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Application of Beckmann rearrangement in the synthesis of indophenazino fused pyrrolo [3,2-*c*] azepine and pyrrolo [3,2-*c*] diazepine derivatives

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ABSTRACT

A variety of ketoximes of indophenazino fused carbazole ***5a*** *and azacarbazoles* ***5(b-e)****, easily prepared from the corresponding ketones* ***4(a-e)*** *undergo the Beckmann rearrangement upon treatment with 2,4,6-trichloro [1,3,5] triazine in N,N-dimethylformamide at room temperature afforded indophenazino fused pyrrolo [3,2-c] azepine* ***(6a)*** *and indophenazino fused pyrrolo [3,2-c] diazepines derivatives* ***6(b-e)*** *in moderate to goog yields.*

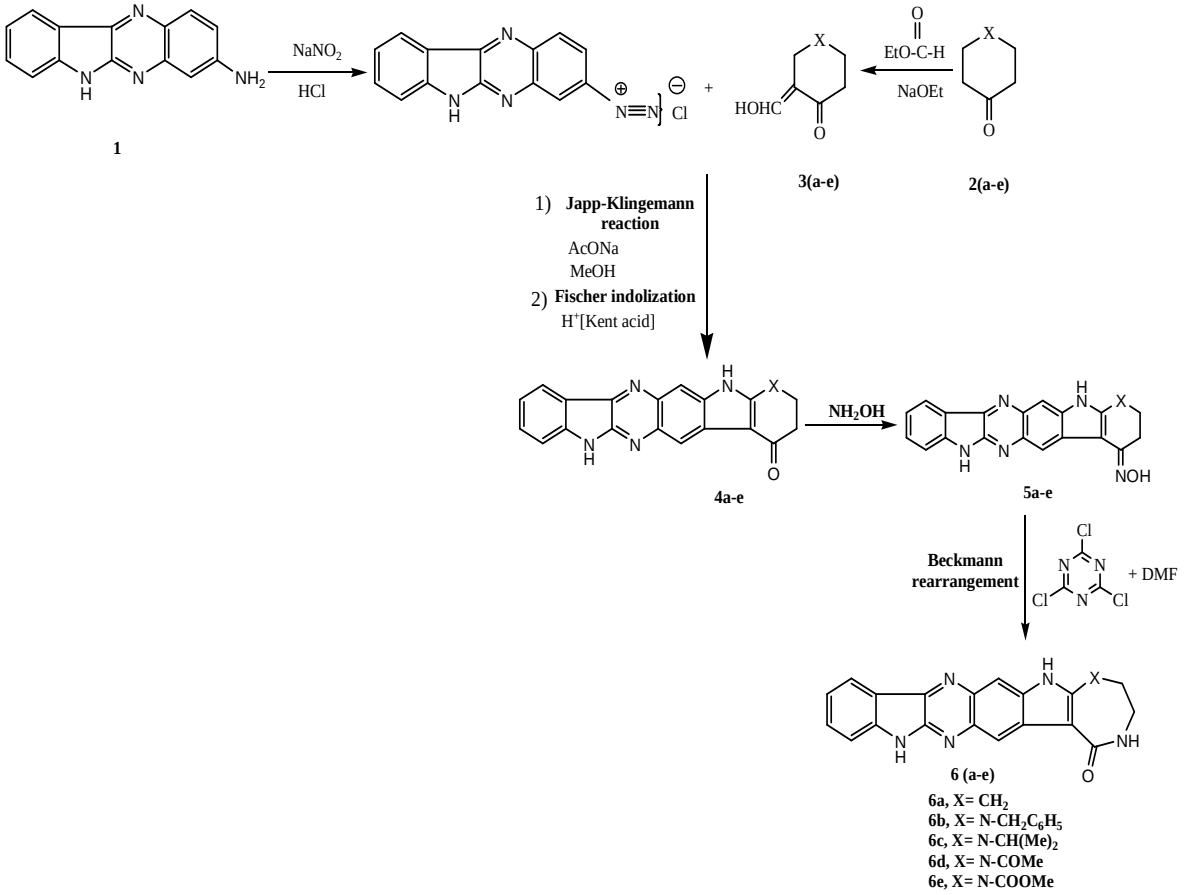
Keywords: Indophenazine, carbazoles, azacarbazoles, Beckmann rearrangement.

