Synthesis and Characterization of Fused Pyrazole Derivatives of Ethoxyphthalimide

Swati Joshi[1], G. L. Talesara[2]
[1, 2]Department of Chemistry
[1]Swami Keshvanand Institute of Technology Management & Gramothan, Jaipur
[2]M.L. Sukhadia University, Udaipur
Email- swt_ojha@yahoo.co.in

Abstract: **In the present reaction series, a convenient method for the synthesis of 1-N-ethoxyphthalimido-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindolyl)alkyl]benz-imidazole (3.1-IVa-c) is described. Phthalic anhydride was made to react with ω-amino acids (glycine/alanine/phenylalanine) (3.1-Ia-c) in dry condition without using any solvent, to yield 1,3-dioxo-1,3-dihydro-2*H*-isoindole-2-yl)acetic/propanoic/2-phenyl acetic acid (3.1-IIa-c). The chemoselective reaction of –COOH group present in (3.1-IIa-c) with o-phenylenediamine led to the formation of 2-[1-(1*H*-benzimidazole-1-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (3.1-IIIa), 2-[1-(1*H*-benzimidazole-2-yl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (3.1-IIIb) and 2-[1-(1*H*-benzimidazole-1-yl)benzyl]-1*H*-isoindole-1,3(2*H*)-dione (3.1-IIIc) respectively. Replacement of imidazole NH proton of (3.1-IIIa-c) from ethoxyphthalimide moiety was carried out by their condensation with phthalimidoxyethyl bromide (2.I-II), resulted in the final compound (3.I-IVa-c). All the compounds were characterized by elemental analysis, IR, NMR and mass spectroscopy.**

