HL
Heterocyclic Letters
(www.heteroletters.org) Vol. 1, No. 1, (2011), 69-72

Synthesis, characterization and biological activity of 1-[6-(2,4-dinitro-phenyl)-3-ethoxy-4-(substitutedphenyl)-5-phenyl-1, 3a, 4, 5-tetrahydro-pyrazolo-[3, 4-c]-pyrazole and 6-(2,4-dinitro-phenyl)-4-ethoxy-3-(substituted-phenyl)-3a, 6-dihydro-3H-pyrazolo-[3, 4-c]-isoxazole

V. Sareen*, V. Khatri, D. Shinde and S. Sareen

Department of Chemistry, University of Rajasthan, Jaipur-302004
e.mail : deeptishinde77@yahoo.co.in

Abstract:

Substituted tetra hydro-pyrazolo-[3,4-c]-pyrazole and dihydro-3H-pyrazolo-[3,4-c]-isoxazole have been prepared by the reaction of 2-(2,4-dinitro-phenyl)-5-ethoxy-4-(substituted benzylidene)-2,4-dihydro-pyrazol-3-one with phenyl hydrazine and hydrazine hydrate in acetic acid and hydroxyl-amine hydrochloride in ethanolic NaOH.

The structures of all these newly synthesized compounds have been confirmed by spectral and analytical data and the compounds have been screened for their antifungal activities against *Macrophomina phaseolina* and *Alternaria burnsii* and insecticidal activities against *Corcyra cephalonica*

Keywords:

2,4-dinitro-phenyl hydrazine, hydrazine hydrate, hydroxyl amine hydrochloride, 2(2,4-dinitro-phenyl) 5-ethoxy-4-(4-fluoro substituted-benzylidene)-2, 4-dihydro-pyrazol-3-one and biological activity.

Introduction

Pyrazole refers to the class of simple aromatic ring organic compounds of the heterocyclic series which are used for their analgesic[1], tranquilisiy muscle relaxing[2] and antibacterial[3] activities, whereas isoxazoles are used as anti-inflammatory, analgesic and antibacterial[4-5] activities.

Pyrazole and isoxazoles are associated with large variety of biological activities.Substituted pyrazolo [3,4-c] pyrazole and isoxazolo [3,4-c] pyrazole were prepared as hemi-azadicarbocyanine dyes and their biological activities were also tested[6]. In continuation of our work[7-10] on heterocyclic compounds we have now synthesized some new pyrazoles and isoxazoles fused derivatives.

Experiment

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a SHIMADZU 8400S FT-IR spectrometer in KBr pellets. ^{1}HNMR spectra were recorded on JEOL DRX-300 spectrometer (300 MHz) using $CDCl_3$ as a solvent. Chemical shifts are expressed in δ ppm. Purity of the compounds were checked by TLC on silica gel plate.

2-(2,4-Dinitro-Phenyl)-5-Ethoxy-4-(4-Fluoro-Benzylidene)-2,4-Dihydro-Pyrazol-3-one-2a

Compound **2a** is prepared by mixing 2-(2,4-dinitro-phenyl)-5-ethoxy-2,4-dihydro-pyrazol-3-one (0.01 mol, 2.9 g) with 4-fluoro-benzaldehyde (0.01 mol, 1.24 g) add 5 ml ethanol and refluxed it in the presence of piperidine on water bath for 8-10 hrs. After the completion of reaction the content were concentrated, cooled and re-crystallized by DMF to yield **2a** (64 %) m.p. (174^{o}C).

1-(2,4-Dinitro-Phenyl)-3-Ethoxy-4-(4-Fluoro-Phenyl)-5-Phenyl-1,3a,4,5-Tetrahydro-Pyrazolo [3,4-c] Pyrazole - 3a

A mixture of (2,4-dinitro-phenyl)-5-ethoxy-4-(4-fluoro-benzylidene)-2, 4-dihydro-pyrazol-3-one (0.01 mol, 4 g) and phenyl hydrazine (0.01 mol, 1.08 g) was refluxed for 5-6 hrs in presence of acetic acid (5 ml) and solid was separated. This solid was crystallized from ethanol to yield **3a** (62 %) m.p. (108^{o}C).