INTRODUCTION

Carbazole and substituted carbazoles fused with heterocyclic ring are of special interest and of contemporary importance on account of the variety of carbazole alkaloids showing antimicrobial, antiviral and cytotoxic properties[1-3]. Indole group of plant alkaloids ellipticine and olivacine have been known since a long time to exhibit anticancer and DNA intercalating properties[4-5]. In view of this, selectively functionalized and annelated carbazoles are interesting targets for the development of antitumour and antibiotically active drugs[6]. Azacarbazoles too seem to have great potential for the development of compounds with analgesic and hypotensive property. It has also been shown that azepine[7] and pyrrolo[1,4]-benzodiazepine[8] also exhibit antitumour activity due to the formation of stable complex with DNA. Recent demonstrations[9] that azepine can be used as potential anti-HIV agents has stimulated further interest on these molecules with yet another perspective.

It has been observed that incorporation of certain bioactive pharmacophores in the existing drug molecules sometimes exert a profound influence on the biological activity of the parent molecules, it was thought of interest to incorporate active pharmacophore like azepine in biologically active indophenzino fused carbazole framework[10], with the hope that it could produce interesting series of compounds with enhanced biological activities. In the present work, we describe the Beckmann rearrangement of ketoximes of indophenazino annulated carbazole **(5a)** and azacarbazoles **5(b-e)** with the organocatalyst derived from 2,4,6-trichloro-[1,3,5]-

triazine and dimethylformamide to generate the synthesis of indophenazino fused pyrrolo[3,2-c] azepine **6a** and indophenazino fused pyrrolo[3,2-c] diazepine **6(b-e)** derivatives.



Scheme:1

MATERIALS AND METHODS

Experimental section

Melting points were determined on an open capillary and are uncorrected. The IR spectra were recorded on Schimadzu FTIR-8400S. ^{1}H NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ on Bruker DRX-300 spectrometer using TMS as internal reference and values are expressed in δ ppm. ^{13}C-NMR spectra were measured on a Joel 68.5 MHz instrument. Mass spectra were taken on a Joel SX-102 (EI/CI/FAB) mass spectrometer at 70 eV.

General procedure for the preparation of 5(a-e) from the ketones 4(a-e):

Formation of Ketoxime

A mixture of **4a** (0.05 mmol), hydroxylamine hydrochloride (0.05 mmol), 0.1 gm of sodium hydroxide in 0.2 ml of rectified spirit and 0.1 ml water was added in portions with shaking, the reaction become too vigorous, the flask was cooled in running tap water. When all the sodium hydroxide was added, attached reflux condenser to the flask and the mixture was refluxed for 30 minutes. Cooled and poured the contents of the flask into a solution of 0.7 ml of concentrated HCl in 10 ml of water. Filtered the product **5a** at the pump, washed and recrystallized it from methanol. Compounds **5(b-e)** were prepared by using similar procedure.

Formation of Caprolactum

2,4,6-Trichloro [1,3,5] triazine (10.0 mmol) was added to DMF (2ml) maintained at 25^0C. After the formation of a white solid, the reaction was monitored (TLC) until complete disappearance of TCT, then ketoxime **5a** (10.0 mmol) in DMF (15 ml) was added. After the addition, the mixture was stirred at room temperature, monitured (TLC) until completion (12Hours). Water (20 ml) was added then the organic phase washed with 15 ml of a saturated solution of Na_2CO_3, followed by 1N HCl and brine. The organic layer was dried (Na_2SO_4) and solvent evaporated to give **6a**. Compounds **6(b-e)** were prepared by using similar procedure.

5a. Yield: 67%; IR (KBr) cm^{-1}: 3600, 2870, 1830, 1430, 1010; NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 10.1 (2H, s, NH-indole ring), 8.07 (2H, s, CH-quinoxaline ring), 8.00 (1H, s, NH-azepine ring), 7.55-7.00 (4H, m, Ar-H), 2.59 (2H, t, CH_2), 2.0 (1H, s, OH), 1.78 (2H, m, CH_2-azepine ring), 1.3 (2H, t, CH_2-azepine ring); ^{13}C NMR 164.6 (C of C=N-OH), 120.5, 121.7, 119.6, 111.0 (4C of Ar-indole), 144.8 (2C of pyrazine), 142.81, 129.4 (4C of quinoxaline), 135.5, 127 (2C of indole), 137, 103 (2C of azepine), 40.0, 28.4, 27.5 ($3CH_2$ of azepine); MS: *m/z* 341 [M^+]; Anal. Calcd. / found for $C_{20}H_{15}N_5O$: C, 70.37/70.31, H, 4.43/4.29, N, 20.52 / 20.48.