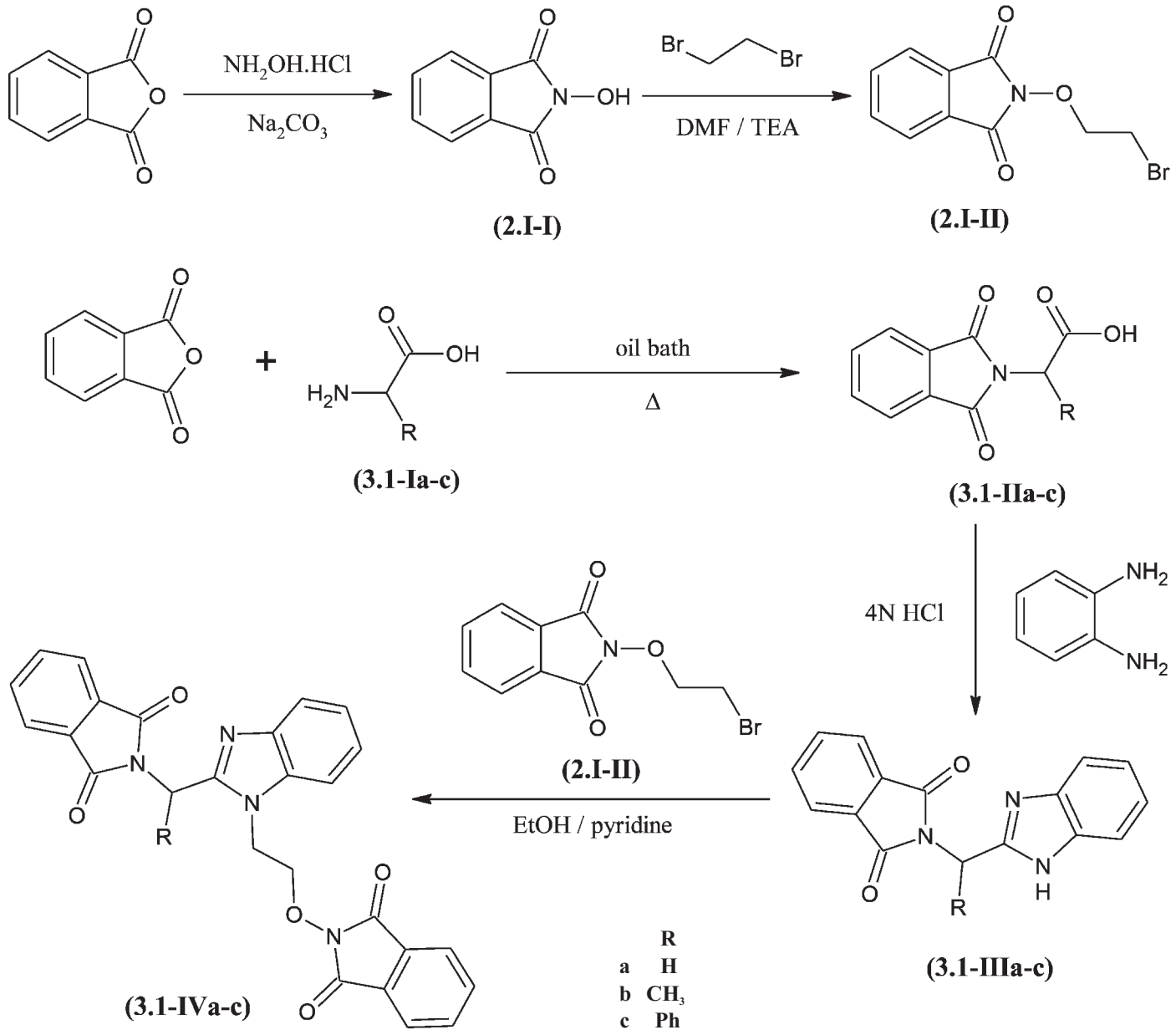
1. INTRODUCTION

Compounds such as thiabendazole, parbendazole and mebendazole are used mainly as antihelmintic agents[1]. Some heterocyclic systems linked to benzimidazole at 2-position have been patented for their marked fungicidal activity[2-4]. Role of benzimidazoles as diuretic and sedative[5], psychotropic[6], antiinflammatory[7] and antiulcer agents[8] is also well documented in the literature. Substituted imidazolinones were found to be exceedingly effective herbicidal agents useful for the control of an exceptionally wide variety of plants[9]. The imidazole nucleus has proven to be unusually fertile source of medicinal agents such as nasal decongestants[10], antiprotozol agents and antifungal agents[11]. Benzimidazole derivatives are of wide interest because of their diverse biological activity. This ring system is present in numerous parasitic, fungicidal, antihelmintic, antiinflammatory and antihypertensive drugs[12-14]. There are reports that benzimidazole compounds have been considered as potential antiviral agents since these were found to inhibit the multiplication of Japanese Encephalitis Virus (JEV), Herpes Simplex Virus type-I (HSV-I), Encephalomycocarditis Virus (EMCV), Influenza Virus (IV) and Semiliki Forest Virus (SFV) in addition to displaying antimicrobial activity[15-16].

Alkoxyphthalimides are a class of compounds well known for a long time and still continue the object of considerable interest, mainly due to their applications in different fields. Several alkoxyphthalimide derivatives have been synthesized[17-18] and are reported to demonstrate a wide range of pharmacological activities like antimalarial, antiepileptic, anticonvulsant etc. These valid observations led us to undertake the synthesis of some new combinational molecules, incorporating above moieties in them with the hope of augmentation in biological activity. Synthetic routes used are shown in Reaction Scheme I.

2. RESULTS AND DISCUSSION

In order to achieve 1,3-dioxo-1,3-dihydro-2*H*-isoindole-2-yl acetic/propanoic/2-phenyl acetic acid (3.1-IIa-c), phthalic anhydride was heated with ω-amino acid (glycine/alanine/phenyl alanine) (3.1-Ia-c) in an oil bath in solvent free condition. The resultant products (3.1-IIa-c) were appeared as sharp melting solids. In ^{1}H NMR spectra signal of OH proton appear as a singlet at δ 9.7 along with signals of aromatic region at δ 7.70-7.77 (3.1-IIa) confirming the formation of (3.1-IIa-c), which was cyclised to 2-[1-(1*H*-benzimidazole-(1-yl-methyl)/(2-yl-ethyl)/(1-yl benzyl))]-1*H*-isoindole-1,3(2*H*)-dione (3.1-IIIa-c) by the condensation with o-phenylenediamine in 4N HCl media. The assigned structure of (3.I-IIIa) was attributed to the presence of band in the region of 3487cm^{-1}, typical for the NH function of imidazole ring. ^{1}H NMR spectra also exhibited one singlet at δ 8.3 arising from NH. Transformation of (3.I-IIa-c) into corresponding ethoxyphthalimide derivatives (3.1-IVa-c) was carried out by the treatment with phthalimidoxyethyl bromide (2.I-II) in the presence of pyridine as a base. The structure of (3.1-IVa-c) was evidenced from their IR, ^{1}H NMR and mass spectral data. IR spectrum exhibited stretching vibration in the region 1380 cm^{-1} for N-O and 1080 cm^{-1} for C-O group together with characteristic bands for CO-N-CO group at 1789-1727 cm^{-1} and ^{1}H NMR spectra revealed signals for alkyl side chain and disappearance of singlet at δ 8.3 of NH proton, as was present in its precursor. The mass spectra of the compounds gave their correct parent ion peaks.



