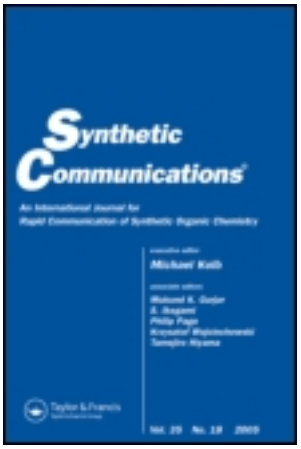

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Convenient Synthesis and Characterization of Pyrazolones and Schiff Bases

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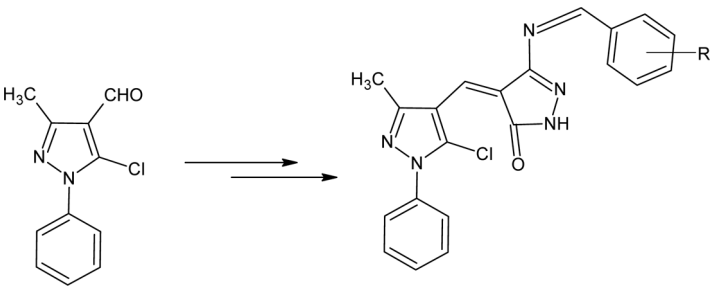
GRAPHICAL ABSTRACT



Abstract *A series of Schiff bases containing the pyrazolylpyrazole moiety has been synthesized in a convenient method at room temperature with good yields. All the compounds were well characterized by spectral and analytical data.*

Keywords Knoevenagel condensation; pyarzoles; pyrazolones; Schiff bases

INTRODUCTION

Pyrazoles and their derivaires are important molecules because they possess anti-inflammatory,[1] selective COX-2 inhibitiory,[2] antiparasitic,[3] and antiviral[4] activities. 5-Amino- and 5-anilinopyrazoles are important molecules from both synthetic and biological points of view.[5] Generally these 5-aminopyrazoles are synthesized by the reaction of hydrazine hydrate and methylenenitriles.[6] Other important methods are the reduction of the 5-azidopyrazoles[7] and the reaction of 5-chloropyrazoles with ammonium hydroxide at higher temperature.[8] In recent years the 5-amino pyrazoles and their derivatives have been synthesized in solid phase.[9] Similarly 5-anilinopyrazoles are synthesized by the Ullmann reaction of 5-aminopyrazoles and bromo/chlorobenzene[5] or by the reaction of benzyolthioacetanilide with substituted hydrazenes.[10] Schiff bases also show various biological activities such as anti-inflammatory, analgesic, and antimicrobial[9c] activities. Keeping in mind these

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properties of pyrazole and Schiff bases and in continuation of our research work on pyrazoles,[11] here we report a series of Schiff bases carrying the pyrazolylpyrazole moiety.

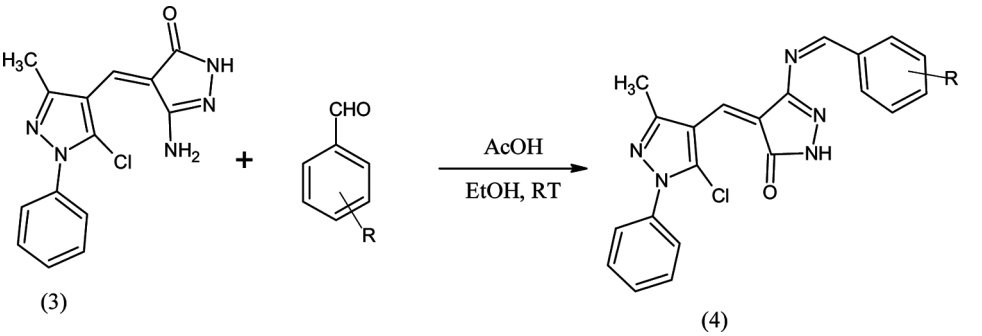
RESULTS AND DISCUSSION

The Knoevenagel condensation of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde **1** with ethylcyanoacetate at 0 °C results in the formation of ethyl-2-cyano-3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-yl)propionate **2**. This propionate, when treated with hydrazine hydrate at room temperature, yielded 5-amino-4-[(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylidine]-2,4-dihydro-3*H*-pyrazol-3-one **3**. When aminopyrazoles are treated with suitably substituted benzldehyde in the presence of a catalytic amount of acetic acid, 5-chloro-3-methyl-4-methylidene[(3^1-substitutedbenzylidineamino)pyrazole-5^1-one]-1-phenyl-1-*H*-pyrazole **4** is obtained. The 5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-carboxaldehyde **1** was synthesized following the literature procedure[11b] (Scheme 1).

