Ortho-Aryloxylation of *N*-Substituted Benzamides: a New Oxidizing Process Induced by the Copper(II)/Trimethylamine *N*-Oxide System

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The oxidation of *N*-(2-hydroxy-4-nitrophenyl)benzamide **1** by the Cu^{II}/trimethylamine *N*-oxide couple has been studied. Under experimental conditions where the concentration quotient, $\alpha = [1]/[Cu]$, of starting benzamide to copper is maintained as low as possible, the benzamide is *ortho*-hydroxylated into the corresponding salicylamide with 88% yield of isolated product. On the other hand, when α is kept as high as possible, a new oxidation process leads to an oxidative cascade: the benzamide is *ortho*-aryloxylated by the phenolic group of a second molecule of itself to afford a 2-aryloxy-*N*-(2-hydroxy-4-nitrophenyl)benzamide, which in turn can undergo another *ortho*-aryloxylation. In intermediate conditions both processes are in competition, thus providing composite compounds such as a 6-aryloxy-2-hydroxy-*N*-(2-hydroxy-4-nitrophenyl)benzamide. Transitory formation of, respectively, Cu^{III}-OH and Cu^{III}-OAr complexes is suggested to be responsible for these *ortho*-selective oxidizing processes. Finally, these results show that the 2-(*N*-amido)-5-nitrophenol group (which is the copper ligand) is a good mediator for the oxidation of a covalently linked aromatic nucleus by the Cu^{II}/TMAO system.

We have recently reported[1,2] a selective and efficient copper-mediated *ortho*-hydroxylation of *N*-substituted benzamides by trimethylamine *N*-oxide (TMAO). The reaction proceeds by oxidation of their corresponding copper(II) salts by TMAO and was assumed to take place through the transitory formation of a hydroxy-copper(III) complex. The intramolecular evolution of the latter accounted for the total *ortho*-selectivity of the oxidation process.

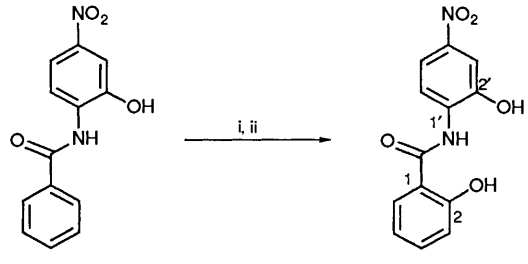
One of the keys to achieving good efficiency in the reaction is the choice of the copper ligand which is present in the substrate. Its major role is to induce the formation of the hydroxylating species (Cu^{III}-OH) at a proper distance from the aromatic nucleus. We have already described one class of substrate for which the copper ligand was the *N*-amido-2-methylalanine group (–CONH–CMe_2–CO_2H).

In the course of our researches concerning the mechanism of the reaction, and aiming at the development of some new copper-ligands as mediators for the oxidation of aromatics, we studied the behaviour of *N*-(2-hydroxy-4-nitrophenyl)benzamide **1**[3] when submitted to the action of the Cu^{II}/TMAO couple.

Results

In previous papers[1,2] we reported two different ways of introducing copper(II) ions: either through corrosion of metallic copper by the starting acidic compound under oxygen atmosphere or by addition of copper(II) hydroxide. The former system is generally better because it produces only half the quantity of poisoning water compared with the latter system.

Oxidation by the Cu^0/O_2/TMAO *System.*—*N*-(2-Hydroxy-4-nitrophenyl)benzamide **1** was submitted to the oxidative Cu^0/O_2/TMAO system under analogous experimental conditions to those previously described[2] for the other benzamidic substrates. A suspension of benzamide **1** and metallic copper powder (1.2 mol equiv.) was heated at 75 °C in a 0.5 mol dm^{-3} anhydrous solution of TMAO (5 mol equiv.) in acetonitrile under oxygen. After complete disappearance of the starting compound **1** (10 h), mild acidic hydrolysis of the dark brown reaction mixture produced the salicylamide **2** in 80% yield of isolated product.



1 **2**

Reagents and conditions: i, Cu^0/O_2/TMAO, MeCN, 75 °C; ii, H_3O^+

Thus, like *N*-benzoyl-2-methylalanine, the benzamide **1** was converted into the corresponding salicylamide in fairly good yield, thereby showing that the 2-(*N*-amido)-5-nitrophenol group is also a mediator ligand for the *ortho*-hydroxylation of aromatics by the Cu^0/O_2/TMAO system.