EXPERIMENTAL

Materials and Instruments:

The reagent grade chemicals were purchased from commercial sources and purified by either distillation or recrystallization before use. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using n-hexane and ethylacetate as solvent system. The visualization of spot was carried out in an iodine chamber. The IR spectra of the compounds were recorded in the 4000-450 cm^{-1} ranges using KBr discs on FTIR IR RX1 Perkin Elmer spectrophotometers and NMR were recorded on a Bruker DRX-300 MHz spectrometer (MeOH) using TMS as an internal standard. The ESI-MS were recorded on a MICROMASS QUATTRO II triple quadrupole mass spectrometer having a JASCOPU-980 HPLC pump commented to it.

Synthesis of N-hydroxy phthalimide (I)[19] :

In a two litre beaker, phthalic anhydride (110.0g), hydroxylamine hydrochloride (65.0g) and sodium carbonate were taken and water (250 ml) was added slowly with constant shaking. This reaction mixture was heated for an hour on water bath. After cooling, a few mL of dilute HCl was added to neutralize the excess of hydroxylamine and sodium carbonate. The crude product thus obtained was filtered and dried in air and then recrystallised from alcohol. Yield 74%, m.p. 226 °C (lit. m.p. 226-229 °C)

1,2-Dibromoethane:

E-Merck and purified by distillation, b.p. 132°C.

Phthalimidoxyethyl bromide (I)[20]:

A typical reaction is described for the preparation of 2-

bromoethoxy-1H-isoindole-1,3(2H)-dione (II). A solution of N-hydroxyphthalimide (I) (16.3g, 0.1 mol) in dimethyl formamide (120 mL) was prepared and 1,2-dibromoethane (37.5g, 28 mL, 0.2 mol) and triethylamine as base were added to it. This was allowed to stand at room temperature with occasional stirring, until the red colour of the mixture had turned colourless (18 hrs.). The precipitate of triethyl-ammonium bromide was filtered at suction. The filtrate was diluted with ice cold water (800 mL) and the solid precipitated was filtered off. The crude product melted at 87°C. This product was washed with petroleum ether (b.p. 40-60°C) to remove excess of dibromoethane and then recrystallized by ethanol. M.P. 79 °C, yield 52%.

Synthesis of (1,3-dioxo-1,3-dihydro-2H-isoindole-2-yl) acetic acid (3.1-IIa) :

Glycine (3.1-Ia, 0.01mol) and phthalic anhydride (0.01) are powdered, mixed in a dry beaker and heated on an oil bath at 180-185°C. The mixture was stirred occasionally. After a few minutes, there occurs complete fusion. Heating is continued till the liquid mass solidifies. The solid obtained was washed with water and recrystallised from ethanol. Similarly (3.1-IIb-c) were prepared, using alanine and phenyl alanine instead of glycine and maintaining the appropriate temperature condition.

3.1-IIa IR(cm^{-1}):

3300 (b, OH str.), 3082 (C-H str., Ar-H), 2932 (C-H str., CH_2), 1715 (C=O str.),

1112 (C-O str.), ^{1}H NMR: 9.7 (s, 1H, OH), 7.70-7.77 (m, 4H, Ar-H), 4.3 (s, 2H, CH_2)

3.1-IIb IR(cm^{-1}):

3280 (b, OH str.), 3072 (C-H str., Ar-H), 2940 (C-H str., CH_2), 1730 (C=O str.),

1089 (C-O str.), ^{1}H NMR: 9.2 (s, 1H, OH), 7.4-7.5 (m, 4H, Ar-H), 3.0 (q, 1H, CH), 1.6 (d, 3H, CH_3)

3.1-IIc IR(cm^{-1}):

3310 (b, OH str.), 3060 (C-H str., Ar-H), 2980 (C-H str., CH_2), 1726 (C=O str.),

1084 (C-O str.), ^{1}H NMR: 9.5 (s, 1H, OH), 7.2-7.8 (m, 9H, Ar-H),3.8 (s, 1H, CH),

Synthesis of 2-[1-(1H-benzimidazole-1-yl)methyl]-1H-isoindole-1,3(2H)-dione (3.1-IIIa):

Compound (3.1-IIa, 0.01mol) and o-phenylenediamine (0.01mol) were refluxed in 4N HCl (30 mL) for 4 hrs.. As soon as the reaction completes, the crystals of product appear during the reflux, which were cooled, filtered, dried and recrystallised from ethanol.

