AN EFFICIENT FACILE AND SELECTIVE HYDROXYLATION OF NITROGEN HETEROCYCLES

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Abstract

Nitrogen heterocycles have been efficiently hydroxylated under mild and neutral conditions by employing Cupric nitrate/phosphate buffer/30% hydrogen peroxide system. The present method afforded the biologically active and important hydroxy heterocycles. The hydroxylation takes place regioselectively without over oxidation.

Introduction

Nitrogen containing heterocycles occupied a prominent position in organic syntheses due to their versatile utility in agriculture and pharmaceutical chemistry i.e Quinolines are found to exhibit antitumour antibiotic activity[1]. Benzimidazoles are associated with antifilarial, Eurokinase inhibition etc[2]. 2-Aminobenzothiazoles are found to posses fungicidal and antibacterial activity [3] where as pyridine is found to be an important constituent of various biologically active molecules[4].

The utility of hydrogen peroxide as source of electrophilic oxygen has gained increasing importance. Various studies on electrophilic hydroxylation of aromatic compounds have been reported including the $AlCl_3$-H_2O_2/urea adducts, with anhydrous HF (in the presence of $AlCl_3$, BF_3 etherate or strong acids such as FSO_3H, FSO_3H-SbF_5/SO_2ClF) and with H_2O_2/HF/pyridine. However, these systems are not always easy to handle and recovery of acid is inconvinient[5] . Recently we have reported an efficient hydroxylation of simple aromatic compounds by employing cupric nitrate in combination with H_2O_2 and phosphate buffer to afford the corresponding phenols[6]. In continuation of this work and in view of the importance of heterocycles in agrochemical and pharmaceuticals, we have extended the study of hydroxylation on some nitrogen heterocyclic compounds, using above reported conditions.

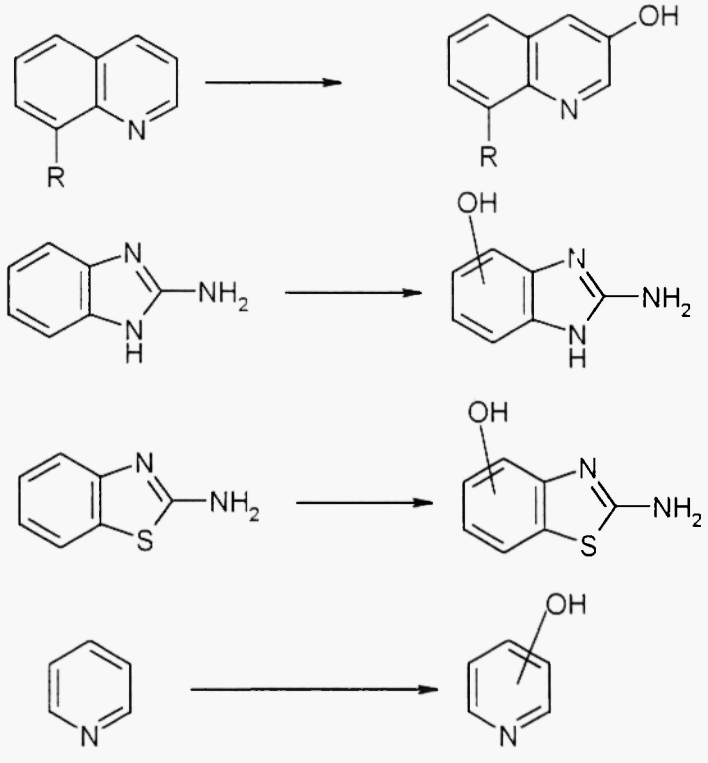
Results and Discussion

Although there is plenty of literature available on aromatic hydroxylation, very few reports are available for hydroxylation of aromatic heterocycles i.e hydroxylation of pyridine, quinoline and other aromatic heterocycles have been carried out by using alkylperoxide anion[7] has a few limitations, i.e. hydroxylation of nitro pyridines, the products are isolated in the form of their pyridones due to over oxidation. Where as in case of 2- nitrothiophene the product 2- nitro-3-hydroxythiophene decomposed

during purification and finally obtained in its salt form. There fore there is a need to carryout the hydroxylation of aromatic heterocycles under mild reaction conditions without over oxidation.

In this communication we wish to report successful hydroxylation of aromatic nitrogen heterocycles by extending our previously reported hydroxylation method[6] (scheme).

