

Reaction of 2-hydrazino-3-methylquinoxaline with aryl-1,3-diketones: A structural reinvestigation

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Abstract

Treatment of 2-hydrazino-3-methylquinoxaline (**1**) with phenyl-1,3-butanedione (**2b**) in THF affords regioisomeric 1-(3'-methylquinoxalin-2'-yl)-3(5)-methyl-5(3)-phenylpyrazoles (**3b** and **4b**) as major products along with the formation of small amount of 1,4-dimethyl-1,2,4-triazolo[4,3-*a*]quinoxaline (**5**) rather than the reported exclusive formation of **5**. Several other regioisomeric 1-(3'-methylquinoxalin-2'-yl)-3,5-disubstituted pyrazoles have similarly been synthesized using other aryl- and heteroaryl-1,3-diketones. The identity of the regioisomeric pyrazoles is based upon NMR (¹H & ¹³C) spectral data and an unambiguous synthesis.

Keywords: 2-Hydrazino-3-methylquinoxaline, 1,3-diketones, regioisomeric pyrazoles, 1-(3'-methylquinoxalin-2'-yl)-3(5)-methyl-5(3)-phenylpyrazoles, 1,4-dimethyl-1,2,4-triazolo[4,3-*a*]quinoxaline

Introduction

The reaction of β -dicarbonyl compounds or synthetic equivalents with hydrazines is the most usual approach for the synthesis of pyrazoles¹. Whereas there is no structural ambiguity concerning the structure of the products obtained in the cases of alkyl- or arylhydrazines, reaction of heterocyclhydrazines with β -dicarbonyl compounds has been reported to yield isomeric products having different structures such as diazepines² or triazepines³. Structure of many of these compounds has been reinvestigated in our laboratory⁴⁻⁹ and by Peet *et al.*¹⁰ and it has been established that all such structures are in error and products are indeed pyrazole derivatives.

As a part of our comprehensive programme to establish the structure of products obtained by the reaction of heterocyclhydrazines with β -diketones, we came across a report by Shiho and Tagami¹¹ describing the exclusive formation of 1,4-dimethyl-1,2,4-triazolo[4,3-*a*]quinoxaline by treating 2-hydrazino-3-methylquinoxaline with phenyl-1,3-butanedione. Such a triazole structure appeared questionable as in the same report these authors have reported the formation of expected pyrazoles while performing the reaction of 2-hydrazinoquinoxalines with a number of

other β -diketones. In view of these anomalous results, we decided to reinvestigate the structure of the products obtained by condensation of 2-hydrazino-3-methylquinoxaline with β -diketones by using NMR spectral studies and also employing an alternate synthesis.

