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The Urea–Hydrogen Peroxide Complex: Solid-State Oxidative Protocols for Hydroxylated Aldehydes and Ketones (Dakin Reaction), Nitriles, Sulfides, and Nitrogen Heterocycles

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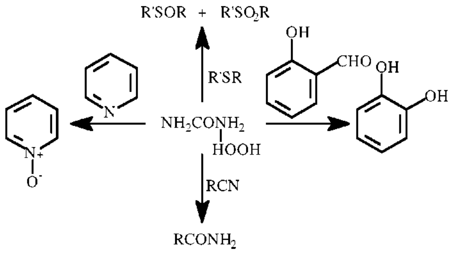
ABSTRACT



An efficient solid-state oxidation of organic molecules is described using a stable, inexpensive, and easily handled reagent, the urea–hydrogen peroxide adduct. The generality of the reaction has been demonstrated in oxidation of several molecules, namely hydroxylated aldehydes and ketones (to hydroxylated phenols), sulfides (to sulfoxides and sulfones), nitriles (to amides), and nitrogen heterocycles (to *N*-oxides).

The oxidation reaction in organic chemistry is a ubiquitous transformation, and numerous oxidizing agents are available to effect this conversion.[1−3] In fine chemical manufacture, environmental constraints are promoting the introduction of catalytic protocols which are replacing the use of stoichiometric amounts of inorganic oxidants, such as persulfate, bromate, and particularly metal oxidants such as chromic acid and permanganate.[4] As an example, metal-catalyzed oxidation with oxygen is employed for the conversion of petroleum hydrocarbons such as alkanes, alkenes, and aromatics to bulk industrial chemicals in processes that involve the use of heterogeneous (metal oxides, in the gas phase) and homogeneous (metal salts, in the liquid phase) catalysts. In the majority of the cases, the use of these toxic or hazardous reagents entails cumbersome and demanding isolation and purification procedures. Consequently, safer and simple protocols are required. The hydrogen peroxide−urea complex, normally called urea−hydrogen peroxide (UHP), is commercially available, can be easily prepared, and has been used in a variety of oxidative transformations in anhydrous organic solvents in the presence of carboxylic anhydrides.[5] So far, all these reactions with UHP have been conducted in organic solvents, including heterogeneous reactions using Ti−β-zeolites.[6] In developing an environ-

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(1) (a) Larock, R. C. *Comprehensive Organic Transformation*; VCH: New York, 1989; p 604. (b) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (c) Procter, G. In *Comprehensive Organic Synthesis*; Ley, S. V., Ed.; Pergamon: Oxford, U.K., 1991; p 7. (d) Griffith, W. P.; Joliffe, J. M. In *Dioxygen Activation and Homogeneous Catalytic Oxidation*; Simandi, L. L., Ed.; Elsevier: Amsterdam, 1991.
(2) *Aldrichim. Acta* **1988**, *21*, 52.
(3) Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015.
(4) Sheldon, R. A. *Top. Curr. Chem.* **1993**, *164*, 22.
(5) (a) Balicki, R.; Kaczmarek, L. *Synth. Commun.* **1993**, *23*, 3149. (b) Astudillo, L.; Galindo, A.; Gonzalez, A. G.; Mansilla, H. *Heterocycles* **1993**, *36*, 1075. (c) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Chem. Lett.* **1990**, 533 and references therein.

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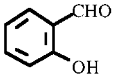
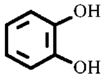
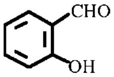
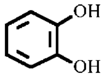
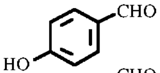
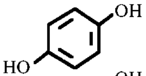
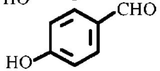
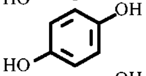
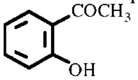
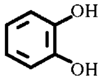
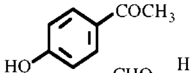
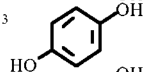
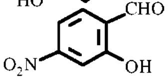
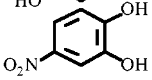
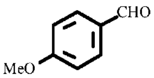
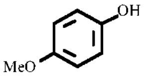
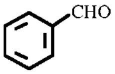
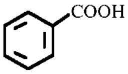
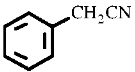
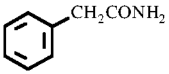
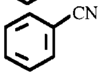
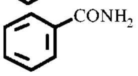
mentally friendly synthetic method, the elimination of the solvent components is especially important, as they are often used in large quantities.[7] Herein, we report an efficient unprecedented solid-state oxidation of organic molecules using urea–hydrogen peroxide adduct. A wide variety of molecules is easily oxidized, such as hydroxylated carbonyls (to hydroxylated phenols), sulfides (to sulfoxides and sulfones), nitriles (to amides), and nitrogen heterocycles (to *N*-oxides).