We have attempted the hydroxylation of quinoline derivatives. The quinoline and 8- hydroxy quinoline undergo selective hydroxylation on 3- position to give the corresponding 3- hydroxy substituted quinolines which are very rare in nature [8]. In particular 8- hydroxy quinoline afforded 3-8-dihydroxyquinoline which is a naturally occuring cytotoxic alkaloid (Jineol)[7] (entry 2b) as an orange amorphous solid (mp 139-141 ^{0}C). The U.V spectrum of obtained product showed maximum absorption at 254 and 264 nm. The IR spectrum exhibited absorptions at 3370, 1595, 1560 and 1200 cm^{-1} suggesting a hydroxy quinoline moiety. These surprising results of regioselective hydroxylation encourage us to check the selectivity in other nitrogen containing heterocycles such as bezimidazoles, benzothiazoles and pyridines.



Reaction Conditions: - Cu ($NO_3)_2.3H_2O$, Phosphate Buffer, 30% H_2O_2, CH_3CN 4-5h, 50 ^{0} C

Scheme

Accordingly 2 aminobenzimidazoles are hydroxylated to afford biologically active hydroxylated products. In particular 2-aminobenzimidazole gives 5-hydroxy 2- aminobenzimidazole, which is a novel eurokinase inhibitor. Other benzimidazoles also gives selective hydroxylated prodcuts without over oxidation (entries 2c-2e).

Table: Hydroxylation of Nitrogen heterocycles

Entry	**Substrate 1**	**Product 2**	**Reaction Time (hr)**	**Yield (%)**
a	Quinoline	3-Hydroxyquinoline	4	85
b	8-Hydroxyquinoline	3,8-Dihydroxyquinoline	4	82
c	2-Aminobenzimidazole	5-Hydroxy-2-aminobenzimidazole	5	75
d	2-Amino-5-methylbenzimidazole	2-Amino-6-hydroxy- 5-methylbenzimidazole	5	74
e	2-Amino-5,6-dimethylbenzimidazole	2-Amino-7-hydroxy -5,6-dimethylbenzimidazole	5	76
f	2-Aminobenzothiazole	5-Hydroxy-2-aminobenzothiazole	4	78
g	4-Methyl-2-aminobenzothiazole	5-Hydroxy-4-methyl-2-aminobenzothiazole	4	76
h	5,6-Dimethyl-2-aminobenzothiazole	7-Hydroxy-5,6-dimethyl-2-aminobenzothiazole	4	74
i	4-Chloro-2-aminobenzothizole	5-Hydroxy-4-chloro-2-aminobenzothiazole	5	78
j	6-Flouro-2-aminobenzothiazole	6-Flouro-5-hydroxy-2-aminobenzothiazole	5	76
k	2-Chloropyridine	2-Chloro-3-hydroxypyridine	5	78
l	6-Chloropyridine	6-Chloro-3-hydroxypyridine	5	84
m	2-Methylpyridine	3-Hydroxy-2-methylpyridine	4	82

2-Aminobenzothiazoles are also hydroxylated efficiently under above reaction conditions. 2-aminobenzothiazoles afforded selectively 2- aminobenzothiazoles (entries 2f-2j) in good yield.

Finally, we have taken up hydroxylation of pyridine derivatives, which are electron deficient and generally resistant to electrophilic substitution reactions under mild reaction condition. As expected pyridines reacted similarly to quinolines. Pyridine, 2- chloropyridine, 6-chloropyridines and 2-methyl pyridine afforded the corresponding monohydroxylated pyridine (entry 2k-2m).

Conclusion

In conclusion we have successfully applied the hydroxylation process to aromatic nitrogen heterocycles to afford the biologically active heterocycles. Furthermore, the process is ecofriendly, the reagents are inexpensive, easy to handle and the procedure follows a simple work-up without over oxidation. Thus it is believed that its an easy facile method for the synthesis of biologically active heterocycles.

Experimental

All the chemicals and solvents were obtained from commercial sources and used without further purification. ^{1}H NMR were recorded at 90 MHz in $CDCl_3$ as solvent, IR spectra were obtained on G.C.FTIR using Varton Nicolet USA apparatus and EI mass spectra were determined by using V.G. Micromass 7070H and Finnigan mal 1020B apparatus. Melting points were determined on Veego digital automatic melting point apparatus and are uncorrected.

General Procedure for Hydroxylation

To a solution of heterocyclic substrate (1a-1 m) (0.01 mole) in acetonitrile (10 ml) was added neutral phosphate buffer (997 mg, 3.6 mmol) in 10 ml of water [The phosphate buffer is an equimolar mixture of disodium hydrogen ortho phosphate (Na_2HPO_4 , 510 mg, 3.6 mmol) and potassium dihydrogen ortho phosphate (KH_2PO_4 , 488 mg, 3.6 mmol) , cupric nitrate (0.5 g, 2.1 mmol) in 2 ml of water followed by the addition of 30% H_2O_2 (7 ml, 0.0618 mole) in three portions. The reaction mixture was heated at 50^0C for 4-5 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (10 ml) , extracted with ethylacetate (15 ml). The organic layer was washed with water and dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was chromatographed over silica gel column using chloroform: ethylacetate (3:1) as eluent to get pure products (2a-2m) in good yields.

