

Copper(II) mediated Aromatic Hydroxylation by Trimethylamine *N*-Oxide

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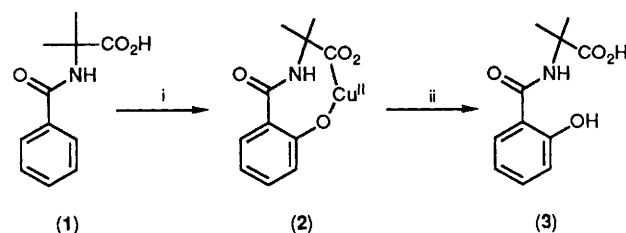
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Quantitative orthohydroxylation of *N*-benzoyl-2-methylalanine (**1**) occurs through its copper(II) salt oxidation by trimethylamine *N*-oxide; transitory formation of a Cu^{III} species is proposed.

Hydroxylation of aromatic compounds¹ by H₂O₂ either through electrophilic (H₂O₂/BF₃² or HF³) or free radical processes (Fenton's⁴ or Udenfriend's⁵ reagent) is usually not selective (partly because the introduction of an OH group activates the ring to further oxidation), except in the case of intramolecular processes leading to stable chelates ('oxidative coppering').⁶ On the other hand, pyrolysis of copper(II) benzoates into salicylates,⁷ which seems to occur *via* nucleophilic attack, is limited by a poor conversion ratio and drastic experimental conditions. In recent years, some examples of oxidation of copper ligands have indicated that the association of copper(I) ions with molecular oxygen⁸ or iodosylbenzene⁹ or copper(II) ions with H₂O₂¹⁰ can promote highly selective aromatic hydroxylation. In earlier papers,¹¹ we have shown how copper(III) species are responsible for various selective oxidations through their intramolecular evolution. We present here some preliminary results dealing with the interaction between copper salts and trimethylamine *N*-oxide (TMAO) as a new source of copper(III) entities and its application to selective and quantitative hydroxylation of aromatic derivatives.

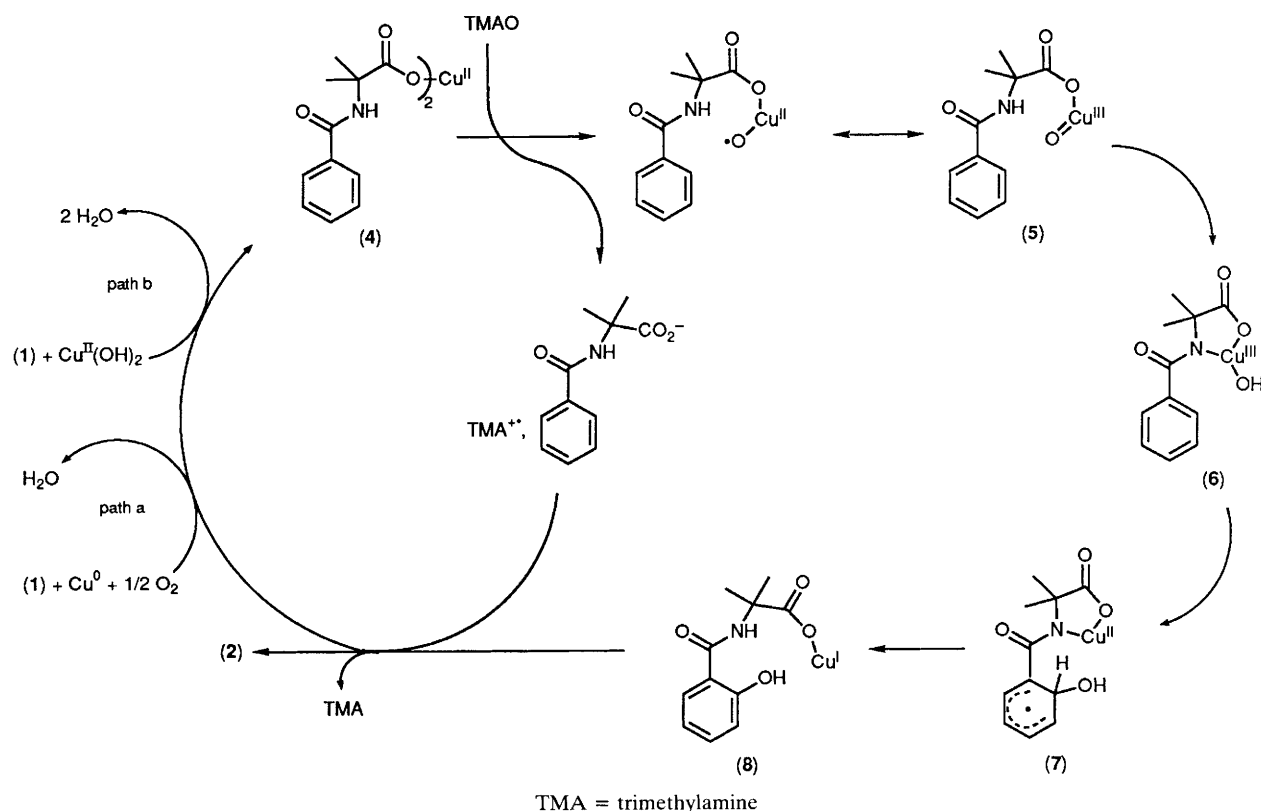
N-Benzoyl-2-methylalanine (**1**),¹² when heated in dry ace-

tonitrile under an oxygen atmosphere with metallic copper powder (1 equiv.) and TMAO (5 equiv.), is quantitatively converted into the blue copper(II) salt (**2**) of *N*-(2-hydroxybenzoyl)-2-methylalanine (**3**) which has been identified[†] after



Scheme 1. Phenyl orthohydroxylation of (**1**) by the Cu⁰/O₂/trimethylamine *N*-oxide system. *Reagents and conditions:* i, Cu⁰/O₂/TMAO, MeCN, 6 h, 75 °C; ii, HCl (0.5 M); ~100%.

