding *N*-oxides with 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane



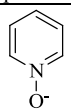
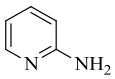
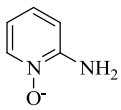
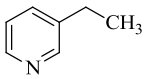
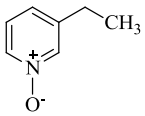
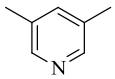
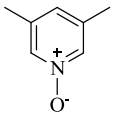
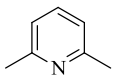
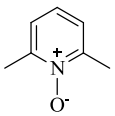
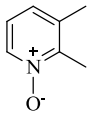
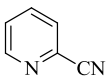
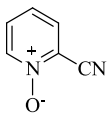
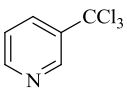
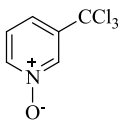
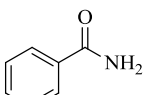
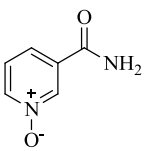
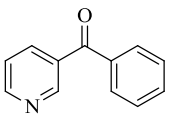
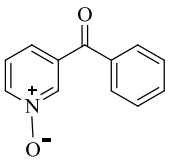
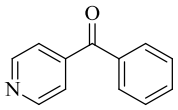
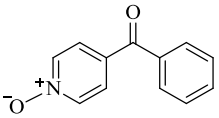
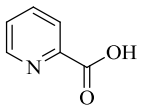
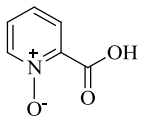
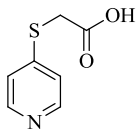
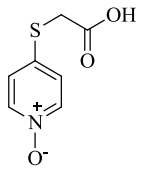
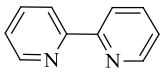
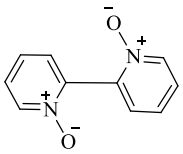
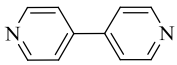
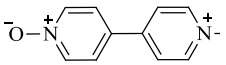
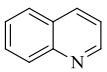
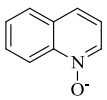
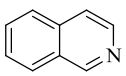
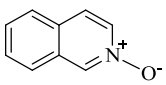
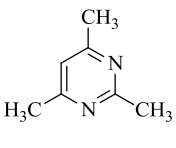
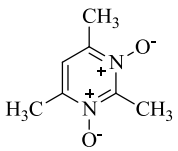
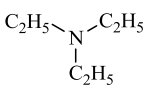
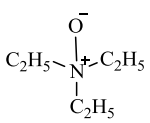
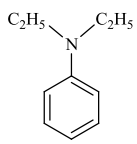
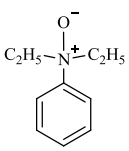
Entry	substrate	product	Time (min)	Yield (%)[b]	M.p. (ºC)[c]
a			3	98	67
b			10	89	166
c			15	91	120
d			8	87	105
e			12	86	115
f			15	78	102
g			5	93	69
h			8	90	180
i			14	87	294
j			120	trace	-

Table 3 continued

Entry	substrate	product	Time (min)	Yield (%)[b]	M.p. (ºC)[c]
k			120	trace	-
l			5	92	162[New]
m			15	93	146[New]
n			11	93	104[New]
o			9	97	120[New]
p			10	93	56
q			13	78	106
r			15	86	57
s			10	86	43
t			7	87	47

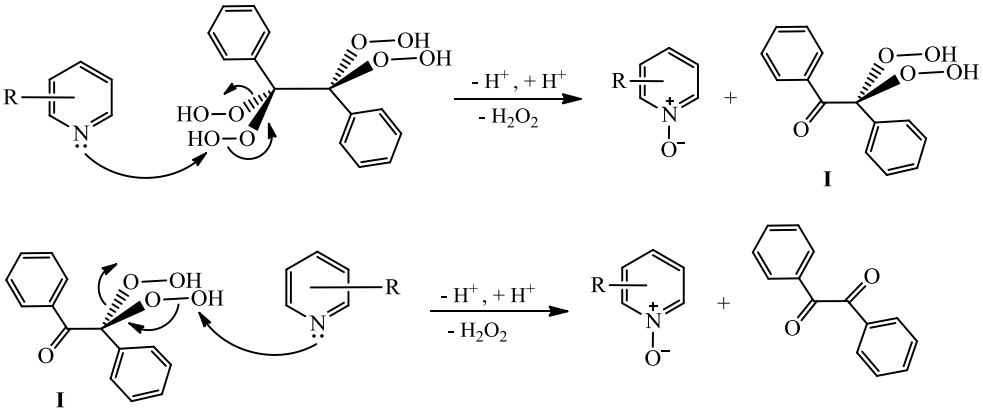
[a] Reaction conditions: substrate (1 mmol), 1,2-diphenyl-1,1,2,2-tetrahydroxyethane (3 mmol), CH3CN (5 mL), r.t

