Int. J. Chem. Sci. : 1 (1), 2003, 25–30

NOVEL SYNTHESIS OF OXYGEN SUBSTITUTED HYDROXYLAMINE DERIVATIVES OF HETEROCYCLIC COMPOUNDS

LALIT KUMAR BAREGAMA, RANJANA SHARMA, BHAWANI SINGH, SHILPI JAIN and G. L. TALESARA*

Synthetic Organic Chemistry Laboratory, Department of Chemistry
M. L. Sukhadia University, Udaipur–313 002 (Raj.), INDIA
E–mail: gtalesara@yahoo.com

ABSTRACT

3–heterocycl–yl propene (**3a–c**) prepared by condensation of allyl bromide (2) with corresponding heterocycles (**1a–c**). It was brominated to give 2,3–dibromo–1–heterocycl–yl propane (**4a–c**). N–hydroxyphthalimide, N–hydroxysuccinimide, benzohydroxamic acid and benzophenone oxime were refluxed separately with (**4a–c**), to give corresponding 2,3–disubstituted–1–heterocycl–yl propane derivatives (**5a–l**).

Key words: Hydroxyphthalimide, Hydroxysuccinimide, Benzohydroxamic acid, Benzophenone oxime, 3–(N–heterocycl–yl) propene.

INTRODUCTION

The importance of heterocyclic derivatives as chemotherapeutic agents is well established and their chemistry has been extensively studied. Imidazole, benzimidazole and benzotriazole derivatives are associated with potent biological activities such as antimicrobial[1–4], anticancer[5,6], herbicidal[7], CNS–depressant[8], anti–inflammatory[9–11] and psychotogenic activities[12,13]. In our previous work on oxygen–substituted hydroxylamine derivatives of heterocycles, a number of such compounds have been prepared and tested for antibacterial[14] and antimalarial[15] activities and found active. Prompted by this, some novel heterocyclic compounds containing imidoxy and related functionalities have been synthesized.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr) were recorded on Perkin–Elmer 1800 (FTIR) and Jasco FTIR–410 spectrophotometer. ^1H NMR spectra ($CDCl_3$) were recorded on a Bruker DRX 300 (300 MHz FT NMR) and Varian spectrometer (270 MHz) using TMS as internal standard and mass spectra were determined on a Jeol D–300 (EI) spectrometer. Purity of compounds were checked on silica gel– TLC plates using benzene and ethyl acetate as solvent. Visualization of spots was carried out in an iodine chamber.

Preparation of 3–Heterocycl–yl propene ***(3a–c)***

Imidazole (**1a**, 0.03 mole) was dissolved in acetone (16 mL) and allyl bromide (**2**, 0.03 mole) was added with constant shaking. It was refluxed for an hour and then added anhydrous K_2CO_3. It was further refluxed for 6 hours. The solvent was removed by distillation under reduced pressure. The residue was used as such for the next step. Compounds (**3b–c**) were also prepared by the similar method.

3a, 59%; **3b,** 54%; **3c,** 51%.

Preparation of 2,3–dibromo–1–heterocycl–yl propane ***(4a–c)***

Semi solid (**3a**) was dissolved in chloroform (15 mL) and a calculated amount of bromine was added slowly with constant stirring till the colour disappeared. Solvent was removed under reduced pressure and light yellow residue was used as such in the next step. Compounds (**4b–c**) were also prepared by the similar method.

4a, 53%; m.p. 128°; **4b,** 51%; m.p. 217°; **4c,** 47%; m.p. 147°

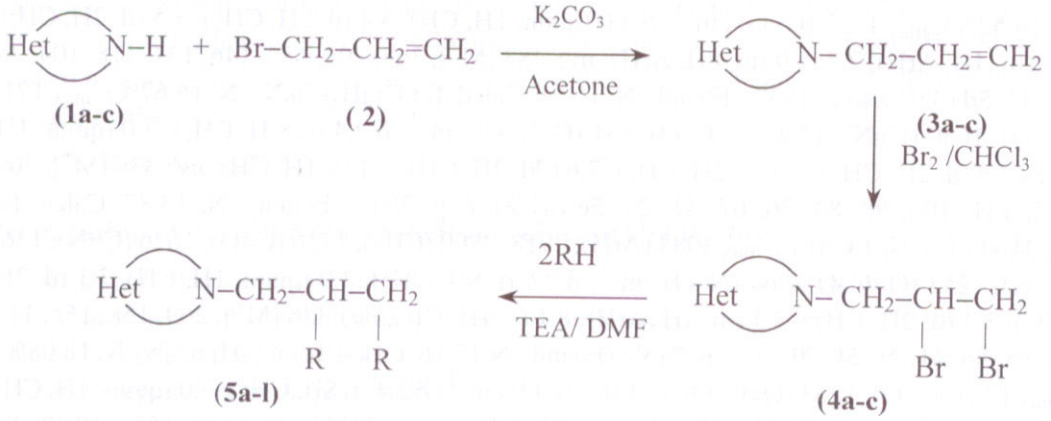
Synthesis of 2,3–bis(oxyphthalimido / oxysuccinimido / oxybenzhydroxamato / benzophenone oxime)–1–heterocycl–yl propane ***(5a–l)***