[†] Spectral and analytical data are in agreement with the proposed structure as confirmed by comparison with an authentic sample (synthesized by condensing acetylsalicyloyl chloride with 2-methylalanine sodium salt).



Scheme 2. Proposed mechanism for (1) orthohydroxylation through the mono-electronic oxidation of its copper(II) salt (4) by trimethylamine *N*-oxide.

acid hydrolysis (Scheme 1). This orthoselective hydroxylation proceeds under mild conditions and constitutes the key step of a new route for transformation of benzoic acids into salicylic acids.

A series of control experiments according to the standard procedure demonstrates that each reactant is necessary for efficient operation: without Cu⁰ or O₂, no reaction can be observed; without TMAO, (1) is converted into its green copper(II) salt (4) which, after acid hydrolysis, releases the starting compound (1). On the other hand, if TMAO is added to (4), hydroxylation proceeds as in the standard procedure together with the renewal of copper corrosion. These facts demonstrate that (4) does not evolve spontaneously and is inert toward O₂ but its association with TMAO produces the active species responsible for hydroxylation. This has been confirmed by another experiment: in similar conditions but under an inert atmosphere (N₂), the Cu^{II}(OH)₂/TMAO couple is also able to promote the hydroxylation of (1) into (2).[‡]

Our results can be rationalized as follows (Scheme 2): the copper(II) salt (4), produced either by copper corrosion with O₂ (path a) or reaction of Cu(OH)₂ with (1) (path b), is oxidized by TMAO. The intramolecular evolution of the

resulting copper(III) species (5) is highly favoured by the proximity of the NH group, ionization of which allows the formation of the hydroxocopper(III) entity (6) according to the well known ability of amidic bonds to particularly stabilize Cu^{III} complexes.¹³ This hypothesis is confirmed by the fact that the *N*-methyl derivative of (1) is not hydroxylated under such conditions.

When the starting benzamide (1) is 3'-fluoro-substituted, the regioselectivity of the hydroxylation gives an *ortho/para* ratio (relative to fluorine) of 0.41,[§] which is quite in agreement with an HO• type attack and not an HO⁺ type (Fenton's hydroxylation¹⁴ and nitration¹⁵ of fluorobenzene give, respectively, *o/p* 0.41 and 0.08). Therefore, the cleavage of the Cu^{III}-OH bond of (6) must be homolytic rather than heterolytic and the transfer of HO• is followed by the rapid intramolecular redox reaction (7) → (8). The copper(I) salt (8) is finally reoxidized by the aminium radical TMA^{•+} into (2) with concomitant liberation of trimethylamine (TMA) which has been trapped as its hydrochloride from gaseous effluents.[¶]

[§] Determined by ¹H NMR spectroscopy (250 MHz, [2H₆]DMSO) of the crude product obtained after acid hydrolysis (quantitative yield). *Selected data for N*-(3-fluoro-2-hydroxybenzoyl)-2-methylalanine: 1.49 (s, 6H, 2 Me), 6.88 (ddd, *J*_F 4.9, *J*_{H4} 8.1, and *J*_{H6} 8.0 Hz; H₅ arom.), 7.38 (ddd, *J*_{H5} 8.1, *J*_{H6} 1.0, and *J*_F 10.8 Hz; H₄ arom.), 7.80 (dd, *J*_{H4} 1.0 and *J*_{H5} 8.0 Hz; H₆ arom.), 8.90 (s, 1H, NH), 11.92 and 12.53 (2 br. s, 2H, 2 OH). *N*-(5-fluoro-2-hydroxybenzoyl)-2-methylalanine: 1.49 (s, 6H, 2 Me), 6.93 (dd, *J*_{H4} 9.0 and *J*_F 4.7 Hz; H₃ arom.), 7.26 (ddd, *J*_{H3} 9.0, *J*_F 8.5, and *J*_{H6} 3.1 Hz; H₄ arom.), 7.77 (dd, *J*_{H4} 3.1 and *J*_F 9.9 Hz; H₆ arom.), 8.87 (s, 1H, NH), 11.92 and 12.53 (2 br. s, 2H, 2 OH).

[¶] Characterized by ¹H NMR spectroscopy and compared with an authentic sample.

[‡] This second method (Scheme 2, path b) is as efficient at the beginning of the reaction [(3) is the only product detected by HPLC] but very slow to reach completion. This can be attributed to the competition for complexation of (4) between TMAO and H₂O, the latter being here produced twice as much as in the corrosion system (path a, see Scheme 2). A similar effect is observed when H₂O is added to the reactive medium or when TMAO·2H₂O is used (formation of a brown insoluble precipitate).

The great stability of (2) in the experimental conditions accounts for the high yield obtained.

Together with the preceding Communication,¹⁶ this is the first example of a copper(II) salt oxidation by an amine *N*-oxide^{||} and it seems to proceed through a one-electron transfer, as has been observed in some cases with iron(III) porphyrin imidazole complexes.¹⁷ This original reaction promises a number of developments, as much for elaboration of new chemical oxidizing preparative systems as for the studies of copper mono-oxygenases (phenylalanine hydroxylase¹⁹ in particular) and their models.

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^{||} To our knowledge, the only previous report of oxidative activity of the Cu/amine *N*-oxide couple describes an intramolecular diphenol oxidative coupling with copper(I) chloride.¹⁸