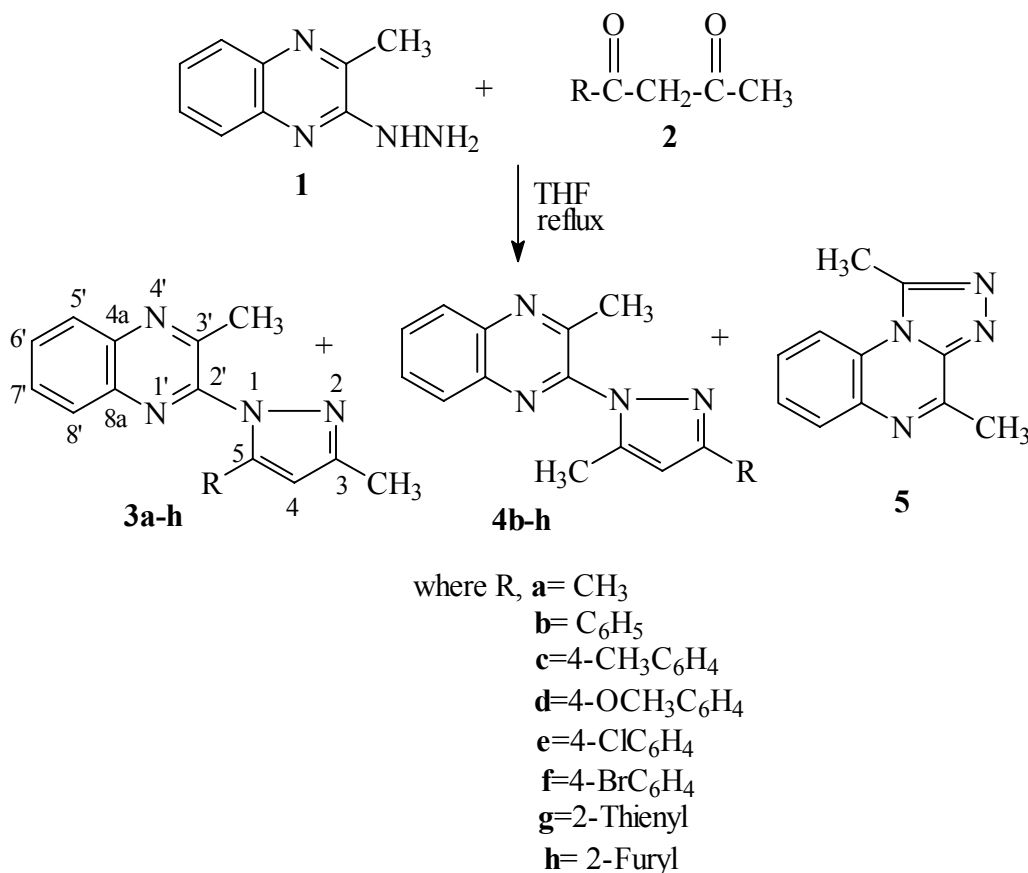
Results and Discussion

Reaction of 2-hydrazino-3-methylquinoxaline (**1**) with pentane-2,4-dione (**2a**) in EtOH or THF afforded an exclusive crystalline product which was identified as 1-(3'-methylquinoxalin-2'-yl)-3, 5-dimethylpyrazole (**3a**), mp 114-116 °C (lit.¹¹ mp 117 °C). ¹H NMR spectrum of **3a** displayed three sharp singlets each of three proton intensity at δ 2.25, 2.29 and 2.69 assigned to CH₃ groups located on C₃ of quinoxaline ring and C₃ & C₅ of pyrazole ring, respectively, and a sharp singlet of one proton intensity at δ 6.0 assigned to C₄-H, besides the aromatic protons of quinoxaline. The difference in chemical shift of C₃-CH₃ and C₅-CH₃ pyrazole signals has been the subject of considerable study in our laboratory and it has been established that the protons of the methyl group located at position-5 are deshielded (~ 0.5 ppm) as compared to those at position-3 and thus can be used as a reliable tool to differentiate between 3-methylpyrazole and its 5-methyl isomer. The deshielding of C₅-CH₃ as compared to C₃-CH₃ can be rationalized on the basis of the lone pair effect of the nitrogen atom of the heteroaromatic ring or perhaps hydrogen bonding and consequent planarity of the system¹². An examination of ¹³C NMR of this compound revealed signals at δ 152.08, 107.48 and 139.55 in agreement with the values recorded for carbon atoms C₃, C₄ and C₅ of pyrazole ring¹².

However, when the reaction of 2-hydrazino-3-methylquinoxaline (**1**) with phenyl-1,3-butanedione (**2b**) was carried out at 130-160 °C (under the conditions specified by Shiho and Tagami¹¹), rather than 1,4-dimethyl-1,2,4-triazolo[4,3-*a*]quinoxaline as a single product, a mixture of three products in the ratio 5.5: 1: 3.5 was obtained as evident from the TLC and ¹H NMR spectrum. In order to examine the effect of reaction conditions on the relative ratio of the three products, a reaction was performed in refluxing THF. This time three products were formed in the ratio 7: 1.5: 1.5 with improved overall yield. (Scheme 1).

Chromatographic work up of the reaction mixture over silica gel using pet. ether and pet. ether-chloroform (0-50% gradient) as eluent, afforded three products in pure form. A crystalline solid, mp 130 °C obtained in the first fraction was characterized as 1-(3'-methylquinoxalin-2'-yl)-3-phenyl-5-methylpyrazole (**4b**) on the basis of elemental analysis and spectral data. ¹H NMR spectra of this compound displayed CH₃ protons resonating as a singlet at δ 2.79 (C₅-CH₃) and at δ 2.42 (quinox-CH₃) and a characteristic signal for one proton as a sharp singlet at δ 6.54 which was assigned to C₄-H of the pyrazole ring. The second fraction afforded a solid, mp 112-114 °C, which was identified as 1-(3'-methylquinoxalin-2'-yl)-3-methyl-5-phenylpyrazole (**3b**) as its ¹H NMR spectrum exhibited three singlets at δ 2.43 (3H, C₃-CH₃), δ 2.45 (3H, quinox-CH₃), and δ 6.46 (C₄-1H), along with aromatic protons. As expected, the CH₃ protons in isomer **4b** were deshielded, and hence the product was characterized as the 5-methyl isomer. These

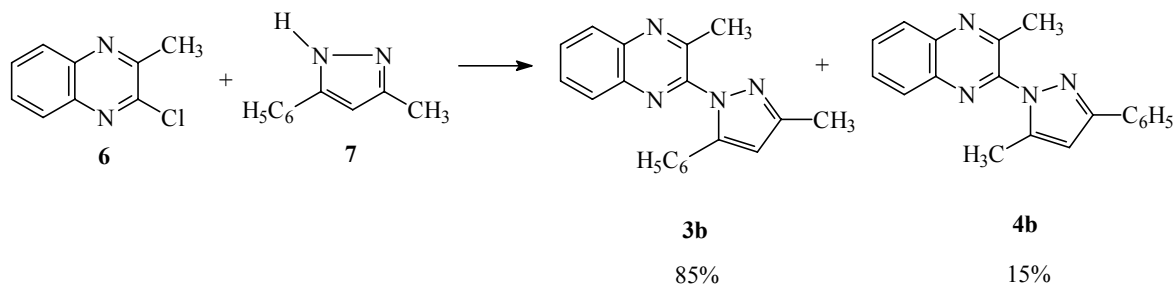
assignments find further support by an inspection of ^{13}C NMR spectral analysis. Analysis of ^{13}C NMR spectra of the isomeric products 5- and 3-isomer showed that carbon atoms C_3 , C_4 and C_5 in the 5-isomer (**4b**) resonated at δ 150.0, 102.53, 139.06 whereas in the 3-isomer, these carbon atoms resonated at δ 151.36, 106.57, 145.35, respectively. The intense signal located at 106 or 102 ppm is characteristic of the pyrazole 4-H. Furthermore, C_3 and C_5 of the pyrazole nucleus resonated at 151 (150) and 145 (139) ppm, respectively in agreement with the literature value.^{1,13} The solid obtained from the last fraction was identified as 1,4-dimethyl-*s*-triazolo[4,3-*a*]quinoxaline (**5**), mp 194-195 °C (lit.¹¹ mp 196 °C). The structure of **5** was confirmed on the basis of mixed mp., co-TLC and ^1H NMR spectrum, which displayed two singlets of three protons intensity at δ 2.9 and δ 3.1 due to two CH_3 groups, one located on quinoxaline ring and other on triazole ring.



Scheme 1

The NMR data thus confirmed the formation and identity of three compounds i.e. 1-(3'-methylquinoxalin-2'-yl)-3-phenyl-5-methylpyrazole (**4b**) and 1-(3'-methylquinoxalin-2'-yl)-3-methyl-5-phenylpyrazole (**3b**) and 1,4-dimethyl-*s*-triazolo[4,3-*a*]quinoxaline (**5**) in this reaction contrary to the reported formation of triazole as sole product.¹¹

Finally, pyrazole structure for compounds **3b** and **4b** was unambiguously established by an alternate synthesis (Scheme 2). Treatment of 2-chloro-3-methylquinoxaline (**6**) with sodium salt of 3(5)-methyl-5(3)-phenyl-1*H*-pyrazole (**7**) in *N,N*-dimethylformamide yielded isomeric pyrazoles **3b** and **4b** in the ratio 85: 15 (on the basis of NMR of crude reaction mixture) which were found to be identical in all respects with the products obtained through the hydrazine route.