3-hydroxyquinoline (2a) :

^{1}HNMR ($CDCl_3$) δ 5.8 (s, 1H, OH), 7.4 (m, 1H, aromatic), 7.6 (m, 3H, aromatic), 8.1 (dd, 1H,aromatic), 8.7 (d, 1H, aromatic); IR : (KBr) 3370, 1595 , 1562 cm^{-1} ; Mass : 144 (m+), 116.

3,8-dihydroxyquinoline (2b) :

^{1}HNMR ($CDCl_3$) δ 5.8 (s, 2H, OH), 7.0 (dd, 1H, aromatic), 7.2-7.3 (dd, 2H, aromatic), 7.6 (d, 1H, aromatic), 8.7 (d, 1H, aromatic); IR : (KBr) 3360, 1585 , 1562 cm^{-1} ; Mass : 161 (m+), 133,104.

5-hydroxy-2-aminobenzimidazole (2c) :

^{1}HNMR ($CDCl_3$) δ 4.6 (s, 3H, NH,NH_2), 5.6 (dd, 1H, aromatic), 5.81 (dd, 1H, aromatic), 5.83 (s, 1H, OH), 6.1 (dd, 1H, aromatic); IR : (KBr) 3410, 1590 , cm^{-1} ; Mass :149 (M+1).

2-amino-6-hydroxy -5-methylbenzimidazole (2d) :

^{1}HNMR ($CDCl_3$) δ 3.2 (s, 3H, CH_3), 4.67 (s, 3H, $NHNH_2$), 5.58 (s, 1H, aromatic), 5.8 (s, 1H, OH), 5.9 (t , 1H, aromatic); IR : (KBr) 3395, 1595 , 1562 cm^{-1} ; Mass : 163 (M+).

2-amino-7-hydroxy-5,6-dimethylbenzimidazole (2e) :

^{1}HNMR ($CDCl_3$) δ 3.2 (s, 6H, CH_3), 4.6 (s, 3H, $NHNH_2$), 5.5 (s, 1H, aromatic), 5.8 (s, 1H, OH); IR : (KBr) 3380, 1595 , 1562 cm^{-1} ; Mass : 177 (M+).

5-hydroxy-2-aminbenzothiazole (2f) :

^{1}HNMR ($CDCl_3$) δ 4.6 (s, 2H, NH_2), 5.5 (s, 1H, aromatic), 5.6 (d, 1H, aromatic), 5.8 (s, 1H, OH), 6.1 (d , 1H, aromatic); IR : (KBr) 3390, 1595 , 1562 cm^{-1} ; Mass : 166(m+).

5-hydroxy-4-methyl- 2-aminbenzothiazole (2g) :

^{1}HNMR ($CDCl_3$) δ 3.2 (s, 3H, CH_3), 4.6 (s, 2H, NH_2), 5.8 (s, 1H, OH), 5.8 (s, 1H, OH), 6.1 (d , 1H, aromatic), 6.2 (d, 1H, aromatic); IR : (KBr) 3350, 1650 , 1450 1050 cm^{-1} ; Mass : 180 (M+).

5,6 dimethyl- 7- hydroxy-2-aminobenzothiazole (2h) :

^{1}HNMR ($CDCl_3$) δ 3.2 (s, 6H, CH_3), 4.6 (s, 2H, NH_2), 5.5 (s, 1H, aromatic), 5.8 (s, 1H, OH); IR : (KBr) 3350, 1659 , 1450 , 1050 cm^{-1} ; Mass : 194 (M+).

4-Chloro-5-hydroxy-2-aminobenzothiazole (2i) :

^{1}HNMR ($CDCl_3$) δ 4.6 (s, 2H, NH_2), 5.8 (s, 1H, OH), 6.2 (d , 1H, aromatic), 6.4 (d , 1H, aromatic); IR : (KBr) 3360, 1655 , 1450 1050 cm^{-1} ; Mass : 202 (M+).

6-Fluoro-5-hydroxy-2-aminobenzothiazole (2j) :

^{1}HNMR ($CDCl_3$) δ 4.6 (s, 2H, NH_2), 5.8 (s, 1H, OH), 6.1 (s , 1H, aromatic), 6.5 (d , 1H, aromatic); IR : (KBr) 3350, 1655 , 1450 1050 cm^{-1} ; Mass : 184 (M+).

