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RESEARCH ARTICLE

SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL ISOXAZOLES AND PYRAZOLES OF CARBAZOLO AND AZACARBAZOLO FUSED QUINOXALINES

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ABSTRACT

Enol ethers 9(a-b) and chalcones 10(a-b) were synthesized from quinoxalino-oxohydrocarbazoles and oxohydroazacarbazoles 8(a-b) using Japp-Klingemaan and Fischer indole synthesis. Isoxazole derivatives of carbazolo and azacarbazolo fused quinoxalines (12a,13a) and pyrazole derivatives of carbazolo and azacarbazolo fused quinoxalines (12b,13b) were prepared by the cyclocondensation reaction of corresponding enol ethers 9(a-b) and chalcones 10(a-b) with hydroxylamine hydrochloride and hydrazine hydrate respectively. The structures of all the compounds have been established on the basis of their elemental analysis and spectral (IR, ¹H NMR and MS) data.

Key words:

Carbazole, Azacarbazole, Chalcones,
Quinoxalines, Isoxazoles, Pyrazoles.

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INTRODUCTION

Quinoxalines have versatile pharmacological property such as anti-tumor (Waring *et al.*, 2002), anti-bacterial (Khan *et al.*, 2007), anti-fungal (Kotharkar *et al.*, 2006), anti-viral (Kleim *et al.*, 1993), anti-inflammatory (Sainz *et al.*, 1999), anti-HIV (Patel *et al.*, 2000), anti-malarial activities (Guillon *et al.*, 2004), *etc.* Similarly, pyrazoles and isoxazoles are the key part in numerous heterocyclic compounds and exhibit extensive pharmacological properties like anti-viral, anti-microbial, anti-tumor, anti-fungal, pesticidal, anti-convulsant, anti-histaminic, anti-toxin stimulant, CNS regulant (Solanki *et al.*, 1996), *etc.* In the synthetic point of view, enol ethers and chalcones are versatile intermediates and offer remarkable open door to scientists to synthesize a wide assortment of heterocyclic compounds. The enol ethers, chalcones, *etc.* show considerable potential as substrates for functional group manipulations and sequential carbon-carbon bond forming transformations and received considerable attention recently due to their synthetic importance in the construction of a variety of alicyclic, aromatic and heterocyclic compounds. Ever since, the enol ethers and chalcones have been developed as adaptable synthons (Martel *et al.*, 2003; Anbazhagan *et al.*, 1997; Biddle

et al., 2007; Ji, Shun-Jun *et al.*, 2004; Potts *et al.*, 1981; Masson *et al.*, 1980; Pozgan *et al.*, 2007; Dineen *et al.*, 2006. The pyrazole and isoxazole moieties on the quinoxalinocarbazoles and azacarbazoles have been synthesized in the present work by using enol ethers and chalcones.

Experimental Work

Chemicals were purchased from Aldrich Chemical Company (USA) and solvents were used after purification by distillation. Melting points were determined in open glass capillaries and are uncorrected. The reaction completion of the compounds was checked by TLC on silica gel G plates. IR spectra were recorded on CE (SHIMADZU) FTIR-8400S. ¹H NMR spectra were recorded on model AC 300F (Bruker) using CDCl₃ and DMSO-d₆ solvents. Chemical shift is expressed in δ ppm. Before analysis, all samples were dried for one hour under reduced pressure. Mass spectra were recorded on a waters QTOF (LCMS) mass spectrometer using Argon/Xenon (6kV, 10mB) gas. Column chromatography was performed on silica gel (Merck). Anhydrous sodium sulfate was used as a drying agent for the organic phase.

Preparation of 6-nitro quinoxaline-2,3-diol (3)

A mixture of 4-nitro-*o*-phenylenediamine (2.03 g, 0.0132 mol) was treated with diethyl oxalate (25 mL). The solid diamine

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slowly became red-orange and heat was evolved but solution did not occur. The mixture was, therefore, refluxed until (after about 2 h) its color had faded. After heating about five minutes, a heavy precipitate of was separated out. After cooling, the solid was filtered, washed with alcohol and dried. After recrystallizations from boiling 50% acetic acid (using decolorizing carbon) the product 3 was obtained in fine bright yellow plates. Yield: 68%; m.p. 267°C.

