AN IMPROVED PROCEDURE FOR THE PREPARATION OF AROMATIC HETEROCYCLIC *N*-OXIDES

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Abstract - An improved procedure for the preparation of aromatic heterocyclic *N*-oxides is described. Nitrogen containing heterocyclic compounds gave their *N*-oxides in excellent yields by the reaction of *m*-CPBA in DMF/MeOH in the presence of HF in a short time under mild reaction conditions. The presence of HF and MeOH is crucial for the reaction.

N-Oxidations of nitrogen containing heterocycles have received much attention due to the usefulness of the *N*-oxides as synthetic intermediates and their biological importances.[1] Heterocyclic *N*-oxides are also useful as protecting groups,[2] auxiliary agents,[3] oxidants,[1a] ligands in metal complexes,[4] and catalysts.[1a] *N*-Oxidations have been generally achieved by various oxidizing agents including peracetic acid,[5] *m*-chloroperbenzoic acid (*m*-CPBA),[6] magnesium monoperphthalate (MMPP),[7] hydrogen peroxide,[8] or dioxiranes.[9] Most of the oxidants could be used sucessfully in the *N*-oxidation reactions, however, some kinds of heterocyclic compounds such as less substituted pyrimidine derivatives gave generally poor yields of *N*-oxides accompanied with some side products.[10]

Recently, we have reported several interesting results of oxidations by *m*-CPBA/HCl/DMF system.[11] For the further development of our oxidation methods, we examined the *N*-oxidation of cytidine by *m*-CPBA/HF/DMF system. We presumed that the use of HF could activate *m*-CPBA and at the same time protect the amino group in cytidine *in situ*., since HF can not be oxidized by *m*-CPBA to generate F^+ as in the case of HCl.[11] However, we observed that the reaction did not show much improvement in yield as compared with that of

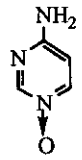
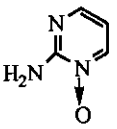
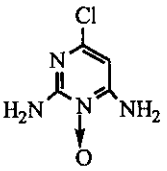
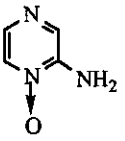
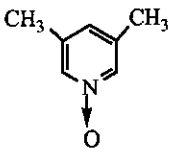
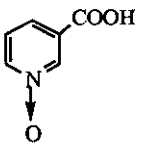
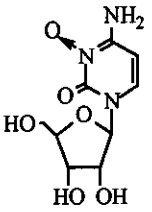
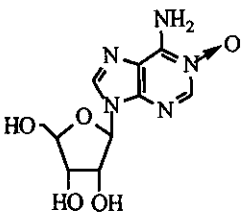
the reported.[12] Remarkably, however, addition of some methanol to the reaction mixture resulted in 90 % yield of cytidine *N*-oxide in a short time. Thus, we examined the *N*-oxidations of some heterocyclic compounds with *m*-CPBA in DMF/MeOH in the presence of HF and found that the novel reaction conditions afforded their *N*-oxides in excellent yields. In general, to a solution of various heterocyclic compounds in DMF/MeOH were added HF (1.1-2.5 equiv) and *m*-CPBA (2.0-2.5 equiv) in one portion, followed by stirring the reaction mixture until the reaction completed. All of the *N*-oxides except two nucleoside *N*-oxides (**7** and **8**) were easily purified by column chromatography on silica gel. For the purifications of **7** and **8**, the crude products were dissolved in MeOH/H_2O (9/1) and triturated into ethyl acetate. The products were identified by the coincidences of their physical and spectroscopic data with those of the reported. The representative results are summarized in **Table 1**. The presence of HF (48% aqueous solution, 1.1-2.5 equiv) and MeOH was crucial to complete the *N*-oxidation reactions of various aromatic heterocyclic compounds. As shown in **Table 1**, 4-aminopyrimidine and 2-aminopyrimidine gave the corresponding *N*-oxides in high yields. 4-Chloro-2,6-diaminopyrimidine 1-oxide (**3**) is an important intermediate for the synthesis of *Minoxidil*[19] which is a valuable antihypertensive agent and used in the treatment of *alopecia*. For the preparation of *Minoxidil*, the *N*-oxidation of 4-chloro-2,6-diaminopyrimidine is a decisive step and a number of reports on the *N*-oxidation were reported,[19] in which various oxidants such as MMPP or dioxirane have been used for the *N*-oxidation and afforded **3** in poor yields even in the vigorous reaction conditions. In contrast to the reported methods, our *N*-oxidation methodology afforded the intermediate (**3**) in high yield (88%). 2-Aminopyrazine, 3,5-lutidine, and nicotinic acid gave their *N*-oxides in excellent yields in a short time at room temperature. But, for the preparation of the *N*-oxides of cytidine and adenosine, somewhat longer reaction time and/or warming was required to complete the reaction.

Although the critical roles of HF and MeOH in the above *N*-oxidation reaction are uncertain, our method can be recommended over other *N*-oxidation procedures of various heterocyclic compounds owing to its high yields, short reaction time under mild reaction conditions.

