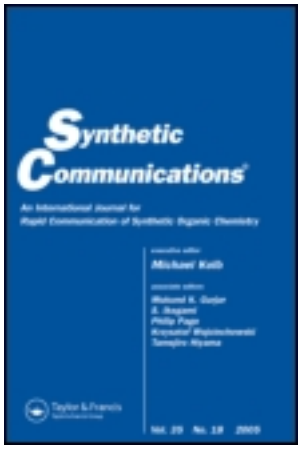

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Noteworthy Mechanistic Precedence in the Exclusive Formation of One Regioisomer in the Beckmann Rearrangement of Ketoximes of 4-Piperidones Annulated to Pyrazolo-indole Nucleus by Organocatalyst Derived from TCT and DMF

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Accepted author version posted online: 24 Jan 2012.Version of record first published: 05 Sep 2012.

To cite this article: Ruchi Tyagi , Navjeet Kaur , Bhawani Singh & D. Kishore (2013): Noteworthy Mechanistic Precedence in the Exclusive Formation of One Regioisomer in the Beckmann Rearrangement of Ketoximes of 4-Piperidones Annulated to Pyrazolo-indole Nucleus by Organocatalyst Derived from TCT and DMF, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:1, 16-25

To link to this article: http://dx.doi.org/10.1080/00397911.2011.589558

Synthetic Communications®, 43: 16–25, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.589558

NOTEWORTHY MECHANISTIC PRECEDENCE IN THE EXCLUSIVE FORMATION OF ONE REGIOISOMER IN THE BECKMANN REARRANGEMENT OF KETOXIMES OF 4-PIPERIDONES ANNULATED TO PYRAZOLO-INDOLE NUCLEUS BY ORGANOCATALYST DERIVED FROM TCT AND DMF

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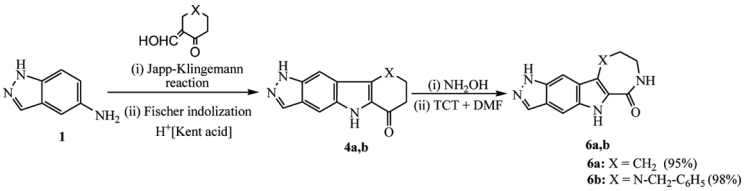
GRAPHICAL ABSTRACT



Abstract *Application of a very mild protocol to the Beckmann rearrangement of ketoximes of pyrazolo annulated oxocarbazole* ***5a*** *and oxoazacarbazole* ***5b*** *with the organocatalyst derived from 2,4,6-trichloro[1,3,5]triazine (TCT) and dimethylformamide (DMF) has been explored to provide a regioselective formation of the corresponding azepine* ***6a*** *and 1,4-diazepine* ***6b*** *respectively in good yield and purity. The mechanistic precedence for the exclusive formation of only one regioisomer has been discussed.*

Keywords Beckmann rearrangement; Fischer indolization; Japp–Kilingemann reaction; oxoazacarbazoles; oxocarbazoles; pyrazole; TCT-DMF complex

INTRODUCTION

1,4-Benzodiazepines represent an important class of privileged templates whose numerous derivatives have been found to have selective activities against a diverse array of biological targets.[1,2] Recent demonstrations that 1,4-benzodiazepine analogs can be used as potential nonnucleoside reverse transcriptase inhibitors and active anticancer agents have stimulated further interest in this nucleus from yet another perspective.[3] Literature pertaining to the one-pot synthetic routes for 1,4-benzodiazepine nucleus from quinazoline,[4] indole,[5] isatin,[6] isatoic anhydride, quinoline azide,[7] 4-quinolone,[8] and 4-isoquinolone[9] has revealed that