Scheme 2

To generalize the formation of these products in this reaction, phenyl-1,3-butanedione (**2b**) was replaced with substituted aryl and heteroaryldiketones **2c-h** (Scheme 1). It was observed that in all these cases, there is formation of isomeric pyrazoles as major products along with smaller amount of the triazole **5**. Ratio of the three products (**3**, **4** and **5**) were calculated on the basis of ^1H NMR of the crude mixtures (Table 1). Distinction between the isomeric pairs was made using NMR (^1H & ^{13}C) spectroscopy. It is evident from the data given in Table 1 that 3-methylpyrazole is the major isomer in all such cases. Mechanistically, predominance of 3-isomer appears more reasonable than 5-isomer as the carbonyl carbon attached to the methyl group is more reactive towards nucleophilic attack by the N of the hydrazines than the other carbonyl which is adjacent to the aryl ring.¹⁴ Careful inspection of the ^{13}C NMR spectra of **3** and **4** reveals that in each case 3-methyl isomer shows resonance signal for C-5 relatively downfield: $\Delta\delta$ 6.29, 5.49, 6.51, 5.32, 5.39, 4.32, for **3b**, **4b**; **3c**, **4c**; **3d**, **4d**; **3e**, **4e**; **3f**, **4f**; **3h**, **4h**, respectively. The comparative deshielding of C-5 in compounds **3** may be attributed to the presence of aryl/heteroaryl group at position-5. The complete assignment of the carbon atoms of compounds **3** and **4** are given in Table 2.

The formation of three products (**3**, **4** and **5**) in these reactions can be explained on the basis of a plausible mechanism involving three intermediates (hydrazones-**A** & **B** and ketoimine-**C**) as outlined in Scheme-3. Intermediate **C** had been isolated and characterized by Zimmer and Amer¹⁵ by super-cooling the reaction mixture of 1-hydrazinophthalazine with polycarbonyl compounds.

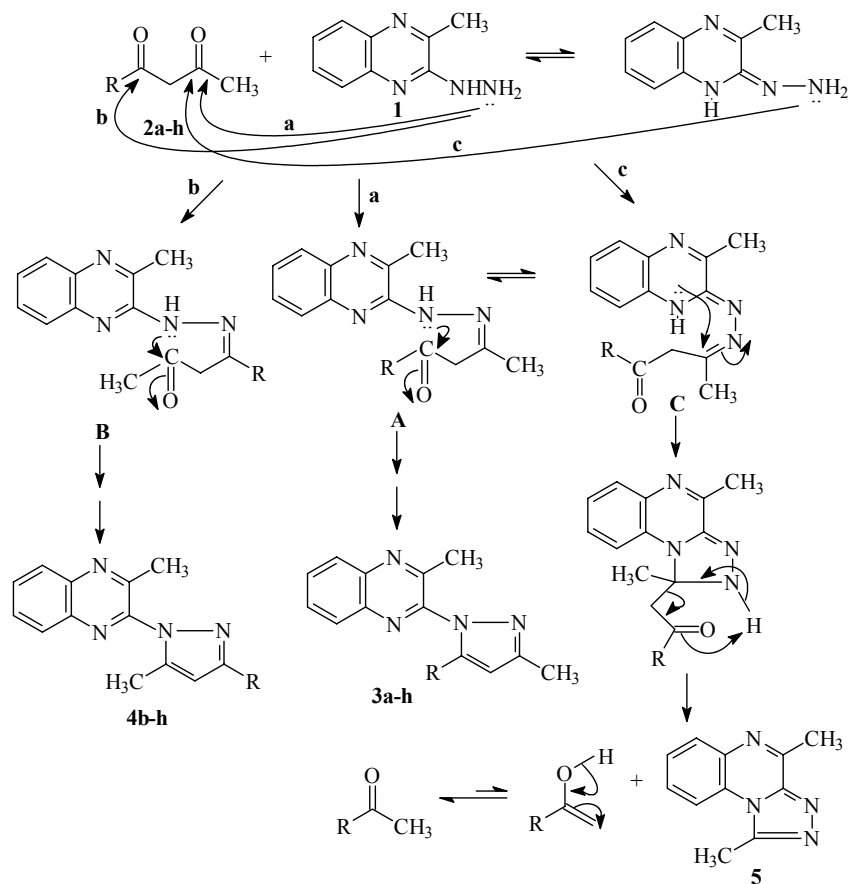
The following conclusions may be drawn as a result of the present study: (a) reaction of 2-hydrazino-3-methylquinoxaline (**1**) with unsymmetrical aryl- and heteroaryldiketones always results in the formation of isomeric pyrazoles as the major products instead of the exclusive

formation of a triazole as reported by Shiho and Tagami.¹¹ (b) 3-methylpyrazole is the predominant isomer thus confirming that carbonyl carbon attached to the methyl group is more susceptible to nucleophilic attack than the carbonyl adjacent to aryl ring. (c) ¹H and ¹³C NMR spectra are important tools for the characterization of isomeric 2'-pyrazolylquinoxalines.

Table 1. Analysis of crude reaction product based on ¹H NMR (Yield %)

Diketone	3-isomer	5-isomer	Triazole
2b	69%	15%	16%
2b*	55%	11%	34%
2c	64%	19%	17%
2d	57%	28%	15%
2e	60%	13%	27%
2f	63%	13%	24%
2g	50%	12%	38%
2h	55%	10%	35%

* Under conditions employed by Shiho and Tagami¹¹ (heating for 20 min. at 130-160 °C).



