Synthesis of amino substituted pyrazoles

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An efficient and convenient synthesis of substituted pyrazoles with aryl and heteroarylamino substituents attached to the C-3 and C-5 positions by the action of hydrazine hydrate on either ketene *N,S*-acetals or mixed *N,N*-aminals hydrate is reported.

Keywords: ketene, pyrazoles, acetal, cyclocondensation, hydrazine

Pyrazoles[1] exhibit a wide range of biological activities such as antipyretic and anti-inflammatory,[1-2] gastric secretion stimulatory,[3] antidepressant,[4] antihypercholesterolemic,[5] antibacterial,[6] antioxidants[7] and against rheumatoid arthritis.[8] Recent reports on the *in vitro* evaluation of pyrazole containing compounds as potent kinase[9] and COX-1[10] inhibitors have increased the interest of pyrazoles into medicinal chemistry. Pyrazole derivatives also are used as herbicides,[11] pesticides and insecticides.[12] In the light of these findings, the synthesis of some new 3(5)-amino substituted pyrazoles has been undertaken as part of our studies on the synthesis of bioactive heterocycles.

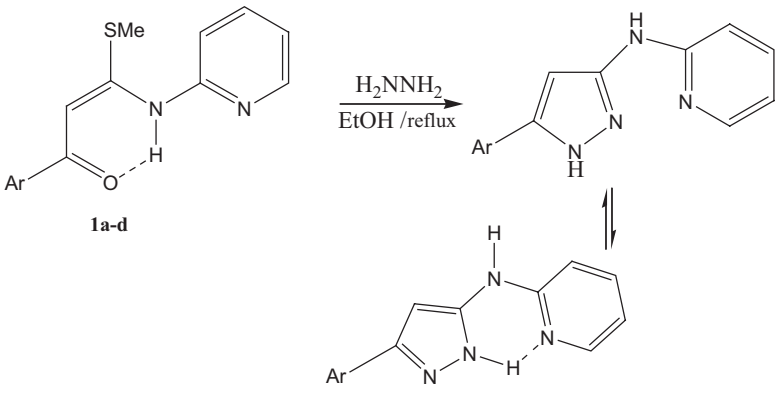
Although synthetic routes for the formation of the pyrazole ring system have been widely described in the literature,[13-17] relatively few convenient methods for the preparation of 3(5)-aminopyrazoles are described. Many of the reported methods for the preparation of 3(5)-substituted aminopyrazoles involve multiple steps using different starting materials. Thus new and facile alternative routes to 3(5)-substituted aminopyrazoles are desirable.

The reaction of *N,S*-acetals with hydrazine hydrate provide a useful synthetic route for novel 3(5)-substituted aminopyrazoles. We previously reported a new and improved synthesis of highly functionalised ketene *N,N*- and *N,S*- acetals.[18] In continuation of our systematic studies on the intramolecular ring cyclisation reactions[19] and cyclocondensation reactions of these acetals, we now report a facile synthesis of amino substituted pyrazoles. Ketene *N,S*-acetals **1a–d** can be converted to the corresponding 3-amino substituted pyrazoles **2a–d** in good yields through a cyclocondensation reaction with hydrazine hydrate. For example, *N,S*-acetal **1a** on refluxing with hydrazine hydrate in ethanol for 3 hr, gave 3-(2-pyridylamino)-5-phenyl-2*H*-pyrazoles **2a** in 82% yield (Scheme 1). The other substituted 3-(2-pyridylamino)-5-aryl-2*H*-pyrazoles (**2b–d)** were similarly obtained in 82–88% overall yields.

3-Pyridylamino substituted ketene acetals **3a–d** also were found to undergo similar reactions with hydrazine hydrate yielding 3-pyridylamino substituted pyrazoles **4a–d** in moderate to good yields (Scheme 2).

We have elaborated the synthetic strategy using mixed *N,N*-aminals **5a–g**. When 3-anilino-1-phenyl-3-(2-aminopyridyl) prop-2-en-1-one **5a** was refluxed with hydrazine hydrate in ethanol for 10 h 3-(2-anilino)-5-phenyl-2*H*-pyrazole **6a** was obtained with 40% yield (Scheme 3). We expected to obtain two different pyrazoles **6a–g** and **2a–d** by reacting the unsymmetrically substituted ketene *N,N*-aminals **5a–g** with hydrazine. However, only **6a–g** was observed, and no traces of 2-aminopyridyl substituted products **2a–d**. 2-Aminopyridine appears to be a better leaving group than the anilino substituents. However, the yields of pyrazoles **6a–d** are much lower than the yields obtained from an earlier reported method.[20] In general *N,N*-aminals are less reactive than *N,S*-acetals in cyclocondensation reactions.