Received March 4, 2011.
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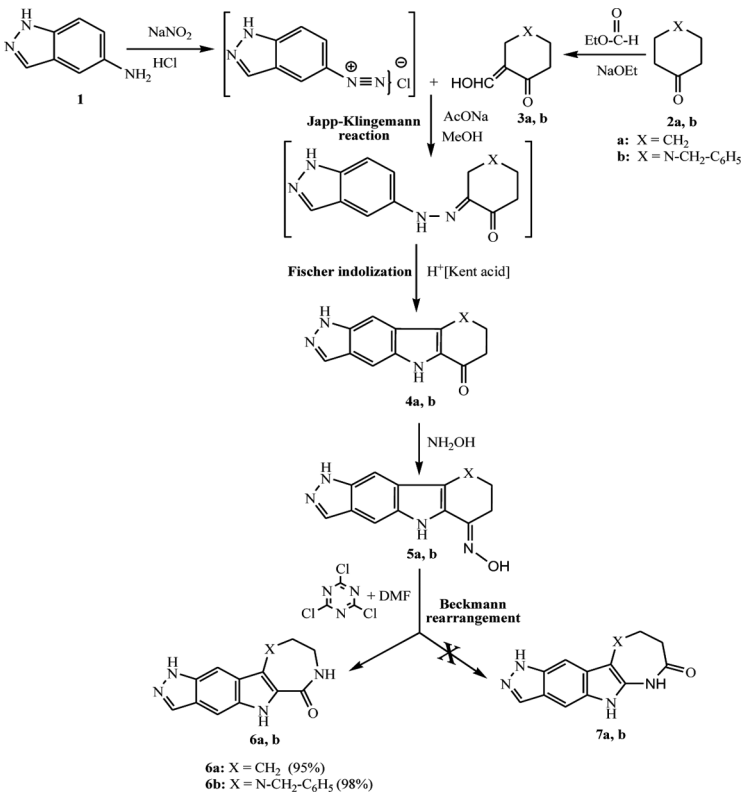
acid-catalyzed Beckmann rearrangement of 4-quinolone oxime provides a very convenient synthetic entry to the benzodiazepine nucleus.[10] It has been demonstrated that the acid-catalyzed Beckmann rearrangement of the ketoximes of *N*-substituted 4-quinolones resulted in the formation of both the regioisomers, viz, 1,4- and 1,5-benzodiazepines, the ratio of which depended upon the nature of the substituent present on the nitrogen atom.[11] This imposed a very serious limitation on the use of this procedure when exclusively only one regioisomer (the 1,4-benzodiazepine) was sought in synthesis.

The discovery of cytotoxic properties in pyridocarbazole derivatives[12] (for example, ellipticene, olivacine, carbazole, and azacarbazole) was hailed as a major step forward in the battle against cancer. Seemingly limitless structural features that their analogs provide, coupled with the impressive biological properties they show, have made them mainstays in cancer chemotherapy.[13] Recently, some azacarbazole derivatives have been reported to be potent and selective cytotoxic agents.[14]

As a part of an ongoing study on the synthesis of biologically active carbazole analogs, this investigation was undertaken to explore the accessibility of some novel carbazole and azacarbazole derivatives, which contained on its one side the biologically active pyrazole nucleus and on the other side the potentially useful anti-HIV-prone 1,4-diazepine class of privileged template, on this premise that their presence in tandem in a single molecular framework of carbazoles and azacarbazoles could produce an interesting series of the biologically active materials typically represented by **6a, b** structures.