EXPERIMENTAL

Melting points were measured with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H Nmr

Table 1. *N*-Oxidations of Heterocyclic Compounds by Using *m*-CPBA in DMF/MeOH in the presence of HF.

Compound	Product	Temp (°C)	Time (min)	Yield (%)	[lit. Yield]
1		25	30	98	[25][13]
2		25	30	90	[68][14]
3		25	30	88	[71][15]
4		25	60	99	[68][14]
5		25	10	85	[30][16]
6		25	180	87	[80][17]
7		50	30	90	[41][12]
8		25	960	95	[95][18]

spectra were recorded on a Varian Gemini-200 nmr Spectrometer with TMS as an internal standard. Mass spectra were recorded on a Shimadzu QP 1000 Spectrometer. Chromatographic separations were performed using 230-400 mesh Kieselgel 60 (E. Merck).

4-Aminopyrimidine 1-oxide (1). To a stirred solution of 4-aminopyrimidine (0.20 g, 2.1 mmol) in DMF/MeOH (15 ml/5 ml) was added HF (48%, 0.1 ml, 2.5 mmol) and *m*-CPBA (85%, 0.90 g, 4.4 mmol). The reaction mixture was stirred for 30 min at 25 °C and poured slowly into cold water (100 ml) with stirring. The precipitated solids were filtered off. The filtrates were concentrated by evaporation. The oily residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH, 8/2/0.1) to afford the product (**1**) as a white solid (0.23 g, 98%); mp 198-201 °C (lit.,[13] 196-197 °C).

2-Aminopyrimidine 1-oxide (2). 2-Aminopyrimidine (0.25 g, 2.6 mmol), HF (0.2 ml, 5.0 mmol), and *m*-CPBA (1.36 g, 6.7 mmol) in DMF/MeOH (15 ml/5 ml) were treated according to the same procedure as above. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH, 8/2/0.1) to afford the product (**2**) as a white solid (0.26 g, 90%); mp 180-183 °C (lit.,[14] 185-187 °C).

4-Chloro-2,6-diaminopyrimidine 1-oxide (3). 4-Chloro-2,6-diaminopyrimidine (0.5 g, 3.46 mmol), HF (0.2 ml, 5.0 mmol), and *m*-CPBA (1.49 g, 7.34 mmol) in DMF/MeOH (15 ml/5 ml) were treated according to the same procedure as above. The viscous brown residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH, 8/2/0.1) to afford the product (**3**) as a white solid (0.49 g, 88 %); mp 185 °C (decomp.) (lit.,[15] 185 °C (decomp.)).

2-Aminopyrazine 1-oxide (4). 2-Aminopyrazine (0.2 g, 2.1 mmol), HF (0.1 ml, 2.5 mmol) , and *m*-CPBA (0.9 g, 4.4 mmol) in DMF/MeOH (30 ml/10 ml) were treated according to the same procedure as above. The oily residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH, 8/2/0.1) to afford the product (**4**) as a brown solid (0.23 g, 99%); mp 170-174 °C (lit.,[14] 178-180 °C).

3,5-Lutidine 1-oxide (5). 3,5-Lutidine (0.5 g, 4.67 mmol) , HF (0.2 ml, 5.0 mmol), and *m*-CPBA (2.0 g, 9.8 mmol) in DMF/MeOH (60 ml/20 ml) were treated according to the same procedure as above. The oily residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 10/1) to afford the product (**5**) as a white solid (0.49 g, 85%); mp 97-99 °C (lit.,[16] 101-102 °C).

Nicotinic acid *N*-oxide (6). Nicotinic acid (0.35 g, 2.84 mmol), HF (0.2 ml, 5.0 mmol), and *m*-CPBA (1.15 g, 5.68 mmol) in DMF/MeOH (60 ml/20 ml) were treated according to the same procedure as above. The oily residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 10/1) to afford the

product (**6**) as a white solid (0.34 g, 87%); mp 260 °C (decomp.) (lit.,[11] 254-255 °C).

Cytidine 3-oxide (**7**). A mixture of cytidine (0.48 g, 2.0 mmol) in DMF/MeOH (20 ml/5 ml) was heated at 50 °C until becoming a clear solution. HF (0.1 ml, 2.5 mmol) and *m*-CPBA (1.0 g, 4.9 mmol) were added and the reaction mixture was stirred for 30 min, and the cooled reaction mixture poured slowly into water (100 ml) with stirring. The solid materials were filtered off. The filtrates were concentrated by evaporation in vacuo. The residue was dissolved in MeOH/H_2O (9/1, 7 ml) and then triturated into ethyl acetate (200 ml) to precipitate the product. After filtration and drying the product (**7**) was obtained as a light brown powder (0.47 g, 90%); mp 160 °C (lit.,[12] > 220 °C).