Pyrazoles **2a–d** may exist in tautomeric equilibrium between **A**, **B** and **C** forms which can be easily distinguished with the help of IR and NMR spectroscopy (Scheme 4). All the pyrazoles **2a–d, 4a–d** and **6a–g** existed as only one



1, **2**, **a**, Ar = C_6H_5 **c**, Ar = p-ClC_6H_4

b, Ar = p-MeC_6H_4 **d**, Ar = p-$MeOC_6H_4$

Scheme 1

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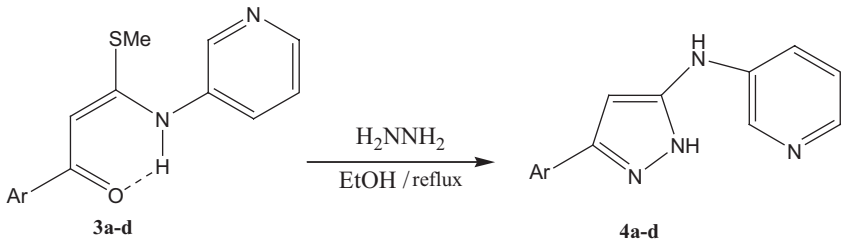
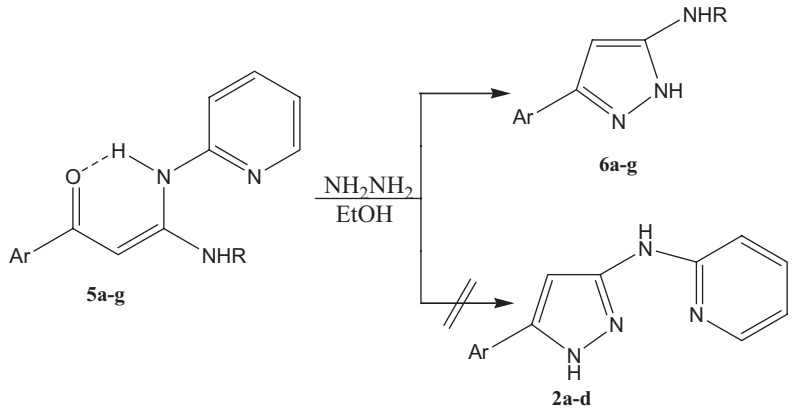


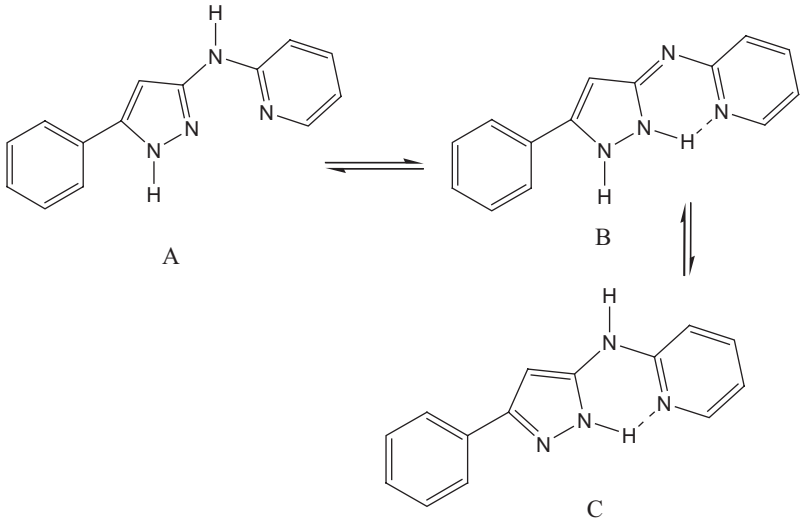
3, **4**, **a**, Ar = C_6H_5 **c**, Ar = p-ClC_6H_4
b, Ar = p-MeC_6H_4 **d**, Ar = p-$MeOC_6H_4$