RESULTS AND DISCUSSION

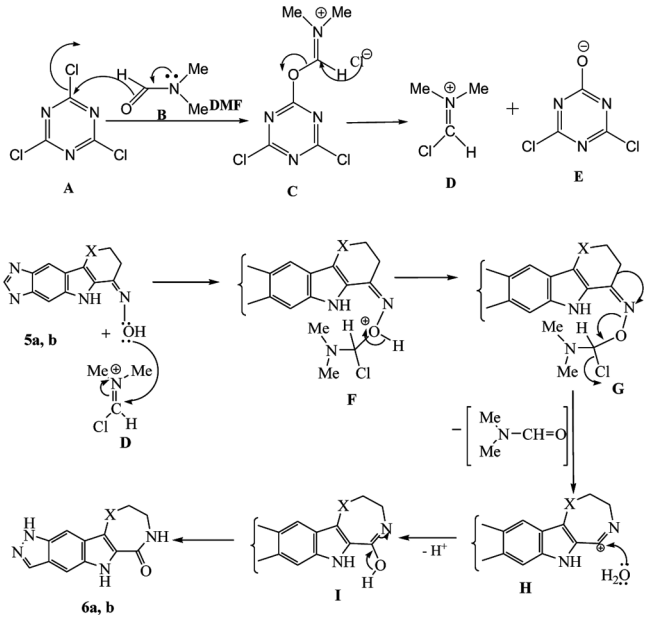
The synthetic plan conceived for the preparation of the materials **6a** and **6b** (Scheme 1) required it to be accomplished in three stages. The first stage of this strategy involved the conversion of 5-indazolyldiazonium chloride to the pyrazolo-fused oxocarbazole **4a, 10**, and oxoazacarbazole **4b** derivatives respectively. These were realized by the interaction of indazolyldiazonium chloride with 2-hydroxymethylidene cyclohexanone **2a** or 2-hydroxymethylidene cyclopentanone **8** and *N*-benzyl-3-hydroxymethylidene-4-piperidone **2b** respectively under the conditions of Japp–Klingemann reaction[15] followed by the Fischer indolization[16] of the resulting hydrazones with Kent's acid (HCl/AcOH; 1:4 v/v). The compounds **3a, b**, and **9** were in turn obtained following the reported procedure,[17] which consisted of treating cyclohexanone, *N*-benzyl-4-piperidone, and cyclopentanone respectively with ethyl formate in the presence of sodium ethoxide. The second stage of the strategy required the conversion of **4a, b**, and **10** to the corresponding ketoximes derivatives **5a, b**, and **11** through their reaction with hydroxylamine hydrochloride in the presence of a base. Though the acid-catalyzed reaction has been most often employed for the rearrangement of ketoximes, but we intended to search for an alternate reagent because of the obvious reasons stated earlier. A search for this revealed that a quantitative conversion of ketoximes into the corresponding lactams under mild conditions with an organocatalyst has been reported.[17,18] This procedure consisted of the reaction of ketoximes with a complex formed by 2,4,6-trichloro[1,3,5]triazine (TCT, cyanuric chloride) and dimethylformamide (DMF). This strategy, when applied to the conversion of ketoximes **5a, b** to the corresponding diazepine derivatives (Scheme 1), yielded exclusively one regioisomer **6a** and **6b** respectively in good



Scheme 1. Synthesis of 1,4-azepinones.

yield and purity. The structures of compounds **4a, b** and **6a, b** were established on the basis of their microanalysis, infrared (IR), ^{1}H NMR, and mass (MS) spectral data. The data presented in the experimental section were found to be in good agreement with the assigned structures. The IR spectra of **4a, b** showed the presence of a strong absorption band near 1700 cm^{-1} for the CO group, whose conversion to the corresponding ketoximes **5a, b** was evident by the disappearance of the peak for CO group. The presence of diazepine ring in **6a, b** was ascertained by the appearance of the CO absorption band at a low frequency at 1660 cm^{-1} and NH str. at 3300 cm^{-1}. The ^{1}H NMR spectrum displayed the peak for NH proton of azepine ring at δ 8.00–8.09 ppm. The most diagnostic evidence that established the formation of the compounds **5a, b** and **6a, b** was the appearance of the proton of indole NH in the region of δ 10.1 in all the compounds. (The NH proton of indazole nucleus appeared at a much downfield region at δ 12.4 ppm). 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.

The mechanistic pathway shown in Scheme 2 rationalizes the formation of **6a, b** from **5a, b**. It is assumed that the reaction proceeded through the formation of a complex formed from 2,4,6-trichloro[1,3,5]triazine (TCT, cyanuric chloride, an inexpensive reagent) and DMF, which allowed the Beckmann rearrangement to take

