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NEW AND CONVENIENT ROUTE FOR THE SYNTHESIS OF SOME NEW PYRAZOL-5-YL-1*H*-IMIDAZOLE DERIVATIVES

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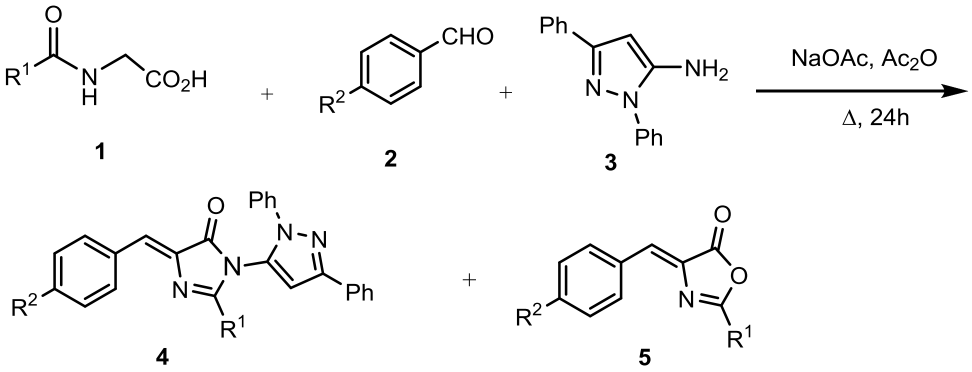
Abstract - A simple and efficient method for the synthesis of some new pyrazol-5-yl-1*H*-imidazoles **4a-h** is described. In this method oxazolones **5a-h** were produced as minor products. The X-ray analysis confirmed the structures of **4** and **5.**

The pyrazole derivatives are well known for their wide range of biological and pharmacological activities, such as antibacterial, fungicidal, herbicidal, insecticidal, anti-HIV, antitumor and other biological activities.[1-8] Various methods have been reported for the synthesis of pyrazole derivatives.[9-13] On the other hand imidazole derivatives are frequently found in biological active natural products or pharmaceutically important drugs. Some of them are useful as antitumor, antifungal, antimicrobial.[14-16] There are some reports for the synthesis of imidazole derivatives.[17-24] Imidazole derivatives were used also as ligands in organomethalic compounds.[25- 27]

There are few reports on the synthesis of systems which contain the imidazole and pyrazole rings.[5,28] Here we wish to report a new and convenient route for the synthesis of pyrazol-5-yl-1*H*-imidazole derivatives **4a-h** under a one-pot and solvent-free conditions in 78-89% yields. In this procedure oxazolones **5a-h** are produced as by-products in 8-15% yields (Scheme 1, Table 1).

We have already reported one-pot and multicomponent synthetic procedures for the synthesis of some heterocyclic compounds.[29-33] In continuation of our request for developing one-pot procedure heterocyclic frameworks, we here report a novel one-pot, multicomponent reaction of acetyl or benzoylglycine **1** and benzaldehyde derivatives **2** and 1,3-diphenyl-1*H*-pyrazol-5-amine **3**[34] in the presence of sodium acetate and acetic anhydride. It is well known that the reaction of acetyl or benzoyl glycine **1**, and benzaldehyde **2** in the presence of sodium acetate, acetic anhydride and heat afforded the oxazolones **5**.[35,36] In this multicomponent reaction, the compounds **5a-h** were produced as by-products in 8-15% yields (their spectroscopic data have already been published[36-43]) and the pyrazol-5-yl-1*H*-imidazoles **4a-h** as the main products in 78 - 88% yields.



R^1 = Me, Ph, R^2 = H, Cl, Br, NO_2, Me, OMe

Scheme 1

Table 1. Yields of products **4** and **5**.

Comp. Entry 4, 5	**R^1**	**R^2**	**Yield % 4**	**Yields % 5**
a	Me	H	85	10[36,37]
b	Me	Cl	82	10[38]
c	Me	Br	83	8[39]
d	Me	NO_2	78	15[40]
e	Ph	H	84	10[36,41]
f	Ph	Me	85	12[36,41]
g	Ph	Br	89	8[42]
h	Ph	OMe	85	8[43]

Recrystalization of **4a** in ethanol and **5a** (4-benzylidine-2-methyloxazol-5-(4*H*)-one) in acetone gave the single crystals suitable for X-ray analysis. X-ray crystal structures of **4a**, **5a** were performed to confirm unambiguously their structures[44] (Figures 1, 2).