The formation of 5-chloro-3-methyl-4-methylidene[(3^1-substituted benzylidineamino)pyrazole-5^1-one]-1-phenyl-1*H*-pyrazole **4** was confirmed by spectral and analytical data. All the newly synthesized compounds show the molecular ion peak in accordance with the proposed structure, which confirms the stability of the compounds. The infrared (IR) spectra of the Schiff bases shows absorption bands at 3300–3450 cm^{-1} for the amide –NH group, 1620–1680 cm^{-1} for the carbonyl group, and 1575–1605 cm^{-1} for the imine group. Absence of peak in the range of 3362 cm^{-1} confirms the absence of an $-NH_2$ group. The formation of these compounds are further confirmed by the ^{1}H NMR spectra, which show two singlets at δ, 8.55–8.73 integrating for one proton each, assigned to the imine proton and alkene proton. The signal from the amide –NH proton is not observed because of the exchange with D_2O of the solvent as the spectra were recorded in $CDCl_3$.

CONCLUSION

In conclusion, this is a convenient method for the preperation of Schiff bases containing the pyrazole moiety. The reactions occur at room temperature in a short



Scheme 1. Synthetic scheme for the reaction of the pyrazolone Schiff's bases.

time with good yield. However, the reported procedure[12] of Knoevenagel condensation is carried out at high temperature. Further, at high temperature this Knoevenagel condensation resulted in the formation of bispyrazoles, whereas at room temperature it gave amino derivatives. It can be concluded that this reaction is highly temperature sensitive.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was confirmed by thin-layer chromatography (TLC) using silica-gel plates in a petroleum ether–ethylacetate (9:1) system as mobile phase. ^{1}H NMR spectra were recorded on a Bruker Avance-II 400-MHz NMR spectrometer using $CDCl_3$ as solvent. Tetramethylsilane (TMS) was employed as internal standard. Chemical shift values are expressed in δ scale down field from TMS. The infrared (IR) spectra were obtained in KBr disc on a Shimadzu-8400 FTIR spectrophotometer. The mass spectra were recorded on a Waters Micromass Q-Tof Micro LC mass spectrometer. CHN analysis was performed on a Vario-El-Elementar III model analyzer.

Ethyl-2-cyano-3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-yl)propionate 2

5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-carboxaldehyde **1** (0.1 mol) was dissolved in 10 mL of ethanol by heating. Ethylcyanoacetate (0.1 mol) was added to this, and the reaction mixture was cooled to 0 °C in an ice–salt mixture. Sodium ethoxide (0.1 mol) in 5 mL ethanol was added to the cold reaction mixture with stirring, and temperature was maintained at 0–5 °C for another 2 h. The solid product was filtered, separated by suction, washed with cold ethanol, dried, and recrystallized from aqueous ethanol. Yield: 87%, mp 74–76 °C (lit.[12] 75–78 °C). CHN: found (cal.): C, 60.75 (60.86); H, 4.58 (4.47); N, 13.24 (13.31). IR: 1516 cm^{-1} (C=N), 1731.46 cm^{-1} (C=O), 2224.08 cm^{-1} (-CN), 2991 cm^{-1}, 2935 cm^{-1}, 3064 cm^{-1} for alkyl group. Mass: *e*/*z*, 316/318 (3:1) $(M^+ + 1)/(M^+ + 3)$. ^{1}H NMR (400 MHz) DMSO-d_6: δ, 1.29–1.33 (t, 3H, ester CH_3), 2.44 (s, 3H, CH_3 of pyrazole), 4.30–4.36 (q, 2H, -CH_2- of ester), 7.56–7.62 (m, 5H, Ar-H), 8.18 (s, 1H, CH=C).

