Hydrogen Peroxide Oxidation of α-(*N*,*N*-Dialkyl)aminoketones

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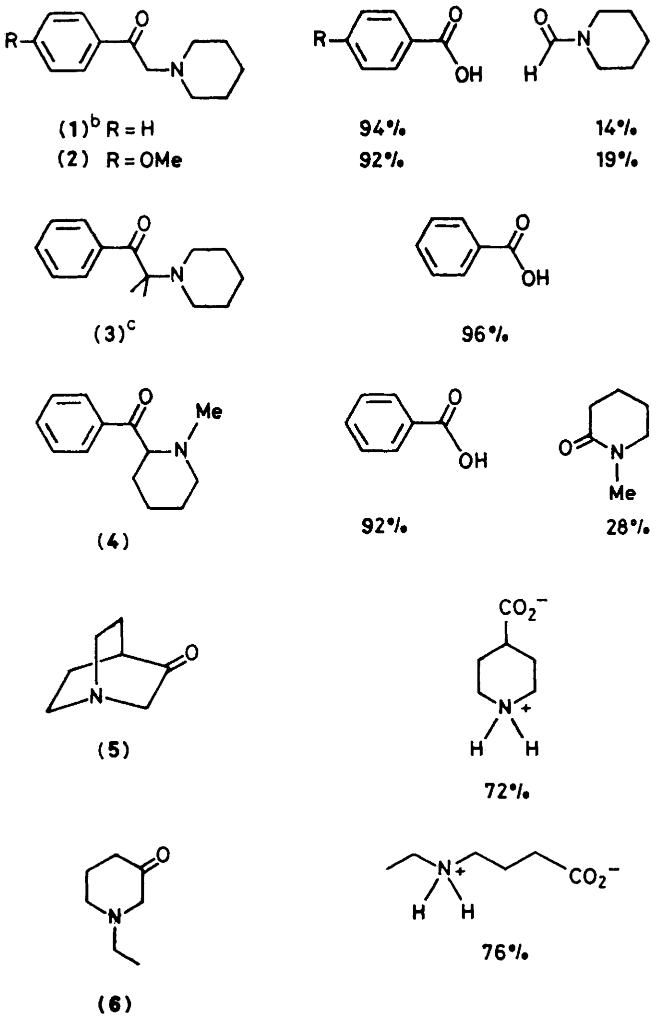
α-(*N*,*N*-Dialkyl)aminoketones are fragmented oxidatively by hydrogen peroxide, leading to carboxylic acids and products derived from iminium intermediates.

During the course of a study of alkaloid synthesis the amine oxide of 1-dimethylaminohexan-2-one was needed as a starting material. As a consequence the aminoketone was exposed to an oxidation with excess of hydrogen peroxide in methanol solution. As shown in equation (1), an unexpected, new reaction was encountered.

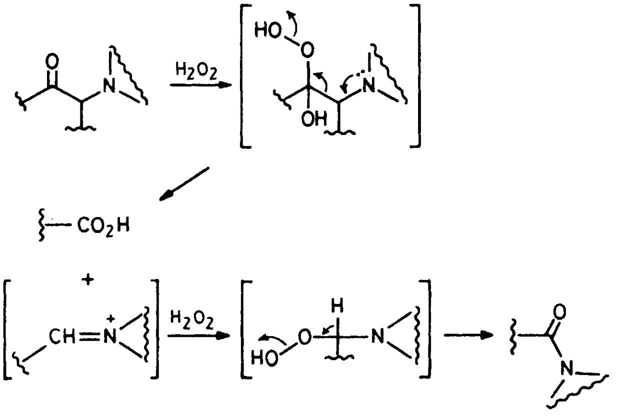


Scheme 1. Reaction of α-aminoketones with 30% H_2O_2 (10 equiv.) in ethanol.[a]
Aminoketone → Isolated products and yields

[a] Reaction times of 1—14 days except for (**5**) (2 h). [b] When the reaction mixture was treated with *N′*,*N*-diphenylethylenediamine and acetic acid, $CH_2PhNCH_2CH_2NPh$ in 47% yield was isolated. [c] When the reaction mixture was treated with 2,4-dinitrophenylhydrazine and sulphuric acid, the 2,4-dinitrophenylhydrazone of acetone was isolated in 54% yield.

$$Me[CH_2]_3COCH_2NMe_2 \rightarrow Me[CH_2]_3CO_2H + HCONMe_2 \quad \text{(only observed products)} \quad (1)$$

In order to ascertain the generality of this reaction, hydrogen peroxide oxidations of a variety of α-(*N*,*N*-dialkyl)-aminoketones were investigated [(**1**)—(**6**), Scheme 1]. Though carboxylic acid products were obtained in high to nearly quantitative yields; amides, when produced, were only formed in low yield. Other products, not isolated upon normal work-up, also resulted from these oxidations as is indicated by the trapping of formaldehyde and acetone for (**1**) and (**3**), respectively (footnotes b and c of Scheme 1).



Scheme 2

Other observations were made in an effort to gain further understanding of the reaction. When a methanol solution of α-(*N*,*N*-diethyl)aminoacetophenone was treated with 10 equiv. of hydrogen peroxide at 0 °C for 30 min and the reaction quenched by an iodide–thiosulphate solution, a 95% yield of benzoic acid was obtained. This made the possible intermediacy of an amine oxide unlikely, as the reaction of the deoxo-compound β-phenylethyldiethylamine with hydrogen peroxide for 5 h under identical conditions led to the recovery of 69% of starting amine and only an 18% yield of its amine oxide.

A mechanism that is consistent with these findings is given in Scheme 2. Addition of hydrogen peroxide to the ketone,[1] followed by a Grob fragmentation,[2] gives a carboxylic acid together with an iminium intermediate, which can be oxidized further to an amide.†

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References

1 *Inter alia.* P. R. Story, B. Lee, C. E. Bishop, D. D. Denson, and P. Busch, *J. Org. Chem.*, 1970, **35**, 3059.
2 C. A. Grob, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 535.
3 See, for example, H. O. House and R. L. Wasson, *J. Org. Chem.*, 1957, **22**, 1157.

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† An alternative mechanism, a Baeyer–Villiger reaction, was deemed less likely, given the inert nature of ketones towards oxidation with hydrogen peroxide and tertiary amines in alcoholic solution and given their known general reluctance to undergo hydroxide-induced oxidation with hydrogen peroxide.[3]