Scheme 3

Table 2. ^{13}C NMR data of compounds **3** and **4**

Carbon	3b	4b	3c	4c	3d	4d	3e	4e	3f	4f	3g	3h	4h	3a
C ₃	151.36	150.0	151.02	152.47	152.06	152.23	151.83	151.81	151.82	151.80	152.59	152.46	150.99	152.08
C ₄	106.57	102.53	105.73	104.82	106.45	104.60	107.45	104.82	107.45	104.81	106.83	105.43	103.54	107.48
C ₅	145.35	139.06	144.94	139.45	145.72	139.21	144.75	139.43	144.82	139.43	142.31	142.76	138.44	139.55
CH ₃	13.14	10.03	12.69	12.43	13.72	12.44	13.70	12.40	13.69	12.39	13.61	13.59	11.17	C ₃ 13.64 C ₅ 12.05
C ₁ '	129.21	127.38	125.98	130.19	122.33	125.78	128.56	131.50	129.18	131.61	Th-2'' 130.73	Fu-2'' 144.20	Fu-2'' 143.93	
C ₂ ', ₆ '	128.10	126.24	126.46	125.74	129.17	127.10	129.16	128.83	128.88	127.37	Th-4'' 127.50	Fu-4'' 111.36	Fu-4'' 110.35	
C ₃ ', ₅ '	127.26	123.43	128.38	129.34	114.15	114.05	128.83	127.07	131.90	131.78	Th-3'' 126.51	Fu-3'' 108.61	Fu-3'' 105.54	
C ₄ '	128.38	126.37	137.40	138.02	159.64	159.72	134.50	133.92	122.71	122.11	Th-5'' 124.37	Fu-5'' 142.20	Fu-5'' 141.25	
4''-			20.10	21.31	55.15	55.32								
CH ₃ /OCH ₃														
2'	150.46	149.55	150.02	152.0	151.01	151.99	151.16	151.32	151.18	151.33	150.98	151.0	147.46	150.21
3'	146.40	143.77	146.11	146.22	147.15	146.12	146.55	146.01	146.63	146.01	146.52	146.82	144.94	146.24
3'-CH ₃	20.88	20.63	20.37	23.05	21.39	23.08	21.55	22.95	21.55	22.94	21.27	21.34	21.67	22.63
5'	129.31	127.92	128.72	129.75	129.76	129.73	129.95	129.87	129.95	129.86	129.89	129.85	128.82	129.67
6'	127.70	125.77	127.26	128.36	128.28	128.35	128.35	128.39	128.35	128.40	128.41	128.38	127.38	128.32
7'	127.83	125.97	127.62	128.76	129.26	128.75	128.43	128.79	128.43	128.79	129.34	129.28	127.81	128.80
8'	130.10	130.59	129.63	130.26	130.67	130.23	130.85	130.46	130.85	130.45	130.98	130.87	129.47	130.22
4a	139.36	137.04	138.99	141.42	140.01	141.39	139.85	141.53	139.85	141.54	139.19	136.21	140.60	141.42
8a	141.35	140.19	140.94	142.49	141.95	142.52	141.97	142.83	141.98	142.84	139.97	139.88	141.17	141.78

Experimental Section

General Procedures. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Buck Scientific IR M-500 spectrophotometer in KBr pellets (ν_{max} in cm^{-1}), ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a Bruker instrument at 300 MHz and 75 MHz, respectively; chemical shifts are expressed as δ values with units of ppm, downfield from TMS (δ 0.0) as an internal standard. Coupling constants (J) are given in Hertz (Hz). Elemental analysis were performed in the RSIC, Lucknow, India. All the compounds gave satisfactory elemental analyses. The reactions were monitored by the TLC carried out on pre-coated silica gel glass plates. Separations were accomplished by column chromatography using silica gel (100-200 mesh) and light petroleum (60-80 °C)- CHCl_3 as eluent.

The starting compounds 2-hydrazino-3-methylquinoxaline (**1**) and aryl- β -diketones (**2c-h**) were prepared according to literature procedures.^{11,16} Pentane-2,4-dione is commercially available.

Synthesis of 1-(3'-methylquinoxalin-2'-yl)-3, 5-disubstituted pyrazoles

1-(3'-Methylquinoxalin-2'-yl)-3, 5-dimethylpyrazole (3a). A solution of 2-hydrazino-3-methylquinoxaline **1** (0.3 g, 1.72 mmol) and **2a** (0.17 g, 1.72 mmol) in EtOH (20 ml) was refluxed for 4 hrs. Excess of EtOH was distilled off and the residue was triturated with petroleum ether. Yield 85%; mp 112-114 °C (Lit.¹¹ mp 117 °C); IR (cm⁻¹): 2921, 1572, 1489, 1413, 1370; ¹H NMR: 2.25 (s, 3H, quinox-3'-CH₃), 2.29 (s, 3H, C₃-CH₃), 2.69 (s, 3H, C₅-CH₃), 6.0 (s, 1H, C₄-H), 7.67-7.69 (dt, 1H, *J*=7.2 Hz, 1.5 Hz, quinox-6'-H), 7.70-7.74 (dt, 1H, *J*=7.2 Hz, 1.5 Hz, quinox-7'-H), 7.94-7.97 (dd, 1H, *J*=7.5 Hz, 1.8 Hz, quinox-5'-H), 7.99-8.02 (dd, 1H, *J*=7.5 Hz, 1.8 Hz, quinox-8'-H). Anal. Calcd. for C₁₄H₁₄N₄: C, 70.58; H, 5.88; N, 23.52; found: C, 70.81; H, 5.75; N, 23.01.

The above compound **3a** was also obtained in 81% yield by refluxing **1** and CH₃COCH₂COCH₃ in THF for 4 hrs.

