Studies with Functionally Substituted *N*-Alkylazoles: The Reactivity of 1-(3,5-Dimethylpyrazol-1-yl)-Acetone towards Electrophilic Reagents

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The reaction of 1-(3,5-dimethylpyrazol-1-yl)acetone **4** with aromatic diazonium salts afforded the corresponding arylhydrazones **5a,b** that were converted into pyridazines **6a,b** and **8** *via* condensation with active methylene nitriles and dimethylformamide dimethylacetal, respectively. Condensation of **4** with phenylhydrazine afforded the phenylhydrazone **10**, which could be converted into the indolylpyrazole **11** on treatment with ethanolic hydrochloric acid. Compound **4** also reacted with nitrous acid, benzylidenemalononitrile to yield a variety of substituted new pyrazoles.

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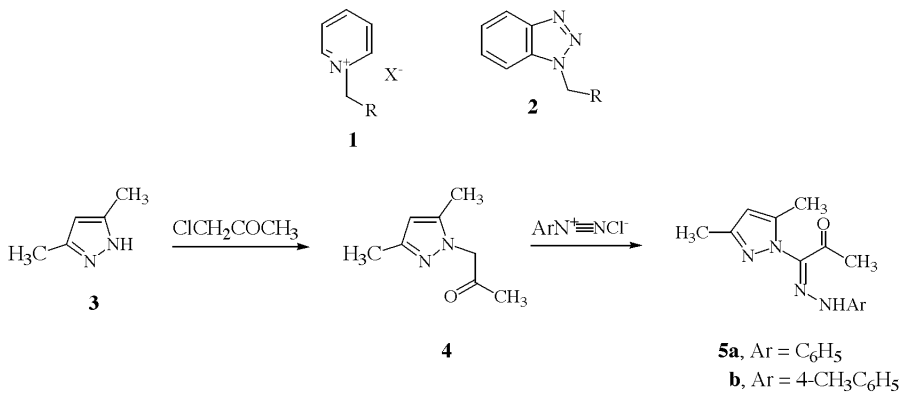
The reactivity of functionally substituted *N*-alkylpyridinium salts **1** and *N*-alkylbenzotriazoles **2** towards electrophiles has been extensively studied in the past [1-6]. Both **1** and **2** are capable of affording carbaniones under mild conditions, as a result of the stabilizing effect of π-deficient ring nitrogen that is exerted on such carbanions. Although carbanions resulting from proton abstraction from *N*-alkylpyrazoles might also be stabilized by the ring nitrogen electron attracting inductive effect, reactivity of such species towards nitrogen and carbon electrophiles has, to our knowledge, not been reported, although this may open new route for preparing otherwise not readily obtainable biologically interesting pyrazole derivatives [7,8]. We report here results of our investigation on the reactivity of **4** towards nitrogen and carbon electrophiles. The work enabled the synthesis of several new pyrazolylazines and functionally substituted pyrazoles that seem interesting as potential agrochemical and/or pharmaceuticals. Thus compound **4** could be readily prepared *via* reacting 3,5-dimethyl-1*H*-pyrazole with chloroacetone in refluxing toluene and in presence of an equimolecular amount of triethylamine. The ^{1}H NMR spectrum of compound **4** displayed three single lines readily recognizable as arising from the methyl groups at C-5 and C-3 at δ = 2.01 and 2.17 ppm respectively and at δ = 2.13 ppm for the acetyl group along with two singlets at δ = 4.70 and 5.83 ppm for the methylene and pyrazolyl 4-H protons. The data thus find parallelism to that reported for similar systems [9].