In organic synthesis, phenols and their derivatives are important substrates and are used extensively. The conversion of hydroxylated benzaldehydes to hydroxylated phenols has been achieved using alkaline hydrogen peroxide,[8] although other oxidants such as peroxybenzoic acid[9a] and peroxyacetic acid[9b] have often been used. In comparison to existing reagents, solid-state oxidation of hydroxylated benzaldehydes with urea–hydrogen peroxide adduct appears to be a superior alternative in terms of shorter reaction time, cleaner product formation, and ease of manipulation (Table 1).

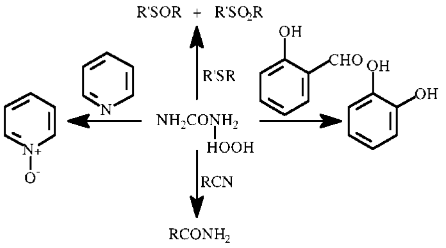
Table 1. Solid-State Oxidation of Aldehydes, Ketones, and Nitriles Using UHP

Entry	Starting Material	Product	Reaction conditions Temp. (°C)	Time	Yield[a]
1			55	1.5h	85
2			85	20 min	80
3			55	3h	83
4			85	75 min	82
5			85	1h	86
6			85	1h	80
7			85	25 min	83
8			85	45 min	80
9			85	20 min	95
10			85	1h	80
11			85	1.5h	85

[a] The yield refers to isolated product.

The hydrolysis of nitriles is often the method of choice for the preparation of carboxylic acid amides (Scheme 1). Traditional methods for the hydration of nitriles usually involve the use of strong mineral acids,[10] although some metals[11] and their oxides[11,12] and complexes[11,13] have also been used for the conversion of carbonitriles to amides. Comparatively better results have been obtained using reagents such as titanium tetrachloride in acetic acid,[14] potassium fluoride on alumina,[15] potassium hydroxide in *tert*-butyl alcohol,[16] sodium percarbonate in aqueous methanol,[17] and some hydroxylamine derivatives.[18] The hydrolysis under basic conditions is restrictively used in view of the hydrolysis of the ensuing amides to carboxylic acid under these conditions. The base-catalyzed hydrolysis of nitriles, originally reported by Radziszewski, works well for aromatic nitriles, but the reaction affords only dismal yields in the case of aliphatic nitriles.[19]

Scheme 1



In the intervening period, several modifications have been advanced wherein hydrogen peroxide is used in dimethyl sulfoxide[20] or under phase transfer conditions.[21] Many of these methods suffer from disadvantages of poor selectivity, longer reaction time, and the use of hazardous reagents.

In our quest for an eco-friendly hydrolysis of nitriles to amide, we now report a facile method using UHP under solvent-free conditions (entries 10 and 11, Table 1).

Selective oxidation of sulfides to sulfoxides or sulfones has been a challenging task for synthetic organic chemists. Among the prominent oxidants used for this conversion are hydrogen peroxide,[22] chromic acid,[23] nitric acid,[24] manganese dioxide,[23] ozone,[25] peracids,[26] selenium dioxide,[27] sodium periodate,[28] hypervalent iodine reagents,[29] sodium perborate,[30] and dinitrogen tetroxide.[31] Most of these processes suffer

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(6) Reddy, T. I.; Varma, R. S. *Chem. Commun*. **1997**, 471.

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(8) Hassall, C. H. *Org. React*. **1957**, *9*, 73.

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(10) (a) Steiger, R. E. *Org. Synth*. **1955**, *3*, 66. (b) Jones, J. H. *Comprehensive Organic Chemistry;* Pergamon Press: Oxford, U.K., 1979; Vol. 2, p 964.

(11) Zilberman, E. N. *Usp. Khim*. **1984**, *53*, 1523; *Chem. Abstr*. **1984**, *101*, 210082h.

(12) Liu, K. T.; Shih, M. H.; Huang, H. W.; Hu, C. J. *Synthesis* **1988**, 715.

(13) Diamond, S. E.; Grant, B.; Tom, G. M.; Taube, H. *Tetrahedron Lett*. **1974**, 4025.