Preparation of 6-amino quinoxaline-2,3-diol (5)

Compound 3 (1.558 g, 0.056 mol) in methanol (25 mL) and conc. HCl (9 mL) were taken in 250 mL round bottom flask and the mixture was heated on water bath. Iron powder (1.28g, 0.022 mol) was added portion wise during one hour with its continuous stirring. The reaction mixture was further refluxed for 1 h and then filtered hot. The filtrate was neutralized with aqueous ammonia (50%) until the dark brown solid has completely separated out and the organic part was extracted with the ethyl acetate. Evaporation of the solvent under reduced pressure gave the crude mass which was recrystallized from ethanol to give fine dark brown compound 5. Yield 65%; m.p. 310°C; IR (KBr) cm^{-1} : 3010 (C-H str.), 3490 (O-H str.), 3250 (N-H str.), 1580 (C=N str.), 1247 (N-H str.), 1130 (C-N str.), 780 (C-H str.); $^1\text{H NMR}$, (δ ppm in CDCl_3): 11.87 (s,2H,OH), 7.42 (d,1H,CH), 7.27 (s,1H,CH), 6.88 (d,1H,CH), 5.32 (s,2H,NH₂); MS: m/z [M^+] = 177.05.

General method for the preparation of 3-hydroxymethylidene cyclohexanone and 1-benzyl-3-hydroxymethylidene-4-piperidone (7a-b)

A mixture of NaOEt (0.6 g, 0.01 mol), dry ether (10 mL), redistilled cyclohexanone (0.9 g, 0.01 mol) or 1-benzylpiperidine-4-one (1.8 g, 0.01 mol), ethyl formate (10 mL) were placed in a two necked flask equipped with a stirrer and stopper. The reaction was initiated by the addition of 3 mL of ethanol to the stirred mixture which was then placed in an ice cold water bath. Stirring was continued for 6 h. After standing overnight, 2.5 mL of ethanol was added. The mixture was stirred for additional 1h. After the addition of 20 mL of water, the reaction mixture was extracted with ether. The aqueous layer was acidified with 5 mL of 6N HCl and the mixture was extracted twice with ether. The ether solution was washed with 5 mL saturated NaCl solution. The compound was dried by the addition of anhydrous MgSO_4 . The ether was evaporated on the steam bath. The residue was distilled under reduced pressure to give 7a and 7b respectively.

Preparation of 2,3-dihydroxy-9,10-dihydro-6H-pyrazino[2,3-b]carbazol-7(8H)-one (8a-b)

(a) Preparation of hydrazone

A solution of 6 (1.6 g, 0.005 mol) in aqueous hydrochloric acid (0.5 mL conc. HCl in 1 mL water) was treated with a cold saturated solution of sodium nitrite (0.1 g in 0.2 mL water) while the temperature was kept at 0-5°C. It was then added portion wise to an ice cooled mixture containing 7a or 7b (0.05 mol), sodium acetate trihydrate (0.3 g), methanol (1.5 mL) and water (1 mL) over a period of 30 min with stirring. The

contents were allowed to stand for further 30 min and the resulting solid mass was filtered, washed with water, dried and recrystallized from ethanol to give the hydrazone. Hydrazone was used as such in the second step without further purification.