2,3–Dibromo–1–imidazol–yl propane (**4a**, 0.1 mole) was dissolved in minimum amount of DMF (20 mL). A concentrated solution of N–hydroxyphthalimide (0.2 mole) in DMF was added slowly with constant stirring. Triethylamine (30 mL) was added all at a time. The reaction mixture was kept for 48 hours at room temperature with occasional shaking. Solid triethylammonium bromide obtained was filtered on vacuum pump. It was washed with two 5.0 mL portion of DMF. The filtrate was poured into 800 g of crushed ice with constant stirring. Semi solid obtained was converted to white dispersible solid (**5a**) by tituration with alcohol. It was filtered and crystallized from absolute alcohol. Compounds (**5b–c**) were also synthesized by similar method but in condensation with N–hydroxysuccinimide, methanol was used as a solvent. The products (**5d–f**) were obtained by cooling the concentrated filtrate. Benzohydroximate compounds (**5g–i**) were obtained by refluxing potassium benzohydroxamates with (**4a–c**) in methanol. The hot contents were filtered and the filtrate gave product on cooling (**5g–i**). The compounds with oxime (**5j–l**) were obtained by refluxing (**4a–c**) with benzophenone oxime in alcoholic KOH solution. White crystals were obtained on cooling the filtrate.

5a (40%), m.p. 210–213° (Found : N, 11.51.Calcd. for $C_{22}H_{16}O_6N_4$; N, 12.96%); $_{max}$ 3048 (ArH), 2926 (CH_2), 1781 (C=O), 1600, 1510, 1460 (C=C), 1376 (CO–O), 1303, 1036 (C–N), 634 (C–N– O) cm^{-1}; δ 2.9 (quint, 1H, CH), 3.2 (d, 2H, CH_2), 3.4 (d, 2H, CH_2), 7.5 (dd, 2H, CH), 7.7 (m, 8H, ArH), 8.5 (s, 1H, CH); *m/z* 432 [M^+], 365, 203, 167, 146, 132, 108, 104,76, 50, 41.
5b: (37%), m.p.286°; (Found : N, 10.64. Calcd. for $C_{26}H_{18}O_6N_4$: N, 11.62%); $_{max}$ 3043 (ArH),