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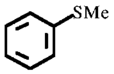
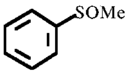
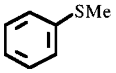
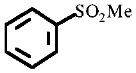
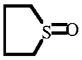
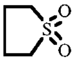
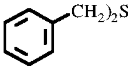
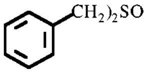
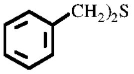
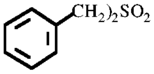
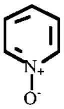
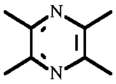
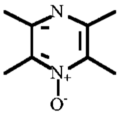
(20) (a) Sawaki, Y.; Ogata, Y. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 793. (b) Katritzky, A. R.; Pilarski, B.; Urogdi, L. *Synthesis* **1989**, 949.

(21) Cacchi, S.; Misiti, D. *Synthesis* **1980**, 243.

from drawbacks such as extended period of time, use of corrosive acids, hazardous peracids, and toxic metallic compounds. Consequently, there is a need for mild and selective methods for the efficient conversion of sulfide to sulfoxides or sulfones. The use of urea−hydrogen peroxide adduct under solvent-free conditions appears to be a viable and safer protocol. Our results for the general oxidation of sulfides to sulfoxides (entries 1, 3, 5, and 7) and sulfones (entries 2, 4, 6, and 8) and nitrogen heterocycles to their corresponding *N*-oxides (entries 9 and 10)[32] are summarized in Table 2.

Table 2. Solid State Oxidation of Sulfides and Nitrogen Heterocycles Using UHP

Entry	Starting Material	Product	Reaction conditions Temp (°C)	Time	Yield[a]
1			85	15 min	80[10]
2			85	1h	87
3	$[CH_3(CH_2)_3]_2S$	$[CH_3(CH_2)_3]_2SO$	85	10 min	85[13]
4	$[CH_3(CH_2)_3]_2S$	$[CH_3(CH_2)_3]_2SO_2$	85	45 min	90
5			85	7 min	87[09]
6			85	1h	88
7			85	30 min	87[11]
8			85	2h	90
9			85	45 min	87
10			85	45 min	92(5)[b]

[a] The yield refers to isolated product, and the results in brackets refer to sulfone. [b] The percentage yield was obtained from GC-MS; results in parentheses refer to dioxide.

Our summarized results for the solid-state oxidation of a variety of organic substrates in Tables 1 and 2 demonstrate the versatility of the UHP reagent under solvent-free conditions. In general, the reaction rate for hydroxylated benzaldehydes is faster when compared to that for hydroxylated acetophenones. Benzaldehyde upon oxidation affords only carboxylic acid and *p*-anisaldehyde gives *p*-methoxyphenol, whereas aliphatic aldehydes lead to the formation of complex products. In the case of nitriles, the reaction rate is faster for aliphatic nitrile, benzylnitrile, as compared to benzonitrile. The selective oxidation of sulfides to sulfoxides or sulfones can be achieved by varying the reaction time (Table 2). Alkyl sulfides get oxidized faster than the aromatic sulfide. Interestingly, no reaction occurs at room temperature for the aforementioned examples.[33,34]

In conclusion, this solvent-free oxidative protocol using an inexpensive, safe, and easily handled reagent, urea−hydrogen peroxide adduct, is a simple and efficient protocol that is applicable to a variety of organic molecules. The operational simplicity, rapid reaction rates, and formation of pure products in high yields at a very moderate temperature make this method superior to existing protocols.

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(33) **General Procedure for UHP Oxidation Reactions.** The starting material (2 mmol) was added to the finely powdered urea−hydrogen peroxide adduct (376 mg, 4 mmol) in a glass test tube, and the reaction mixture was placed in an oil bath at 85 °C for the specified time (Tables 1 and 2). After completion of the reaction, monitored by TLC (8:2 v/v, hexane:EtOAc), the reaction mixture was extracted into ethyl acetate and the combined extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford the crude product, which was purified by chromatography to deliver pure product, as confirmed by the spectral analysis.

(34) **Typical Procedure for Oxidation of Sulfides: Preparation of Methyl Phenyl Sulfoxide and Sulfone.** In a typical experiment, methyl phenyl sulfide (248 mg, 2 mmol) was added to the finely powdered urea−hydrogen peroxide adduct (376 mg, 4 mmol) in a glass test tube, and the reaction mixture was placed in an oil bath at 85 °C for 15 min for complete conversion of sulfide to sulfoxide with a trace amount (10%) of sulfone. For complete conversion of sulfide to sulfone, the reaction time was extended to 1 h (see Table 2). After completion of the reaction, monitored by TLC (8:2 v/v, hexane:EtOAc), the reaction mixture was extracted into ethyl acetate and the combined extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford the crude product, which was purified by chromatography on a silica gel column; fractions obtained with pure hexane as eluent afforded pure product (80% of sulfoxide), as confirmed by the spectral analysis.