Cyclisation of hydrazone

A solution of hydrazone (1.7 g, 0.005 mol) in a mixture of acetic acid (0.5 mL) and hydrochloric acid (0.2 mL) was refluxed on an oil bath preheated to 125-130°C for 0.5 h. The content were then cooled and poured in ice cooled water with continuous stirring. The separated brown solid 8a was purified by passing through a column of silica gel using 50 % benzene in pet. ether as eluant to give 8a. Similarly compound 8b was prepared. (8a): Yield 70%; m.p. 300-02°C; IR (KBr) cm^{-1} : 3460 (O-H str.), 3309 (N-H str.), 2940 (C-H str.), 1705 (C=O str.), 1635 (C=N str.), 1335 (N-H str.), 1070 (C-N str.), 945 (C-H str.); $^1\text{H NMR}$, (δ ppm in CDCl_3): 11.96 (s,1H,NH), 11.87 (s,2H,OH), 8.07 (s,2H,CH), 3.01 (t,2H,CH₂), 2.58 (t,2H,CH₂), 2.11 (m,2H,CH₂); MS: m/z [M^+] = 269.08 (8b): Yield 50%; m.p. 312-15°C; IR (KBr) cm^{-1} : 3510 (O-H str.), 3310 (N-H str.), 2930 (C-H str.), 1730 (C=O str.), 1660 (C=N str.), 1332 (N-H str.), 930 (C-H str.); $^1\text{H NMR}$, (δ ppm in CDCl_3): 11.87 (s,2H,OH), 11.63 (s,1H,NH), 8.07 (s,2H,CH), 7.33-7.23 (m,5H,ArH), 4.51 (s,2H,CH₂), 3.39 (t,2H,CH₂), 2.63 (t,2H,CH₂); MS: m/z [M^+] = 360.12.

Preparation of 8-(ethoxymethylene)-2,3-dihydroxy-9,10-dihydro-6H-pyrazino[2,3-b]carbazol-7(8H)-one (9a-b)

To a solution of 10% sodium methoxide (10 mL) in benzene (50 mL) at 0°C, a solution of ethyl formate (10 mmol) in dry benzene (25 mL) was added and 8a (2.25 g, 10 mmol) in benzene (25 mL) was added. The mixture was stirred for 4 h at room temperature and allowed to stand. It was then diluted with cold water, acidified with dil. HCl and extracted with ether. The solvent was evaporated and the resultant compound was recrystallised from ethanol to give pure 9a. Similarly, compound 9b was prepared. (9a): Yield 57%; m.p. 300-02°C; IR (KBr) cm^{-1} : 3550 (O-H str.), 3420 (N-H str.), 2920 (C-H str.), 1670 (C=O str.), 1490 (C=N str.), 1330 (CN str.); $^1\text{H NMR}$, (δ ppm in CDCl_3): 11.87 (s,2H,OH), 11.19 (s,1H,NH), 8.07 (s,2H,CH), 6.09 (s,1H,CH), 4.49 (q,2H,CH₂), 3.03 (t,2H,CH₂), 2.83 (t,2H,CH₂), 1.21 (t,3H,CH₃); MS: m/z [M^+] = 325.11 (9b): Yield 60%; m.p. 288-90°C; IR (KBr) cm^{-1} : 3550 (O-H str.), 3450 (N-H str.), 3000 (C-H str.), 1590-1450 (C=C str.), 1610 (C=O str.), 1550 (C=N str.), 1330 (C-N str.); $^1\text{H NMR}$, (δ ppm in CDCl_3): 11.87 (s,2H,OH), 11.63 (s,1H,NH), 8.07 (s,2H,CH), 7.33-7.23 (m,5H,ArH), 7.11 (s,1H,CH), 4.49 (q,2H,CH₂), 3.73 (s,1H,CH₂), 4.71 (s,1H,CH₂), 1.21 (t,3H,CH₃); MS: m/z [M^+] = 416.15

Preparation of 8-benzylidene-2,3-dihydroxy-9,10-dihydro-6H-pyrazino[2,3-b]carbazol-7(8H)-one (10a-b)