1-(3'-Methylquinoxalin-2'-yl)-3-methy-5-phenylpyrazole (3b), 1-(3'-methylquinoxalin-2'-yl)-3-phenyl-5-methylpyrazole (4b) and 1, 4-dimethyl-s-triazolo[4,3-*a*]quinoxaline (5). A solution of **1** (0.3 g, 1.72 mmol) and **2b** (0.28 g, 1.72 mmol) in THF (20 ml) was refluxed for 4 hrs. Excess of THF was distilled off and the residue obtained on cooling was found to be a mixture of products as evidenced by the TLC and ¹H NMR spectrum. The residue was subjected to column chromatography over silica gel using mixtures of petroleum ether/ CHCl₃ of increasing polarity as eluent to yield compound **4b** as a white solid and compound **3b** as a light yellow solid and the compound **5** in last fraction. **3b.** Yield 62%; mp 112-114 °C; IR (cm⁻¹): 3063, 1607, 1558, 1496, 1364; ¹H NMR: 2.43 (s, 3H, C₃-CH₃), 2.45 (s, 3H, quinox-3'-CH₃), 6.46 (s, 1H, C₄-H), 7.21-7.25 (m, 5H, Ph-H), 7.71-7.77 (dt, 1H, *J*=7.2 Hz, 1.5 Hz, quinox-6'-H), 7.78-7.84 (dt, 1H, *J*=7.5 Hz, 1.5 Hz, quinox-7'-H), 8.04-8.07 (d, 1H, *J*=8.1 Hz, quinox-5'-H), 8.07-8.11 (d, 1H, *J*=8.1 Hz, quinox-8'-H). Anal. Calcd. for C₁₉H₁₆N₄: C, 76.0; H, 5.33; N, 18.66; found: C, 75.89; H, 5.49; N, 18.22.

1-(3'-Methylquinoxalin-2'-yl)-3-phenyl-5-methylpyrazole (4b). Yield 12%; mp 130-132 °C; IR (cm⁻¹): 3069, 1569, 1472, 1446, 1368; ¹H NMR: 2.42 (s, 3H, quinox-3'-CH₃), 2.79 (s, 3H, C₅-CH₃), 6.54 (s, 1H, C₄-H), 7.27-7.38 (m, 3H, Ph-H), 7.68-7.71 (dt, 1H, *J*=7.2 Hz, 1.2 Hz, quinox-6'-H), 7.72-7.76 (dt, 1H, *J*=7.2 Hz, 1.5 Hz, quinox-7'-H), 7.79-7.83 (m, 2H, Ph-H), 7.96-7.99 (dd, 1H, *J*=7.5 Hz, 1.8 Hz, quinox-5'-H), 8.02-8.05 (dd, 1H, *J*=7.5 Hz, 1.8 Hz, quinox-8'-H). MS: *m/z* (%) 301.139 (21.9) (M+1)⁺, 300.137 (100) M⁺. Anal. Calcd. for C₁₉H₁₆N₄: C, 76.0; H, 5.33; N, 18.66; found: C, 76.21; H, 5.37; N, 18.18.

1,4-Dimethyl-s-triazolo[4,3-*a*]quinoxaline (5). Yield 33%; mp 194-195 °C (Lit.¹¹ mp 196 °C); IR (cm⁻¹): 2919, 1678, 1589, 1491; ¹H NMR: 2.92 (s, 3H, quinox-3'-CH₃), 3.10 (s, 3H, CH₃), 7.55-7.56 (m, 1H, quinox-6'-H), 7.57-7.58 (m, 1H, quinox-7'-H), 7.98-8.01 (dd, 1H, *J*=6.9 Hz, 2.7 Hz, quinox-5'-H), 8.06-8.09 (dd, 1H, *J*=6.9 Hz, 2.7 Hz, quinox-8'-H); ¹³C NMR: 14.18, 20.04, 29.91, 113.96, 125.30, 126.43, 127.52, 129.22, 135.43, 144.20, 146.50, 151.93. Anal. Calcd. for C₁₁H₁₀N₄: C, 66.66; H, 5.05; N, 28.28; found: C, 66.81; H, 5.21; N, 28.21.

All other compounds were synthesized according to the procedure mentioned for **3b** and **4b** using 2-hydrazino-3-methylquinoxaline (**1**) and different β -diketones (**2c-h**). The characterization data for **3c-h**, **4c-h** are given below:

1-(3'-Methylquinoxalin-2'-yl)-3-methyl-5-(4''-methylphenyl)pyrazole (3c). Yield 58%; mp 118-120°C; IR (cm⁻¹): 2960, 1619, 1563, 1511, 1434, 1364; ¹H NMR: 2.18 (s, 3H, Ph-4''-CH₃), 2.30 (s, 3H, C₃-CH₃), 2.36 (s, 3H, quinox-3'-CH₃), 6.34 (s, 1H, C₄-H), 6.91-6.94 (d, 2H, *J*=7.8 Hz, Ph-3'', 5''-H), 6.98-7.01 (d, 2H, *J*=7.8 Hz, Ph-2'', 6''-H), 7.64-7.74 (m, 2H, quinox-6'-H, 7'-H) 7.96-8.01 (m, 1H, quinox-5'-H), 8.03-8.07 (m, 1H, quinox-8'-H). Anal. Calcd. for C₂₀H₁₈N₄: C, 76.43; H, 5.73; N, 17.83; found: C, 76.63; H, 5.39; N, 17.80.

1-(3'-Methylquinoxalin-2'-yl)-3-(4''-methylphenyl)-5-methylpyrazole (4c). Yield 15%; mp 124-128°C; IR (cm⁻¹): 2919, 1612, 1566, 1514, 1364; ¹H NMR: 2.32 (s, 3H, Ph-4''-CH₃), 2.41 (s, 3H, quinox-3'-CH₃), 2.79 (s, 3H, C₅-CH₃), 6.51 (s, 1H, C₄-H), 7.15-7.17 (d, 2H, *J*=8.1 Hz, Ph-3'', 5''-H), 7.65-7.68 (d, 2H, *J*=8.1 Hz, Ph-2'', 6''-H), 7.69-7.72 (dt, 1H, *J*=7.8 Hz, 1.8 Hz, quinox-6'-H), 7.73-7.75 (dt, 1H, *J*=7.8 Hz, 1.8 Hz, quinox-7'-H) 7.95-7.99 (dd, 1H, *J*=7.8 Hz, 1.2 Hz, quinox-5'-H), 8.05-8.08 (dd, 1H, *J*=7.8 Hz, 1.2 Hz, quinox-8'-H). Anal. Calcd. for C₂₀H₁₈N₄: C, 76.43; H, 5.73; N, 17.83; found: C, 76.18; H, 5.96; N, 17.69.

