Regioselective Synthesis and Structural Correlations of Aryl Pyrazole Framework

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Abstract: **A regioselective synthesis of medicinally important methoxylated aryl pyrazole frameworks *viz.* 1-methyl-5-(2,4,6-trimethoxyphenyl)-1*H*-pyrazole 6 and 1-methyl-3-(2,4,6-trimethoxy-phenyl)-1H-pyrazole 7 were achieved by varying the addition sequence of methyl iodide and sodium hydride. The structures of the regioisomers were confirmed using 1D and 2D NMR techniques.**

Keywords: Pyrazole, N-alkylation, Regioselectivity, HMBC.

I. INTRODUCTION

Heterocycles are an extremely important and unique class of organic compounds having a wide range of chemical and biological properties.[1] These are widely distributed in nature and play an important role in metabolic processes because of their existence in many natural products, as well as numerous pharmaceuticals, agrochemicals, and many others. [2] In addition to naturally occurring heterocycles, an enormous number of synthetic heterocyclic compounds with significant pharmacological properties are also known. [3] These compounds offer frameworks on which pharmacophores can assemble to yield potent bioactive molecules. [4] Nitrogen containing heterocycles are one of the important classes of heterocyclic compounds exhibit numerous biological activities. [5] Pyrazoles are well-known nitrogen containing aromatic heterocycles with two nitrogen atoms in their five-membered rings, and possess a wide spectrum of biological activities. [6] In recent years, several drugs like celecoxib, rimonabant, fomepizole, difenamizole, betazole, etc. have been developed from pyrazole derivatives. [7] The pyrazole containing heterocycles are also of considerable interest due to their wide synthetic utility. [8]

In light of the importance of pyrazole framework in numerous areas, mostly in medicinal chemistry, in the present work we focus on the regioselective synthesis of methoxylated aryl pyrazole framework and their structural investigations using 2D NMR techniques.

II. EXPERIMENTAL SECTION

Materials and methods

All the chemicals and reagents used in experiment were of analytical grade purchased from Sigma Aldrich and used as obtained. All the reactions were monitored by thin–layer chromatography (TLC), performed on aluminum sheets pre-coated with silica gel, kiesel gel 60 F_{254} (Merck) and the spots were visualized under UV lamp (254 nm). Melting points were determined with digital thermometer and were uncorrected. The IR spectra were performed on infrared FT-IR spectrometer, Nicolet iS10; Thermo Electron Scientific, USA and values were represented in cm^{-1}. The mass spectra were confirmed on Shimadzu LCMS-2010 EV. NMR (1D and 2D) spectra were recorded on 400 and 500 MHz NMR spectrometer, Bruker AVIII, Switzerland, using $CDCl_3$ solvent and chemical shift values were recorded in parts per million on δ scale. Coupling constants (*J*) are referred in Hertz (Hz).

Synthesis of 1-methyl-5-(2,4,6-trimethoxy-phenyl)-1*H*-pyrazole (6):

5-(2,4,6-Trimethoxy-phenyl)-1*H*-pyrazole **5** (2.34 gm, 10 mmol) was dissolved in dry DMF (15 ml) under inert atmosphere. The flask is cooled in an ice bath and methyl iodide (2.84 gm, 1.25 ml, 20 mmol) was added to it. To this reaction mixture, sodium hydride (60 % in oil, 0.48 gm, 12 mmol) was added in small portions and the resulted mixture was then allowed to stir at 0°C for 15 min. The reaction mixture was then poured over crushed ice and the solid obtained was filtered off, dried and recrystallized from ethanol to obtain regioisomer **6** in pure form. The filtrate was then extracted with ethyl acetate (3 x 25 ml). The combined

organic extract was washed with water. After drying over anhydrous $MgSO_4$, the solvent was distilled off under reduced pressure. The resulted residue was purified by column chromatography to obtain compound **7** in pure form.

Yield: 82 %; m.p. 147-149 ºC; IR (KBr, cm^{-1}): 3064, 2962, 2943, 2841, 1612, 1584, 1549, 1473, 1458, 1234, 1161; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (s, 1H, Pyr-*H*), 6.20 (m, 3H, 2xAr*H*, Pyr-*H*), 3.87 (s, 3H, O*CH*$_3$), 3.75 (s, 6H, 2xO*CH*$_3$), 3.65 (s, 3H, N*CH*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 162.25 (w, C), 159.32 (m, C), 137.91 (m, CH), 135.52 (w, C), 107.44 (m, CH), 100.69 (w, C), 90.54 (s, CH), 55.75 (s, CH_3), 55.40 (m, CH_3), 36.66 (m, CH_3); 135-DEPT: 137.89 (+), 107.44 (+), 90.53 (+), 55.75 (+), 55.40 (+), 36.65 (+); MS (ESI): m/e 249 (M+1).