5-Amino-4-[(5-chloro-3-methyl-1-phenyl-1*h*-pyrazol-4-yl)methylene]-2,4-dihydro-3*H*-pyrazol-3-one 3

The ethyl-2-cyano-3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-yl)propionate **2** (0.1 mol) was dissolved in 10 mL ethanol. Hydrazine hydrate (0.1 mol) was added to this solution with stirring. The reaction mixture was stirred at room temperature for 4 h. The solid was separated, filtered, washed with cold ethanol, dried, and recrystallized from ethanol. Yield: 85.48%, mp 98–100 °C. CHN: found (cal.): C, 55.79 (55.73); H, 4.16 (4.06); N, 23.11 (23.21). IR: 1528 cm^{-1}, 1600 cm^{-1} (C=N), 1628 cm^{-1} (amideC=O), 2959 cm^{-1} (-CH_3), 3202 cm^{-1} (-NH), 3362 cm^{-1} (-NH_2). Mass: *e*/*z*, 302/304 (3:1) $(M^+ + 1)/(M^+ + 3)$. ^{1}H NMR (400 MHz) $CDCl_3$: δ, 2.64 (s, 3H, -CH_3), 7.44–7.60 (m, 5H, Ar-H), 8.67 (s, 1H, CH=C). The signals due to -NH_2

and –NH protons are not observed possibly because of the D_2O exchange with the solvent.

5-Chloro-3-methyl-4-methylidene[(3^1-substitutedbenzylidineamino) pyrazole-5^1-one]-1-phenyl-1*H*-pyrazole 4

The 5-amino-4-[(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene]-2,4--dihydro-3*H*-pyrazol-3-one **3** (0.1 mol) was taken in 10 mL ethanol. Suitably substituted benzaldehyde (0.1 mol) and a catalytic amount of acetic acid were added. The reaction mixture was stirred at room temperature for 6 h. The separated product was filtered, washed with alcohol, dried, and recrystallized from an ethanol–DMF mixture. The characterization data of all the newly synthesized compounds are summerized in Table 1.

Spectral Data of Some of the Other Represented Compounds

Compound 4b. Mass: e/z, 356/358 $(M^+ + 1)/(M^+ + 3)$. IR (KBr pellet): 1679 cm^{-1} (NH-C=O), 3326 cm^{-1} (-NH), 2922 cm^{-1} (alkyl streching), 1602 cm^{-1} (N=CH), 1523 cm^{-1} (pyrazole N=CH).

Compound 4c. Mass: e/z, 386/388 $(M^+ + 1)/(M^+ + 3)$. ^{1}H NMR (400 MHz) (DMSO-d_6): δ, 2.51 (s, 3H, pyrazole-CH_3), 3.84 (s, 3H, -OCH_3), 7.05–7.07 (d, $J = 8.64$ Hz, 2H, ortho protons of *p*-anisyl), 7.55–7.61 (m, 5H, Ar-H), 7.84–7.86 (d, $J = 8.6$ Hz, 2H, meta protons of *p*-anisyl), 8.59 (s, 1H, CH=C), 8.6673 (s, 1H, N=CH).

Table 1. Characterization data of 5-chloro-3-methyl-4-methylidene[(3^1-substitutedbenzylidineamino) pyrazole-5^1-one]-1-phenyl-1*H*-pyrazole **4**