2916 (CH_2), 1723 (C=O), 1634 (C=N) cm^{-1}; δ 2.8 (quint, 1H, CH), 3.1 (d, 2H, CH_2), 3.3 (d, 2H, CH_2), 7.5 (m, 4H, ArH), 7.7 (m, 8H, ArH), 8.5 (s, 1H, CH); *m/z* 482 [M^+], 365, 203, 158, 146, 132, 117, 104, 76, 50, 41. **5c** (30%), m.p. 203°; (Found : N, 13.02. Calcd. for $C_{25}H_{16}O_6N_5$; N, 14.52%); $_{max}$ 1727 (C=O) cm^{-1}; δ 3.0 (quint, 1H, CH), 3.4 (d, 2H, CH_2), 3.5 (d, 2H, CH_2), 7.4 (m, 4H, ArH), 7.8–7.9 (m, 8H, ArH); m/z 483 [M^+], 365, 203, 159, 146, 132, 118, 104, 76, 50, 41. **5d** (43%), m.p. 183°; (Found : N, 16.01. Calcd. for $C_{14}H_{16}O_6N_4$; N, 16.67%); $_{max}$ 1711 (C=O), 1630 (C=N), 1260 (O=C–O), 631 (C–N–O) cm^{-1}; δ 2.4 (t, 8 H, CH_2), 3.0 (quint, 1H, CH), 3.3 (d, 2H, CH_2), 3.4 (d, 2H, CH_2), 7.6 (dd, 2H, CH), 8.4 (s, 1H, CH); *m/z* 336 [M^+], 269, 155, 141, 108, 98, 84, 56, 67, 41, 28. **5e** (31%), m.p. 263°; (Found : N, 13.87. Calcd. for $C_{18}H_{18}O_6N_4$; N, 14.50%); $_{max}$ 3084 (ArH), 2918, 2860 (CH_2), 1726 (C=O), 1626 (C=N), 1369 (C–N), 1253 (O=C–O), 964 (N–O) cm^{-1}; δ 2.5 (t, 8H, CH_2), 3.0 (quint, 1H, CH), 3.1 (d, 2H, CH_2), 3.3 (d, 2H, CH_2), 7.3 (m, 4H, ArH), 8.1 (s, 1H, CH); *m/z* 386 [M^+], 269, 158, 155, 117, 98, 84, 56, 41, 28. **5f** (29%), m.p. 215°; (Found : N,17.16. Calcd. for $C_{17}H_{17}O_6N_5$ N, 18.08%); ν_{max} 1721 (C=O), 1263 (O=C–O), 631 (C–N–O) cm^{-1}; δ 2.4 (t, 8H, CH_2), 3.0 (quint, 1H, CH), 3.1 (d, 2H, CH_2), 3.4 (d, 2H, CH_2), 7.6 (m, 4H, ArH), *m/z* 387 [M^+], 269, 159, 155, 118, 98, 84, 56, 41, 28. **5g** (41%), m.p. 231° (Found : N, 14.07. Calcd. for $C_{20}H_{20}O_4N_4$; N, 14.73%); ν_{max} 3410 (N–H), 3056 (ArH), 1720 (C=O), 1361 (C–N), 1269 (O=C–O) cm^{-1}; δ 3.0 (quint, 1H, CH), 3.1 (d, 2H, CH_2), 3.2 (d, 2H, CH_2), 5.9 (s, 1H, NH), 7.5 (dd, 2H, CH), 7.8 (m, 10H, ArH), 8.8 (s, 1H, CH); *m/z* 380 [M^+], 313, 117, 108, 105, 77, 67, 51, 41. **5h** (37%), m.p. 211°; (Found : N, 12.60. Calcd. for $C_{24}H_{22}O_4N_4$; N, 13.02%); ν_{max} 3406 (N–H), 3071 (ArH), 2871 (CH_2), 1726 (C=O), 1369 (C–N), 1286 (O=C–O), 631 (O–C–N) cm^{-1}; δ 3.0 (quint, 1H, CH), 3.2 (d, 2H, CH_2), 3.3 (d, 2H, CH_2), 5.8 (s, 1H, NH), 7.6 (m, 4H, ArH), 7.8 (m, 10H, ArH), 8.3 (s, 1H, CH); *m/z* 430 [M^+], 313, 177, 158, 117, 105, 77, 51, 41. **5i** (40%), m.p 276°; (Found : N, 15.63; Calcd. for $C_{23}H_{21}O_4N_5$; N, 16.24%); ν_{max} 3396 (N–H), 3036 (ArH), 1716 (C=O), 1338 (C–N), 1267 (O=C–O), 643 (O–C–N) cm^{-1}; δ 2.9 (quint, 1H, CH), 3.1 (d, 2H, CH_2), 3.3 (d, 2H, CH_2), 5.8 (s,1H, NH), 7.4 (m, 4H, ArH), 7.8 (m, 10H, ArH); *m/z* 431 [M^+], 313, 177, 159, 118, 105, 77, 51, 41. **5j** (29%), m.p. 192° (Found : N, 10.75. Calcd. for $C_{32}H_{28}O_2N_4$; N, 11.20%); ν_{max} 3030 (Ar–H), 2916 (CH_2), 1734 (C=O), 1641 (C=N), 1580, 1476 (C=C), 1263 (O=C–O), 1349 (C–N), 956 (N–O), 618 (C–N–O) cm^{-1}; δ 3.0 (quint, 1H, CH), 3.4 (d, 2H, CH_2), 3.4 (d, 2H, CH_2), 5.8 (s, 1H, NH), 7.4 (dd, 2H, CH), 7.7–7.8 (m, 20H, Ar–H), 8.2 (s, 1H, CH); *m/z* 433 [M^+], 237, 180, 108, 103, 77, 67, 51, 41. **5k** (43%), m.p. 241°; (Found : N, 9.32. Calcd. for $C_{36}H_{30}O_2N_4$; N, 10.18%); ν_{max} 3077 (ArH), 2930 (CH_2), 1725 (C=O), 1653 (C=N), 1351 (C–N), 1256 (O=C–N), 960 (C–O), 619 (C–N–O) cm^{-1}. δ 3.0 (quint, 1H, CH), 3.2 (d, 2H, CH_2), 3.4 (d, 2H, CH_2), 7.3 (m, 4H, ArH), 7.6–7.8 (m, 20H, ArH), 7.9 (s, 1H, CH), *m/z* 550 [M^+], 433, 237, 180, 158, 117, 103, 77, 51, 41. ***5l*** (44%), m.p. 213°; (Found : N, 12.03. Calcd. for $C_{35}H_{29}O_2N_5$; N, 12.70%); $_{max}$ 3090 (ArH), 2920 (CH_2), 1710 (C=O), 1284 (O=C–N), 960 (N–O) cm^{-1}. δ 3.0 (quint, 1H, CH), 3.2 (d, 2H, CH_2), 3.4 (d, 2H, CH_2), 7.3 (m, 4H, ArH), 7.6–7.8 (m, 20H, ArH), 7.9 (s, 1H, CH); *m/z* 551 [M^+], 433, 237, 180, 159, 118, 103, 77, 51, 41.