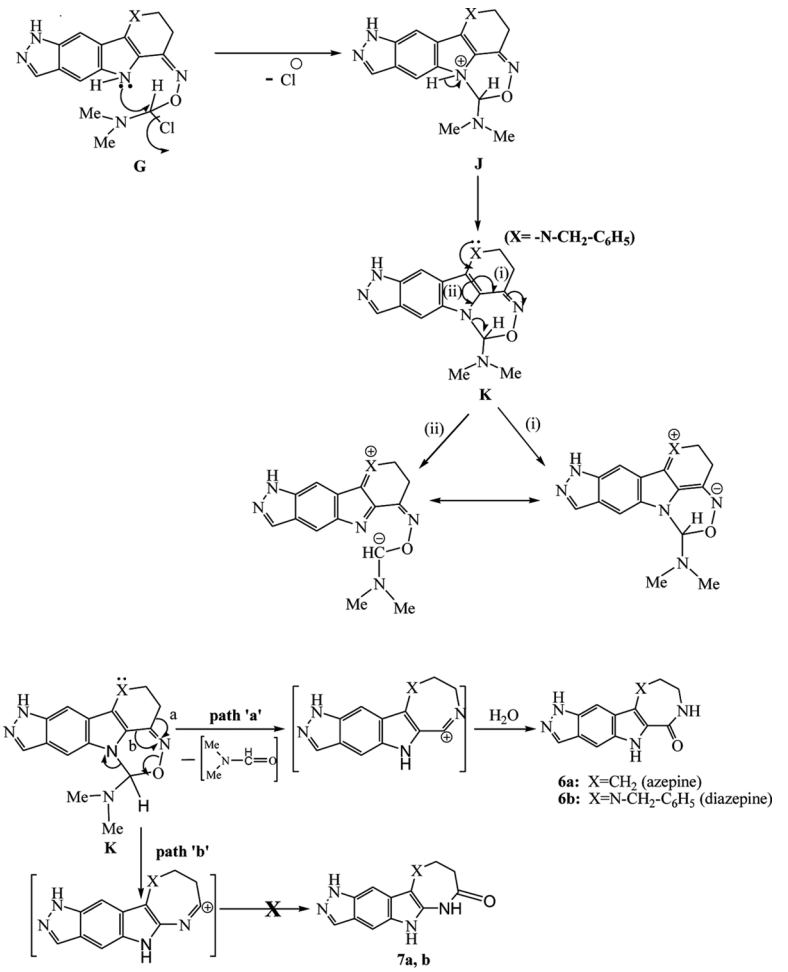


Scheme 2. Mechanistic pathway of TCT-DMF-catalyzed Beckmann rearrangement.

place on **5a, b** to generate **6a, b** respectively. The mechanistic scheme for this rearrangement shown in Scheme 2 is based on the earlier precedence for this reaction in the literature.[17,18]

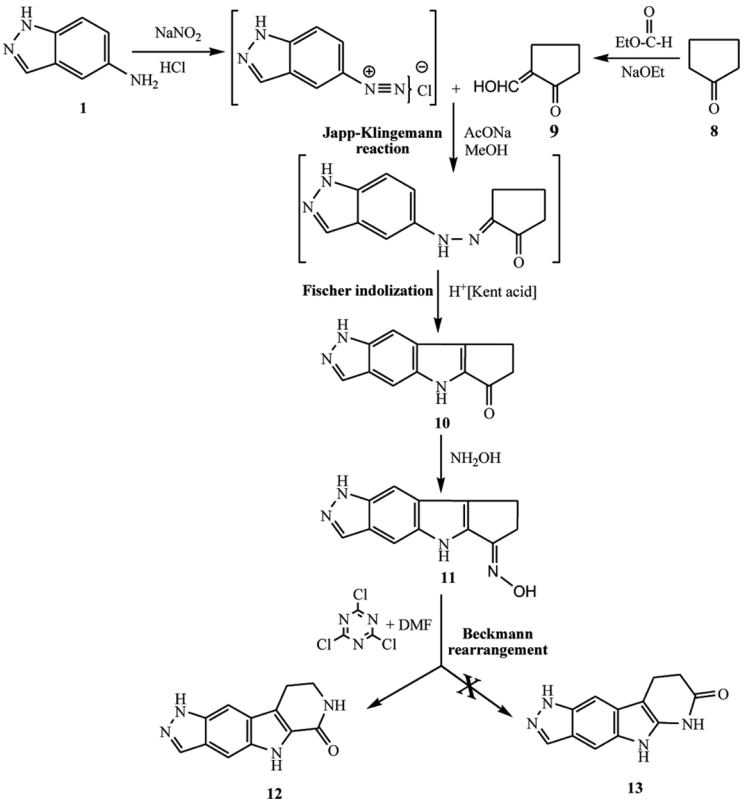
A plausible mechanistic scheme for the exclusive formation of **6a** (95%) and **6b** (98%) from the rearrangement of the corresponding ketoximes **5a** and **5b** respectively with TCT and DMF is shown in Scheme 3. The reaction is believed to proceed by a pathway similar to that outlined in Scheme 2. It is suggested that the species **G** generated in Scheme 2 presumably facilitates the departure of its chlorine atom by the indole nitrogen, which initiates an intramolecular nucleophilic attack on the carbon-bearing the chlorine atom to generate a relatively more stable species **K** via the intermediacy of **J** (Scheme 3). The indicated orientation that the species G acquires facilitates on one hand the rearrangement to occur only through path **a** and on the other hand precludes its reaction in proceeding through path **b** to form the other regioisomers **7a** and **7b**. It is apparent that the rearrangement through path **a** would allow **6a** and **6b** to be exclusively formed in the reaction.