Adenosine 3-oxide (**8**). Adenosine (0.27 g, 1 mmol) was dissolved in DMF/MeOH (50 ml/10 ml) at an ambient temperature. HF (0.1 ml, 2.5 mmol) and *m*-CPBA (0.43 g, 2.1 mmol) were added and stirred for 16 h at room temperature. The reaction mixture was poured slowly into ice-water (300 ml) with stirring. The precipitated solids were filtered off and the filtrates were concentrated by evaporation in vacuo. The residue was dissolved in MeOH/H_2O (9/1, 10 ml) and then triturated into ethyl acetate (150 ml) to precipitate the product. After filtration and drying the product (**8**) was obtained as a light brown powder (0.27 g, 95%); mp 158 °C (lit.,[18] 155 °C (decomp.)).

REFERENCES

1. (a) A. Albini and S. Pietra, " Heterocyclic N-Oxides", CRC Press, Boca Raton, 1991. (b) A. Albini, *Synthesis*, 1993, 263. (c) A. Katritzky and J. M. Lagowski, " Chemistry of Heterocyclic N-Oxides, Academic Press, London, 1971.
2. (a) Y. Mizuno, K. Ikeda, T. Endo, and K. Tsuchida, *Heterocycles*, 1977, **7**, 1189. (b) M. MacCoss, E. K. Ryu, R. S. White, and R. L. Last , *J. Org. Chem.*, 1980, **45**, 788.
3. (a) M. Ochiai, O. Aki, A. Morimoto, T. Okata, and T. Kaneko, *Tetrahedron Lett.*, 1972 , 2345. (b) K. Iwamatsu, K. Shudo, and T. Okamoto, *Heterocycles*, 1983, **20**, 5.
4. (a) J. D. Lee, D. S. Brown, and B. G. A. Melsom, *Acta Crystallogr., Sect.* B, 1969, **25**, 1378. (b) C. J. O'connor, E. Sinn, and R. L. Carlin, *Inorg. Chem.*, 1977, **16**, 3314.
5. T. J. Kress, *J. Org. Chem.*, 1985, **50**, 3073.

6. L. R. Subbaraman, J. Subbaraman, and E. J. Behrman, *Biochemistry*, 1969, **8**, 3059.

7. P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney, and N. Thompson, *Synthesis*, 1987, 1015.

8. (a) A. Pollak, B. Stanovink, and M. Tisler, *J. Org. Chem.*, 1970, **35**, 2478. (b) D. Kyriacou, *J. Heterocycl. Chem.*, 1971, **8**, 697.

9. (a) A. R. Gallopo and J. O. Edwards, *J. Org. Chem.*, 1981, **46**, 1684. (b) R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, 1985, **50**, 2847.

10. (a) D. J. Brown, " The Pyrimidines ", Wiley Interscience, New York, 1970, Supplement I. (b) D. J. Brown, " The Pyrimidines ", Wiley Interscience, New York, 1962.

11. (a) H. R. Kim, J. H. Jung, J. N. Kim, and E. K. Ryu, *Synth. Commun.*, 1990, **20**, 637. (b) H. J. Kim, H. R. Kim, J. N. Kim, and E. K. Ryu, *Bull. Korean Chem. Soc.*, 1990, **11**, 184. (c) K. H. Chung, K. M. Kim, J. N. Kim, and E. K. Ryu, *Synth. Commun.*, 1991, **21**, 1917. (d) H. R. Kim, K. H. Chung, H. J. Kim, and E. K. Ryu, *Bull. Korean Chem. Soc.*, 1992, **13**, 579. (e) K. M. Kim, K. H. Chung, J. N. Kim, and E. K. Ryu, *Synthesis*, 1993, 283.

12. T. J. Delia, M. J. Olsen, and G. B. Brown, *J. Org. Chem.*, 1965, **30**, 2766.

13. M. V. Jovanovic, *Can. J. Chem.*, 1984, **62**, 1176.

14. L. W. Deady, *Synth. Comm.*, 1977, **7**, 509.

15. (a) J. P. Allaigre and J. Desbois, Fr. Denmande FR 2632954 (*Chem. Abstr.*, 1990, **113**, 212009m). (b) J. M. McCall, R. E. TenBrink, and J. J. Ursprung, *J. Org. Chem.*, 1975, **40**, 3304.

16. F. M. Hershenson and L. Bauer, *J. Org. Chem.*, 1969, **34**, 655.

17. E. C. Taylor and A. J. Crovetti, *J. Chem. Soc.*, 1954, 1633.

18. (a) M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, 1958, **80**, 2755. (b) T. Fujii, T. Saito, and T. Nakasaka, *Chem. Pharm. Bull.*, 1989, **37**, 2601.

19. (a) W. C. Anthony (Upjohn Co.), Ger. Offen. 2,114,887 (*Chem. Abstr.*, 1972, **76**, 34284e). (b) Upjohn Co., Neth. Appl. 6,615,385 (*Chem. Abstr.*, 1968, **68**, 21947h). (c) J. M. McCall, R. E. TenBrink, and J. J. Ursprung, *J. Org. Chem.*, 1975, **40**, 3304. (d) H. J. Schostarez, PCT Int. Appl. WO 9208705 (*Chem. Abstr.*, 1992, **117**, 90319x).

Received, 13th October, 1994