However, HPLC monitoring of the reaction showed the formation of two minor products **3** and **4**. The first one is mainly produced at the very beginning of the reaction while the second one appears mostly at the end of the reaction (see Fig. 1).

Oxidation by the $Cu^{II}(OH)_2$/TMAO *System.*—A suspension of substrate **1** and copper(II) hydroxide (1.2 mol equiv.) in an anhydrous 0.5 mol dm^{-3} solution of TMAO (5 mol equiv.) in acetonitrile under a gaseous current [either O_2 or N_2, in order to remove trimethylamine (TMA) continuously from the medium] was heated at 75 °C. After complete conversion of compound **1**, formation of the same compounds **2**, **3** and **4** was observed. However, the proportions of the products were completely different compared with those obtained with the former system (corrosion): production of compounds **3** and **4** increased at least six-fold whereas the yield of *ortho*-hydroxylated product **2** fell 30% (see Fig. 2).

Here again, HPLC monitoring of the reaction emphasized the preferential formation of compound **3** at the beginning of the reaction and of compound **4** at the end. Furthermore, when

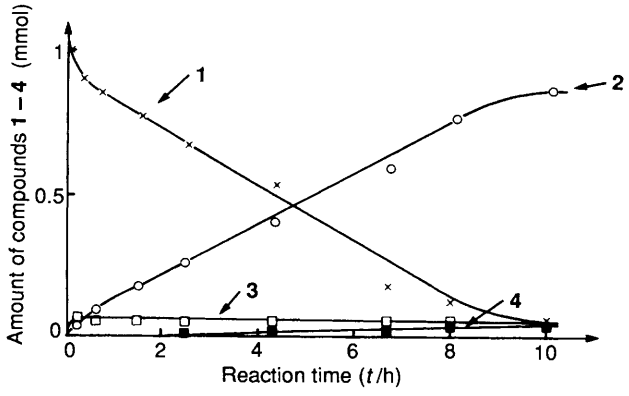
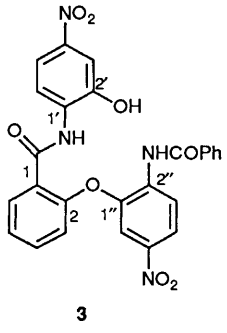


Fig. 1 HPLC monitoring of the oxidation of the benzamide **1** by the Cu^0 (1.2 mol equiv.)/O_2/TMAO (5 mol equiv.) system with simultaneous introduction of all the reactants, and temperature set at 75 °C [here as in following Figs. 2 and 3, the quantities of compounds **3**, **4** and **6** (Fig. 3) have been respectively multiplied by 2, 2 and 3, their degree of condensation from starting benzamide **3**]

the experiment was continued after complete conversion of starting compound **1**, although formation of *ortho*-hydroxylated product **2** had stopped, production of **4** still continued while product **3** disappeared.

We have been able to purify compounds **3** and **4** by preparative HPLC. Their structures have been elucidated by NMR spectroscopy and confirmed by mass spectroscopy.



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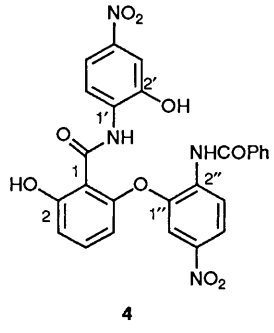

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Consequently, we were confronted with two competitive oxidative processes: one is the already well known *ortho*-hydroxylation reaction which leads to compounds **2** and **4** from, respectively, **1** and **3**; the other one is the '*ortho*-aryloxylation' of substrate **1** by another molecule of substrate, giving rise to the formation of compound **3**. This oxidation process is quite original; the only example of a related oxidation we have found in the literature is the intramolecular conversion of β-binaphthol into binaphthylene dioxide,[4] which was also mediated by copper(II) ion (CuO) in nitrobenzene (presumed to be involved as an oxygen carrier).