Scheme 2



5, **6**, a, Ar = C_6H_5 ; R = C_6H_5 e, Ar = C_6H_5 ; R = o-ClC_6H_4
b, Ar = p-MeC_6H_4 ; R = C_6H_5 f, Ar = p-MeC_6H_4; R = o-ClC_6H_4
c, Ar = p-ClC_6H_4 ; R = C_6H_5 g, Ar = p-$MeOC_6H_4$; R = o-ClC_6H_4
d, Ar = p-$MeOC_6H_4$; R = C_6H_5

Scheme 3



Scheme 3

tautomer, which was evident from their sharp melting points. Spectral data supports the existence of the tautomeric form **C**. The IR spectra strongly indicate a hydrogen-bonded NH stretching vibration at 3310–3340 cm^{-1}, suggesting its position with the intramolecularly associated hydrogen. ^1H NMR spectra of these pyrazoles in deuteriochloroform showed a characteristic chelated NH proton far downfield near δ 12–13 ppm, assigned to the amino group which participated in a strong hydrogen bond with the nitrogen or carbon of the substituted pyridyl or the aryl compound in a six- membered, planar chelate (Scheme 4). A broad (singlet) peak at δ 9–10 ppm indicates the presence of the NH proton of the corresponding aryl or pyridyl substituents.

^{13}C NMR spectra further confirms the existence of a single tautomeric form, which showed three signals for the pyrazole ring carbons in the expected ranges, the one for C4 near 109 ppm and the two for C3 and C5 downfield, near 155 and 145 ppm. Apparently it appears that the strong intramolecular

hydrogen bonding directs the overall configuration of the pyrazole tautomers.

Pyrazoles **2a–d** possesses a good structural framework for behaving as conventional ligands. A recent report[21] on metal–ligand coordination studies of pyrazoles mentioned the difficulties of synthesising functionalised side chain at the pyrazole 3-position. The introduction of the functionalised amino substituents like 2-amino pyridine in **2a–d** enhances the scope of our studies on these heterocycles. Further studies on the metal complexation of the pyrazole heterocycles will be communicated in the near future.

In conclusion we have demonstrated the synthetic application of *N,S*-ketene aminals **1a–d** and **3a–b** as efficient 1,3-bielectrophilic reagents to prepare pyrazoles **2a–d** and **4a–b** in high yields. The method was extended to mixed *N, N*-aminals **5a–g** to yield arylamino substituted pyrazoles **6a–g** instead of the heteroarylamino substituted pyrazoles.

Experimental

The IR spectra were recorded on a Perkin Elmer 983 spectrometer in KBr pellets with absorption given in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Varian EM-390 (300 MHz) spectrometer. The Chemical shifts (δppm) and the coupling constants (Hz) are reported in the standard fashion with reference to internal tetramethyl silane (TMS). Elemental analyses were performed on a Heraus CHN-O-Rapid Analyser. Ketene *N,S*-acetals and mixed *N,N*-aminals required for the present investigation were prepared according to our previously reported[18,19] procedure.

General procedure: Synthesis of pyrazoles **2a–d** *and* **4a–d**

Hydrazine hydrate (6 mmol) was added to a solution of the appropriate *N,S*- acetal (5 mmol) in distilled ethanol (20 ml) and the reaction mixture was refluxed for 3–4 h (monitored by TLC). The solvent was evaporated and the residue was diluted with water (100 ml), extracted with chloroform (2 × 50 ml). The organic layer was washed with water (100 ml), dried (Na_2SO_4), and evaporated to give the crude pyrazoles, which were further purified by column chromatography over silica gel using hexane/ethyl acetate (20:1) as eluent to yield colourless crystals of **2a–d** and **4a–d**.

*3-(2-Aminopyridyl)-5-phenyl-2*H-*pyrazole* (**2a**): M.p. 210°C; yield 82%; IR (KBr): 3340, 3275 (NH), 1602 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): 6.69–6.73 (m, 2H, H-4 and pyridyl H), 7.19–7.34 (m, 3H, three ArH), 7.41–7.46 (m, 1H, pyridyl H), 7.53–7.58 (m, 1H, pyridyl H), 7.72–7.74 (m, 2H, ArH), 8.15–8.16 (m, 1H, pyridyl H), 9.31 (brs, 1H, NH), 12.61 (s, 1H, N–H); ^{13}C NMR ($CDCl_3$): 109, 114, 125, 127, 128, 129, 137, 147, 155; Anal. Calcd. for $C_{14}H_{12}N_4$(236): C, 71.17; H, 5.12; N, 23.71. Found: C, 71.78; H, 5.20; N, 23.00.