6-(2,4-Dinitro-Phenyl)-4-Ethoxy-3-(4-Fluoro-Phenyl)-3a, 6-Dihydro-3H-Pyrazolo [3, 4-c] Isoxazole 4a

Dihydro-3H-pyrazolo [3, 4-c] isoxazole is obtained by refluxing 2-(2, 4-dinitro-phenyl)-5-ethoxy-4-(4-fluoro-benzylidene)-2,4-dihydro-pyrazol-3-one with hydroxylamine hydrochloride in ethanolic NaOH for 4-5 hrs on water bath and solid was separated. The separated solid was dried and crystallized by ethanol to yield **4a** (50 %) m.p. 160^{o} c.

All compounds from **3a-4d** were prepared in similar manner. Their names and m.p.'s are given in **Table I**.

Result and discussion

In our comprehensive work, we have described the synthesis of tetrahydro-pyrazolo-[3,4-c]-pyrazole and dihydro-3H-pyrazolo-[3,4-c]-isoxazole derivatives from 2-(2,4-dinitro-phenyl)-5-ethoxy-4-(substituted benzylidene)-2,4-dihydro-pyrazol-3-one **(2a)**. Compound **2a** shows significant characteristic absorption band in the region of $\nu_{max.}$: 1710 (>C=O), 1670 (C=C), 1345-1390 (NO_2) cm^{-1}.

IR spectra of 5-tetrahydro-pyrazolo-[3,4-c]-pyrazole and dihydro-3H-pyrazolo-[3,4-c]-isoxazole showed absorption band in the region of $\nu_{max.}$: 1480-1515 (>C=N–), 3000-3100 (Aromatic), 1365-1400 (NO_2), 760-800 ($\geq$C–F) cm-^{1}.

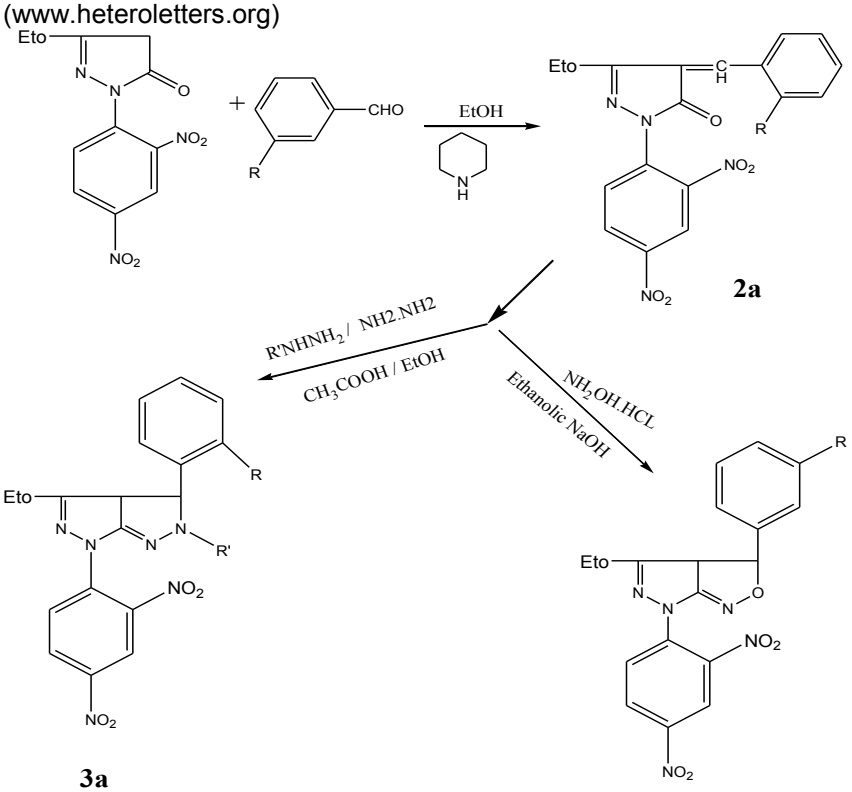
^{1}HNMR spectra of tetrahydro-pyrazolo-pyrazole and dihydro-3H-pyrazolo-isoxazole showed signals in the range of δ 1.21-1.25 (s, 3H, –CH_3), δ 2.14 (s, 1H, >CH), δ 3.4 (>C–H), δ 6.95-7.30 (m, Aromatic–H) ppm. δ 3.56(q,4H,-OCH_2)