Synthesis of 1-methyl-3-(2,4,6-trimethoxy-phenyl)-1*H*-pyrazole (7):

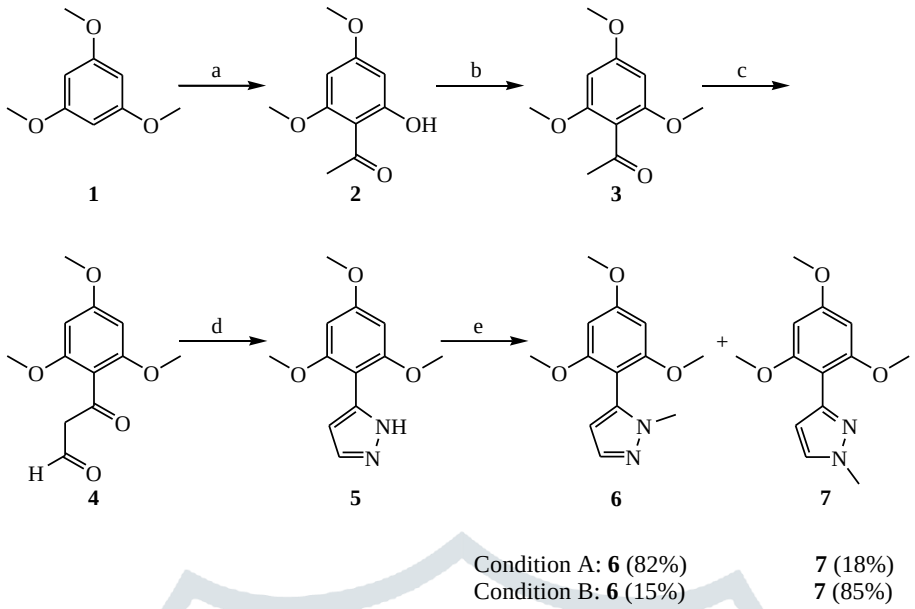
5-(2,4,6-Trimethoxy-phenyl)-1*H*-pyrazole **5** (2.34 gm, 10 mmol) was dissolved in dry DMF (15 ml) under inert atmosphere. The flask is cooled in an ice bath and sodium hydride (60 % in oil, 0.48 gm, 12 mmol) was added to it. To this reaction mixture, methyl iodide (2.84 gm, 1.25 ml, 20 mmol) was added in small portions and the resulted mixture was then allowed to stir at 0ºC for 15 min. The reaction mixture was then poured over crushed ice and the small amount of solid obtained was filtered off (regioisomer **6)**. The filtrate was then extracted with ethyl acetate (3 x 25 ml). The combined organic extract was washed with water, dried over anhydrous $MgSO_4$ and the solvent was distilled off under reduced pressure to obtain orange colored viscous oil. The resulted viscous residue was purified by column chromatography using petroleum: ethyl acetate (8:2) as eluting solvent to obtain regioisomer **7** in pure form.

Yield: 85 %; MP: 104-106 ºC; IR (KBr, cm^{-1}): 3130, 2992, 2956, 2834, 1613, 1586, 1505, 1474, 1224, 1161; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, J = 2.8 Hz, 1H, Pyr-*H*), 6.31 (d, J = 2.8 Hz, 1H, Pyr-*H*), 6.20 (s, 2H, 2xAr*H*), 3.97 (s, 3H, N*CH*$_3$), 3.85 (s, 3H, O*CH*$_3$), 3.76 (s, 6H, 2xO*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 161.07 (w, C), 159.37 (m, C), 144.40 (w, C), 130.13 (m, CH), 107.81 (m, CH), 104.51 (w, C), 90.55 (s, CH), 55.91 (s, CH_3), 55.27 (m, CH_3), 38.92 (m, CH_3); 135-DEPT: 130.11 (+), 107.81 (+), 90.56 (+), 55.93 (+), 55.28 (+), 38.94 (+); MS (ESI): m/e 249 (M+1).