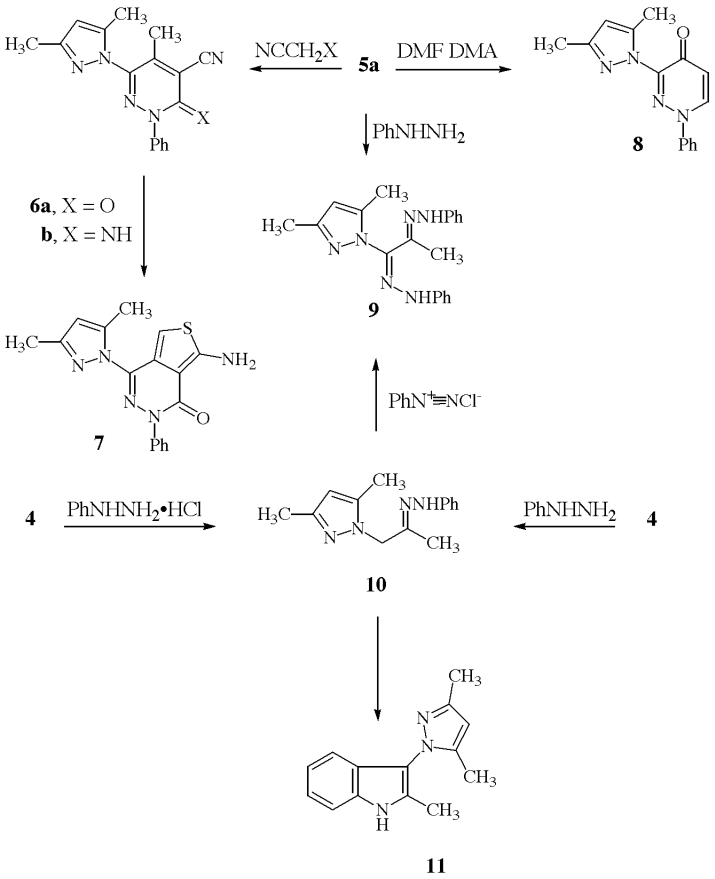
Compound **4** coupled readily with aromatic diazonium salts in ethanolic sodium hydroxide to yield the corresponding arylhydrazones **5a,b** in good yields (Scheme 1).

Similar to the reported behavior of acetylarylhydrazonyl derivatives [10-12], compound **5a** condensed readily with ethyl cyanoacetate and with malononitrile to yield the pyridazin-6-ones **6a** and pyridazin-6-imines **6b** respectively. Typical to the reported behavior of 4-methylpyridazine-5-carbonitriles [13-14] towards sulfur, coumpound **6a** reacted with sulfur in refluxing DMF and in presence of piperidine to yield the thienopyridazines **7**. Compound **5a** also condensed with dimethylformamide dimethylacetal to yield the pyrazolylpyridazines **8** Compound **5a** condensed with

Scheme 1

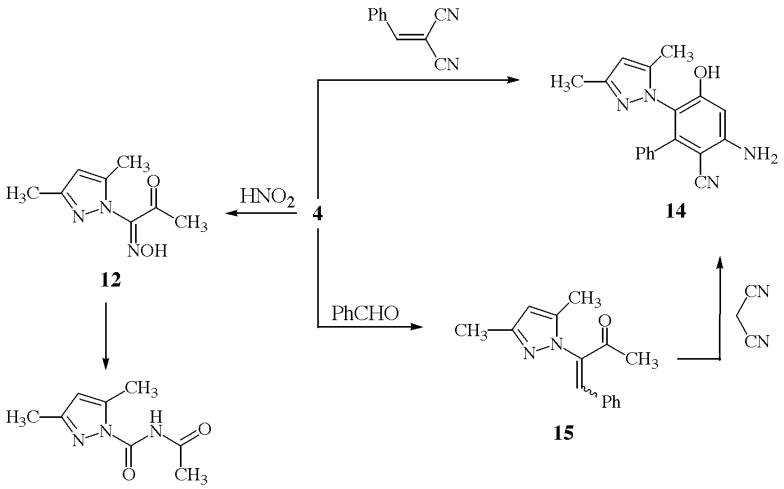


Scheme 2



phenylhydrazine to yield the diphenylhydrazone **9** that has also been obtained by an alternative method, *via* coupling the phenylhydrazone **10** with benzenediazonium chloride. The reaction of **4** with phenylhydrazine hydrochloride resulted directly in the formation of indoylpyrazoles **11**, which most likely resulted from the rearrangement of intermediary **10**. Compound **10** could be prepared *via* condensing **4** with phenylhydrazine in refluxing acetic acid. This could be rearranged into **11** on reflux in ethanolic hydrochloric acid (Scheme 2).

