AN EFFICIENT SYNTHESIS OF A METABOLITE OF VASOPRESSIN V2 RECEPTOR ANTAGONIST, OPC-31260, BY METALLOPORPHYRIN-CATALYZED DEMETHYLATION

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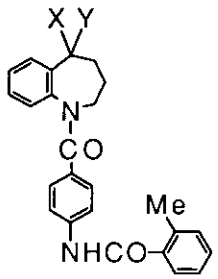
Abstract - A secondary amine (**3**) as a metabolite of the vasopressin V2 receptor antagonist, OPC-31260 (**1**), was efficiently prepared through selective demethylation of the corresponding *N*,*N*-dimethylalkylamine *N*-oxide (**2**) with *meso*-(tetraphenylporphinato)iron(III) chloride [Fe(TPP)]Cl, where tetrazole as an additive played a crucial role in the achievement of high chemical yields.

The oxidative *N*-dealkylation[1] of xenobiotics containing amino function is an important metabolic reaction which is catalyzed by cytochrome P-450 enzymes and hence, widely investigated in a variety of chemical models.[2] While these model reactions are often performed with *N*,*N*-dimethylaniline and related derivatives including *N*,*N*-dialkylarylamines in the presence of several iron complexes and alternative oxygen sources, some research groups[3] reported the use of *N*,*N*-dimethylaniline *N*-oxide as both the oxygen donor and, thereafter, the substrate in the enzymatic reaction. On the other hand, the dealkylation of trialkylamines has been only slightly studied.[4] We wish to report herein our findings that the *N*,*N*-dimethylalkylamine *N*-oxide (**2**) is efficiently demethylated using several metalloporphyrins with additives to afford the corresponding secondary amine (**3**) which has been proposed as one of the

metabolites of a new vasopressin V2 receptor antagonist, OPC-31260 (**1**)[5] (5-dimethylamino-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine), in the rat, dog and human.



1; X = NMe_2, Y = H
2; X = $N(O)Me_2$, Y = H
3; X = NHMe, Y = H
4; X, Y = O
5; X = $\dot{N}^{+}Me_2$, Y = H

The results are shown in Table 1. Initially, when 1.0 eq of **2** was treated with 0.1 eq of *meso*-(tetraphenylporphinato)iron(III) chloride [Fe(TPP)]Cl and 1.0 eq of imidazole in dichloromethane at room temperature according to the method reported by Oae *et al.*,[3a] no detectable reaction took place (entry 1). The stoichiometric amount of [Fe(TPP)]Cl, however, promoted the reaction quite efficiently to give a mixture of demethylated product (**3**) and deoxygenated product (**1**) (entry 2). This observation may suggest that the turnover number of [Fe(TPP)]Cl as a catalyst is very small in this model reaction and the product composition is remarkably influenced by the property of the metalloporphyrin employed. Actually, the product ratio was certainly changed in the reaction using another metalloporphyrin (entries 3 and 4). Next, replacement of the additive as an axial ligand of the iron complex was examined in order to control the catalytic activity of iron(III) to some extent. Thus, improvement in the chemical yield of **3** was achieved using a base[6] other than imidazole. Especially, the addition of tetrazole showed a remarkable increase (entry 6).[7] It turned out that the reaction in other solvent such as benzene, acetonitrile-water was not effective and afforded unsatisfactory results. The formation of a ketone (**4**) was not observed in the cases reported in Table 1. Although the precise role of additives is unclear, there is an explanation for the observed chemoselectivity. Thus, tetrazole may act as a base to abstract a proton preferably from the less hindered methyl group of the ammonium radical cation (**5**) formed in the reaction.

In conclusion, the structure of the metabolite (**3**) was identical with the corresponding synthetic

compound based on NMR and MS comparisons, and high-performance liquid chromatographic (HPLC)

Table 1. Products of metalloporphyrin promoted reactions of **2**[a)]

			yield (%)[b)]		
entry	metalloporphyrins	additives	**3**	**1**	recovered **2**
1[c)]	Fe(TPP)Cl	imidazole	0	0	82
2	Fe(TPP)Cl	imidazole	68	25	0
3	Mn(TPP)Cl	imidazole	35	30	21
4	Ru(TPP)CO	imidazole	0	0	64
5	Fe(TPP)Cl	1,2,4-triazole	69	12	13
6	Fe(TPP)Cl	tetrazole	86	0	0
7[c)]	Fe(TPP)Cl	tetrazole	39	0	40

a) 1.0 eq each of metalloporphyrin and additive was used to 1.0 eq of **2**. *b)* Isolated yields based on **2**. *c)* Fe(TPP)Cl (0.1 eq for entry 1, 0.5 eq for entry 7) was employed.

behavior,[8] moreover, the present study demonstrates the simple preparation method for a secondary amine in high yield from the corresponding *N*,*N*-dimethylalkylamine *N*-oxide. This transformation might provide an alternative and practical methodology for the construction of various metabolites containing *N*,*N*-dialkyl substituted secondary amines.

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6. The use of Et_3N, pyridine, *N*-methylimidazole, thiazole or $PhCH_2SH$ instead of imidazole as an additive under the reaction conditions of entry 2 gave no improvement.
7. Typical procedure: To a stirred solution of **2** (50 mg, 0.11 mmol) in dichloromethane (5 mL) was added Fe(TPP)Cl (82 mg, 0.11 mmol) and tetrazole (8.0 mg, 0.11 mmol) at rt and the mixture was stirred for 16 h at the same temperature in the dark. Standard workup procedure followed by preparative TLC (dichloromethane/MeOH, 10/1) gave 40 mg (86 %) of **3** as a pale yellow oil.
8. **3** : NMR ($CDCl_3$) δ: 1.3-3.3 (m with three s at δ 2.43, 2.46, and 2.56, 12H), 3.70-3.80 (m, 1 x 1/3H) 4.03-4.06 (m, 1 x 2/3H), 4.45-4.65 (m, 1 x 2/3H), 5.05-5.26 (m, 1 x 1/3H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.90-7.70 (m, 12H). MS *m/z* (%) 413 (M^+, 1), 384 (5), 238 (70), 180 (72), 144 (55), 119 (100). HPLC (column, TSK-ODS 80TM, 4.6 x 150 mm; solvent, acetonitrile:water:acetic acid = 25:75:1; flow rate, 1.0 ml/min; detector, UV 280 nm). retention time, 8.5 min.

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