In view of establishing the generality of this reaction, the Beckmann rearrangement of the corresponding cyclopentanone oxime **11** was also examined. The required oxime **11** was realized in a straightforward manner in three steps from **9** (Scheme 4), on allowing the same strategy to operate on **9** that had resulted the formation of **5a** from **3a** (Scheme 1). The rearrangement of **11** with TCT-DMF produced exclusively **12** in 82% yield. The minor amounts of other products formed were not examined. The same mechanism (Scheme 2) that allowed the formation of **6a** and **6b** from **5a** and **5b** was presumed to operate also in the formation of



Scheme 3. Mechanism for the exclusive formation of one-regioisomer **6a** and **6b** only.

12 from **11**. We believe that in both the reactions the indole nitrogen has played a determining role in allowing the formation of the one regioisomer only. In the ^{1}H NMR spectrum of **12**, the occurrence of two downfield triplets for the protons of two CH_2 groups at δ 3.40 and 2.83 clearly indicated these to be present in close proximity to nitrogen atom. Had **13** been formed, the two CH_2 groups would have been present close to CO group and the protons of the CH_2 group would have appeared in an upfield region. In the ^{1}H NMR spectrum of **6b** (containing the N-benzyl group), the two CH_2 groups were found to be flanked in between the two nitrogen atoms, and this caused the two triplets of the CH_2 protons to appear much downfield in the region of δ 3.25 and 3.15. Had the **7b** been formed, it would have caused the CH_2 protons lying close to CO group to appear in the upfield region. As this was not observed, it clearly ruled out the possibility of the formation of **7b**.



Scheme 4. Synthesis of 3,4-dihydropyazolo[4,3-b]azacarbazole-1(2*H*)-one.

EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on a Schimadzu FTIR-8400S. ^{1}H NMR spectra were recorded using $CDCl_3$ on Bruker DRX-300 spectrometer using tetramethylsilane (TMS) as internal reference, and values are expressed in δ ppm. Mass spectra were taken on a Jeol SX-102 mass spectrometer at 70 eV. 5-Aminoindazole required in synthesis was prepared from the reduction[19] of commercially available 5-nitroindazole.

Preparation Using Japp–Klingemann Reaction

A solution of 5-indazolyl amine **1** (1.0 g, 0.050 mol) in aqueous HCl (2 ml concentrated HCl in 4 ml water) was treated with a cold saturated solution of sodium nitrite (0.7 g in 2 ml water) while the temperature was kept at 0 to 5 °C. The solution was kept aside for 10 min. It was then added portionwise to an ice-cooled mixture containing (E)-1-benzyl-3-(hydroxymethylidine)-piperidin-4-one **3b** (1.30 g, 0.050 mol) or 2-hydroxymethylene cyclopentanone **9** and sodium acetate trihydrate (1.80 g) in methanol (10 ml) and water (6 ml) over a period of 0.5 h with stirring.

The contents were allowed to stand for a further 0.5 h and the resulting solid mass was filtered, washed with water, dried, and recrystallized from ethanol. Similarly the cyclohexan-1-one-2-[5-indazolyl]hydrazone was prepared. These were employed in the next step for Fischer indolization without further purification to give **4a, 4b**, and **10** respectively.

General Method for the Preparation of 4a, 4b, and 10

A solution of hydrazone (0.01 mol) suspended in a mixture of acetic acid and HCl (3:1 ml) was refluxed on a preheated oil bath to 125–130 °C for 0.5 h. The contents were then cooled and poured into ice-cold water with stirring and basified with ammonia. The separated brown solid was purified by passing through a column of silica gel using 50% benzene in petroleum ether as eluant to give **4a, 4b**, and **10** respectively.