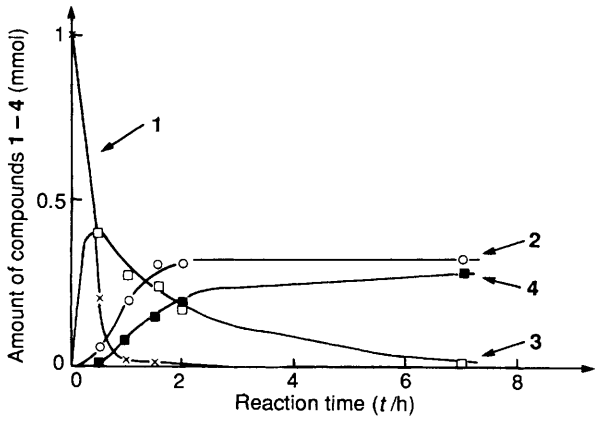


Fig. 2 HPLC monitoring of the oxidation of the benzamide **1** by the $Cu(OH)_2$ (1.2 mol equiv.)/O_2/TMAO (5 mol equiv.) system with simultaneous introduction of all the reactants, and temperature set at 75 °C

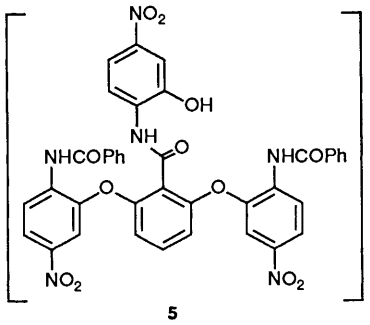
Experiments varying the Introduction Method of Copper and Substrate **1**.—(a) When benzamide **1** was slowly added (8 h) to a suspension of metallic copper powder (1.2 mol equiv.) in an anhydrous solution of 0.5 mol dm^{-3} TMAO (5 mol equiv.) in acetonitrile under oxygen at 75 °C, only 5% of aryloxylation products **3** and **4** could be detected (HPLC) and the yield of isolated product **2** rose to 88%.

This improvement has to be attributed to the lower concentration of substrate **1** during the oxidizing process compared with the first above described experiment where all the substrate was added at once.

(b) On the other hand, when a quantity of copper(II) hydroxide (0.3 mol equiv.) was slowly (5 h) added to a dry solution of substrate **1** and 0.5 mol dm^{-3} TMAO (5 mol equiv.) in acetonitrile at 55 °C, neither of the hydroxylated products **2** and **4** could be detected. If the reaction was stopped after 30% conversion of substrate **1**, the yield of aryloxylated product **3** was quantitative as determined by NMR analysis of the crude material obtained after acidic hydrolysis. However, when the reaction was allowed to continue, the yield of compound **3** reached a plateau value and several secondary products appeared thereafter (Fig. 3). Among these, compound **6** has been isolated by preparative HPLC. Its NMR analysis, correlated with NMR data for compounds **1**–**4**, led us to propose the structure shown.

Formation of this product is most probably due to a Smiles-type rearrangement from an *ortho,ortho'*-bisaryloxylated intermediate **5**. This can be explained by the higher nucleophilic character of the amidic function of postulated intermediate **5** compared with that of compound **3** and is supported by a very similar example previously reported by Tozer and Smiles.[5]

Therefore, from this last experiment, we can conclude that when the copper(II) ion concentration is maintained as low as possible, aryloxylation becomes the major oxidation process.



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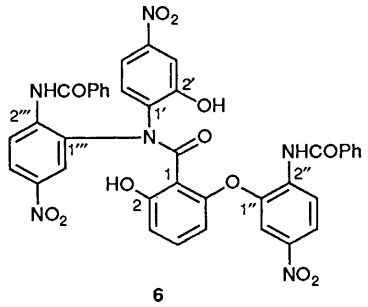
Smiles



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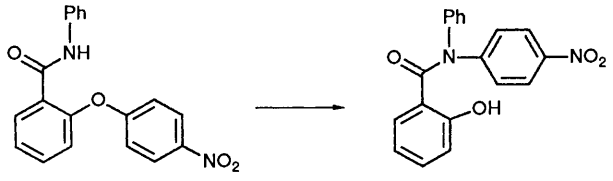


Reagents and conditions: NaOH, aq. acetone, 18 °C, 30 min (ref. 5)