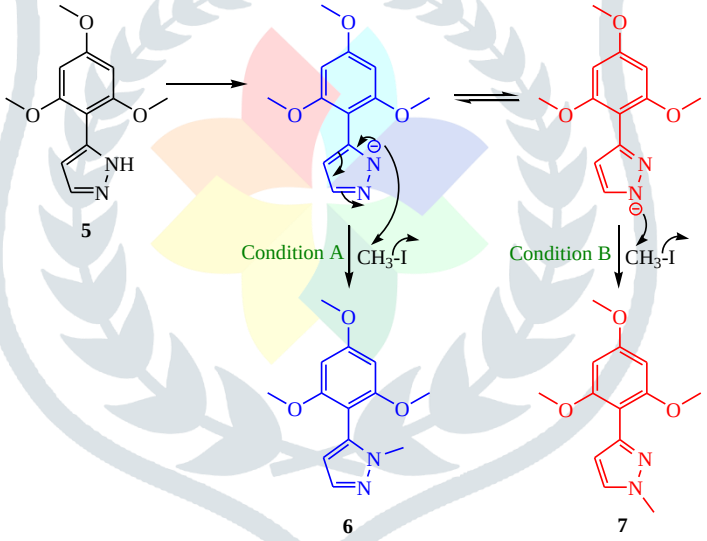
III. RESULTS AND DISCUSSION

In our earlier reports we have unveiled the regioselective synthesis of key intermediates 1-methyl-5-(2,4,6-trimethoxyphenyl)-1*H*-pyrazole **6** with excellent yield. [9] In the present work, regioselective synthesis of 1-methyl-3-(2,4,6-trimethoxy-phenyl)-1H-pyrazole **7** was achieved by optimizing the reaction conditions as illustrated in **Scheme 1**. The preparation of 1-(2-Hydroxy-4,6-dimethoxy-phenyl)-ethanone **2** was achieved by the Friedel-Craft acetylation of 1,3,5-trimethoxybenzene **1**, and successive O-methylation of the resulting 1-(2-hydroxy-4,6-dimethoxy-phenyl)-ethanone **2** using dimethyl sulphate and flame dried potassium carbonate in acetone under reflux condition furnished 1-(2,4,6-trimethoxyphenyl)ethanone **3** in excellent yield. Then the formylation of ketone **3** with ethyl formate and sodium hydride offered 3-oxo-3-(2,4,6-trimethoxyphenyl)propanal **4**, which on subsequent treatment with hydrazine hydrate afforded the corresponding 5-(2,4,6-trimethoxyphenyl)-1*H*-pyrazole **5** in 96% yield.

A cooled mixture of 5-(2,4,6-trimethoxyphenyl)-1*H*-pyrazole **5** and methyl iodide in dry DMF taken in a round bottomed flask under nitrogen atmosphere and sodium hydride was added in small portions with stirring afforded exclusively regioisomer **6** in the form of yellow solid. On the other hand, when a mixture of 5-(2,4,6-trimethoxyphenyl)-1*H*-pyrazole **5** and sodium hydride in dry DMF was stirred under nitrogen atmosphere and methyl iodide was added slowly to the resulting solution we obtain regioisomers **7** predominantly which is retained in aqueous layer. In later case, resonance stabilization of negative charge leads to the formation of regioisomers **7** (**Scheme 2**). The small precipitate obtained of compound **6** was filtered off and resulting aqueous layer extracted thrice with ethyl acetate. On evaporation of ethyl acetate dark orange colored oil was obtained which on chromatographic purification furnished white crystals of regioisomers **7**.



Scheme 1: Reagents and conditions: (a) CH_3COCl, $AlCl_3$ (anh.), Et_2O, N_2, 0°-rt; (b) Me_2SO_4, K_2CO_3, acetone, reflux, 12 h; (c) HCOOEt, NaH, THF, N_2, rt; (d) $NH_2NH_2.H_2O$, rt; (e) Condition A: MeI, NaH, DMF, N_2, 0°; Condition B: NaH, MeI, DMF, N_2, 0°



Scheme 2. Effect of resonance stabilization on formation of regioisomers

The structural investigations of the regioisomers **6** and **7** were carried out by using 1D ^1H, ^{13}C NMR spectra, 135-DEPT and 2D NMR experiments (^1H-^1H COSY, ^1H-^{13}C HMBC, ^1H-^{13}C and HSQC), which were scanned on Bruker AV-400MHz and 500MHz instruments. These regioisomers were only differ in the position of methyl group on pyrazole nucleus, therefore, the ^1H and ^{13}C NMR chemical shifts were appear to be almost similar. Thus, the structures of these two regioisomers were only established with the help of 2d NMR experiments such as HMBC, HSQC and COSY correlations. The most important HMBC and COSY correlations are summarized in Figure **1** and the complete chemical shift assignment is shown in **Table 1** and **Table 2**. According to a Heteronuclear Multiple Bond Correlation (HMBC) experiment performed with regioisomer **6**, the HMBC correlation observed between H-13 (δ_H 3.65) and C-3 (δ_C 135.5) and with regioisomer **7,** the HMBC correlation observed between H-13 (δ_H 3.97) and C-1 (δ_C 130.12) allowing to unambiguous identification of the regioisomer **6** and **7**. Additionally, Heteronuclear Single Quantum Coherence (HSQC) experiment was used to assign proton signals to the corresponding carbon signals. There is a strong ^1H-^1H COSY correlation observed between H-1 and H-2.