8,9-Dihydropyrazolo[4,3-*b*]carbazol-6(1*H*,5*H*,7*H*)-one 4a. This was prepared following the general procedure mentioned above. Yield: 65%; mp 238–240 °C; IR (KBr) cm^{-1}: 3290, 2920, 1720, 1510, 1020; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ ppm: 12.4 (1H, s, NH), 10.1 (1H, s, NH), 8.20 (1H, s, CH), 7.60 (1H, s, ArCH), 7.44 (1H, s, ArCH), 2.43 (2H, t, CH_2), 2.10 (2H, m, CH_2), 1.89 (2H, t, CH_2); MS m/z (percent abundance): 225 [M^+] (25%), 109 (38%), 165 (50%), 136 (56%), 91 (88%); Analytical data calcd./found for $C_{13}H_{11}N_3O$: N, 18.52/18.69; C, 69.32/69.54; H, 4.92/5.08.

9-Benzyl-7,8-dihydropyrazolo[4,3-b]carbazol-6(1*H*,5*H*,7*H*)-one (4b). This was prepared following the general procedure mentioned above. Yield: 70%; mp 277–279 °C; IR (KBr) cm^{-1}: 3220, 2910, 1735, 1520, 1040; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 11.9 (1H, s, NH), 10.8 (1H, s, NH), 8.15 (1H, s, CH), 7.79–7.57 (2H, m, ArH), 7.14–7.06 (5H, m, ArH), 4.32 (2H, t, CH_2), 3.39 (2H, t, CH_2), 2.63 (2H, s, CH_2); MS m/z (percent abundance): 316 [M^+](18%), 288 (26%), 221 (40%), 147 (52%), 91 (81%). Analytical data calcd./found for $C_{19}H_{16}N_4O$: N, 17.71/17.94; C, 72.13/72.31; H, 5.10/5.29.

Pyrazolo[4,3-*b*]-1,2-dihydrocyclopentan[b]indol-3(4*H*)-one 10. The general method mentioned above was applied to the synthesis of **10**. Yield: 71%; mp 210–212 °C; IR(KBr) cm^{-1}: 3250, 29350, 1710, 1540, 1040; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 12.1 (1H, s, NH), 10.3 (1H, s, NH), 8.15 (1H, s, CH), 7.63 (1H, s, ArH), 7.57 (1H, s, ArH), 2.67 (2H, t, CH_2), 2.71 (2H, t, CH_2); MS: m/z 211 [M^+]. Analytical data calcd./found for $C_{13}H_{11}N_3O$: N, 19.89/20.09; C, 68.24/68.44; H, 4.29/4.38.

Preparation of Ketoxime 5a, 5b, and 11

To a mixture of 0.137 mol of **4a/b** or **10,** hydroxylamine hydrochloride (0.216 g, 0.06 M), 0.1 g of sodium hydroxide (pellet form) in 0.2 ml of rectified spirit, and 0.1 ml water were added in portions with shaking. As the reaction became too vigorous, the flask was cooled in running tap water. When all the sodium hydroxide was added, a reflux condenser was attached to the flask, and the mixture was refluxed for 20 min, cooled, and poured into 5 ml of water. The precipitate (oxime) was

filtered at the pump, washed, and recrystallized from methanol to give ketoxime **5a:** yield 70%, mp 245–46 °C; **5b:** yield 76%, mp 224–226 °C; **11:** yield 66%, mp 170 °C.

Preparation of 1,4,5,6,8-Pentahydroimidazolo[7,8-*b*]indolo-7(5*H*)-[6,5-f]azepine (3*H*)-2-one 6a

