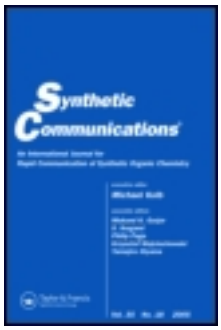

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A Facile and Efficient Regioselective Synthesis of 1-(3′-Substitutedquinoxalin-2′-yl)-3-Aryl/Heteroaryl-5-Methylpyrazoles

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A FACILE AND EFFICIENT REGIOSELECTIVE SYNTHESIS OF 1-(3'-SUBSTITUTEDQUINOXALIN-2'-YL)-3-ARYL/HETEROARYL-5-METHYLPYRAZOLES

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Abstract

This report describes an efficient and practical approach for regioselective synthesis of 1-(3'-substitutedquinoxalin-2'-yl)-3-aryl/heteroaryl-5-methylpyrazoles **(3a-j)**. Reaction of 2-chloro-3-substitutedquinoxalines **(1)** with 3(5)-methyl-5(3)-aryl-1H-pyrazoles **(2)** in presence of sodium hydride furnished the title compounds in excellent yields exhibiting high level of regioselectivity. The present protocol is superior to the existing method which yielded a mixture of regioisomeric pyrazoles **(I, II)** and triazolo[4,3-a]quinoxalines **(III)**.

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KEYWORDS: 2-Chloro-3-substitutedquinoxalines; 3(5)-methyl-5(3)-aryl-1*H*-pyrazoles; regioselective synthesis; 1-(3'-substitutedquinoxalin-2'-yl)-3-aryl/heteroaryl-5-methylpyrazoles

INTRODUCTION

ACCEPTED MANUSCRIPT

Pyrazoles and their derivatives exhibit many diverse type of pharmaceutical activities such as herbicidal,[1] cholecystokinin 1 (CCK 1) receptor antagonist[2] besides being selective monoamine oxidase[3] and human complement component (C1s) inhibitors.[4] The introduction of celecoxib, a COX-2 inhibitor, for the treatment of chronic inflammatory diseases like rheumatoid and osteoarthritis has stimulated further interest in the pyrazole chemistry.[5] Recently, there has been a growing interest in developing general and versatile synthetic methods for the synthesis of this heterocyclic nucleus. In addition, quinoxaline ring has attracted considerable attention as a result of their pharmacological properties. Several potentially useful antibiotics e.g. echinomycin, levomycin, actinoleutin based on this pharmacophore have been developed in recent years,[6,7] but there is still an ample scope for further exploration of this system. Therefore, it was thought of interest to synthesize some pharmacologically active pyrazole derivatives bearing quinoxaline nucleus.

Synthetic routes available for the construction of pyrazole include 1,3-dipolar intermolecular [2+3] cycloadditions of diazoalkanes to alkynes,[8] oxidation of pyrazolines[9–11] and cyclocondensation of hydrazines with 1,3-difunctionalized compounds which include β-keto esters, aldehydes, nitriles, substituted α,β-unsaturated ketones and β-diketones[12–14] etc. A 1,3-diketone is the classical 3-atom synthon which has a wide scope not only because of its ready availability but also because one carbonyl of the starting diketone may be replaced by an acetal, a hemiacetal, a chlorovinyl group and a dihalide. Although very frequently used, unsymmetrical 1,3-diketones and

hydrazines suffer not only from the drawback of regioselectivity but some reports also mention the formation of isomeric diazepines and triazepines.[15–18]

Recently, we have undertaken the study of reaction of 2-hydrazino-3-methylquinoxaline with several aryl/heteroaryl-1,3-diketones[19] and it was observed that the reaction furnished a mixture of three products namely: regioisomeric 1-(3'-methylquinoxalin-2'-yl)-3-methyl-5-substitutedpyrazole **I**, 1-(3'-methylquinoxalin-2'-yl)-5-methyl-3-substitutedpyrazole **II** and an unexpected 1,4-dimethyl-*s*-triazolo[4,3-*a*]quinoxaline **III** **(**Scheme 1**)**.