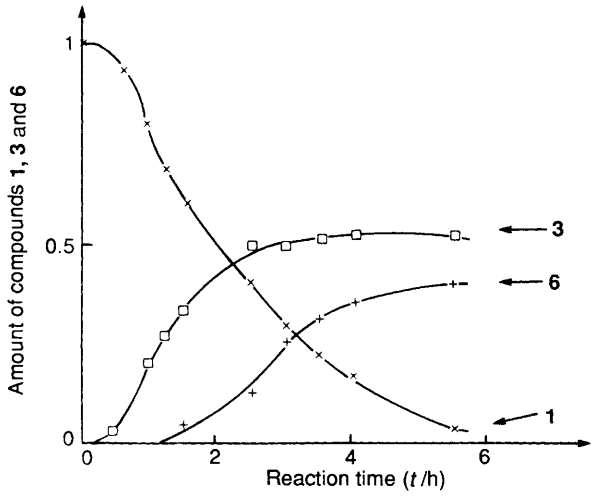
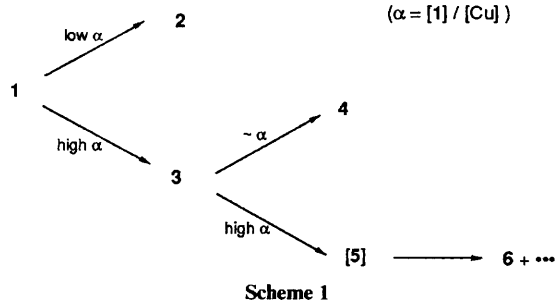


Fig. 3 HPLC monitoring of the oxidation of the benzamide **1** by the $Cu(OH)_2$ (0.3 mol equiv.)/O_2/TMAO (5 mol equiv.) system with gradual (5 h) introduction of copper(II) ion to a solution of substrate **1** and TMAO at 55 °C

Furthermore, in all cases, we observed a higher aryloxylation/hydroxylation quotient at the beginning of the reaction than at the end. This can be related to a decreasing value of $\alpha = [\mathbf{1}]/[Cu]$, the concentration quotient of substrate to copper in solution: whatever the introduction method of copper, its concentration is increasing with time because the copper(II) salts of the products are completely soluble, but neither $Cu(OH)_2$ nor, of course, metallic copper are. At the same time, substrate **1** is consumed, and its own concentration is lowered with time.

Discussion

From all these observations we can deduce that the main factor determining the major route of oxidation of the benzamide **1** is the relative concentration of substrate to that of copper: a low α-value favours hydroxylation and the benzamide **1** is converted into the salicylamide **2**; a high α-value favours aryloxylation affording compounds **3**, **5** and **6** as well as some unidentified products; under intermediate conditions (cases where all the reactants are added at once), combination of both oxidation processes leads to the formation of composite product **4** (see Scheme 1).