Reaction sequence:



(1a-c) **(2)** **(5a-l)** **(4a-c)**

(1a),(3a),(4a): Het = Imidazole

(1b),(3b),(4b): Het = Benzimidazole

(1c),(3c),(4c): Het = Benzotriazole

Compounds	Het	R
5a	Imidazole	Phthalimidoxy
5b	Benzimidazole	Phthalimidoxy
5c	Benzotriazole	Phthalimidoxy
5d	Imidazole	Succinimidoxy
5e	Benzimidazole	Succinimidoxy
5f	Benzotriazole	Succinimidoxy
5g	Imidazole	Benzohydroxymate
5h	Benzimidazole	Benzohydroxymate
5i	Benzotriazole	Benzohydroxymate
5j	Imidazole	Benzophenone oxime
5k	Benzimidazole	Benzophenone oxime
5l	Benzotriazole	Benzophenone oxime

Scheme–I

RESULTS AND DISCUSSION

3–bromopropene (**2**) was condensed with imidazole, benzimidazole and benzotriazole in presence of K_2CO_3 in acetone. Active hydrogen present on the nitrogen of these heterocyclic compounds were replaced by allyl group and gave substituted heterocycl–yl propene (**3a–c**). It was confirmed by disappearance of N–H peak around 3300 cm^{-1} in IR spectra and PMR signal at δ 5.2 and appearance of a new C–N band around 1351cm^{-1}. It was brominated and light yellow solids of 2,3–dibromo–1–heterocycl–yl propane (**4a–c**) were separated when the solvent was distilled under reduced pressure. The dibromo compounds (**4a–c**) were condensed with N–hydroxyphthalimide, N–hydroxysuccinimide, potassium benzohydroxamate and benzophenone oxime (experimental, *vide supra*) to give corresponding bis compounds (**5a–*l*).** The reaction was further confirmed by mass spectral studies where M+2 peak present in (**4a–c**) was found absent in their products and a C–O band appeared at 960 cm^{-1} in IR.

ACKNOWLEDGMENT

The authors are thankful to the Head, Department of Chemistry , M. L. Sukhadia University, Udaipur for facilities and to the Head, RSIC, CDRI, Lucknow, for spectral studies and elemental analysis.

REFERENCES

1. S. M. El–Khawas and N. S. Habib, J. Heterocyclic Chem., **26**, 177 (1989).
2. L. L. Bannett (Jr) and H. I. Baker, J. Org. Chem., **22**, 707 (1957).
3. S. Rao and A. S. Mitra, Indian J. Chem., **15B**, 1060 (1977).
4. L. K. Baregama, B. Singh, T. Banu and G. L. Talesara, Indian J. Heterocyclic Chem., **11**, 203 (2002).
5. A. Boido, I. Vazzana and F. Sparatore, Studi. Sassar. Sez., **57**, 787,(1979); Chem. Abstr., **93**, 239320 m (1980).
6. P. R. Marshm, J. Heterocyclic Chem., **31**, 603 (1994).
7. A. Steigmann, Brit. J. Photo., **94**, 256 (1946).
8. V. Mues, W. Brandes and V. Paul, German Offen. de., **105**, 433 (1946).
9. A. K. Sengupta, M. P. Bajaj and U. Chand, J. Indian Chem. Soc., **55**, 992 (1978).
10. S. N. Sowhney, D. R. Kodali, G. S. Dhindsa and S. P. Singh, Indian J. Chem., **22B**, 584 (1983).
11. W. C. Campbell, J. Am. Med. Assoc., **216**, 2143 (1971).
12. H. H. Pennes and P. H. Hoch, Am. J. Psychiat., **113**, 887 (1957).

13. A. S. Halasz, Psychopharmacologia , **4**, 385 (1963).
14. S. Rajora, T. Banu, D. Khatri and G. L. Talesara, Asian J. Chem., **11**,1528 (1999).
15. G. L. Talesara and K. S. Suresh, Asian J. Chem., **9**, 635 (1997).
16. W. R. Orndroff and D. S. Pratt, Am. Chem. J., **47**, 89 (1912).
17. V. B. Ranadive and S. D. Samant, Indian J. Chem., **34B**, 364 (1995).

Accepted 20.3.2003