3.1-IIIa IR(cm^{-1}):

3487 (N-H str.), 3024 (C-H str., Ar-H), 2923, 2857 (C-H str., CH_2), 1711, 1641 (C=O str.), 1600 (C=N str.), ^{1}H NMR: 8.3 (s, 1H, NH), 7.3-7.8 (m, 8H, Ar-H), 4.67 (s, 2H, CH_2)

Compounds (3.1-IIIb-c) were similarly prepared with minor change in reflux time.

3.1-IIIb IR(cm^{-1}):

3480 (N-H str.), 3036 (C-H str., Ar-H), 2970 (C-H str., CH_2), 1720, 1660 (C=O str.), 1602 (C=N str.), ^{1}H NMR: 8.2 (s, 1H, OH), 7.1-7.7 (m, 8H, Ar-H), 3.2 (q, 1H, CH), 1.58 (d, 3H, CH_3)

3.1-IIIc IR(cm^{-1}):

3472 (N-H str.), 3015 (C-H str., Ar-H), 2956 (C-H str., CH_2), 17150, 1670 (C=O str.), 1594 (C=N str.), ^{1}H NMR: 8.12 (s, 1H, OH), 7.2-7.9 (m, 13H, Ar-H), 3.87 (s, 1H, CH),

Synthesis of 1-N-ethoxyphthalimido-2-[(1,3-dioxo-1,3-dihydro-2H-isoindole-1-yl)methyl]benzimidazole (3.1-IVa):

An equimolar mixture of (3.1-IIIa, 0.01 mol) and phthalimidoxyethyl bromide (2.I-II, 0.01 mol) in absolute ethanol were heated under reflux for 18 hrs. using pyridine (0.02 mol) as a base. Reaction mixture was cooled and poured on crushed ice to get the grayish coloured product of 3.1-IVa, which was recrystallised from DMF.

3.1-IVa IR(cm^{-1}):

3069 (C-H str., Ar-H) , 2982 (C-H str., CH_2), 1789, 1727 (C=O str.), 1592 (C=N str.), 1380 (N-O str.), 1080 (C-O str.) , ^{1}H NMR: 7.0-7.8 (m, 12H, Ar-H), 4.65 (t, 2H, OCH_2), 4.30 (s, 2H, CH_2), 3.50 (t, 2H, NCH_2), Mass m/z: 466 $[M]^{+\cdot}$, 428 $[M- C_3H_2]^{+\cdot}$, 414 $[M- C_4H_4]^{+\cdot}$, 357 $[M- C_5H_3NO_2]^{+\cdot}$, 311 $[M- C_5H_5N_3O_3]^{+\cdot}$, 267 $[M- C_{10}H_3N_2O_3]^{+\cdot}$, 239 $[M- C_{11}H_5N_3O_3]^{+\cdot}$, 221 $[M- C_{12}H_{11}N_3O_3]^{+\cdot}$

Compounds (3.1-IVb-c) were prepared similarly with minor modification in reaction conditions.

3.1-IVb IR(cm^{-1}):

3080 (C-H str., Ar-H) , 2980 (C-H str., CH_2), 1790, 1710 (C=O str.), 1599 (C=N str.), 1385 (N-O str.), 1056 (C-O str.), ^{1}H NMR: 6.9-7.79 (m, 12H, Ar-H), 4.68 (t, 2H, OCH_2), 3.52 (t, 2H, NCH_2), 3.2 (q, 1H, CH), 1.58 (d, 3H, CH_3), Mass m/z: 480 $[M]^{+\cdot}$, 442 $[M- C_3H_2]^{+\cdot}$, 428 $[M- C_4H_4]^{+\cdot}$, 357 $[M- C_6H_5NO_2]^{+\cdot}$, 325 $[M- C_5H_5N_3O_3]^{+\cdot}$, 281 $[M- C_{10}H_3N_2O_3]^{+\cdot}$, 253 $[M- C_{11}H_5N_3O_3]^{+\cdot}$, 221 $[M- C_{13}H_{13}N_3O_3]^{+\cdot}$

3.1-IVc IR(cm^{-1}):

3072 (C-H str., Ar-H) , 2970 (C-H str., CH_2), 1780, 1715 (C=O str.), 1594 (C=N str.), 1390 (N-O str.), 1076 (C-O str.), ^{1}H NMR: 7.1-7.77 (m, 17H, Ar-H), 4.60 (t, 2H, OCH_2), 3.50 (t, 2H, NCH_2), 3.8 (s, 1H, CH), Mass m/z: 542 $[M]^{+\cdot}$, 504 $[M- C_3H_2]^{+\cdot}$, 490 $[M- C_4H_4]^{+\cdot}$, 357 $[M- C_{11}H_7NO_2]^{+\cdot}$, 387 $[M- C_5H_5N_3O_3]^{+\cdot}$, 343 $[M- C_{10}H_3N_2O_3]^{+\cdot}$, 315 $[M- C_{11}H_5N_3O_3]^{+\cdot}$, 297 $[M- C_{12}H_{11}N_3O_3]^{+\cdot}$