Scheme 1

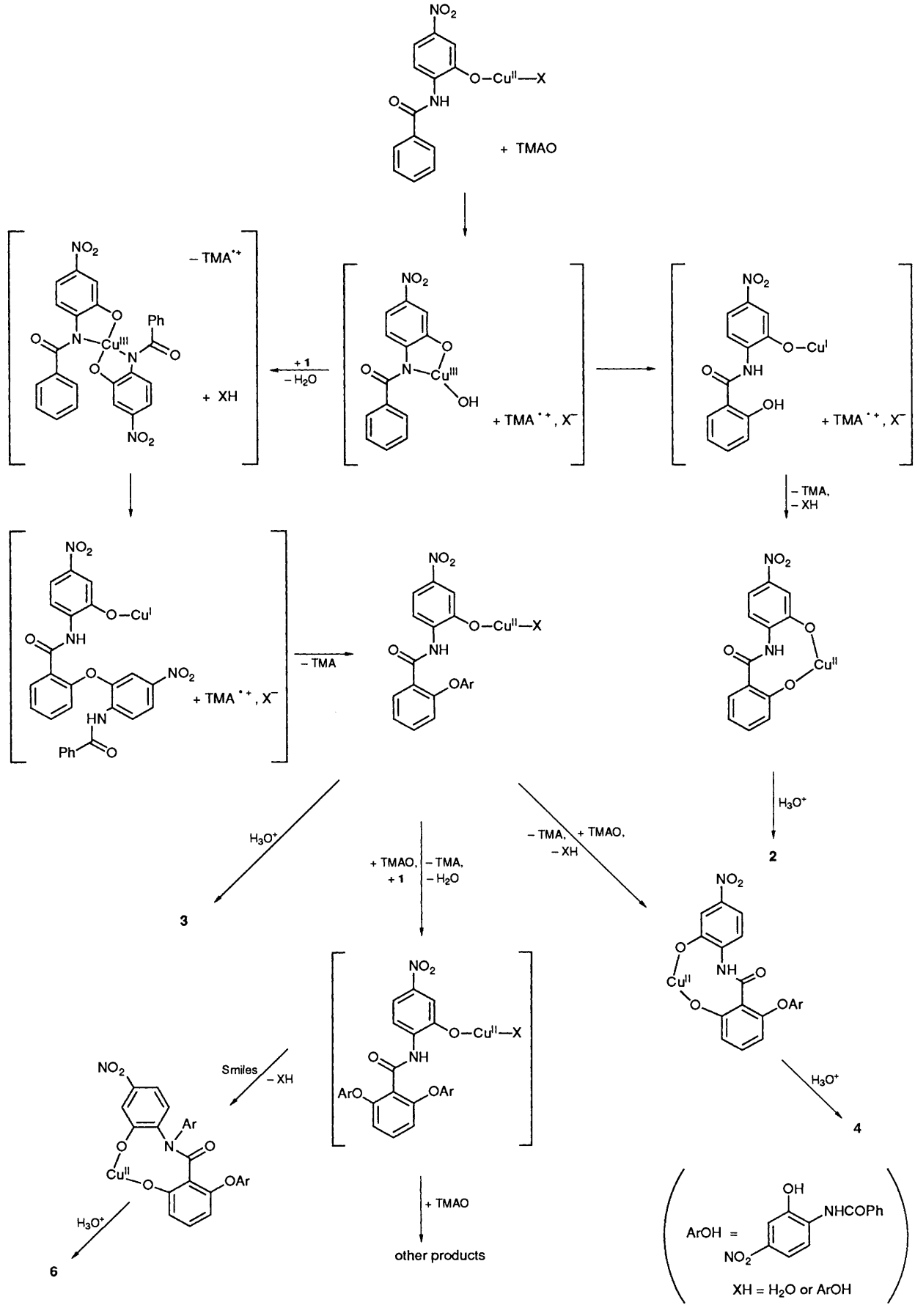
Proposed Mechanism.—To account for these results we propose the transitory formation of an aryloxy-copper(III) complex to be responsible for the aryloxylation process. Its formation could be due to the interception, by another molecule of substrate **1**, of the hydroxy-copper(III) species which is the hydroxylating entity and which results from the oxidation of a copper(II) salt of a substrate by TMAO.[1] Indeed, reaction of Cu^{III}-OH with substrate **1** will be favoured by experimental conditions where the [**1**]/[copper] α-value is high. The intramolecular evolution of Cu^{III}-OAr species accounts for the *ortho*-selectivity of the aryloxylation process as does that of Cu^{III}-OH species for hydroxylation.[1] The deprotonation of another amidic function arising from the second molecule of substrate **1** will provide a negatively charged copper(III) complex. Hence, as it is protected against a reverse attack from hydroxide, this intermediate will evolve toward aryloxylation of the benzamidic moiety of one of its ligands by the phenolic function of the other ligand. This is supported by a number of studies which show that the proximity of a copper(III) species significantly increases the acidity of amidic functions of its ligands[6] which, when ionized, are particularly qualified to stabilize copper(III).[6,7]

These assumptions led us to the following deductions: (i) the more nucleophilic the ligand is, the more favoured is the interception of the hydroxylating Cu^{III}-OH species by a substrate molecule toward formation of aryloxylating Cu^{III}-OAr species; (ii) the more acidic the amidic function of the ligand, the more favoured is the second deprotonation giving rise to a negatively charged Cu^{III}-OAr complex. These two points account for the difference in behaviour between *N*-benzoyl-2-methylalanine and substrate **1**: the ligand of the former has an acidic function which is less nucleophilic and an amidic function which is less acidic than the 2-(*N*-amido)-5-nitrophenol group of the latter. This explains the lack of any oxidation process other than *ortho*-hydroxylation when *N*-benzoylamino-2-methylalanine is submitted to the action of the Cu^{II}/TMAO couple under the same experimental conditions as those for substrate **1**.