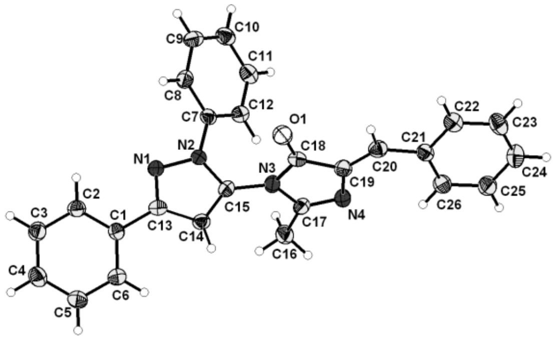


Figure 1: X-Ray crystal structure of **4a**

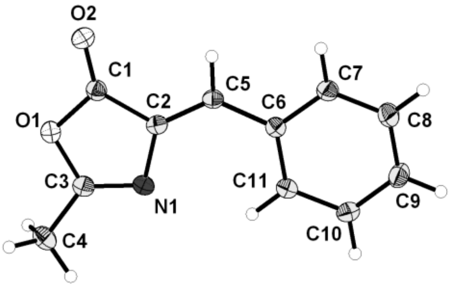


Figure 2: X-Ray crystal structure of **5a**

This procedure is optimized as following: To a mixture of acetyl- or benzoylglycine **1** and benzaldehydes **2**, anhydrous sodium acetate in acetic anhydride were added gently at 0 °C and heated for 5-7 h. Then 1,3-diphenyl-1*H*-pyrazol-5-amine **3** was added to the reaction mixture and heated for 16-18 h. The product **4** was purified by column chromatography and recrystalized from ethyl acetate or ethanol.

Structures **4** were assigned on the basis of their elemental analysis, IR, ^{1}H, ^{13}C NMR and MS data. The MS of compounds **4a-h** displayed molecular ion peaks at appropriate m/z values. For pyrazol-5-yl-1*H*-imidazole derivatives **4**, initial fragmentation involved the loss of the phenyls also pyrazole and imidazole ring side groups. ^{1}H NMR and ^{13}C NMR spectra of **4a-h** displayed resonances in agreement with their structures.

In summary, we report an efficient multicomponent reaction for synthesis of some new pyrazol-5-yl-1*H*-imidazole derivatives under a one-pot and solvent-free conditions. In this method novel extended π-conjugated heterocyclic system with a pyrazole and imidazole rings were produced in fairly high yields. Further investigations of this method are currently in progress to establish its scope and utility.

EXPERIMENTAL

Chemicals and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Compound **3** was synthesized according to the procedure.[34] Isolation and determination of the by-products **5a-h** were according to references.[36-43] Columns chromatography were performed on silica Gel (0.015-0.04 mm, mesh-size) and TLC on precoated plastic sheets (25 $DC_{UV\text{-}254}$) respectively. Melting points were measured on Barnstead Electrothermal melting point apparatus and were not corrected. Elemental analyses for C, H and N were performed using a Thermo Finnigan Flash EA1112 instrument. IR spectra were measured on a Bruker EQUINOX 55 spectrophotometer by ATR method. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ on a Brucker 500 spectrophotometer and chemical shifts were expressed in ppm downfield from tetramethylsilane. Mass spectra were recorded on a Finnigan-MAT 8430 spectrometer at an ionization potential of 70 ev.

General Procedure:

To a magnetically stirred mixture of acetyl- or benzoylglycine **1** (2mmol) and benzaldehyde derivatives **2** (2.5 mmol), anhydrous sodium acetate (3 mmol) in acetic anhydride (3 mmol) were added and heated for 5-7 h. Then 1, 3-diphenyl-1*H*-pyrazol-5-amine **3** (2 mmol) was added to the above mixture and was heated for 16-18 h. The brown residue was purified by column chromatography using silica gel and EtOAc: *n*-hexane (1:4) as co-solvent. The products **4a-h** were recrystalized from EtOAc or EtOH.

4-Benzylidine-2-methyl-1-(1,3-diphenyl-1*H*-pyrazol-5-yl)-1*H*-imidazol-5(4*H*)-one (4a).

Light yellow crystals; mp 145 °C; ν_{max}: 1724 (C=O), 1643, 1623 (C=N), 1524, 1500 (C-N) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 2.14 (3H, s, CH_3), 6.86 (1H, s, olefinic), 7.41-7.44, 7.47-7.49, 7.52-7.53, 7.94-7.96, 8.18-8.20 (16H, 5m, aromatic and pyrazole); δ_C (125 MHz): 16.22 (CH_3), 104.28 (olefinic), 124.28, 126.12, 128.97, 129.01, 129.20, 129.27, 130.05, 130.09, 131.21, 132.49, 132.81, 132.84, 134.10, 137.42, 138.39 (aromatic), 152.58, 160.60 (C=N), 170.01 (C=O); MS: m/z: 404, 327, 260, 116, 77; Anal. Calcd for $C_{26}H_{20}N_4O$: C, 77.21; H, 4.98; N, 13.85. Found: C, 77.20; H, 4.96; N, 13.88.