1-(3'-Methylquinoxalin-2'-yl)-3-methyl-5-(4''-methoxyphenyl)pyrazole (3d). Yield 60%; mp 117-118°C; IR (cm⁻¹): 2961, 1606, 1509, 1438, 1246 (OCH₃); ¹H NMR: 2.31 (s, 3H, C₃-CH₃), 2.52 (s, 3H, quinox-3'-CH₃), 3.63 (s, 3H, Ph-4''-OCH₃), 6.30 (s, 1H, C₄-H), 6.63-6.66 (d, 2H, *J*=8.7 Hz, Ph-3'', 5''-H), 7.01-7.04 (d, 2H, *J*=8.4 Hz, Ph-2'', 6''-H), 7.63-7.67 (t, 1H, *J*=7.8 Hz, quinox-6'-H), 7.68-7.73 (t, 1H, *J*=7.5 Hz, quinox-7'-H) 7.96-7.98 (d, 1H, *J*=7.5 Hz, quinox-5'-H), 8.01-8.05 (d, 1H, *J*=7.8 Hz, quinox-8'-H). MS: *m/z* (%) 331.150 (22.1) (M+1)⁺, 330.146 (100) M⁺. Anal. Calcd. for C₂₀H₁₈N₄O: C, 72.72; H, 5.45; N, 16.96; found: C, 72.57; H, 5.69; N, 16.80.

1-(3'-Methylquinoxalin-2'-yl)-3-(4''-methoxyphenyl)-5-methylpyrazole (4d). Yield 12%; mp 120-122°C; IR (cm⁻¹): 2929, 1612, 1570, 1428, 1365, 1243 (OCH₃); ¹H NMR: 2.41 (s, 3H, quinox-3'-CH₃), 2.80 (s, 3H, C₅-CH₃), 3.78 (s, 3H, Ph-4''-OCH₃), 6.47 (s, 1H, C₄-H), 6.87-6.90 (d, 2H, *J*=9.0 Hz, Ph-3'', 5''-H), 7.65-7.70 (m, 2H, quinox-6', 7'-H), 7.72-7.75 (d, 2H, *J*=8.1 Hz, Ph-2'', 6''-H), 7.96-7.99 (dd, 1H, *J*=7.5 Hz, 1.2 Hz, quinox-5'-H), 8.01-8.04 (dd, 1H, *J*=7.5 Hz, 1.2 Hz, quinox-8'-H). MS: *m/z* (%) 331.150 (23.2) (M+1)⁺, 330.147 (100) M⁺. Anal. Calcd. for C₂₀H₁₈N₄O: C, 72.72; H, 5.45; N, 16.96; found: C, 72.69; H, 5.72; N, 16.68.

1-(3'-Methylquinoxalin-2'-yl)-3-methyl-5-(4''-chlorophenyl)pyrazole (3e). Yield 60%; mp 142-144°C; IR (cm⁻¹): 2930, 1605, 1492, 1362; ¹H NMR: 2.44 (s, 3H, C₃-CH₃), 2.48 (s, 3H, quinox-3'-CH₃), 6.45 (s, 1H, C₄-H), 7.12-7.18 (dd, 2H, *J*=8.7 Hz, 2.1 Hz, Ph-2'', 6''-H), 7.19-7.22 (dd, 2H, *J*=8.4 Hz, 2.1 Hz, Ph-3'', 5''-H), 7.72-7.80 (dt, 1H, *J*=7.2 Hz, 1.5 Hz, quinox-6'-H), 7.81-7.86 (dt, 1H, *J*=7.2 Hz, 1.8 Hz, quinox-7'-H) 8.00-8.04 (dd, 1H, *J*=8.4 Hz, 1.5 Hz, quinox-5'-H), 8.06-8.09 (dd, 1H, *J*=8.4 Hz, 1.5 Hz, quinox-8'-H). Anal. Calcd. for C₁₉H₁₅ClN₄: C, 68.16; H, 4.48; N, 16.74; found: C, 67.91; H, 4.75; N, 16.78.

1-(3'-Methylquinoxalin-2'-yl)-3-(4''-chlorophenyl)-5-methylpyrazole (4e). Yield 12%; mp 170-172°C; IR (cm⁻¹): 2924, 1612, 1570, 1427, 1367; ¹H NMR: 2.41 (s, 3H, quinox-3'-CH₃),

2.78 (s, 3H, C₅-CH₃), 6.51 (s, 1H, C₄-H), 7.30-7.33 (dd, 2H, *J*=8.7 Hz, 2.1 Hz, Ph-2'', 6''-H), 7.66-7.72 (m, 2H, quinox-6', 7'-H), 7.73-7.76 (d, 2H, *J*=8.7 Hz, Ph-3'', 5''-H), 7.96-7.99 (dd, 1H, *J*=8.1 Hz, 1.2 Hz, quinox-5'-H), 8.02-8.06 (dd, 1H, *J*=8.1 Hz, 1.2 Hz, quinox-8'-H). MS: *m/z* (%) 335.09 (28.3) (M+1)⁺, 334.098 (100) M⁺. Anal. Calcd. for C₁₉H₁₅ClN₄: C, 68.16; H, 4.48; N, 16.74; found: C, 68.33; H, 4.58; N, 16.96.

1-(3'-Methylquinoxalin-2'-yl)-3-methyl-5-(4''-bromophenyl)pyrazole (3f). Yield 57%; mp 166-168°C; IR (cm⁻¹): 2925, 1606, 1486, 1397; ¹H NMR: 2.36 (s, 3H, C₃-CH₃), 2.40 (s, 3H, quinox-3'-CH₃), 6.37 (s, 1H, C₄-H), 6.97-7.04 (d, 2H, *J*=8.7 Hz, Ph-2'', 6''-H), 7.25-7.29 (d, 2H, *J*=8.4 Hz, Ph-3'', 5''-H), 7.71-7.76 (m, 2H, quinox-6'-H, 7'-H) 7.92-7.95 (dd, 1H, *J*=8.4 Hz, 1.5 Hz, quinox-5'-H), 7.97-8.01 (dd, 1H, *J*=8.4 Hz, 1.5 Hz, quinox-8'-H). Anal. Calcd. for C₁₉H₁₅BrN₄: C, 60.15; H, 3.95; N, 14.77; found: C, 60.36; H, 3.66; N, 14.80.