Biological activity

The synthesized compounds were screened to evaluate their antifungal properties against two plant pathogenic fungi viz. *Alternaria burnsii* and *Macrophomina phaseolina*, adopting food poison technique and insecticidal properties using penultimate larvaes of *Corcyra cephalonica* compound no. **3a,3b** and **3a** with dinitro group and one fluorine atom in the molecule exhibited significantly higher level of antifungal property (47.77 to 75.03 percent inhibition of *A. burnsii* at 500 ppm) and insecticidal activity (61.6 to 72 percent kill of test insect in 5 days past treatment). Remaining compounds showed relatively low level of bioactivity.

TABLE – I

Compd No.	R	R′	M. F.	M.P.'s (°C)	Yield (%)	Elemental Ana. Found (Calcd.)
						N
3a	4–F	$–C_6H_5$	$C_{24}H_{19}FN_6O_5$	108	62	16.92 (17.14)
3b	4–F	$–COCH_3$	$C_{20}H_{17}FN_6O_6$	115	60	18.34 (18.41)
3c	–H	$–C_6H_5$	$C_{24}H_{20}N_6O_5$	135	55	17.68 (17.79
3d	–H	$–COCH_3$	$C_{20}H_{18}N_6O_6$	122	55	19.04 (19.17)
3e	4–OCH_3	$–C_6H_5$	$C_{25}H_{22}N_6O_6$	125	61	16.65 (16.73)
3f	4–OCH_3	$–COCH_3$	$C_{21}H_{20}N_6O_7$	110	50	17.85 (17.94)
3g	2–OH	$–C_6H_5$	$C_{24}H_{20}N_6O_6$	155	58	17.13 (17.21)
3h	2–OH	$–COCH_3$	$C_{20}H_{18}N_6O_7$	145	64	18.42 (18.50)
4a	4–F	---	$C_{18}H_{14}FN_5O_6$	160	50	16.73 (16.86)
4b	–H	---	$C_{18}H_{15}N_5O_6$	260	50	17.56 (17.63)
4c	4–OCH_3	---	$C_{19}H_{17}N_5O_7$	225	63	16.28 (16.39)
4d	2–OH	---	$C_{18}H_{15}N_5O_7$	195	62	16.86 (16.94)



SCHEME

R= 4-F, 4-OCH_3 , -H, -2-OH

R'= -C_6H_5 , -$COCH_3$

REFERENCES

1 Gursoy, S. Demirayak, G. Capan, K. Erol and K. Vural; Eur. J. Med. Chem. **35**, 364 (2000).
2 E. L. Anderson, J. E. Cosly, Jr. L. C. Green, J. L. Lafferty and H. E. Reiff; J. Med. Chem. **7**, 259 (1965)
3 T. Okamoto, T. Trikura, S. Suzne, K. Ushiyama, Y. Matsui, Y. Nagatsu, S. Sato, H. Yakayama and S. Saito; J. P. Pat. 1983, 7372193; Chem. Abstr. **80**, 37015r (1984).
4 H.Agirbas, S.guner, F.Budak, S.keceli, F.Kandemirli, N.shvets,V.Kovalishyh and A.Dimoglo, bioorganic and medicinal chemistry **15**, 2322(2007)
5 K.R.R Kumar, H.Mallisha,K.S.Rangappa, Arch.Pharm.Med. Chem. **336**,159(2003)
6 A.I.M. Koraiem, J.P.Pat. 1983,7372193,Chem. Abstr. 80, 37015r (1984)
7 V.Sareen .U.Gupta, V.Khatri and S.Chugh ,Indian J. Heterocyclic Chem. **18**,239,(2009)
8 V.Sareen, V.Khatri,P.Jain and K.Sharma, Phosphorous, Sulphur and Silicon **185**,146(2010)
9 V. Sareen, V. Khatri, D. Shinde and S. Chugh and S. Sareen ,Heterocyclic Communications, **16,**33 (2010).
10 V. Sareen, V. Khatri, D. Shinde and S. Sareen, J. Indian Chem. Soc. **87**, 1415 (2010)