5b. Yield: 67%; IR (KBr) cm^{-1}: 3600, 2850, 1850, 1430, 1030; NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 10.1 (2H, s, NH-indole ring), 8.07 (2H, s, CH-quinoxaline ring), 8.00 (1H, s, NH-azepine ring), 7.55-7.00 (4H, m, Ar-H), 24.32 (2H, s, CH_2), 3.28 (2H, t, CH_2), 2.0 (1H, s, OH), 1.6 (2H, t, CH_2-azepine ring); ^{13}C NMR 164.6 (C of C=N-OH), 128.3, 128.1, 126.8, 120.5, 121.7, 119.6, 111.0 (8C of Ar-Benzene), 144.8 (2C of pyrazine), 135.5, 127.6 (4C of pyrrole attached with benzene), 137 (C of benzyl), 62.2 (CH_2 of benzyl), 142.8, 129.6,129.4 (6C of quinoxaline), 124.0, 102.0, (2C of pyrrole attached with azepine), 51.9, 39.7 (CH_2 of azepine ring); MS: *m/z* 432 [M^+]; Anal. Calcd. / found for $C_{26}H_{20}N_6O$: C, 72.21/ 72.19, H, 4.66/4.62, N, 19.43 / 19.40.

5c. Yield: 67%; IR (KBr) cm^{-1}: 3600, 2850, 1850, 1430, 1030; NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 10.1 (2H, s, NH-indole ring), 8.07 (2H, s, CH-quinoxaline ring), 8.00 (1H, s, NH-azepine ring), 7.55-7.00 (4H, m, Ar-H), 3.28 (2H, t, CH_2), 2.97 (1H,q,CH attached with N-piperidine), 2.0 (1H, s, OH), 1.05 (6H, d, CH_3); ^{13}C NMR 164.6 (C of C=N-OH), 120.5, 121.7, 119.6, 111.0 (4C of Ar-Benzene), 144.8 (2C of pyrazine), 135.5 (C of pyrrole attached with benzene), 142.8 (2C of benzene attached with pyrazine), 142.8, 129.6,129.4 (4C of quinoxaline), 127.6, 124.0 (2C of pyrrole), 52.6 (CH of azepine ring), 49.5, 40.0 (CH_2 of azepine), 21.6 (2C of CH); MS: *m/z* 384 [M^+]; Anal. Calcd. / found for $C_{22}H_{20}N_6O$: C, 68.73/68.69, H, 5.24/5.21, N, 21.86 / 21.82.

5d. Yield: 67%; IR (KBr) cm^{-1}: 3600, 2830, 1830, 1450, 1030; NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 10.1 (2H, s, NH-indole ring), 8.07 (2H, s, CH-quinoxaline ring), 8.00 (1H, s, NH-azepine ring), 7.55-7.00 (4H, m, Ar-H), 3.60 (2H, t, CH_2), 2.02 (3H,s,CH_3), 2.0 (1H, s, OH), 1.5 (2H, t, CH_2 of azepine); ^{13}C NMR 166.4 (C of CO group), 164.6 (C of C=N-OH), 120.5, 121.7, 119.6, 111.0 (4C of Ar-Benzene), 144.8 (2C of pyrazine), 135.5 (C of pyrrole attached with benzene), 142.8 (2C of benzene attached with pyrazine), 142.8, 129.6,129.4 (4C of quinoxaline), 127.6, 124.0 (2C of pyrrole), 45.6 (CH_2 of azepine ring), 39.2 (CH_2 of azepine toward C=N-OH), 15.4 (C attached with CO group); MS: *m/z* 384 [M^+]; Anal. Calcd. / found for $C_{21}H_{16}N_6O_2$: C, 65.62/65.59, H, 4.20/4.17, N, 21.86 / 21.81.

5e. Yield: 67%; IR (KBr) cm^{-1}: 3600, 2860, 1850, 1470, 1030; NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 10.1 (2H, s, NH-indole ring), 8.07 (2H, s, CH-quinoxaline ring), 8.00 (1H, s,

NH-azepine ring), 7.55-7.00 (4H, m, Ar-H), 3.67 (3H, t, COMe), 3.18(2H,t,CH_2), 2.0 (H,s,C=N-OH), 1.6 (2H, t, CH_2 of azepine); ^{13}C NMR 153.0 (C of CO group), 164.6 (C of C=N-OH), 120.5, 121.7, 119.6, 111.0 (4C of Ar-Benzene), 144.8 (2C of pyrazine), 135.5 (C of pyrrole attached with benzene), 142.8 (2C of benzene attached with pyrazine), 142.8, 129.6,129.4 (4C of quinoxaline), 127.6, 124.0 (2C of pyrrole), 47.4 (CH_2 of azepine ring), 39.1 (CH_2 of azepine toward C=N-OH), 48.1 (C of COMe group); MS: *m/z* 400 [M^+]; Anal. Calcd. / found for $C_{21}H_{16}N_6O_3$: C, 62.99/62.94, H, 4.03/4.00, N, 20.99 / 20.95.