2-Chloro-3-hydroxypyridine (2k) :

^{1}HNMR ($CDCl_3$) δ 5.8 (s, 1H, OH), 7.5 (t , 1H, aromatic), 7.7 (s , 1H, aromatic), 8.5 (d, 1H,aromatic) ; IR : (KBr) 3340, 1658 cm^{-1} ; Mass : 129 (M+).

6-Chloro-3-hydroxypyridine (2l) :

^{1}HNMR ($CDCl_3$) δ 5.8 (s, 1H, OH), 7.5 (d , 1H, aromatic), 7.7 (s , 1H, aromatic), 8.7 (s, 1H, aromatic) ; IR : (KBr) 3345, 1657 cm^{-1} ; Mass : 129 (M+).

3-hydroxy-2-methylpyridine (2m) :

^{1}HNMR ($CDCl_3$) δ 2.8 (s, 3H, CH_3), 5.8 (s, 1H, OH), 7.2-7.3 (d , 2H, aromatic), 8.3 (t , 1H, aroamtic) ; IR : (KBr) 3370, 1655 cm^{-1} . Mass : 144 (M+).

References

1. (a) R. Elderfield *Heterocycl. Compd.* 4, 1 (1952) ; (b) O. Meth-Chon., B. Narine. *Tetrahedron 19*, 2045 **(1978)**.

2. (a) R. J. Anderson., D. J. Bendell., M. Hooper., D. Cairns., S. P Mackay., S. P. Hiremath., A. S. Jivinagi., S. Badami., J. S. Biradar., S. Townson., *J. Pharm. Phramac. 53*, 89 **(2001)** ; (b) P. J. Hajduk., S. Boyd., D. Nettesheim., V. Nienaber., J. Severin., R. Smith., D. Davidson., T. Rockway., S. W. Fesik. *J. Med. Chem. 43*, 3862 **(2000)**; (c) R. Rastogi., S. Sharma. *Synthesis* 861 **(1983)**.

3. (a) A. M. Dave., K. N. Bhatt., N. K. Undavia., P. B. Trivedi. *J. Indian.Chem. Soc.*.365 **(1988)**; (b) T. Dimmhing., H. Hein. *Arzeneion-Forsch. 2*, **515 (1952)**; (c) J. Hata. *J. Pharm. Soc. Japan. 74*, 254 **(1954)**; (d) G. Tartler., W., *Wevffen. Pharmazie (Ger), 21*, 425 **(1966)**.

4. (a) M. Makosza., K. Sienkiewiez. *J. Org. Chem 63*, 4199 **(1998)** and references cited there in ; (b) M. Makosza., J. Golinski., A. Rykowski. *Tetrahedron Lett.* 3277 **(1983)**; (c) Z. Owezarezyk. Ph. D. Thesis, Icho-PAN **(1988)**.

5. (a) G. A. Olah., T. Keumie., A. P. Fung. *Synthesis*, 536 **(1979)** ; (b) J. Sugano, Y. Kariyama., Y. Ishinshin., K. Minamikawa. *Japanese Kokai 234*,7407, **(1974)** *Chem Abstr. 80*, 120535 **(1974)** ; (c) J. A. Vesely, L. Schmerling. *J. Org. Chem. 35*, 4028 **(1970)** ; (d) J. A. Vesely. *U. S. Patent* 3839467 **(1974)** : *Chem Abstr. 82*, 3974 **(1975)** ; (e) M. E. Kurz.; G. J. Johnson. *J. Org. Chem. 29*, 2397 **(1964)** ; (f) J. D. McClure., P. H. Williams. *J. Org. Chem. 27*, 124 **(1962)** ; (g) J. Varagnut. *Ind. Eng. Chem. Prod. Res. Dev. 15*, 212 **(1976)** ; (h) G. A. Olah., R. Ohnishi. *J. Org. Chem. 43*, 865 **(1978)**.

6. A. Nasreen., S. R. Adapa. *Org. Prep. Proc. Intl. 32*, 375. **(2000)**.

7. (a) M. Makosza. *Synthesis*, 103 **(1991)** ; (b) M. Makosza., E. Kwast. *Tetrahedron, 51*,8339 **(1995)**.

8. J. P. Michel. *Natural Prod. Rep. 11*, 163 **(1994)**.

9. S. SikMoon., N. Cho., J. Shin., Y. Seo., C. O. Lee., S. U. Choi. *J. Nat. Prod. 59*, 777 **(1996)**.

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