A mixture of 8a (2.3 g, 0.01 mol), benzaldehyde (1.2 g, 0.01 mol) and fused sodium acetate (1.2 g, 0.015 mol) in glacial acetic acid was refluxed for 5 h. The reaction mixture was cooled in an ice water. The resulting solid was filtered, washed with water and recrystallised from aqueous ethanol to give pure

compound 10a. Same procedure was followed in the preparation of compound 10b. (10a): Yield 68%; m.p. 298-99°C; IR (KBr) cm^{-1} : 3530 (O-H str.), 3460 (N-H str.), 2980 (C-H str.), 1670 (C=O str.), 1350 (C-N str.), 730 (C-H str.); ^1H NMR, (δ ppm in CDCl_3): 11.87 (s,2H,OH), 11.18 (s,1H,NH), 8.07 (s,2H,CH), 7.60-7.33 (m,5H,ArH), 7.25 (s,1H,CH), 3.03 (t,2H, CH_2), 2.83 (t,2H, CH_2); MS: m/z [M^+]= 357.11 (10b): Yield 70%; m.p. 260-61°C; IR (KBr) cm^{-1} : 3530 (O-H str.), 3430 (N-H str.), 2950 (C-H str.), 1600 (C=O str.), 1530 (C-N str.), 770 (C-H str.); ^1H NMR, (δ ppm in CDCl_3): 11.87 (s,2H,OH), 11.63 (s,1H,NH), 8.07 (s,2H,CH), 7.60-7.23 (m,10H,ArH), 7.45 (s,1H,CH), 4.71 (s,2H, CH_2), 3.73 (s,2H, CH_2); MS: m/z [M^+]= 448.47

Preparation of 5,12-dihydro-4H-isoxazolo[3,4-a]pyrazino[2,3-h]carbazole-8,9-diol (12a)

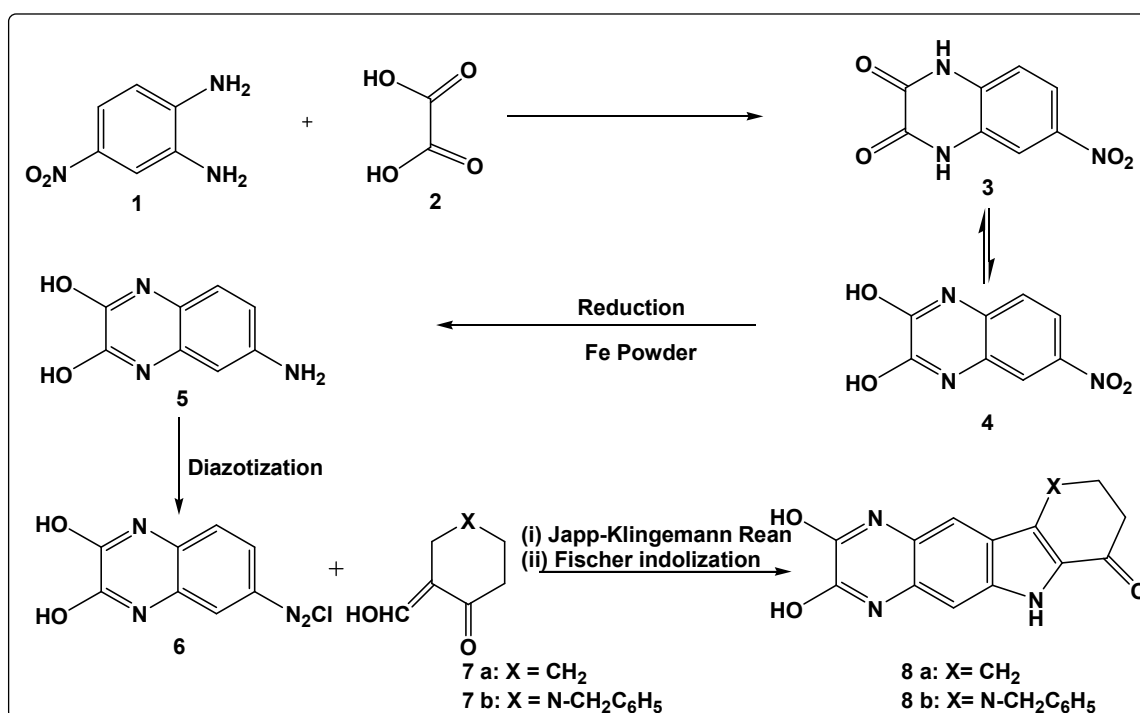