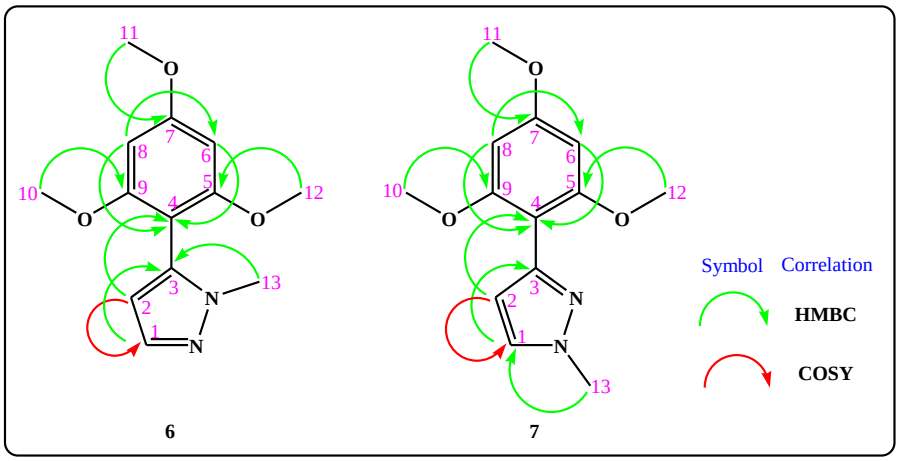


Figure 1: HMBC (^{1}H - ^{13}C) and ^{1}H-^{1}H COSY correlations

Table 1. ^{1}H, ^{13}C NMR, 135-DEPT and ^{1}H-^{1}H COSY, HSQC and HMBC correlations in compound **6**.

Position	^{1}H NMR (δ/ppm)	^{13}C NMR (δ/ppm)	DEPT	Correlations		
				COSY	HSQC	HMBC
1	7.558 (d, 1H)	137.905	CH	2H	1C	3C
2	6.206 (m, 3H)	107.441	CH	1H	2C	3C, 4C
3	-	135.516	C	-	-	-
4	-	100.688	C	-	-	-
5, 9	-	159.320	C	-	-	-
6, 8	6.206 (m, 3H)	90.542	CH	-	6C, 8C	4C, 5C, 6C, 7C, 8C, 9C
7	-	162.252	C	-	-	-
10, 12	3.753 (s, 6H)	55.748	CH_3	-	10C, 12C	5C, 9C
11	3.877 (s, 3H)	55.398	CH_3	-	11C	7C
13	3.658 (s, 3H)	36.656	CH_3	-	13C	3C

Table 2. ^{1}H, ^{13}C NMR, 135-DEPT and ^{1}H-^{1}H COSY, HSQC and HMBC correlations in compound **7.**

Position	^{1}H NMR (δ/ppm)	^{13}C NMR (δ/ppm)	DEPT	Correlations		
				COSY	HSQC	HMBC
1	7.413 (d, 1H)	130.12	CH	2H	1C	2C, 3C, 13C
2	6.316 (d, 1H)	107.82	CH	1H	2C	1C, 3C, 4C
3	-	144.42	C	-	-	-
4	-	104.42	C	-	-	-
5, 9	-	159.38	C	-	-	-

6, 8	6.202 (s, 2H)	90.92	CH	-	6C, 8C	4C, 5C, 6C, 7C, 8C, 9C
7	-	161.08	C	-	-	-
10, 12	3.768 (s, 6H)	55.92	CH_3	-	10C, 12C	5C, 9C
11	3.852 (s, 3H)	55.25	CH_3	-	11C	7C
13	3.972 (s, 3H)	38.94	CH_3	-	13C	1C

IV. CONCLUSION

In conclusion, the facile regioselective synthesis methoxylated aryl pyrazole frameworks were achieved by simply altering the sequence of addition of reagents. As simple ^{1}H NMR technique failed to assign the structures of regioisomeric pyrazole frameworks, the structures were confirmed by 1D (^{1}H, ^{13}C NMR and DEPT) and 2D NMR techniques (HMBC, HSQC and COSY). These regioisomeric frameworks may be utilized for the diversity oriented synthesis of bioactive molecules.

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