



## Trichloroacetonitrile–hydrogen peroxide: a simple and efficient system for the selective oxidation of tertiary and secondary amines



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### ABSTRACT

A variety of tertiary and secondary amines were efficiently oxidized to their corresponding *N*-oxides and nitrones, respectively, using the trichloroacetonitrile–hydrogen peroxide system. The in situ generated trichloromethylperoxyimidic acid is the active reagent for the oxidation processes.

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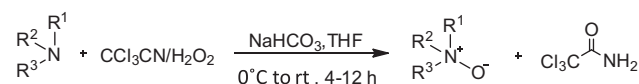
Hydrogen peroxide is an environmentally safe oxidant that produces only water as a by-product, however, it has low reactivity because of the poor leaving group activity of the hydroxide ion. Methods for activation of hydrogen peroxide have drawn the attention of numerous research groups. Hydrogen peroxide activation has been reported using transition metal catalysts,<sup>1</sup> or by reacting with peroxy-carboxylic acids,<sup>2</sup> and anhydrides.<sup>3,4</sup> Excessive use of corrosive acids, the application of transition metals, and production of stoichiometric amounts of acid by-products are some disadvantages of these processes. It has become clear that the use of an organic nitrile in combination with hydrogen peroxide or a urea-hydrogen peroxide addition complex in basic media are surprisingly active reagents for several oxidation reactions. Activation of hydrogen peroxide in the presence of acetonitrile and benzonitrile under controlled pH was first described by Payne.<sup>5</sup> The procedure involves the initial formation of a peroxy-carboximidic acid, which reacts with the double bond of an olefin to produce epoxides.<sup>6</sup> The in situ generated peroxy-carboximidic acid is too reactive to be isolated, but its existence has been proved by vibrational spectroscopy.<sup>7</sup> The by-product amide is obtained stoichiometrically from the reaction of peroxy-carboximidic acid with an alkene and hydrogen peroxide.<sup>5</sup> Studies on selective oxidation using peroxy-carboximidic acids have focused primarily on

Baeyer–Villiger oxidation of ketones into esters,<sup>8</sup> epoxidation of olefins,<sup>6,9</sup> and oxidation of amines.<sup>7</sup>

Trichloroacetonitrile–hydrogen peroxide has been reported to be a useful Payne-type oxidation system for the oxidation of *N*-alkylimines<sup>10</sup> and *N*-sulfonylimines<sup>11</sup> into oxaziridine derivatives. The present study has found that this system also has the ability to oxidize selectively tertiary and secondary amines into their corresponding *N*-oxides and nitrones. Tertiary amine *N*-oxides and nitrones are useful synthetic intermediates in heterocyclic chemistry.<sup>12,13</sup> They are important functional chemical building blocks for synthesizing pharmaceuticals such as HIV-1 inhibitors,<sup>14</sup> therapeutics in age-related diseases,<sup>15</sup> and are used as oxidants<sup>16</sup> and ligands in metal complexes.<sup>17</sup> Selective oxidations of tertiary and secondary amines to give *N*-oxides,<sup>18–20</sup> and nitrones<sup>12</sup> have been reported using several synthetic methods.

This letter describes the synthesis of *N*-oxides via oxidation of tertiary amines with the CCl<sub>3</sub>CN/H<sub>2</sub>O<sub>2</sub> (30 wt %, aqueous solution) system. The process is outlined in Scheme 1.

Initially, pyridine was chosen as a model substrate. This oxidation system is highly dependent on the nature of the solvent. Oxidation of pyridine was carried out in solvents such as methanol,



**Scheme 1.** *N*-oxidation of tertiary amines using trichloroacetonitrile–hydrogen peroxide.

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**Table 1**  
Optimization of the reaction conditions for the oxidation of pyridine to pyridine *N*-oxide<sup>a</sup>

| Entry | Nitrile/H <sub>2</sub> O <sub>2</sub> /NaHCO <sub>3</sub> | Nitrile          | Time (h) <sup>b</sup> | Yield (%) <sup>d</sup> |
|-------|---|------------------|-----------------------|------------------------|
| 1     | 0:2:0   | —                | 24                    | n.r                    |
| 2     | 0:2:0.5   | —                | 24                    | n.r                    |
| 3     | 1.1:1.1:0.5   | TCA <sup>c</sup> | 12                    | 85                     |
| 4     | 1.1:1.1:0   | TCA              | 12                    | 70                     |
| 5     | 2:2:0.5   | TCA              | 8                     | 88                     |
| 6     | 2:2:0   | TCA              | 12                    | 75                     |
| 7     | 2:2:0.5   | TCA              | 12                    | 88                     |
| 8     | 2:2:0.5   | MeCN             | 48                    | 80                     |
| 9     | 2:2:0.5   | BnCN             | 48                    | 70                     |
| 10    | 2:2:0.5 <sup>e</sup>                                      | TCA              | 12                    | 75                     |
| 11    | 2:2:0.5 <sup>f</sup>                                      | TCA              | 12                    | 80                     |