Intrigued by the formation of a mixture of products, we intended to develop an efficient alternative synthesis involving nucleophilic aromatic substitution (S_NAr) which is a versatile approach to prepare a wide range of functionalized heterocycles.[20] We wish to report here a regioselective synthesis of 1-(3'-substitutedquinoxalin-2'-yl)-3-aryl/heteroaryl-5-methylpyrazoles involving the reaction of 2-chloro-3-substitutedquinoxaline with sodium salt of 3(5)-methyl-5(3)-aryl/heteroaryl-1*H*-pyrazole.

RESULTS AND DISCUSSION

3(5)-Methyl-5(3)-phenyl-1*H*-pyrazole **(2a)**, obtained by condensation of hydrazine hydrate with benzoylacetone, on treatment with equimolar amount of 2-chloro-3-methylquinoxaline **(1a)** in presence of NaH in *N*,*N*-dimethylformamide (DMF) under reflux led to the formation of 1-(3'-methylquinoxalin-2'-yl)-5-methyl-3-phenylpyrazole **(3a)** as the exclusive product (on the basis of TLC and NMR of crude reaction mixture).

The compound was found to be identical in all respects (mixed mp, co-TLC and ^{1}H NMR spectrum) with the product obtained by the reaction of an equimolar amount of 2-hydrazino-3-methylquinoxaline with phenyl-1,3-butanedione in THF under reflux.[19]

Success of this reaction encouraged us to examine the generality of this reaction by reacting 2-chloro-3-methyl/phenylquinoxalines **(1a-b)** with sodium salts of a variey of 3(5)-methyl-5(3)-aryl/heteroaryl-1*H*-pyrazoles **(2)** in DMF **(**Scheme 2**)** under similar reaction conditions. Except in case of reaction of **1a** with **2b** and **1b** with **2a** (where formation of small amount of 3-methyl isomers **4b** and **4f** was observed), 5-methyl isomer **(3a-j)** was formed as an exclusive isomer in all the cases as shown in Table 1. The known products **3a-e** and **4b** were identified by comparison of mps with those reported in the literature.[19] The structure of new compounds **3f-j** and **4f** was confirmed from their spectral data (IR, ^{1}H NMR and HRMS) and elemental analysis.

The IR spectra of compounds **3f-j** and **4f** showed the disappearance of a band due to -NH stretch in the range 3100-3400 cm^{-1} which was present in 3(5)-methyl-5(3)-aryl/heteroaryl-1*H*-pyrazoles **2**, indicating that nucleophilic substitution has occurred. High resolution ^{1}H NMR spectrum of **3f** showed the singlet of 5-methyl at δ 2.14 appeared as a doublet due to allylic coupling with C_4-H having coupling constant of ^4J= 0.68 Hz. Similarly, a singlet of one proton intensity appeared as a quartet rather than a singlet at δ 6.48 ppm (^4J= 0.68 Hz) for pyrazole 4-H and it was characterized as 1-(3'-phenylquinoxalin-2'-yl)-5-methyl-3-phenylpyrazole. Similarly, in ^{1}H NMR spectra of **3g-j** a sharp singlet for three protons (CH_3) appeared upfield at δ 2.04-2.17 probably due to

shielding of methyl protons due to phenyl ring at position 3' of quinoxaline ring and a singlet of one proton intensity at □ 6.34-6.54 for pyrazole 4-H, besides the aromatic protons of quinoxaline. However, ^{1}H NMR spectra of **4f** revealed CH_3 protons resonating as a singlet at δ 2.49 (C_3-CH_3) and a characteristic signal for one proton as a sharp singlet at □ 6.19 which was assigned to C_4-H of the pyrazole ring, alongwith aromatic protons.

It is evident from the results given in Table 1 that 5-methylpyrazole is the exclusive/major isomer in all such cases. Ratio of the two products **3** and **4** depends on the tautomeric equilibrium of the 3(5)-methyl-5(3)-aryl/heteroaryl-1*H*-pyrazoles **(2)**. As the 5-methyl isomer **3a-j** is predominant than 3-isomer **4b,f** this indicates that the ratio of equilibrium between tautomers of **2** may be more towards 3-aryl/heteroaryl-5-methyl-1*H*-pyrazoles.