1-(3'-Methylquinoxalin-2'-yl)-3-(4''-bromophenyl)-5-methylpyrazole (4f). Yield 14%; mp 172-173°C; IR (cm⁻¹): 2967, 1563, 1465, 1364, 1260; ¹H NMR: 2.41 (s, 3H, quinox-3'-CH₃), 2.78 (s, 3H, C₅-CH₃), 6.51 (s, 1H, C₄-H), 7.46-7.49 (d, 2H, *J*=8.4 Hz, Ph-2'', 6''-H), 7.66-7.69 (d, 2H, *J*=8.4 Hz, Ph-3'', 5''-H), 7.71-7.76 (m, 2H, quinox-6', 7'-H), 7.96-7.99 (dd, 1H, *J*=7.8 Hz, 1.8 Hz, quinox-5'-H), 8.02-8.06 (dd, 1H, *J*=7.8 Hz, 1.8 Hz, quinox-8'-H). MS: *m/z* (%) 379.046 (42.4) (M+1)⁺, 378.049 (100) M⁺. Anal. Calcd. for C₁₉H₁₅BrN₄: C, 60.15; H, 3.95; N, 14.77; found: C, 60.33; H, 4.19; N, 14.75.

1-(3'-Methylquinoxalin-2'-yl)-3-methyl-5-(2''-thienyl)pyrazole (3g). Yield 55%; mp 128°C; IR (cm⁻¹): 3111, 1583, 1506, 1433, 1366; ¹H NMR: 2.34 (s, 3H, C₃-CH₃), 2.40 (s, 3H, quinox-3'-CH₃), 6.41 (s, 1H, C₄-H), 6.70-6.72 (d, 1H, *J*_{3''}, *J*_{4''}=3.6 Hz, Th-3''-H), 6.76-6.79 (t, 1H, *J*_{4''}, *J*_{5''}=5.1 Hz, *J*_{3''}, *J*_{4''}=3.6 Hz, Th-4''-H), 7.09-7.11 (d, 1H, *J*_{4''}, *J*_{5''}=5.1 Hz, Th-5''-H), 7.66-7.72 (t, 1H, *J*=7.8 Hz, quinox-6'-H), 7.73-7.77 (t, 1H, *J*=8.1 Hz, quinox-7'-H) 8.01-8.04 (dd, 1H, *J*=8.1 Hz, 1.8 Hz, quinox-5'-H), 8.05-8.08 (dd, 1H, *J*=8.1 Hz, 1.5 Hz, quinox-8'-H). Anal. Calcd. for C₁₇H₁₄N₄S: C, 66.66; H, 4.57; N, 18.30; found: C, 66.45; H, 4.91; N, 18.18.

1-(3'-Methylquinoxalin-2'-yl)-3-(2''-thienyl)-5-methylpyrazole (4g). Yield 12%; mp 140°C; IR (cm⁻¹): 3011, 1583, 1566, 1463, 1365; ¹H NMR: 2.48 (s, 3H, quinox-3'-CH₃), 2.86 (s, 3H, C₅-CH₃), 6.54 (s, 1H, C₄-H), 7.08-7.11 (t, 1H, *J*_{4''}, *J*_{5''}=5.1 Hz, *J*_{3''}, *J*_{4''}=3.6 Hz, Th-4''-H), 7.29-7.31 (d, 1H, *J*_{4''}, *J*_{5''}=5.1 Hz, Th-5''-H), 7.42-7.43 (d, 1H, *J*_{3''}, *J*_{4''}=3.6 Hz, Th-3''-H), 7.77-7.79 (dt, 1H, *J*=7.5 Hz, 1.5 Hz, quinox-6'-H), 7.80-7.82 (dt, 1H, *J*=7.5 Hz, 1.5 Hz, quinox-7'-H) 8.05-8.08 (dd, 1H, *J*=7.8 Hz, 1.8 Hz, quinox-5'-H), 8.11-8.13 (dd, 1H, *J*=8.1 Hz, 1.8 Hz, quinox-8'-H). Anal. Calcd. for C₁₇H₁₄N₄S: C, 66.66; H, 4.57; N, 18.30; found: C, 66.61; H, 4.86; N, 18.44.

1-(3'-Methylquinoxalin-2'-yl)-3-methyl-5-(2''-furyl)pyrazole (3h). Yield 56%; mp 128°C; IR (cm⁻¹): 3111, 1610, 1542, 1497, 1360; ¹H NMR: 2.34 (s, 3H, C₃-CH₃), 2.46 (s, 3H, quinox-3'-CH₃), 5.95-5.96 (d, 1H, *J*_{3''}, *J*_{4''}=3.3 Hz, Fur-3''-H), 6.19-6.21 (dd, 1H, *J*_{3''}, *J*_{4''}=3.3 Hz, *J*_{4''}, *J*_{5''}=1.8 Hz, Fur-4''-H), 6.48 (s, 1H, C₄-H), 7.17-7.18 (d, 1H, *J*_{4''}, *J*_{5''}=1.8 Hz, Fur-5''-H), 7.66-7.72 (t, 1H, *J*=8.4 Hz, quinox-6'-H), 7.73-7.79 (t, 1H, *J*=8.1 Hz, quinox-7'-H) 7.99-8.03 (m, 1H, quinox-5'-H), 8.06-8.1 (m, 1H, quinox-8'-H). Anal. Calcd. for C₁₇H₁₄N₄O: C, 70.34; H, 4.82; N, 19.31; found: C, 70.77; H, 5.12; N, 19.03.

