Int. J. Chem. Sci. : 1 (3), 2003, 267–271

SYNTHESIS OF IMINO–ETHER TYPE COMPOUNDS THROUGH SULFONYLATION OF N–ACYL–O–ALKYL HYDROXYLAMINES

A. S. SINGHA* AND B. S. KAITH

Department of Applied Sciences,
National Institute of Technology (NIT), HAMIRPUR–177 005 (H. P.) INDIA

ABSTRACT

A number of imino–ether type of compounds (IV) have been prepared by sulfonylation of O–alkyl arylcarbohydroximic acids in pyridine. Sulfonylation was carried out by using different sulfonylating agents such as p–toluence sulfonyl chloride, benzene sulfonyl chloride, p–nitro benzene sulfonyl chloride and methane sulfonyl chloride. The structural elucidation of various compounds thus synthesized was done by physical and spectroscopic techniques.

Key words: Imino–ethers, Sulfonylation, N–Acyl–O–alkyl hydroxylamines

INTRODUCTION

Sulfonylation of O–alkyl hydroxamic acids and their derivatives is not a well investigated field. Cooley *et al.*[1] were the first to attempt sulfonylation of a number of O–alkyl hydroxamic acids and reported the formatin of p–toluene sulfonyl–N–benzyloxy benzimino–ehter when sodium salt of O–benzyl benzohydroxamic acid was reacted with p–toluence sulfonyl chloride in benzene. The reaction of acetyl chloride with potassium or silver salt of N–acyl–O–alkyl hydroxylamines can lead to the formation of both; O–and N–acylated products[2]. Misra *et al.*[3,4] have also reported synthesis of few imino–ether and isoimides. Imino–ethers are useful starting materials for the preparation of amidines, hydroxamic alkyl ethers and thioesters[5]. Recently, these compiunds have been screened for their anti–cancer activity by National Institute of Health, USA and have been found as potential anti–cancer agents[6]. Encouraged by this finding, we have started a comprehensive research work in our laboratory to synthesise imino–ether type compounds through sulfonylation of some N–acyl–O–alkyl hydroxylamines expected to show a wide spectrum of biological activity[7–12].

EXPERIMENTAL

Melting points reported were taken in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel G. IR, ^{1}H NMR and MS were recorded on Perkin–Elmer 2378, Jeol FT–100 and Jeol D–300 instruments, respectively. Various N–acyl–O–alkyl hydroxylamines were prepared by the reported methods in the literature.[13–14]

General method for the sulfonylation of N–acyl–O–alkyl hydroxylamines : N–acyl–O–alkyl hydroxylamine (0.01 mol) was treated with alkyl/aryl sulfonyl chloride (0.01 mol) in 25 mL of pyridine. The mixture was stirred for 72 hours and the progress of the reaction was monitored by TLC. After the completion of the reaction, the excess of the pyridine was removed and the residue was washed with water followed by extraction with chloroform (3 x 50 mL). The chloroform layer was washed successively with saturated sodium bicarbonate solution (2 x 50 mL) and 10% HCl (1 x 50 mL). The solution was dried over anyhydrous sodium sulphate and then concentrated to half of its volume. After storage in a refrigerator, the product was separated and recrystallised.

p–Nitrobenzene sulfonyl N–benzyloxy benziminoether (IVa) : It was isolated as solid material (60%), M. P. 116–117°; $C_{20}H_{16}N_2O_6S$ calcd for: C, 58.25; H, 3.88; N, 6.79; S, 7.76% (Found: C, 58.21; H, 3.92; N, 6.81; S, 7.72%); IR (KBr) 1644 (C=N), 1370 (SO_2), 1155 (OSO_2), 1360 (C–NO_2), 835 cm^{-1} (Ar); ^1H NMR δ ($CDCl_3$) 4.91 (2H, m, OCH_2), 7.35–8.2 (14 H, m, Ar–H).

p–Nitrobenzene sulfonyl–N–benzyloxy–p–methoxylbenzo iminoether (IVb): It was obtained as a solid (48%), M. P. 105–106 °C; IR (KBr) 1630 (C=N), 1340 (SO_2), 1160 (OSO_2), 1365 (C–NO_2), 825 cm^{-1} (Ar); ^1H NMR δ ($CDCl_3$) 4.93 (2H, m, OCH_2), 7.2–7.6 (13H, m, Ar–H).

p–Nitrobenzene sulfonyl N–benzyloxy p–chlorobenziminoether (IVc) : It was a light yellow solid (55%), M.P. 162-163°C; IR (KBr) 1590 (C=N), 1365 (SO_2), 1155 (OSO_2), 1360 (C-NO_2), 835 cm^{-1} (Ar); ^1H NMR δ ($CDCl_3$) 4.93 (2H, m, OCH_2), 7.2-7.6 (13H, m, Ar-H).

p–Nitrobenzene sulfonyl N–benzyloxy p–nitrobenziminoether (IVd): It was obtained as a yellow ppt. (50%), M. P. 170–171 °C; IR (KBr) 1605 (C=N), 1370 (SO_2), 1156 (OSO_2), 1355 (C–NO_2), 835 cm^{-1} (Ar); ^1H NMR δ ($CDCl_3$) 4.98 (2H, m, OCH_2), 7.2–7.8 (13H, m, Ar–H).