6a. Yield: 70%; IR (KBr) cm^{-1}: 3100, 2900, 1810, 1750, 1480, 1030; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 10.1 (2H,s,NH- indole ring), 8.07 (2H,s,CH- quinoxaline ring), 8.00 (1H,s,NH- azepine ring), 7.55-7.00 (4H,m,Ar-H), 2.96 (2H,q,CH_2), 2.59 (2H,t,CH_2), 1.82 (2H,q,CH_2) ; ^{13}C NMR 167.9 (C of CO group in azepine ring), 144.8 (2C of pyrazine attached with pyrrole), 142.8(2C of pyrazine attached with benzene), 137.0 C of pyrrole attached with azepine towards CH_2), 135.0 (C of pyrrole attached with benzene in indole ring), 129.4 (2C of quinoxaline attached with pyrrole), 129.6 (2C of quinoxaline ring), 127.6 (C of pyrrole attached with benzene in indole ring), 121.7, 120.5, 119.6, 111.0 (4C of Ar-Benzene), 103 (C of pyrrole attached with azepine towards CO group), 42.9,34.5, 26.0 (3C of CH2 of azepine ring); MS: *m/z* 341 [M^+]; Anal. Calcd. / found for $C_{20}H_{15}N_5O$: C, 70.37/ 70.31, H, 4.43/4.29, N, 20.52 / 20.48.

6b. Yield: 62%; IR (KBr) cm^{-1}: 3200, 2920, 1840, 1750, 1460, 1010; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 10.1 (2H, s, NH- indole ring), 8.00 (1H,s,NH- diazepine ring), 8.07 (2H,s,CH- quinoxaline ring), 7.55-7.00 (9H,m,Ar-H), 4.32 (2H,s,CH_2-Benzyl Proton), 3.32 (2H,t,CH_2), 3.19 (2H,q,CH_2); ^{13}C NMR 167.9 (C of CO group in azepine ring), 144.8, 142.8 (4C of pyrazine ring), 129.6 (2C of quinoxaline), 129.4 (2C of quinoxaline attached with pyrrole), 128.3,128.1, 126.8, 121.7, 120.5, 119.6, 111.0 (9C of Ar Benzene), 124, 102 (2C of azepine attached with pyrrole), 58.0, 42.9 (2C of CH_2 of azepine ring), 61.8 (C of CH attached with N of azepine), 2.16 (2C of CH_3 group); MS: *m/z* 432 [M^+]; Anal. Calcd. / found for $C_{26}H_{20}N_6O$: C, 72.21/72.18, H, 4.66/4.62, N, 19.43 / 19.39.

6c. Yield: 60%; IR (KBr) cm^{-1}: 3200, 2900, 1820, 1750, 1460, 1040; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 10.1 (2H,s,NH- indole ring), 8.07 (2H,s,CH- quinoxaline ring), 8.00 (1H,s,NH- diazepine ring), 7.55-7.00 (4H, m,Ar-H), 3.32 (2H,t,CH_2), 3.19 (2H,q,CH_2), 2.97 (1H,m,CH), 1.05 (6H,d,CH_3); ^{13}C NMR 167.7 (C of CO group in azepine ring), 144.8, 142.8 (4C of pyrazine ring), 129.6 (2C of quinoxaline), 129.4 (2C of quinoxaline attached with pyrrole), 121.7, 120.5, 119.6, 111.0 (4C of Ar Benzene), 124, 102 (2C of azepine attached with pyrrole), 55.6, 42.9 (2C of CH_2 of azepine ring), 52.2 (C of CH attached with N of azepine), 2.16 (2C of CH_3 group); 384 [M^+]; Anal. Calcd. / found for $C_{22}H_{20}N_6O$: C, 68.73/68.69, H, 5.24/5.20, N, 21.86 / 21.82.