Scheme 3



Compound **4** reacted with nitrous acid to yield a product of molecular formula $C_8H_{11}N_3O_2$ that could be **12** or **13.** Structure **13** is established based on the ^{13}C NMR which revealed the presence of two carbonyl carbons resonating at δ = 178.4 and 176.2 ppm. Moreover signals at 1680 and 1695 cm^{-1} in the IR spectra reveal the presence of two-carbonyl groups and a signal at 3210 cm^{-1} reveals the presence of an NH group. Compound **4** also reacted with benzylidenemalononitrile to yield the addition product **14** and elimination of hydrogen molecule. Several isomeric structures seemed possible for the reaction product as initial addition of both active methylene and active methyl in **4** can be envisioned. Structures **14** could be established for the reaction product *via* initially condensing **4** with benzaldehyde and subsequent treatment of the formed arylidene derivative **15** with malononitrile (Scheme 3).

In conclusion, it may be stated that a pyrazolyl moiety activates adjacent *N*-methylene to proton loss in a fashion similar to what is established for benzotriazolyl moiety.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded as KBr disks on a Pye Unicam SP 1000 spectrometer. ^1H NMR spectra were obtained on a Varian EM 390-300MHz spectrometer with DMSO-d_6 or $CDCl_3$ as solvent and TMS as an internal standards and chemical shifts expressed ppm (δ). Elemental analyses were obtained from the Microanalytical Unit at Cairo University, Giza, Egypt.

3,5-Dimethylpyrazol-1-yl-acetone (**4**).

A solution of 3,5-dimethylpyrazole (0.96 g, 10 mmoles) in dry toluene (30 ml) was treated with chloroacetone (0.92 g, 10 mmoles) in presence of triethylamine (1 ml). The reaction mixture was refluxed for 5 hours. The solvent was evaporated under vacuum and the solid product, so formed, was collected by filtration and crystallized from benzene to give beige crystals; yield: 1.21 g (80%), mp 67-68°; ir: 2960, 2840 (CH_3), 1685 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.01 (s, 3H, $CH_{3\text{pyrazolyl C-5}}$), 2.13 (s, 3H, $CH_{3\text{pyrazolyl C-3}}$), 2.17 (s, 3H, $COCH_3$), 4.70 (s, 2H, CH_2), 5.83 (s, 1H, pyrazolyl 4-H); ms: m/z 152 (M^+).

Anal. Calcd. for $C_8H_{12}N_2O$ (152.19): C, 63.13; H, 7.95; N, 18.41. Found: C, 62.99; H, 8.10; N, 18.28.

General Procedure for the Preparation of (**5a,b**).

A cold solution of aryldiazonium chloride (30 mmoles), prepared as described earlier [4], was added to a solution of **4** (10 mmoles) in ethanol (50 ml) containing sodium acetate (3 g). The reaction mixture was stirred at room temperature for 2 hours, and left overnight in the refrigerator. The solid product, so formed, was collected by filtration and crystallized from ethanol.

1-(3,5-Dimethylpyrazol-1-yl)-1-phenylhydrazonopropan-2-one (**5a**).

Compound **5a** was obtained in 76% yield (1.92 g), mp 84-85°; ir: 3215 (NH), 1679 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H, $CH_{3\text{pyrazolyl C-5}}$), 2.15 (s, 3H, $CH_{3\text{pyrazolyl C-3}}$), 2.19 (s, 3H, $COCH_3$), 5.85 (s, 1H, pyrazolyl 4-H), 7.21-7.78 (m, 5H, arom. H), 9.85 (s, 1H, NH); ms: m/z 256 (M^+).

Anal. Calcd. for $C_{14}H_{16}N_4O$ (256.30): C, 65.60; H, 6.29; N, 21.86. Found: C, 65.48; H, 6.20; N, 21.85.

1-(3,5-Dimethylpyrazol-1-yl)-1-*p*-tolylhydrazonopropane-2-one (**5b**).

Compound **5b** was obtained in 83% yield (2.24 g), mp 168-169°; ir: 3210 (NH), 1679 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 1.85 (s, 3H, $CH_{3\text{pyrazolyl C-5}}$), 2.02 (s, 3H, $CH_{3\text{pyrazolyl C-3}}$), 2.15 (s, 3H, $CH_{3\text{ tolyl C-4}}$), 2.18 (s, 3H, $COCH_3$), 5.85 (s, 1H, pyrazolyl 4-H), 7.21-7.92 (m, 4H, arom. H), 9.38 (s, 1H, NH); ms: m/z 270 (M^+).