A solution of 9a (2.8 g, 10 mmol) in glacial acetic acid (25 mL) was stirred with hydroxylamine hydrochloride (1.3 g, 15 mmol) for 6-8 h at 70-80°C. The solvent was removed under reduced pressure and the residue was diluted with water. It was extracted with ethyl acetate, washed with saturated NaHCO_3 solution, water, brine solution and dried over Na_2SO_4 . The solvent was removed and the crude product was purified by recrystallization from ethanol to give 12a. Same procedure was followed in the preparation of compound 12b by using of hydrazine hydrate at place of hydroxylamine hydrochloride. (12a): Yield 52%; m.p. 230-32°C; IR (KBr) cm^{-1} : 3490 (O-H str.), 2950 (C-H str.), 1690 (C=N str.), 770 (C-H bending), 1310 (C-N str.); ^1H NMR, (δ ppm in CDCl_3): 11.87 (s,2H,OH), 11.63 (s,1H,NH), 8.07 (s,2H,CH), 7.60-7.23 (m,10H,ArH), 7.45 (s,1H,CH), 4.71 (s,2H, CH_2), 3.73 (s,2H, CH_2); MS: m/z [M^+]= 294.08. (12b): Yield 52%; m.p. 230-32°C; IR (KBr) cm^{-1} : 3490 (O-H str.), 3430 (N-H str.), 2950 (C-H str.), 1600 (C=O str.), 1530 (C-N str.), 770 (C-H str.); ^1H NMR, (δ ppm in CDCl_3): 11.87 (s,2H,OH), 11.34 (s,1H,NH), 8.07 (s,2H,CH), 8.1 (s,1H,CH), 2.93 (t,2H, CH_2), 2.87 (t,2H, CH_2); MS: m/z [M^+]= 448.47.