6d. Yield: 70%; IR (KBr) cm^{-1}: 3200, 2900, 1820, 1750, 1450, 1040; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 10.1 (2H,s,NH- indole ring), 8.07 (2H,s,CH- quinoxaline ring), 8.07 (1H,s,NH- diazepine ring), 7.55-7.00 (4H,m,Ar-H), 3.64 (2H,t,CH_2), 3.11 (2H,q,CH_2), 2.02 (3H,s,CH_3); ^{13}C NMR 167.7 (C of CO group in azepine ring), 166.4 (C of COMe group) 144.8, 142.8 (4C of pyrazine ring), 129.6 (2C of quinoxaline), 129.4 (2C of quinoxaline attached with pyrrole), 121.7, 120.5, 119.6, 111.0 (4C of Ar Benzene), 51.7, 42.1 (2C of CH_2 of azepine ring), 52.2 (C of CH attached with N of azepine), 15.4 (C of CH_3 group attached with CO group); MS: *m/z* 384 [M^+]; Anal. Calcd. / found for $C_{21}H_{16}N_6O_2$: C, 65.62/65.59, H, 4.20/4.17, N, 21.86 / 21.81,.

6e. Yield: 66; IR (KBr) cm^{-1}: 3200, 2870, 1820, 1750, 1430, 1020; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 10.1 (2H,s,NH- indole ring), 8.07 (2H,s,CH- quinoxaline ring), 8.00 (1H,s,NH- diazepine ring), 7.55-7.00 (4H,m,Ar-H), 3.67 (3H,s,CH_3), 3.24 (2H,t,CH_2), 3.22 (2H,q,CH_2); ^{13}C NMR 153.0 (C of COOMe group), 144.8, 142.8 (4C of pyrazine ring), 129.6 (2C of quinoxaline), 129.4 (2C of quinoxaline attached with pyrrole), 121.7, 120.5, 119.6, 111.0 (4C of Ar Benzene), 53.5, 42.0 (2C of CH_2 of azepine ring), 48.1 (C of CH_3 group in COOMe); MS: *m/z* 514 [M^+]; Anal. Calcd. / found for $C_{29}H_{18}N_6O_4$: C, 62.99/62.95, H, 4.03/4.00, N, 16.33 / 16.29.

RESULTS AND DISCUSSION

The synthetic strategy for the preparation of the materials **6(a-e)** (scheme-1) involved the conversion of diazotised indophenazine to the indophenazino fused oxocarbazole and oxoazacarbazole derivatives[10] **4(a-e)** respectively. These were realized by the interaction of diazotised indophenazine with 2-hydroxymethylidene cyclohexanone **(3a)** and various N-substituted piperidones **3(b-e)** respectively under the conditions of Japp-Klingemann reaction, followed by the Fischer indolization of the resulting hydrazones with Kent's acid (HCl:AcOH; 1:4 v/v). The compounds **3(a-e)** were inturn obtained, following the reported procedure[12] which consisted of treating cyclohexanone and various N-substituted piperidone with ethyl formate in presence of sodium ethoxide. The second stage of the strategy required the conversion of **4(a-e)** to the corresponding ketoximes derivatives **5(a-e)** using hydroxylamine hydrochloride in prescence of a base. A search for an efficient organocatalyst for Beckmann rearrangement for use under mild conditions and following our latest interest in the use of [1,3,5]-triazine[13] derivatives in organic synthesis, we report a very mild and selective procedure for the quantitative conversion of ketoximes **(5a-e)** into the corresponding lactams **(6a-e)**. The procedure is based on the reaction of a complex formed by 2,4,6-trichloro[1,3,5]triazine (TCT), a very inexpensive reagent, and DMF, in a DMF solution of 1 mol equiv of the ketoxime. The last stage of this strategy required the conversion of ketoximes **(5a-e)** to the corresponding diazepine derivatives **6(a-e)** using Beckmann rearrangement. The structure of compounds **5(a-e)** and **6(a-e)** were established on the basis of their microanalysis IR, ^{1}HNMR, ^{13}CNMR and MS spectral data. The data shown in experimental section was found in good agreement to the assigned structures. The IR spectra of all the compounds showed the presence of a strong absorption band near 1700cm^{-1} for CO group. The presence of azepine ring in **6(a-e)** was ascertained by the appearance of a band for NH str. at 3200cm^{-1} . The ^{1}HNMR spectrum displayed the peak for proton of NH of azepine ring at 8.00 ppm The most diagnostic evidence which established the formation of the compounds **5(a-e)** and **6(a-e)** was the appearance of the proton of indole NH in the region of δ 10.1 in all the compounds. The appearance of the M^+ peaks corresponding to their molecular formula in MS spectra substantiated further the formation of the compounds and unequivocally established their structures.

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