4-(4-Chlorobenzylidine)-2-methyl-1-(1,3-diphenyl-1*H*-pyrazol-5-yl)-1*H*-imidazol-5(4*H*)-one (4b).

Light yellow crystals; mp 157 °C; ν_{max}: 1726 (C=O), 1648, 1621 (C=N), 1529, 1503 (C-N), 904 (C-Cl) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 2.12 (3H, s, CH_3), 6.85 (1H, s, olefinic), 7.31-7.32, 7.42-7.44, 7.45-7.47, 7.48-7.50, 7.93-7.95, 8.12-8.14 (15H, 6m, aromatic and pyrazole); δ_C (125 MHz): 16.24 (CH_3), 104.27 (olefinic CH), 124.29, 126.11, 128.37, 129.01, 129.20, 129.55, 130.10, 132.59, 132.74, 133.95, 134.08, 137.28, 137.69, 138.35 (aromatic), 152.60, 161.04 (C=N), 169.82 (C=O); MS: m/z: 440, 438, 363, 361, 286, 284, 219, 77; Anal. Calcd for $C_{26}H_{19}ClN_4O$: C, 71.15; H, 4.36; N, 12.77. Found: C, 71.14; H, 4.37; N, 12.80.

4-(4-Bromobenzylidine)-2-methyl-1-(1,3-diphenyl-1*H*-pyrazol-5-yl)-1*H*-imidazol-5(4*H*)-one (4c).

Yellow crystals; mp 178 °C; ν_{max}: 1738 (C=O), 1645, 1616 (C=N), 1552, 1510 (C-N), 826, 765 (C-Br) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 2.11 (3H, s, CH_3), 6.84 (1H, s, olefinic), 7.14-7.15, 7.28-7.29, 7.40-7.42, 7.43-7.48, 7.49-7.51, 7.58-7.60, 7.92-7.94, 8.03-8.05 (15H, 8m, aromatic and pyrazole); δ_C (125 MHz): 16.25 (CH_3), 104.26 (olefinic CH), 124.28, 125.86, 126.11, 128.41, 129.00, 129.06, 129.20, 130.10, 132.31, 132.53, 132.74, 132.98, 134.10, 137.82, 138.34 (aromatic), 152.61, 161.11 (C=N), 169.82 (C=O); MS: m/z: 482, 484, 327, 260, 116, 77; Anal. Calcd for $C_{26}H_{19}BrN_4O$: C, 64.61; H, 3.96; N, 11.59. Found: C, 64.59; H, 3.97; N, 11.62.

4-(4-Nitrobenzylidine)-2-methyl-1-(1,3-diphenyl-1*H*-pyrazol-5-yl)-1*H*-imidazol-5(4*H*)-one (4d).

Yellow crystals; mp 174 °C; ν_{max}: 1737 (C=O), 1650, 1627 (C=N), 1526, 1512 (C-N), 1563, 1311 (NO_2)

cm^{-1}; δ_H (500 MHz, $CDCl_3$): 2.15 (3H, s, CH_3), 6.85 (1H, s, olefinic), 7.20-7.21, 7.40-7.41, 7.42-7.44, 7.47-7.50, 7.93-7.94, 8.29-8.34 (15H, 6m, aromatic and pyrazole); δ_C (125 MHz): 16.38 (CH_3), 104.29 (olefinic CH), 124.24, 124.31, 126.03, 126.11, 129.09, 129.20, 129.23, 130.16, 133.22, 138.26, 140.12, 148.58 (aromatic), 152.70, 163.41 (C=N), 169.51 (C=O) ; MS: m/z: 449, 434, 372, 295, 237, 135, 116, 77; Anal. Calcd for $C_{26}H_{19}N_5O_3$: C, 69.48; H, 4.26; N, 15.58. Found: C, 69.47; H, 4.24; N, 15.61.

4-Benzylidine-2-phenyl-1-(1,3-diphenyl-1*H*-pyrazol-5-yl)-1*H*-imidazol-5(4*H*)-one (4e).