As it can be seen in the proposed mechanism (Scheme 2), in order to react with TMAO the copper(II) salt must have one of its ligands displaced. On one hand the introduction of a hydroxy (phenolic) group onto the substrate changes the nature of the copper-ligand which becomes bidentate and therefore a much better complexing agent of copper(II) ion than the monodentate substrate is. This explains the stability of compounds **2**, **4** and **6** in this oxidizing medium although they are intrinsically more oxidizable. On the other hand, the introduction of an aryloxy group onto substrate **1** does not change the nature of the ligand much. These facts account for the oxidative cascade which takes place under experimental conditions which favour the aryloxylation process: substrate **1** is converted into compound **3** which is then oxidized to give compound **5** which is still a good substrate for over-oxidation unless a Smiles rearrangement converts it into compound **6**. Again, the presence of a second hydroxy group on compound **6** deactivates its copper(II) complex toward TMAO (as for compounds **2** and **4**) and explains why compound **6** is the only tertiary oxidized product we have been able to isolate under such conditions.

Experimental

General.—M.p.s were determinated on a digital melting point apparatus. ^1H NMR spectra were obtained in $(CD_3)_2SO$ (standard $SiMe_4$) on a Bruker AM-250 spectrometer (250 MHz). *J*-Values are given in Hz. Mass spectra were recorded on a VG ZAB instrument using electron-impact (EI) or on a R 30-10 Nermag using fast-atom bombardment (FAB). Where



Scheme 2 Proposed mechanism for the oxidation of the benzamide **1** by the Cu^{II}/TMAO couple

mass spectral measurements were used to establish molecular formulae, the purity of the sample was checked by TLC and HPLC in more than one solvent system as well as by NMR measurements.

HPLC.—The HPLC analysis and purifications were carried out on a Lichrosorb (5 μm) diol column (250 × respectively, 4.6 and 22.0 mm) using a Gilson solvent-delivery system. The mobile phase was an n-hexane–CH_2Cl_2–ethyl acetate–acetic acid (70:20:10:2) mixture. Flow rate was, respectively, 1 and 10 cm^3 min^{-1} and absorbance at 254 nm was monitored. Quantifications were performed by comparison with calibration curves obtained with known amounts of compounds **1**–**5**. HPLC monitoring of the reaction was managed as follows: samples (25 mm^3) were taken from the reaction mixture, acidified with 2% H_2SO_4 (two drops), saturated with NaCl, and extracted with ethyl acetate (1 cm^3). A fraction (10 mm^3) was injected into the HPLC analytic system.

Materials.—Most reagents are commercially available. MeCN was distilled from P_4O_{10} and kept over molecular sieves (3 Å). Dry TMAO was obtained by azeotropic distillation of TMAO·$2H_2O$ with toluene and kept as a 1 mol dm^{-3} solution in anhydrous MeCN.

The benzamide **1**[3] was synthesized according to the procedure described in ref. 8; δ_H 7.55 (t, $J_{3,5}$ 7, 4-H), 7.58 (t, $J_{2,4}$ 7, 3-H and $J_{4,6}$ 7, 5-H), 7.75 (d, $J_{5'}$ 2.5, 3′-H), 7.79 (dd, $J_{6'}$ 8.8, $J_{3'}$ 2.5, 5′-H), 7.98 (d, J_3 7.2, 2- and 6-H), 8.24 (d, $J_{5'}$ 8.8, 6′-H), 9.6 (1 H, s, NH) and 11.17 (1 H, s, OH).