1-(3'-Methylquinoxalin-2'-yl)-3-(2''-furyl)-5-methylpyrazole (4h). Yield 10%; mp 138°C; IR (cm⁻¹): 2930, 1619, 1552, 1488, 1368; ¹H NMR: 2.37 (s, 3H, quinox-3'-CH₃), 2.73 (s, 3H, C₅-CH₃), 6.41-6.43 (dd, 1H, *J*_{3''}, *J*_{4''}=3.3 Hz, *J*_{4''}, *J*_{5''}=1.8 Hz, Fur-4''-H), 6.47 (s, 1H, C₄-H), 6.67-6.68 (d, 1H, *J*_{3''}, *J*_{4''}=3.3 Hz, Fur-3''-H), 7.41-7.42 (d, 1H, *J*_{4''}, *J*_{5''}=1.8 Hz, Fur-5''-H), 7.66-7.71 (dt, 1H, *J*=6.9 Hz, 1.5 Hz, quinox-6'-H), 7.73-7.75 (dt, 1H, *J*=6.9 Hz, 1.5 Hz, quinox-7'-H) 7.96-7.99 (dd, 1H, *J*=7.8 Hz, 1.8 Hz, quinox-5'-H), 8.02-8.06 (dd, 1H, *J*=8.1 Hz, 1.8 Hz, quinox-8'-H). Anal. Calcd. for C₁₇H₁₄N₄O: C, 70.34; H, 4.82; N, 19.31; found: C, 70.15; H, 4.62; N, 19.44.

Unambiguous synthesis of 1-(3'-methylquinoxalin-2'-yl)-3-methy-5-phenylpyrazole (3b), 1-(3'-methylquinoxalin-2'-yl)-3-phenyl-5-methylpyrazole (4b)

A solution of 3(5)-methyl-5(3)-phenyl-1*H*-pyrazole (**7**) (790 mg, 5 mmol) in anhydrous *N,N*-dimethylformamide (20 ml) was stirred with a suspension of sodium hydride (60%, 240 mg, 10 mmol) at room temperature for 30 minutes. Subsequently, 2-chloro-3-methylquinoxaline (**6**) (890 mg, 5 mmol) was added slowly and the reaction mixture was heated in an oil bath at 140-150 °C for 12 hr. After distilling the excess of *N,N*-dimethylformamide, the residue was poured into ice-water (50 ml) and extracted with ethyl acetate (3 x 20 ml). The combined extract was dried over anhydrous Na₂SO₄ and ethyl acetate was distilled off. The crude solid thus obtained was purified by column chromatography using light petroleum-chloroform as eluent, which afforded first **4b**, mp 130-132 °C, yield 10%. Further elution of the column with light petroleum-chloroform afforded **3b**, mp 112-114 °C, yield 54%.

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References

- (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry I*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, Chapter 4.04. (b) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W., Scriven, E. F. V. Eds.; Pergamon Press: Oxford, 1995; Vol. 3, Chapter 3.01.
- (a) Surana, A.; Tyagi, R. P.; Joshi, B. C. *Philipp. J. Sci.* **1972**, *101*, 49. (b) Singhal, R. K.; Joshi, B. C. *Philipp. J. Sci.* **1978**, *107*, 219.

3. (a) Alaka, B. V.; Patnaik, D.; Rout, M. K. *J. Indian Chem. Soc.* **1982**, *9*, 1168. (b) Mahajan, M. P.; Sondhi, S. M.; Ralhan, N. K. *Aust. J. Chem.* **1977**, *30*, 2053. (c) Lancelot, J. C.; Laduree, D.; Kashef, H. E.; Robba, M. *Heterocycles* **1985**, *23*, 909.
4. (a) Singh, S. P.; Seghal, S.; Singh, L.; Dhawan, S. N. *Indian J. Chem.* **1987**, *26 B*, 154. (b) Singh, S. P.; Diwarkar, P.; Vaid, R. K. *Indian J. Chem.* **1986**, *26 B*, 1054. (c) Singh, S. P.; Sehgal, S.; Diwakar, P.; Vaid, R. K. *Indian J. Chem.* **1988**, *27 B*, 573.
5. (a) Singh, S. P.; Vaid, R. K.; Prakash, I.; Prakash, O. *Indian J. Chem.*, **1986**, *25 B*, 945. (b) Singh, S. P.; Tarar, L. S.; Vaid, R. K.; Elguero, J.; Martinez, A. *J. Heterocycl. Chem.* **1989**, *26*, 733.
6. Singh, S. P.; Kumar, D. *Heterocycles* **1990**, *31*, 855.
7. Singh, S. P.; Savita; Kumar, D. *Indian J. Chem.* **1993**, *32 B*, 262.
8. Singh, S. P.; Kapoor, J. K.; Kumar, D. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1703.
9. Singh, S. P.; Kodali, D. R.; Prakash, I.; Prakash, O.; Sawhney, S. N. *Indian J. Chem.* **1984**, *23 B*, 125.
10. (a) Peet, N. P.; Sunder, S.; Barbuch, R. J.; Whalon, M. R. *J. Heterocycl. Chem.* **1988**, *25*, 543. (b) Peet, N. P.; Sunder, S. *Heterocycles* **1986**, *24*, 3213.
11. Shiho, D.; Tagami, S. *J. Am. Chem. Soc.* **1960**, *82*, 4044.
12. Singh, S. P.; Sehgal, S.; Tarar, L. S. *Indian J. Chem.* **1989**, *28 B*, 27.
13. Heinisch, G.; Holzer, W. *Heterocycles* **1988**, *27*, 2443.
14. (a) Barry, W. J. *J. Chem. Soc.* **1958**, 1171. (b) Barry, W. J.; Finar, I. L.; Simmonds, A. B. *J. Chem. Soc.* **1956**, 4974.
15. Zimmer, H.; Amer, A. *Heterocycles* **1987**, *26*, 1177.
16. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Text Book of Practical Organic Chemistry*; 5th Edn.; Longman Group: England, 1991; p 634.