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Table 3.1-I: Physical data and elemental analysis of synthesized compounds

Compd No.	X	Molecular Formula	Mol. weight	m.p. (^{0}C)	Yield (%)	Found/ calculated (%) N
3.1-IIa	H	$C_{10}H_7NO_4$	205	196	92	6.76/6.82
3.1-IIb	CH_3	$C_{11}H_9NO_4$	219	210	91	6.28/6.39
3.1-IIc	Ph	$C_{16}H_{11}NO_4$	281	240	86	4.87/4.98
3.1-IIIa	H	$C_{16}H_{11}N_3O_2$	277	>300	83	15.03/15.16
3.1-IIIb	CH_3	$C_{17}H_{13}N_3O_2$	291	>300	79	14.33/14.43
3.1-IIIc	Ph	$C_{22}H_{15}N_3O_2$	353	>300	74	11.36/11.89
3.1-IVa	H	$C_{26}H_{18}N_4O_5$	466	>300	65	11.99/12.01
3.1-IVb	CH_3	$C_{27}H_{20}N_4O_5$	480	>300	60	11.34/11.66
3.1-IVc	Ph	$C_{32}H_{22}N_4O_5$	542	>300	62	10.16/10.33

REFERENCES

[1] Marxer A and Schier O; In, Progress in Drug Research, Vol.21, edited by Ernst Jucker (Birkhouse Verlag, Basel, Stottgart), 1977, 27.

[2] Frohberg P E and Weigand C; Ger., 1966, 1209799; Chem. Abstr., 64, 1966, 14900g.

[3] Hennart C; Fr., 1967, 1484776; Chem. Abstr., 68, 1968, 38526t.

[4] Merk and Co. Inc., Neth. Appl., 1966, 6510290; Chem. Abstr., 65, 1966, 68986k.

[5] Ursprung J J; US, 1967, 3337579; Chem. Abstr., 68, 1968, 68986k.

[6] Makoto S and Masahiro A; Japan Kokai, 1977, 7787176; Chem. Abstr., 88, 1978, 37793d.

[7] Singh P, Hingoran L L, Trivedi G K and Vara J; Indian J. Chem., 29B, 1990, 596.

[8] Tomoya Y, Kazue Y and Masahi S; Japan Kokai, 1990, 2167268; Chem. Abstr., 113, 1990, 191360b.

[9] Wepplo P J; Pest. Sci., 29, 1990, 293.

[10] Julia M; Bull. Chem. Fr., 1956, 1365.

[11] Varma P, Dandiya P C, Chaudhary A and Parmar S S; J. Pharm. Sci., 63, 1974, 1740; Chem. Abstr., 82, 1975, 51385y.

[12] Perozo-Rondon M L, Costarrosa L, Martin-Aranda R M, Rojas-Cervantes M L and Vicente-Rodriguez M A; Applied Surface Science, 252(17), 2006, 6067.

[13] Sarvanan S, Senthamil Selvan P, Gopal N, Gupta G K and De B; Archivder Pharmazie, 338(10), 2005, 488.

[14] Khalif-Nezhad A, Soltani Rad M N, Mohabatkar H, Asrari Z and Hemmateeenejad B; Bioorg. Med. Chem., 13(6), 2006, 1931.

[15] Pandey V K, Bishnoi A, Saxena R, Joshi M N and Bajpai S K; Indian J. Chem., 41B, 2002, 1978.

[16] Pandey V K, Tusi Z, Tusi S, Joshi M N and Bajpai S K; Indian J. Heterocycl. Chem., 111, 2002, 309.

[17] Sharma R, Nagda D P and Talesara G L, Arkivoc, (i), 2006, 1.

[18] Alexander M S, Stables J P, Rutkowska M C, Hurshthousu M B, Hibbs D E, Edafiogho I O, Farrak V A, Moore J A and Scott R R, Eur. J. Med. Chem., 31, 1996, 787.

[19] Orndroff W R and Pratt D S; Am. Chem. J., 47, 1917, 89.

[20] Bauer L and Suresh K S; J. Org. Chem., 28, 1963, 1604.

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