Oxidation of the Benzamide **1** *by the* Cu^0/O_2/TMAO *System.*—A mixture of the benzamide **1** (258 mg, 1 mmol) and Cu^0 powder (200 mesh; 76 mg, 1.2 mmol, 1.2 mol equiv.) was vigorously stirred, with O_2 bubbling, in dry MeCN (5 cm^3). A 1 mol dm^{-3} solution of TMAO (5 cm^3, 5 mol equiv.) was then added and the temperature was set at 75 °C. After 10 h, the reaction mixture was allowed to cool to room temp., filtered on a Büchner filter (in order to remove the excess of Cu^0), and poured dropwise onto ice-cold 0.5 mol dm^{-3} HCl (10 cm^3). The precipitated product was collected by filtration, washed successively with diethyl ether (3 × 5 cm^3) and then with ice-cold ethyl acetate (3 cm^3), and finally dried over KOH, then P_4O_{10} *in vacuo* to afford the salicylamide **2** as tan-yellow crystals (220 mg, 80%); m.p. 256 ± 0.5 °C (from aq. MeOH), unchanged through three successive recrystallizations (lit.,[9] 271–272 °C) (Found: C, 56.7; H, 3.7; N, 10.1. Calc. for $C_{13}H_{10}N_2O_5$: C, 56.93; H, 3.68; N, 10.22%); δ_H 7.00 (t, $J_{4,6}$ 7.5, 5-H), 7.04 (d, J_4 7.5, 3-H), 7.44 (td, $J_{3,5}$ 7.5, J_6 1.7, 4-H), 7.74 (d, $J_{5'}$ 2.6, 3′-H), 7.80 (dd, $J_{6'}$ 8.9, $J_{3'}$ 2.6, 5′-H), 8.03 (dd, J_5 7.5, J_4 1.7, 6-H), 8.68 (d, $J_{5'}$ 8.9, 6′-H), 11.27 (1 H, s, NH) and 11.35 and 11.95 (2 H, 2 br s, 2 × OH).

To a suspension of Cu^0 powder (200 mesh; 76 mg, 1.2 mmol, 1.2 mol equiv.) vigorously stirred with O_2 bubbling in a dry 0.5 mol dm^{-3} MeCN solution of TMAO (5 cm^3, 5 mol equiv.) at 75 °C was progressively added the starting benzamide **1** (258 mg, 1 mmol) during 8 h. After 2 more hours of heating, the reaction mixture was treated as described above to afford the salicylamide **2** (240 mg, 88%).

Oxidation of the Benzamide **1** *by the* $Cu(OH)_2$/TMAO *System.*—A suspension of the benzamide **1** (258 mg, 1 mmol) was vigorously stirred at the required temperature with either O_2 or N_2 bubbling in a 0.5 mol dm^{-3} dry MeCN solution of TMAO (5 cm^3, 5 mol equiv.). $Cu(OH)_2$ was then added over the desired period (117 mg, 1.2 mol equiv. added at once or 30 mg, 0.3 mol equiv. added during 5 h at 55 °C, depending on the experiment) and the temperature was set at 75 °C. The reaction is stopped by pouring the mixture onto ice-cold 0.5 mol dm^{-3} HCl (10 cm^3). The crude precipitated product obtained by filtration is washed with water (3 × 5 cm^3) and dried *in vacuo* over KOH and then P_4O_{10}. The crude product could be either subjected to NMR analysis for quantitative determination of compounds **1**–**4** or partly dissolved in ethyl acetate and injected into the preparative HPLC system. The collected fractions of each purified product **1**–**4** were concentrated under reduced pressure, first in a rotary evaporator, then in a vacuum desiccator containing KOH where the product was kept for over 24 h.

2-Aryloxybenzamide **3**: tan crystals, m.p. 292 °C (decomp.) (Found: M^+, 514.1126. $C_{26}H_{18}N_4O_8$ requires M, 514.1125); *m/z* (EI) 514 (M^+), 496 (M − H_2O), 484 (M − NO), 368, 284, 256, 210, 167 and 105; δ_H 7.07 (d, J_4 7.5, 3-H), 7.36 (t, $J_{6,4}$ 7.5, 5-H), 7.44 (t, $J_{2''',4'''}$ 7.5, 3‴-H and $J_{4''',6'''}$ 7.5, 5‴-H), 7.55 (td, $J_{3,5}$ 7.5, J_6 1.5, 4-H), 7.56 (t, $J_{3''',5'''}$ 7.5, 4‴-H), 7.625 (d, $J_{5'}$ 2.4, 3′-H), 7.77 (dd, $J_{3'}$ 2.4, $J_{6'}$ 9.0, 5′-H), 7.77 (d, $J_{3'''}$ 7.5, 2‴- and 6‴-H), 8.01 (d, $J_{4''}$ 2.5, 6″-H), 8.08 (dd, J_5 7.5, J_4 1.5, 6-H), 8.20 (dd, $J_{3''}$ 9.1, $J_{6''}$ 2.5, 4″-H), 8.47 (d, $J_{5'}$ 9.0, 6′-H), 8.55 (d, $J_{4''}$ 9.1, 3″-H), 10.47 (2 H, s, 2 × NH) and 11.1 (1 H, br s, OH).