2,4,6-Trichloro[1,3,5]triazine (1.83 g, 10.0 mmol) was added to DMF (2 ml) and maintained at 25 °C. After formation of white solid, the reaction was monitored (by TLC) until complete disappearance of TCT, and then ketoxime of 7,8,9-trihydropyrazolo[4,5-b] carbazol-6(3*H*)-one **5a** (1.10 g, 10.0 mmol) in DMF (15 ml) was added. After the addition, the mixture was stirred at room temperature and monitored (by TLC) until the completion of the reaction (20 h). Water (20 ml) was added, and then the organic phase was washed with 15 ml of a saturated solution of Na_2CO_3 followed by brine solution. The organic layer was dried over the sodium sulfate. Evaporation of solvent gave **6a**. Yield: 1.27 g (95%), mp 155–156 °C. IR (KBr) cm^{-1}: 3340, 2930, 1660, 1600, 1490, 1090, 800; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 12.53 (1H, s, NH), 10.55 (1H, s, NH), 8.19 (1H, s, CH pyrazole ring), 8.09 (1H, t, NH), 7.88–7.76 (2H, s, ArH), 2.58 (2H, t, CH_2), 2.13 (2H, t, CH_2), 1.66 (2H, m, CH_2). MS m/z (percent abundance): 240 [M^+] (21%), 212 (28%), 165 (50%), 91 (78%); Analytical data calcd./found for $C_{13}H_{12}N_4O$: N, 23.22/23.41: C, 64.99/65.17: H, 5.03/5.26.

Preparation of 6-Benzyl-1,4,5,8-tetrahydroimidazolo[7,8-b]indolo-7(5*H*)-[6,5-f]-azepine (3*H*)-2-one 6b

Compound **6b** was prepared by the method used for preparation of **6a**. Yield: 98%, mp 164–165 °C. IR (KBr) cm^{-1}: 3300, 2900, 1665, 1580, 1490, 1025, 825; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 12.3 (1H, s, NH), 10.6 (1H, s, NH), 8.14 (1H, s, CH pyrazole ring), 8.09 (1H, t, NH), 7.82–7.10 (7H, m, ArH), 4.37 (2H, s, CH_2), 3.25 (2H, t, CH_2), 3.15 (2H, t, CH_2). MS m/z (percent abundance): 331 [M^+] (17%), 303 (22%), 286 (43%), 191 (51%), 109 (58%), 91 (81%). Analytical data calcd./found for $C_{19}H_{17}N_5O$: N, 21.73/21.94; C, 68.87/69.08; H, 5.17/5.36.

Preparation of 3,4-Dihydro-pyrazolo-2*H*-pyrido[3,4-b]indol-(6*H*,10*H*)-one 12

Compound **12** was prepared by the method used for preparation of **6a** and **6b**. Yield 1.10 g (82%), mp 190 °C. IR (KBr) cm^{-1}: 3310, 2920, 1710, 1650, 1090, 830; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 12.72 (1H, s, NH), 10.05 (1H, s, NH), 8.21 (1H, s, CH pyrazole ring), 8.10 (1H, t, NH), 7.71 (1H, s, ArH), 7.74 (1H, s, ArH), 3.40 (2H, t, CH_2), 2.83 (2H, t, CH_2); MS: m/z 226 [M^+]. Analytical data: calcd./found for $C_{13}H_{12}N_4O$: N, 23.22/23.41; C, 63.71/63.88; H, 4.46/4.61.

CONCLUSION

In conclusion, two noteworthy features from the strategy employed in synthesis of the reported compounds are apparent from our study. First, it established that the

Fischer indolization of 2-(2-indazolylhydrazono)cyclohexan-1-one and 1-benzyl-3-(2-indazolylhydrazono)piperidin-4-ones provided a very convenient, one-pot synthetic entry to the corresponding pyrazolo fused oxocarbazole **4a** and oxoazacarbazole **4b** derivatives. The study further established the versatility of the Japp–Klingemann reaction to provide a one-step synthetic approach to the preparation of hetero aryl hydrazones (on to the adjacent methylene carbon of a cyclic carbonyl species), which are not normally accessible by conventional procedures. Second, it established that the Beckmann rearrangement of the ketoximes of the indole ring incorporated 4-piperidones by the organocatalyst derived from TCT + DMF provided an elegant one-step approach to the regioselective formation of one regioisomer only, in high purity and good yield. The versatility of this process pathway on other substrates is under study.

ACKNOWLEDGMENTS

The authors are thankful to CDRI, Lucknow, for providing the spectral data of the compounds, and are grateful for the financial support provided by the Department of Science and Technology (DST), New Delhi, to Banasthali Center for Education and Research in Basic Sciences under the CURIE (Consolidation of University Research for Innovation and Excellence in Women Universities) program.

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