Anal. Calcd. for $C_{15}H_{18}N_4O$ (270.33): C, 66.66; H, 6.71; N, 20.73. Found: C, 66.36; H, 6.70; N, 20.72.

General Procedure for the Preparation of (**6a,b**).

Each of malononitrile (0.66 g, 10 mmoles) or ethylcyanoacetate (1.13 g, 10 mmoles) was added to **5a** (2.56 g, 10 mmoles) in the presence of acetic acid (1 ml) and anhydrous ammonium acetate (1 g). The reaction mixture was heated at 120° for 15 minutes, then triturated with ethanol. The solid product, so formed, was collected by filtration and crystallized from ethanol.

6-Oxo-4-methyl-1-phenyl-3-(3',5'-dimethylpyrazol-1'-yl)-pyridazine-5-carbonitrile (**6a**).

Compound **6a** was obtained in 90% yield (2.74 g), mp 169-170°; ir: 2231 (CN), 1683 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H, $CH_{3\text{pyrazolyl C-5}}$), 2.19 (s, 3H, $CH_{3\text{pyrazolyl C-3}}$), 2.50 (s, 3H, $CH_{3\text{ pyridazinyl C-4}}$), 5.85 (s, 1H, pyrazolyl 4-H), 7.52-7.85 (m, 5H, arom. H); ms: m/z 305 (M^+).

Anal. Calcd. for $C_{17}H_{15}N_5O$ (305.33): C, 66.87; H, 4.95; N, 22.94. Found: C, 66.68; H, 4.90; N, 22.86.

6-Imino-4-methyl-1-phenyl-3-(3',5'-dimethylpyrazol-1'-yl)-pyridazine-5-carbonitrile (**6b**).

Compound **6b** was obtained in 86% yield (2.61 g), mp 185-186°; ir: 3215 (NH), 2204 cm^{-1} (CN); ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, $CH_{3\text{pyrazolyl C-5}}$), 2.15 (s, 3H, $CH_{3\text{pyrazolyl C-3}}$), 2.61 (s, 3H, $CH_{3\text{ pyridazinyl C-4}}$), 5.85 (s, 1H, pyrazolyl 4-H), 7.50-7.85 (m, 5H, arom. H), 9.15 (s, 1H, NH); ms: m/z 304 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_6$ (304.35): C, 67.08; H, 5.30; N, 27.62. Found: C, 67.09; H, 5.29; N, 27.41.

7-Amino-2-phenyl-4-(3',5'-dimethylpyrazol-1'-yl)-thieno-[3,4-*d*]-pyridazin-1-one (**7**).

Elemental sulfur (0.32 g, 10 mmoles) was added to a solution of **6a** (3.05 g, 10 mmoles) in dimethylformamide (30 ml) in the presence of piperidine (0.5 ml). The reaction mixture was heated for 5 hours. The solvent was reduced to half its volume, poured onto water and neutralized with hydrochloric acid. The solid product, so formed, was collected by filtration and crystallized from ethanol; yield: 2.02 (60%), mp 195-196°; ir: 3420, 3310 (NH_2), 1680 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.05 (s, 3H, $CH_{3\text{pyrazolyl C-5}}$), 2.19 (s, 3H, $CH_{3\text{pyrazolyl C-3}}$), 5.75 (s, 1H, thienyl 5-H), 6.26 (s, 1H, pyrazolyl 4-H), 7.05-7.75 (m, 7H, arom. H, NH_2); ms: m/z 337 (M^+).

Anal. Calcd. for $C_{17}H_{15}N_5OS$ (337.33): C, 60.53; H, 4.48; N, 20.76. Found: C, 60.62; H, 4.36; N, 20.75.

1,4-Dihydro-3-(3',5'-dimethylpyrazol-1'-yl)-1-phenylpyridazin-4-one (**8**).