[b] Isolated yield

[c] The melting points of the known products were compared with those reported in the literature [10, 20, 30, 49–52]

undergoes similar reaction with a second molecule of pyridine to provide the expected *N*-oxide and benzil as identified in the reaction mixture.

Structures of the products were established on the basis of their physical and spectroscopic (IR, ^{1}HNMR, and ^{13}CNMR) analysis and those of the known products are



Scheme 3 Proposed mechanism for the *N*-oxidation of pyridine derivatives and tertiary amines with 1,2-diphenyl-1,1,2,2-tetrahydroperoxyethane

compared with the reported data (Table 2). The characteristic data for the new products **3l–o** are given below.

2-Carboxypyridine-1-oxide (3l): White solid, mp 160–162 °C; ^{1}HNMR (90 MHz, DMSO-d_6/TMS): δ 7.54 (t, 1H), 7.950 (t, 1H), 8.60 (d, 1H), 8.64 (d, 1H), 8.13 (t, 1H) ppm; ^{13}C NMR (100 MHZ, DMSO-d_6): δ 128.9, 127.9, 137.9, 149.8, 166.8, 167.8 ppm; IR (KBr) (ν_{max}/cm^{-1}): 3444, 3092, 1713, 1660, 1598, 1521, 1454, 1379, 1294, 998, 834; Anal. Calcd for $C_6H_5NO_3$: C, 51.79; H, 3.59; N, 10.07 %. Found: C, 51.53; H, 3.38; N, 9.92.

4-(Carboxymethylthio)pyridine-1-oxide (3 m): White solid, mp 144–146 °C; ^{1}HNMR (90 MHZ, $CDCl_3$/TMS): δ 8.671 (s, 1H), 7.860 (d, 4H), 2.48 (s, 2H) ppm; ^{13}C NMR (100 MHZ, DMSO-d_6): δ 33.0, 129.0, 129.1, 167.4, 167.7, 170.2 ppm; IR (KBr) (ν_{max}/cm^{-1}): 3424, 3160, 3073, 2960, 1720, 1693, 1620, 1564, 1482, 1326, 1298, 1053, 906, 651; Anal. Calcd for $C_7H_7NO_3S$: C, 45.40; H, 3.78; N, 7.56 %. Found: C, 45.24; H, 3.52; N, 7.38.

[2,2′-Bipyridine]-1,1′-dioxide (3n): Pink solid, mp 102–104 °C; ^{1}HNMR (90 MHz, DMSO-d_6/TMS): δ 7.513 (d, 2H), 8.248 (t, 2H), 8.753 (t, 2H), 9.033 (d, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 129.0, 129.7, 131.1, 133.3, 167.7; IR (KBr) (ν_{max}/cm^{-1}): 3436, 3068, 1602, 1583, 1454, 1326, 1274, 1175, 1026, 760, 619; Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.24; N, 14.89 %. Found: C, 63.13; H, 4.57; N, 15.19.

4,4′-Bipyridine-1,1′-dioxide (3o): Violet solid, mp 118–120 °C; ^{1}H NMR (90 MHz, DMSO-d_6/TMS): δ 7.804 (d, 4H), 8.750 (d, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 121.9, 145.0, 150.7 ppm; IR (KBr) (ν_{max}/cm^{-1}): 3424, 3044, 1626, 1374, 1124, 1012, 825, 665; Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.24; N, 14.89 %. Found: C, 63.43; H, 4.54; N, 14.49.

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