Benzensulfonyl N–benzyloxy p–methoxybenziminoether (IV e) : It was obtained as a liquid (62%), IR (KBr) 1590 (C=N), 1350 (SO_2), 1155 (OSO_2), 825 cm^{-1} (Ar); ^1H NMR δ ($CDCl_3$) 3.75 (3H, s, OCH_3), 4.97 (2H m, OCH_2), 6.8–8.2 (14H, m, Ar–H).

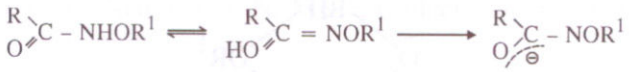
Methanesulfonyl N–benzyloxy p–methoxybenziminoether (IVf) : It was also obtained as a liquid (60%), IR (KBr) 1600 (C=N), 1360 (SO_2), 1160 (OSO_2), 810 cm^{-1} (Ar); ^1H NMR δ ($CDCl_3$) 3.7 SO_2 (3H, s, SO_2CH_3), 3.8 (3H, s, OCH_3), 5.1 (2H, m, OCH_2), 6.8–8.3 (9H, m, Ar–H).

p–Nitrobenzenesulfonyl N–propargyloxybenziminoether (IVg) : It was a yellow solid (70%), M. P. 112–113°C, $C_{16}H_{12}N_2O_6S$ calcd for: C, 53.33; H, 3.33; N, 7.78; S, 8.88% (found: C, 53.35; H, 3.37; N, 7.75; S, 8.86%); IR (KBr) 1645 (C=N), 1330 (SO_2), 1170 (OSO_2), 1360 (CNO_2), 790 cm^{-1} (Ar), ^1H NMR δ ($CDCl_3$), 2.8 (1H, s, C ≡ CH), 4.1 (2H, s, OCH_2) 6.8–7.4 (9H, m, Ar–H); MS m/z 360 (M^+ 58%), 175 (M^+–185, 100), 121 (M^+–185–54, 50), 105 (40), 77 (25).

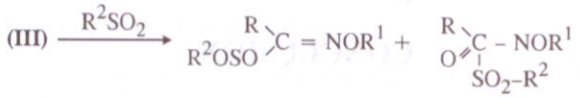
p–Nitrobenzenesulfonyl N–propargyloxy p–Nitrobenziminoether (IVh): It was a dirty white solid (63%), M.P. 126–127 °C, IR (KBr) 1647 (C=N), 1330 (SO_2), 1170 (OSO_2), 1360 (C–NO_2), 790 cm^{-1} (Ar); ^1H NMR δ ($CDCl_3$) 2.7 (1H, s, C=CH), 4.1 (2H, s, OCH_2), 6.9–7.8 (8H, m, Ar–H).

RESULTS AND DISCUSSION

Sulfonylation of N–acyl–O–alkyl hydroxylamine was carried out at room temperature in pyridine in the presence of a variety of sulfonylating agents. O–alkyl hydroxamic acid (I) tautomerises to O–alkyl hydroximic acid (II) which upon treatment with pyridine leads to the formation of an ambident anion (III). This anion on sulfonylation could afford isoimide (IV) and imide (V) products. This is because of the fact that the anion (III) has two active sites which could lead to the formaitn of O– or N– sulfonylated products. In polar aprotic solvent pyridine, the negative charge of the ambident anion is located on the more electronegative oxygen atom. Upon treatment of this anion with sulfonyl halide, sulfonyl group becomes preferentially attached to more electronegative oxygen atoms to give the product (IV)[15]. N–sulfonylated product (V) if at all formed, could not be isolated.



(I) **(II)** **(III)**



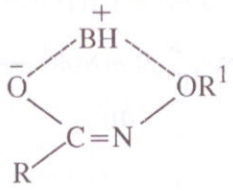
(IV) **(V)**

Compound	R	R^1	R^2
(IVa)	C_6H_5	$CH_2C_6H_5$	$C_6H_4NO_2$
(IVb)	$CH_3OC_6H_4$	$CH_2C_6H_5$	$C_6H_4NO_2$
(IVc)	Cl–C_6H_4	$CH_2C_6H_5$	$C_6H_4NO_2$
(IVd)	$NO_2C_6H_4$	$CH_2C_6H_5$	$C_6H_4NO_2$
(IVe)	$CH_3OC_6H_4$	$CH_2C_6H_5$	C_6H_5
(IVf)	$CH_3OC_6H_4$	$CH_2C_6H_5$	CH_3
(IVg)	C_6H_5	$CH_2C \equiv CH$	$C_6H_4NO_2$
(IVh)	$NO_2C_6H_4$	$CH_2C \equiv CH$	$C_6H_4NO_2$

Preferential O–sulfonylation can be explained with Kornblum theory[16] concerning the orientation of the alkyl group on the ambident anion derived from N–acyl–O–alkyl hydroxylamine. All the O–sulfonylated products in IR spectra show absorption at 1155–1170 cm^{-1} assigned to the –OSO_2 group, 1330–1370 cm^{-1} assigned to SO_2 and between 1590–1645 cm^{-1} attributed to the C=N functional group.