<sup>a</sup> All reactions were run with pyridine as the substrate, NaHCO<sub>3</sub> as the base, and THF as the solvent.

<sup>b</sup> 10 min at 0 °C, then warmed to rt.

<sup>c</sup> Trichloroacetonitrile.

<sup>d</sup> Isolated yield of pyridine *N*-oxide.


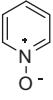
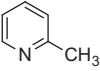
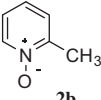
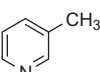
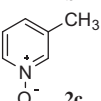
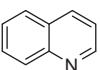
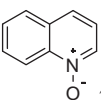
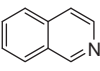
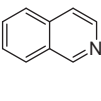
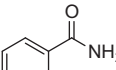
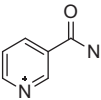
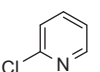
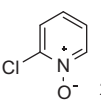

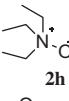

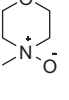

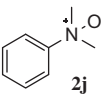
<sup>e</sup> Na<sub>2</sub>CO<sub>3</sub> was used as the base.

<sup>f</sup> K<sub>2</sub>CO<sub>3</sub> was used as the base.

ethanol, water, acetonitrile, dichloromethane, toluene, tetrahydrofuran, or free of any additional solvent. Although toluene and dichloromethane have been reported to be suitable solvents for the oxidation of imines using this system,<sup>10,11</sup> they only produce moderate activity (10% pyridine conversion). The best result was obtained in tetrahydrofuran, so it was decided to optimize the reaction conditions using THF as the solvent (Table 1). The oxidation of pyridine was carried out under vigorous stirring in a 10 mL glass flask placed in an ice-water bath. In a typical run, THF (2 mL), pyridine, (1 mmol) and different amounts of trichloroacetonitrile and base were mixed in the flask. Next, hydrogen peroxide (30 wt % aqueous solution) was added, and the mixture was allowed to warm to room temperature. After an appropriate amount of time, the solvent was evaporated under vacuum, and acetonitrile (2 mL) was added. The trichloroacetamide precipitate was removed by filtration and the filtrate was concentrated and purified by column chromatography.

A blank experiment showed that no oxidation occurred in the absence of trichloroacetonitrile, even in the presence of a base, and the pyridine remained unchanged after 24 h (Table 1, entries 1 and 2). In the presence of trichloroacetonitrile (1.1 mmol), the

**Table 2**  
Oxidation of tertiary and secondary amines using CCl<sub>3</sub>CN/H<sub>2</sub>O<sub>2</sub> (30%)<sup>a</sup>

| Entry | Substrate  | Product  | Time <sup>b</sup> (h) | Yield <sup>c</sup> (%) | Refs. |
|-------|--|--|-----------------------|------------------------|-------|
| 1     | <br><b>1a</b>   | <br><b>2a</b>  | 8                     | 88                     | 22    |
| 2     | <br><b>1b</b> | <br><b>2b</b> | 12                    | 78                     | 23    |
| 3     | <br><b>1c</b> | <br><b>2c</b> | 12                    | 75                     | 22    |
| 4     | <br><b>1d</b> | <br><b>2d</b> | 12                    | 80                     | 22    |
| 5     | <br><b>1e</b> | <br><b>2e</b> | 12                    | 75                     | 22    |
| 6     | <br><b>1f</b> | <br><b>2f</b> | 12                    | 65                     | 24    |
| 7     | <br><b>1g</b> | <br><b>2g</b> | 12                    | 70                     | 22    |
| 8     | <br><b>1h</b> | <br><b>2h</b> | 4                     | 85                     | 24    |
| 9     | <br><b>1i</b> | <br><b>2i</b> | 4                     | 89                     | 13    |
| 10    | <br><b>1j</b> | <br><b>2j</b> | 8                     | 80                     | 24    |

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