						CHN analysis found (Calc.)		
Compound	R	Mol. formula	Mol. wt	Yield (%)	Mp (°C)	C	H	N
4a	H	$C_{21}H_{16}ClN_5O$	389.5	79	141–144	67.66 (64.7)	4.25 (4.14)	17.82 (17.96)
4b	4-CH_3	$C_{22}H_{18}ClN_5O$	403.5	78	218–220	65.35 (65.43)	4.56 (4.49)	17.79 (17.39)
4c	4-OCH_3	$C_{22}H_{18}ClN_5O_2$	419.5	89	222–225	62.66 (62.93)	4.18 (4.32)	16.42 (16.68)
4d	3,4-dimethoxy	$C_{23}H_{20}ClN_5O_3$	449.5	93	227–230	61.59 (61.40)	4.30 (4.48)	15.63 (15.57)
4e	4-OH	$C_{21}H_{16}ClN_5O_2$	405.5	91	226–227	62.34 (62.15)	4.13 (3.97)	17.14 (17.26)
4f	4-Cl	$C_{21}H_{15}Cl_2N_5O$	424	96	214–215	59.61 (59.45)	3.25 (3.56)	16.78 (16.51)
4g	4-F	$C_{21}H_{15}ClFN_5O$	407.5	76	222–226	61.88 (61.85)	3.68 (3.71)	17.12 (17.17)
4h	4-Br	$C_{21}H_{15}BrClN_5O$	468.5	99	146–148	53.76 (53.81)	3.36 (3.23)	14.82 (14.94)
4i	2-Cl	$C_{21}H_{15}Cl_2N_5O$	424	80	223–224	59.54 (59.45)	3.23 (3.56)	16.42 (16.51)
4j	3,4-Dichloro	$C_{21}H_{14}Cl_3N_5O$	458.5	96	208–212	55.07 (54.98)	3.00 (3.08)	15.08 (15.27)
4k	3-Br	$C_{21}H_{15}BrClN_5O$	468.5	69	225–226	53.92 (53.81)	3.46 (3.23)	14.88 (14.94)
4l	4-NO_2	$C_{21}H_{15}ClN_6O_3$	434.5	92	179–183	58.13 (58.00)	3.24 (3.48)	19.54 (19.33)
4m	3-NO_2	$C_{21}H_{15}ClN_6O_3$	434.5	89	225–227	58.04 (58.00)	3.39 (3.48)	19.46 (19.33)

Note. Solvent for recrystallization: 1:1 mixture of ethanol–DMF.

Compound 4d. Mass: e/z, 416/418 $(M^+ + 1)/(M^+ + 3)$. IR (KBr pellet): 1629 cm^{-1} (NH-C=O), 3305 cm^{-1} (-NH), 2920 cm^{-1} & 2958 cm^{-1} (alkyl streching), 1597 cm^{-1} (N=CH), 1569 cm^{-1} (pyrazole N=CH).

Compound 4f. Mass: e/z, 390/392/394 $(M^+ + 1)/(M^+ + 3)/(M^+ + 5)$. IR (KBr pellet): 1627 cm^{-1} (NH-C=O), 3388 cm^{-1} (-NH), 2936 cm^{-1} (alkyl streching), 1577 cm^{-1} (N=CH), 1529 cm^{-1} (pyrazole N=CH).

Compound 4h. Mass: e/z, 435/437 $(M^+ + 1)/(M^+ + 3)$. ^1H NMR (400 MHz) (DMSO-d_6): δ, 2.65 (s, 3H, pyrazole-CH_3), 7.45–7.61 (m, 7H, Ar-H & 2 ortho protons of *p*-bromophenyl), 7.71–7.73 (d, $J = 8.4$ Hz, 2H, meta protons of *p*-bromo phenyl), δ, 8.62 (s, 1H, CH=C), 8.697 (s, 1H, N=CH).

Compound 4l. Mass: e/z, 401/403 $(M^+ + 1)$ / $(M^+ + 3)$. ^1H NMR (400 MHz) (DMSO-d_6): δ, 2.64 (s, 3H, pyrazole-CH_3), δ, 7.464–7.6058 (m, 5H, Ar-H), 8.014–8.036 (d, $J = 8.7$ Hz, 2H, ortho protons of p-nitro phenyl), 8.31–8.334 (d, $J = 8.7$ Hz, 2H, meta protons of *p*-nitro phenyl), 8.7239 (s, 1H, CH=C), 8.7360 (s, 1H, N=CH). IR (KBr pellet): 1631 cm^{-1} (NH-C=O), 3452 cm^{-1} (-NH), 2976 cm^{-1} (alkyl streching), 1577 cm^{-1} (N=CH), 1529 cm^{-1} (pyrazole N=CH), 1567 cm^{-1} (NO_2 assymmetric), 1419 cm^{-1} (NO_2 symmetric).

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