Preparation of 3-phenyl-3a, 4, 5, 12-tetrahydro-4H-isoxazolo [3,4-a]pyrazino[2,3-h] carbazole-8,9-diol (13a)

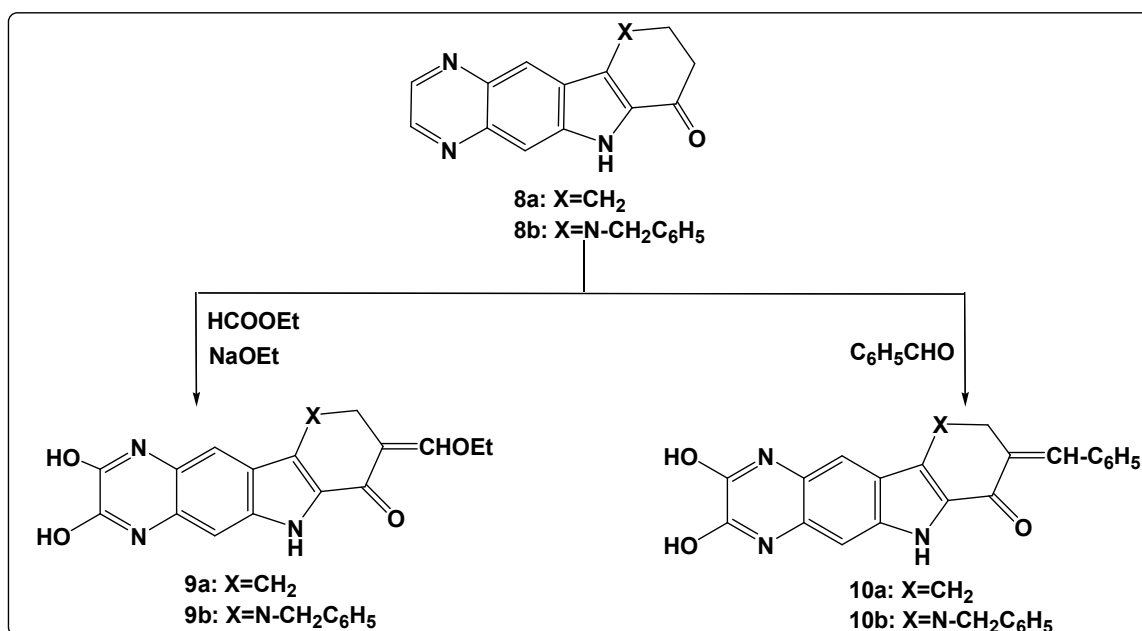
Anhydrous sodium acetate (1.0 g, 0.001 mol) dissolved in a minimum amount of acetic acid was added to a solution of hydroxylamine hydrochloride (0.5 mL, 0.01 mol) in ethanol. This was added to a solution of 10a (3 g, 0.01 mol) in ethanol (15 mL). The mixture was refluxed on a sand-bath for 2-3 h. The contents were poured into crushed ice, filtered and recrystallised from ethanol to give 13a. Same procedure was followed in the preparation of compound 13b by using of hydrazine hydrate at place of hydroxylamine hydrochloride. (13a): Yield 62%; m.p. 251-52°C; IR (KBr) cm^{-1} : 3520 (O-H str.), 3132 (N-H str.), 3010 (C-H str.), 2983, 2854 (C-H str.), 1728 (C=N), 1604-1450 (C=C), 1337 (C-N str.), 1342 (C-H str.); ^1H NMR, (δ ppm in CDCl_3): 11.87 (s,2H,OH), 11.63 (s,1H,NH), 7.38-7.36 (m,5H,ArH), 4.5 (d,1H,CH), 2.68 (t,2H, CH_2), 2.0 (q,1H,CH), 1.74 (q,2H, CH_2); MS: m/z [M^+]= 370.11 (13b): Yield 70%; m.p. 248-50°C; IR (KBr) cm^{-1} : 3510 (O-H str.), 2980 (C-H str.), 1620 (C=N str.), 1510-1400 (C=C), 1310 (C-N str.), 780 (C-H str.); ^1H NMR, (δ ppm in CDCl_3): 11.87 (s,2H,OH), 7.0 (s,1H,NH), 7.40-7.27 (m,5H,ArH), 3.9 (d,1H,CH), 2.68 (t,2H, CH_2), 2.1 (q,1H,CH), 1.6 (q,2H, CH_2); MS: m/z [M^+]=369.12.