Light yellow crystals; mp 167 °C; ν_{max}: 1736 (C=O), 1654, 1630 (C=N), 1531, 1511 (C-N) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 6.95 (1H, s, olefinic), 7.20-7.22, 7.29-7.34, 7.41-7.42, 7.47-7.53, 7.95-7.98, 8.31-8.32 (21H, 6m, aromatic and pyrazole); δ_C (125 MHz): 103.96 (olefinic CH), 124.38, 126.15, 128.51, 128.56, 128.61, 128.91, 129.02, 129.15, 129.30, 129.68, 131.13, 131.40, 132.22, 132.92, 133.27, 133.72, 134.39, 137.70, 138.29 (aromatic), 152.48, 158.83 (C=N), 170.59 (C=O) ; MS: m/z: 466, 389, 312, 247, 116, 77; Anal. Calcd for $C_{31}H_{22}N_4O$: C, 79.81; H, 4.75; N, 12.01. Found: C, 79.79; H, 4.75; N, 12.04.

4-(4-Methylbenzylidine)-2-phenyl-1-(1,3-diphenyl-1*H*-pyrazol-5-yl)-1*H*-imidazol-5(4*H*)-one (4f).

Light yellow crystals; mp 173 °C; ν_{max}: 1724 (C=O), 1647, 1621 (C=N), 1559, 1510 (C-N) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 2.46 (3H, s, CH_3), 6.94 (1H, s, olefinic), 7.20-7.22, 7.28-7.32, 7.39-7.50, 7.95-7.97, 8.19-8.21 (20H, 5m, aromatic and pyrazole); δ_C (125 MHz): 22.24 (CH_3), 103.96 (olefinic CH), 124.38, 126.16, 128.47, 128.57, 128.69, 128.89, 129.00, 129.15, 129.67, 130.13, 131.40, 131.76, 132.07, 132.76, 132.97, 133.34, 133.84, 136.99, 138.34, 140.27 (aromatic), 152.45, 158.21 (C=N), 170.62 (C=O); MS: m/z: 480, 326, 203, 116, 100, 98, 57; Anal. Calcd for $C_{32}H_{24}N_4O$: C, 79.98; H, 5.03; N, 11.66. Found: C, 79.99; H, 5.02; N, 11.68.

4-(4-Bromobenzylidine)-2-phenyl-1-(1,3-diphenyl-1*H*-pyrazol-5-yl)-1*H*-imidazol-5(4*H*)-one (4g).

Yellow crystals; mp 186 °C; ν_{max}: 1729 (C=O), 1638, 1611 (C=N), 1560, 1492 (C-N), 817, 762 (C-Br) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 6.94 (1H, s, olefinic), 7.18-7.20, 7.29-7.30, 7.31-7.33, 7.39-7.41, 7.48-7.50, 7.94-7.96, 8.15-8.17 (20H, 7m, aromatic and pyrazole); δ_C (125 MHz): 16.70 (CH_3), 103.96 (olefinic CH), 124.37, 126.15, 128.12, 128.41, 128.53, 128.66, 128.94, 129.07, 129.16, 129.42, 129.70, 132.40, 132.58, 132.87, 133.27, 133.56, 134.46, 138.10, 138.26 (aromatic), 152.50, 159.27 (C=N), 170.40 (C=O); MS: m/z: 544, 546, 467, 469, 390, 392, 168, 116, 118, 77; Anal. Calcd for $C_{31}H_{21}BrN_4O$: C, 68.26; H, 3.88; N, 10.27. Found: C, 68.25; H, 3.87; N, 10.30.

4-(4-Methoxybenzylidine)-2-phenyl-1-(1,3-diphenyl-1*H*-pyrazol-5-yl)-1*H*-imidazol-5(4*H*)-one (4h).

Light yellow crystals; mp 188 °C; ν_{max}: 1727 (C=O), 1635, 1614 (C=N), 1563, 1508 (C-N) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 3.91 (1H, s, OCH_3), 6.92 (1H, s, olefinic), 7.03-7.05, 7.26-7.29, 7.50-7.57, 7.61-7.66, 8.14-8.16, 8.19-8.24 (20H, 6m, aromatic and pyrazole); δ_C (125 MHz): 55.18 (OCH_3), 103.91 (olefinic CH), 124.29, 126.10, 127.17, 128.39, 128.50, 128.62, 128.84, 129.03, 129.26, 129.72, 130.11, 130.81, 131.38, 132.44, 133.44, 133.88, 134.19, 135.85, 137.53 (aromatic), 152.53, 159.16 (C=N), 170.11 (C=O);

MS: m/z: 496, 464, 419, 387, 167, 105, 77, 57; Anal. Calcd for $C_{32}H_{24}N_4O_2$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.41; H, 4.86; N, 11.30.

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44. Crystallographic data for the structures of compounds **4a, 5a** reported in this paper have been deposited with the Cambridge Crystallographi Data Center as supplementary publication No. CCDC 776000, 775999. These data can be obtained free of charge via www.ccdc.com.ac.uk/data_request/cif.