A mixture of **5a** (2.56 g, 10 mmoles) in dimethylformamide dimethylacetal (1.19 g, 10 mmoles) in toluene (30 ml) was heated for 16 hours. The solvent was evaporated under vacuum and the

solid product, so formed, was collected by filtration and crystallized from ethanol to give red crystals; yield: 2.08 g (78%), mp 137-138°; ir: 1710 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 1.99 (s, 3H, $CH_{3pyrazolyl\ C-5}$), 2.19 (s, 3H, $CH_{3pyrazolyl\ C-3}$), 6.07 (s, 1H, pyrazolyl 4-H), 7.02-7.85 (m, 7H, arom H).

Anal. Calcd. for $C_{15}H_{14}N_4O$ (266.29): C, 67.65; H, 5.30; N, 21.04. Found: C, 67.52; H, 5.30; N, 21.03.

3',5'-Dimethyl-1-(1,2-diphenylhydrazonopropanyl)-pyrazole (**9**).

Method A.

A mixture of **5a** (2.56 g, 10 mmoles) and phenylhydrazine (1.08 g, 10 mmoles) and acetic acid (1 ml) was heated at 120° for 10 minutes. The reaction mixture was triturated with ethanol, the solid product, so formed, was collected by filtration and crystallized from ethanol to give red crystals in a yield of 75%.

Method B.

A cold solution of benzenediazonium chloride (prepared as previously discussed in compound **5a**), was added to a solution of compound **10** (1.82 g, 10 mmoles) in 50 ml ethanol containing 2 g NaOH. The reaction mixture was stirred for 1 hour. at room temperature and was left overnight in the refrigerator. The solid product, so formed, was collected by filtration and crystallized from ethanol to give red crystals in a yield of 64%; yield: 2.60 g (75%), mp 167-168°; ir: 3431 (NH), 2980, 2850 (CH_3) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.89 (s, 3H, $CH_{3pyrazolyl\ C-5}$), 2.55 (s, 3H, $CH_{3pyrazolyl\ C-3}$), 2.65 (s, 3H, CH_3), 6.35 (s, 1H, pyrazole 4-H), 7.28-7.83 (m, 10H, arom. H), 8.12 (br s, 1H, NH), 8.15 (br s, 1H, NH).

Anal. Calcd. for $C_{20}H_{22}N_6$ (346.42): C, 69.34; H, 6.40; N, 24.26. Found: C, 69.35; H, 6.42; N, 24.48.

1-(3′,5′-Dimethylpyrazol-1′-yl)-2-phenylhydrazonopropane (**10**).

A mixture of **4** (1.52 g, 10 mmoles) and phenylhydrazine in presence of acetic acid (1 ml) was heated at 120° for 10 minutes. The reaction mixture was triturated with ethanol, the solid product, so formed, was collected by filtration and crystallized from ethanol to give yellow crystals; yield: 2.17 (90%), mp 128-129°; ir: 3238 cm^{-1} (NH); ^1H NMR (DMSO-d_6): δ 1.89 (s, 3H, $CH_{3pyrazolyl\ C-5}$), 2.52 (s, 3H, $CH_{3pyrazolyl\ C-3}$), 2.65 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 6.82 (s, 1H, pyrazolyl 4-H), 7.23-7.55 (m, 5H, arom H.), 8.20 (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{18}N_4$ (242.32): C 69.39, H 7.49, N 23.12; found C 69.19, H 7.60, N 23.30.

3-(3',5'-Dimethylpyrazol-1'-yl)-2-methylindole (**11**).

A mixture of compound **4** (1.52 g, 10 mmoles) and phenylhydrazine hydrochloride (1.44 g, 10 mmoles) in dioxane (30 ml) was heated for 5 hours. The solvent was evaporated under vacuum and crystallized from ethanol as brown crystals; yield: 1.80 g (80%), mp 259-260° ; ir: 3.210 cm^{-1} (NH); ^1H NMR (DMSO-d_6): δ 2.02 (s, 3H, $CH_{3pyrazolyl\ C-5}$), 2.19 (s, 3H, $CH_{3pyrazolyl\ C-3}$), 2.21 (s, 3H, $CH_{3\ indolyl\ C-2}$), 6.04 (s, 1H, pyrazolyl 4-H), 6.99-7.38 (m, 4H, arom. H.), 11.33 (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{15}N_3$ (225.28): C, 74.64; H, 6.71; N, 18.65. Found: C, 74.66; H, 6.67; N, 18.67.