^{1}H NMR spectrum of p–nitrobenzene sulfonyl N–propargyloxy benzimino-ether showed absorptions at δ 2.8 (1H, s, ≡ CH), δ 4.1 (2H, s, OCH_2) and 6.8–7.4 (9H, m, Ar–H). It is interesting to note that OCH_2 proton showed a little up–field absorption as compared to the OCH_2 protons in the starting N–benzoyl–O–propargyl hydroxylamine (2H, s, 4.7). This indicates that OCH_2 protons of the compounds (IV) are little shielded due to the presence of p–nitro phenyl group and such a shielding can be obsrved if it has isomide structure (IV). Misra *et al.*[17] have also observed that upon sulfonylation of sodium salt of N–acyl–O–alkyl hydroxylamine in benzene, products having iminoether type structure are obtained.

Ei mass spectrum of p–nitrobenzene sylfonyl N–propargyloxy benziminoether exhibited the molecular ion peak at m/z 360 (58%) with strong peaks at m/z 175 (M^+–SO_2 $C_6H_4NO_2$, 100%), 121 (M^+–$SO_2C_6H_4NO_2$–HC=C–CHO, 50%), 105 (M^+–185–54–16, 40%), 77 (M^+–185–54–16–28, 25%). Similar fragmentation pattern for the mass spectroscopic behaviour of methane sulfonyl N–benzyloxy benziminoether has already been proposed by Misra *et al.*[18]. These studies clearly establish that the iminoether is best represented by structure (IV) in which the sulfonyl group is atached to the oxygen. Formation of the structure (IV) could result through transition state (VI) involving a protonated base (BH).



CONCLUSION

Imino–ether type of compounds (IV) prepared by sulfonylation of O–alkyl arylcarbohydroximic acids in pyridine have been found to exhibit anti–cancer activities. Sulfonylation of N–acyl–O–alkyl hydroxylamines affords the better path for the synthesis of iminoether type compounds. The various compounds reported in this paper are already under testing for various biological ctivities. These compounds also serve as the precursors for the synthesis of a wide variety of organic compounds such as amidines, hydroxamic alkyl ethers, thioesters etc.

REFERENCES

1. J. H. Cooley, B. N. Misra, J. R. Throckmorton and W. D. Wills, J. Med. Chem., **II**, 196 (1969).
2. A. D. Ward and M. T. W. Hearn, Aust. J. Chem., **22**, 1731 (1969).
3. B. N. Misra, A. S. Singha, G. S. Chauhan and R. P. Sharma, Ind. J. Chem. Sect. B, **23**, 728 (1984).
4. B. N. Misra, R. P. Sharma and Disha, Ind. J. Chem. **25B**, 118 (1986).

5. R. Delabi, Bull. Soc. Chim. Fr. **12**, 152, 954 (1945); **11**, 227, 234 (1944).
6. V. L. Narayanan, National Cancer Institute, Maryland, USA, Private Comm.
7. A. S. Singha and B. N. Misra, Ind. J. Chem., **21B**, 361 (1982).
8. C. Indiani, A. Feis, B. D. Howes, M. P. Marzocchi and G. Smulevich, J. Am. Chem. Soc, **122**, 7368 (2000).
9. C. T. Supuran and A. Scozzafava, Eur. J. Pharm. Sci., **10**, 67 (2000).
10. A. Scozafava and C. T. Supuran, Eur. J. Med. Chem., **35**, 299 (2000).
11. M. G. William, Q.–Z. Ye, F. Molina, L. L. Johnson, D. F. Ortwine, A. Pavlovski, J. R. Rubin, R. Skean, A. D. White and T. L. Blundell, Croa Chem. Acta, **72**, 575 (1999).
12. Q.–Z. Ye, L. L. Johnson, D. J. Hupe, D. F. Ortwine, J. B. Dunbar, J. R. Rubin, A. Pavlovski, C. Humblet and T. L. Blundell, Structure, **4**, 375 (1996).
13. B. N. Misra, C. S. Pandey, R. K. Mahajan, J. K. Jassal and I. K. Mehta, Ind. J. Chem., **49**, (1977).
14. J. H. Cooley, W. D. Bills and J. R. Throckmorton, J. Org. Chem. **25**, 1734 (1960).
15. S. Lakhanpal, C. G. Rao and B. N. Misra, Collect. Czech. Chem. Commun., **57**, 540 (1992).
16. H. Kornbulum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, J. Am. Chem. Soc., **77**, 6269 (1955).
17. B. N. Misra, Ind. J. Chem., **1**, 546 (1973).
18. N. Sharma and B. N. Misra, Collect. Czech. Chem. Commun. **54**, 2738 (1989).

Accepted : 8.7.2003