2-Hydroxy-6-aryloxybenzamide **4**: pale yellow crystals, m.p. 300 °C (decomp.) [Found: (M$^+$ − H_2O), 512.0968. $C_{26}H_{18}N_4O_9$ requires (M − H_2O), 512.0972]; *m/z* (EI) 530 (M^+), 512 (M − H_2O), 500 (M − NO), 408, 392, 290, 272, 256, 227, 210, 121 and 105; δ_H 6.56 (d, J_4 8.2, 5-H), 6.82 (d, J_4 8.2, 3-H), 7.35 (t, $J_{3,5}$ 8.2, 4-H), 7.46 (t, $J_{2''',4'''}$ 7.5, 3‴- and 5‴-H), 7.58 (t, $J_{3'''}$ 7.5, 4‴-H), 7.64 (d, $J_{5'}$ 2.5, 3′-H), 7.73 (dd, $J_{3'}$ 2.5, $J_{6'}$ 8.8, 5′-H), 7.81 (d, $J_{3'''}$ 7.5, 2‴-H and $J_{5'''}$ 7.5, 6‴H), 7.99 (d, $J_{4''}$ 2.5, 6″-H), 8.14 (dd, $J_{6''}$ 2.5, $J_{3''}$ 9.0, 4″-H), 8.34 (d, $J_{5'}$ 8.8, 6′-H), 8.47 (d, $J_{4''}$ 9.0, 3″-H), 10.22 and 10.25 (2 H, 2 s, 2 × NH) and 11.18 and 11.48 (2 H, 2 s, 2 × OH).

N-Aryl-6-aryloxy-2-hydroxybenzamide **6**: orange crystals, m.p. 174 °C (decomp.); *m/z* (FAB) 770 (M^-) 769 (M − 1); δ_H 6.79 (d, J_3 8.05, 4-H), 7.02 (d, J_3 8.05, 2-H), 7.2–7.5 (10 H, m, 2 × Ph), 7.5 (t, $J_{2,4}$ 8.05, 3-H), 7.5 (d, $J_{5'}$ 2.5, 3′-H), 7.65 (dd, $J_{3'}$ 2.5, $J_{6'}$ 9.1, 5′-H), 7.68 (d, $J_{4''}$ 2.6, 6″-H), 7.83 (dd, $J_{3''}$ 9.1, $J_{6''}$ 2.6, 4″-H), 7.89 (d, $J_{5'''}$ 2.5, 3‴-H), 8.20 (d, $J_{5'}$ 9.1, 6′-H), 8.23 (dd, $J_{3'''}$ 2.5, $J_{6'''}$ 9.2, 5‴-H), 8.30 (d, $J_{4''}$ 9.1, 3″-H), 8.92 (d, $J_{5'''}$ 9.2, 6‴-H), 9.93 and 10.30 (2 H, 2 s, 2 × NH) and 10.89 and 11.015 (2 H, 2 s, 2 × OH).

Conclusions.—Finally, we have shown that *N*-(2-hydroxy-4-nitrophenyl)benzamide **1** can be *ortho*-hydroxylated to the corresponding salicylamide **2** in high yield (88%) by the Cu^0/O_2/TMAO oxidizing system, thereby showing that the 2-(*N*-amido)-5-nitrophenol group is a good ligand for this copper-mediated hydroxylation process.

This study has also described a new oxidative process within the aryloxylation of benzamide **1** induced by the Cu^{II}/TMAO system. As far as we know, this is the first example of aryloxylation of a non-phenolic aromatic substrate, *i.e.* which does not come from the coupling between two phenoxy radicals.

The complete *ortho*-selectivity of this oxidizing process suggests the transitory formation of a Cu^{III}-OAr complex by analogy with the Cu^{III}-OH species evoked to account for the *ortho*-hydroxylation of the benzamide **1** as well as some other benzamidic substrates[1,2] by the same oxidizing system. Both processes can be in competition but experimental conditions leading to an exclusive oxidation pathway have been highlighted.

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