1-(3',5'-Dimethylpyrazol-1'-yl)-*N*-acetylformamide (**13**).

To a cold solution of **4** (1.52 g, 10 mmoles) in (30 ml) acetic acid, a solution of sodium nitrite was added (0.7 g, 10 mmoles) was added drop wise at 0° . The reaction mixture was left overnight. The solid product obtained was collected by filtration and crystallized from benzene as white crystals; yield: 1.26 g (70%), mp 259-260° ; ir: 3210 (NH), 1680, 1695 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.06 (s, 3H, $CH_{3pyrazolyl\ C-5}$), 2.56 (s, 3H, $CH_{3pyrazolyl\ C-3}$), 2.35 (s, 3H, CH_3), 6.35 (s, 1H, pyrazole H-4), 8.12 (br s, 1H, NH); ^{13}C NMR (DMSO): δ 178.4 (CO), 176.2 (CO), 132.3, 129.6, 106.2 (pyrazolyl C), 24.30, 24.10, 22.5 ($3CH_3$); ms: m/z 181 (M^+).

Anal. Calcd. for $C_8H_{11}N_3O_2$ (181.19): C, 53.03; H, 6.12; N, 23.19. Found: C, 53.17; H, 6.08; N, 23.06.

6-Amino-4-hydroxy-2-phenyl-3-(3',5'-dimethylpyrazol-1'-yl)benzonitrile (**14**).

Method A.

To a solution of **4** (1.52 g, 10 mmoles) in dioxan (30 ml), benzylidenemalononitrile (1.54 g, 10 mmoles) was added in the presence of few drops of piperidine. The reaction mixture was heated under reflux for 6 hours. The solvent was reduced under vacuum, diluted with water and acidified with dilute HCl. The solid product obtained was collected by filtration and crystallized from ethanol as green crystals in a yield of 70%.

Method B.

To a solution of **15** (2.40 g, 10 mmoles) in dioxan (30 ml), malononitrile (0.66 g, 10 mmoles) was added in the presence of few drops of piperidine. The reaction mixture was heated under reflux for 6 hours. The solvent was reduced under vacuum, diluted with water and acidified with dilute HCl. The solid product obtained was collected by filtration and crystallized from ethanol as green crystals 63%; yield: 2.12 g (70%) (method A), mp 141-142°; ir: 3465 (OH), 3420, 3328 (NH_2), 2208 cm^{-1} (CN); ^1H NMR (DMSO-d_6): δ 2.01 (s, 3H, $CH_{3pyrazolyl\ C-5}$), 2.25 (s, 3H, $CH_{3pyrazolyl\ C-3}$), 6.35 (s, 1H, pyrazole 4-H), 7.35-7.65 (m, 6H, arom. H), 8.72 (br s, 2H, NH_2), 9.65 (s, 1H, OH); ms: m/z304 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_4O$ (304.34): C, 71.03; H, 5.30; N, 18.41. Found: C, 57.19; H, 7.88; N, 25.30.

2-(3',5'-Dimethylpyrazol-1'-yl)-1-phenylbutene-3-one (**15**).

To a solution of **4** (1.52 g, 10 mmoles) in dioxan (30 ml), benzaldehyde (1.06 g, 10 mmoles) was added in the presence of few drops of piperidine. The reaction mixture was heated under reflux for 15 minutes. The solvent was reduced under vacuum, diluted with water and acidified with dilute HCl. The solid product obtained was collected by filtration and crystallized from ethanol as yellow crystals; yield: 1.99 g (83%), mp 123-124°; ir: 1710 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 2.05 (s, 3H, $CH_{3pyrazolyl\ C-5}$), 2.35 (s, 3H, $CH_{3pyrazolyl\ C-3}$), 2.65 (s, 3H, CH_3), 5.67 (s, 1H, olefinic-H), 6.35 (s, 1H, pyrazolyl 4-H), 7.25-7.68 (m, 5H, arom. H). ms: m/z 240 (M^+).

Anal. Calcd. for $C_{15}H_{17}N_2O$ (240.29): C, 74.97; H, 6.71; N, 11.66. Found: C, 74.66; H, 6.97; N, 11.61.

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