Finally, the present approach is significant as this alternative route not only eliminates the formation of triazoloquinoxaline **III** but also provides the 5-methyl isomer as the exclusive/major product which otherwise was a minor product in the reaction of 2-hydrazino-3-methylquinoxaline with 1,3-diketones.

EXPERIMENTAL SECTION

General Procedure

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}). Low and high resolution ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker

instrument at 300 MHz and 400 MHz respectively. ^{13}C NMR spectra was recorded in $CDCl_3$ on a Bruker instrument at 50 MHz and 75 MHz; 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). All the compounds gave satisfactory elemental analyses. The reactions were monitored by the TLC carried out on pre-coated silica gel glass plates. Isolation of product was accomplished *via* crystallization in ethanol in those reactions where a single product was obtained. Wherever, a mixture of products was obtained, separation was done by column chromatography using silica gel (100-200 mesh) and ethyl acetate- pet. ether as eluent.

The starting materials 2-chloro-3-methylquinoxaline **(1a)** and 2-chloro-3-phenylquinoxaline **(1b)** were prepared *via* the chlorination of 2-hydroxy-3-methylquinoxaline and 2-hydroxy-3-phenylquinoxaline, respectively, with phosphorus oxychloride.[21] 3(5)-Methyl-5(3)-aryl/heteroaryl-1*H*-pyrazoles **(2a-e)** were prepared according to the literature procedure.[22]

Synthesis Of 1-(3'-Methylquinoxalin-2'-Yl)-5-Methyl-3-Phenylpyrazole (3a)

A solution of 3(5)-methyl-5(3)-phenyl-1*H*-pyrazole **(2a)** (790 mg, 5 mmol) in anhydrous *N*,*N*-dimethylformamide (20 ml) was refluxed with a suspension of sodium hydride (240 mg, 10 mmol) for 30 minutes. Subsequently, 2-chloro-3-methylquinoxaline **(1a)** (890 mg, 5 mmol) was added slowly and the reaction mixture was heated at **150 C** for **13 hr.** After distilling the excess of *N*,*N*-dimethylformamide, the residue was poured into water (50 ml) and extracted with DCM (3 x 20 ml). The combined extracts were dried over

anhydrous Na_2SO_4 and DCM was distilled off. The crude solid thus obtained was recrystallised in ethanol to obtain **3a** as a crystalline solid.

mp 130-132 □C (Lit[19] mp 132 □C), yield 71%.

All other compounds were synthesized according to the procedure mentioned for **3a** using 2-chloro-3-substitutedquinoxaline **(1)** with different 3(5)-methyl-5(3)-aryl-1*H*-pyrazoles **(2).** Column chromatographic workup using ethyl acetate- pet. ether as eluent, was performed for reaction between **1a** and **2b** which afforded **3b** in the initial fractions followed by **4b** in the next fractions. Similarly, a mixture of **3f** and **4f**, obtained by reaction between **1b** with **2a** was also separated by column chromatography.

The Characterization Data For 3f: 3f: 1-(3'-Phenylquinoxalin-2'-Yl)-5-Methyl-3-Phenylpyrazole

mp 110-112 °C; yield 68.4%; IR (cm^{-1}): 3063, 1597, 1443, 1366; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 2.14 (d, 3H, ^4J= 0.68 Hz, C_5-CH_3), 6.48 (q, 1H, ^4J= 0.68 Hz, C_4-H), 7.30-7.39 (m, 6H, $C_{3'}$-Ph, Ph^a- 4H), 7.48-7.50 (m, 2H, Ph^a- 2H, 6H), 7.70-7.72 (m, 2H, Ph^a- 3H, 5H), 7.81-7.88 (m, 2H, quinox-6'H, 7'H), 8.18-8.19 (m, 1H, quinox-5'H), 8.20-8.21 (m, 1H, quinox-8'H); ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 11.68, 104.90, 126.03, 127.58, 128.05, 128.39, 128.50, 128.54, 129.17, 129.30, 129.49, 130.05, 130.21, 130.30, 140.17, 141.87, 143.40, 144.87, 151.34, 152.83. HRMS (*m/z*) (Ir, %): 363.1603 (M^++1) (33), Anal. Calcd. for $C_{24}H_{18}N_4$: C, 79.54; H, 5.01; N, 15.46 %. Found: C, 79.70; H, 4.91; N, 15.70 %.