RESULTS AND DISCUSSION

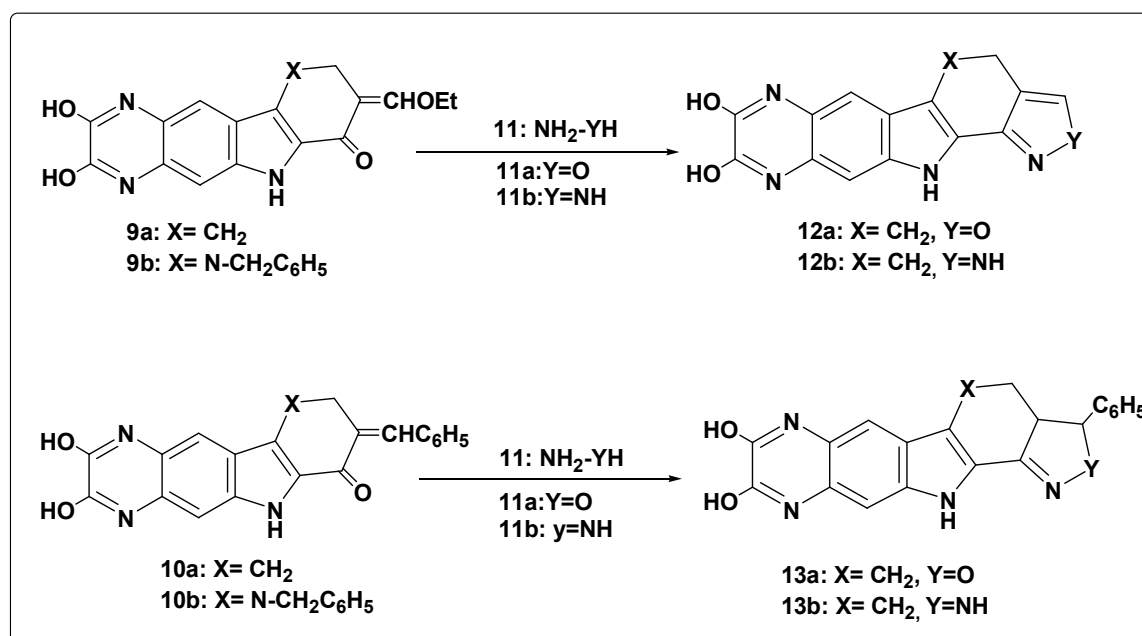
In the present work, the condensation of 4-nitro-*o*-phenylenediamine (1) with oxalic acid (2) followed by reduction of the nitro group of 4 with iron powder in the subsequent step to give corresponding amine 4 (Thakuria *et al.*, 2006). Formation of the compound 5 from 4 was confirmed by chemical tests as well as by IR spectra in which peaks of nitro group of compound 4 at 1560 and 1346 cm^{-1} disappeared and peaks of amino group of compound 5 at 3472 and 3368 cm^{-1} appeared. Compound 5 was diazotized with NaNO_2 and HCl at temperature 0-5°C which was allowed to undergo Japp-



Scheme-1



Scheme-2



Scheme-3

Klingemann reaction (Prasad *et al.*, 1994) with 2-hydroxymethylidene cyclohexanone (7a) and 3-hydroxymethylidene piperidone (7b) generated *in situ* from the reaction of cyclohexanone and piperidone with ethyl formate in presence of NaOEt. This underwent concomitant ring closure with acid under the conditions of Fischer indolization furnished the compounds 8(a-b) [Scheme-1] which in the subsequent step was treated separately with (i) ethyl formate + sodium ethoxide (Padmawati *et al.*, 2000) and (ii) benzaldehyde (Singh *et al.*, 2004) to give (9a-b) and (10a-b) respectively [Scheme-2]. Formation of the enol ethers and chalcones was confirmed by the ¹H NMR signals in which signals of CH₂ around 4.51-2.58δppm of compounds 8a-b were disappeared in the enol

ethers (9a-b) and chalcones (10a-b). The synthesis of pyrazole and isoxazole derivatives was carried out by the cyclocondensation of enol ethers and chalcones with hydrazine hydrate and hydroxylamine hydrochloride respectively. Thus, when 9(a-b) and 10(a-b) were allowed to react with hydroxylamine hydrochloride in presence of a base, the corresponding isoxazole derivatives 12a and 13a were obtained in good yield. In a likewise manner, 9(a-b) and 10(a-b) reacted smoothly with hydrazine hydrate to yield the corresponding pyrazole derivatives 12b and 13b respectively [Scheme-3]. Cyclization of the compounds (9a-b and 10a-b) to the compounds (12a-b and 13a-b) was confirmed by the IR spectra in which peaks of the carbonyl group around 1670 cm⁻¹ of the

compounds (9a-b and 10a-b) disappeared in the compounds (12a-b and 13a-b).

Conclusions

A practical and efficient synthesis isoxazole derivatives of carbazolo and azacarbazolo fused quinoxalines (12a,13a) and pyrazole derivatives of carbazolo and azacarbazolo fused quinoxalines (12b,13b) by the cyclocondensation reaction of corresponding enol ethers 9(a-b) and chalcones 10(a-b) with hydroxylamine hydrochloride and hydrazine hydrate respectively has been reported.

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