Complete experimental and spectral details are available online in the Supplementary Materials.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version.

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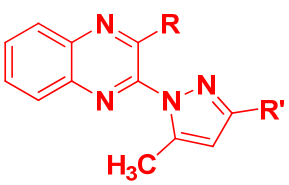
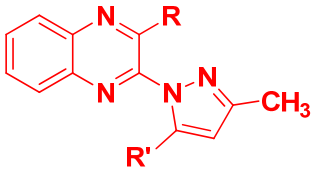
Table 1 Ratio of the products calculated from ^{1}H NMR of the crude reaction mixture

(Yield %)



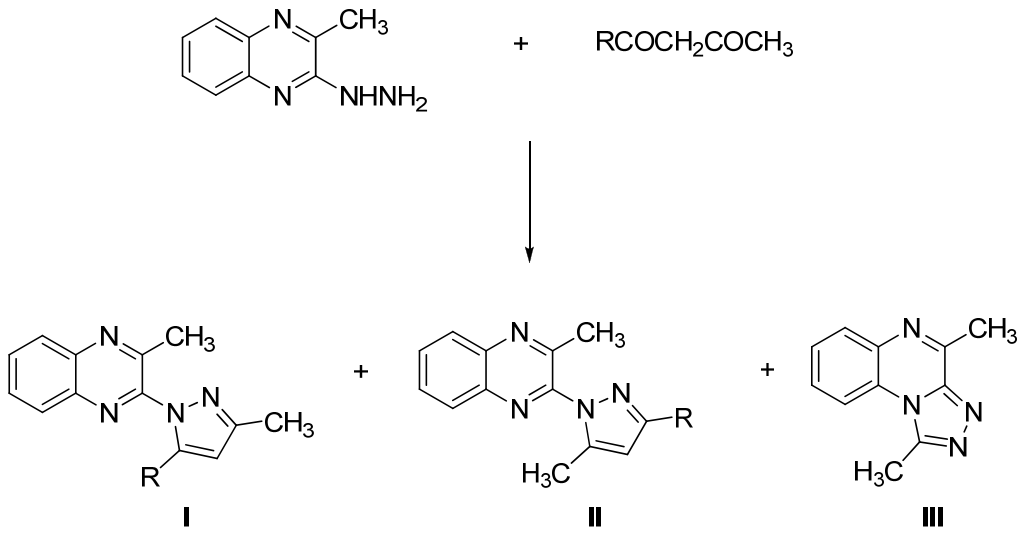
5-Isomer
Exclusive/Major
3a-j



3-Isomer
Negligible/Minor
4b,f

3,4	R	R'	(3a-j) 5-isomer	(4b,f) 3-isomer
a	CH_3	C_6H_5	**100 %**	Nil
b	CH_3	4-$CH_3C_6H_4$	90 %	10 %
c	CH_3	4-$OCH_3C_6H_4$	**100 %**	Nil
d	CH_3	4-ClC_6H_4	**100 %**	Nil
e	CH_3	2-Thienyl	**100 %**	Nil
f	C_6H_5	C_6H_5	70 %	30 %
g	C_6H_5	4-$CH_3C_6H_4$	**100 %**	Nil
h	C_6H_5	4-$OCH_3C_6H_4$	**100 %**	Nil
i	C_6H_5	4-ClC_6H_4	**100 %**	Nil
j	C_6H_5	2-Thienyl	**100 %**	Nil

Scheme 1 Synthesis of regioisomeric pyrazoles **I**, **II** and triazole **III**.



I II III

R= alkyl, aryl, heteroaryl

Scheme 2 Synthesis of compounds **3a-j** and **4b,f**.