*3-(2-Aminopyridyl)-5-(*p-*methylphenyl)-2*H-*pyrazole*(**2b**): M.p. 215–217°C, yield 85%; IR (KBr): 3340, 3275 (NH), 1602 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 2.38 (s, 3H, CH_3), 6.55 (s, 1H, H-4), 6.77 (m, 1H, pyridyl H), 6.90 (m, 1H, pyridyl H), 7.16 (d, 2H, *J* = 8.4 Hz, ArH), 7.36 d, 2H, *J* = 8.4 Hz, ArH), 7.50 (m, 1H, pyridyl H), 8.22 (m, 1H, pyridyl H) 9.30 (brs, 1H, NH), 12.56 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6): 20, 108, 113, 126, 129, 133, 137, 138, 148, 149, 155, 161; Anal. Calcd. for $C_{15}H_{14}N_4$ (250): C, 71.98; H, 5.64; N, 22.38. Found C, 71.90; H, 5.37; N, 22.56.

*3-(2-Aminopyridyl)-5-(*p-*chlorophenyl)-2*H-*pyrazole*(**2c**):M.p.236°C, yield 82%; IR (KBr): 3323, 3273 (NH), 1601 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 6.50 (s, 1H, H-4), 6.73 (m, 1H, pyridylH), 6.95 (m, 1H, pyridyl H), 7.50 d, 2H, *J* = 8.0 Hz, ArH), 7.90–8.19 (m, 3H, two ArH and one pyridyl H), 8.25 (m, 1H, pyridyl H), 9.30 (brs, 1H, NH), 12.50 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6): 90, 108, 112.5, 128, 129.5, 134, 135.5, 138, 148, 149, 155.5, 160.3; Anal. Calcd. For $C_{14}H_{11}N_4Cl$ (270.5): C, 62.11; H, 4.10; N, 20.70. Found C, 62.20; H, 4.20; N, 20.50.

*3-(2-Pyridylamino)-5-(*p-*methoxyphenyl)-2*H-*pyrazole* (**2d**): M.p. 240°C, yield 88%; IR (KBr): 3318, 3275 (NH), 1634, 1604 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 3.73 (s, 3H, OCH_3), 6.45 (s, 1H, H-4), 6.65 (m, 1H, pyridyl H), 6.80 (m, 1H, pyridyl H), 6.95 (d, 2H, *J* = 7.5 Hz), 7.55 (d, 2H, *J* = 9.0 Hz), 7.74 (m, 1H, pyridyl H), 8.11 (m, 1H, pyridyl H), 9.10 (brs, 1H, NH), 12.35 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6): 56, 91, 109.5, 114, 115.6, 128, 129.5, 138, 149, 149.7, 155, 161, 162.5; Anal. Calcd. for $C_{15}H_{14}N_4O$ (266): C, 67.65; H, 5.30; N, 21.04. Found C, 67.60; H, 5.20; N, 21.12.

*3-(3-Pyridylamino)-5-phenyl-2*H-*pyrazole* (**4a**): M.p. 196°C, yield 62%; IR (KBr): 3340, 3275 (NH), 1602 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 6.40 (s, 1H, H-4), 7.10 (m, 1H, ArH), 7.20 (m, 1H, pyridyl H), 7.30 (m, 2H, ArH), 7.41–7.50 (m, 3H, two ArH and one pyridyl H), 8.20 (m, 1H, pyridyl H), 8.55 (m, 1H, pyridyl H), 9.20 (brs, 1H, NH), 12.45 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6): 91, 122, 125, 127.5, 129, 129.5, 137, 137.5, 139, 146, 149.5, 156; Anal. Calcd. For $C_{14}H_{12}N_4$ (236): C, 71.17; H, 5.12; N, 23.71. Found: C, 71.20; H, 5.10; N, 23.00.

*3-(3-Pyridylamino)-5-(*p-*methylphenyl)-2*H-*pyrazole* (**4b**): M.p. 217°C, yield 65%; IR (KBr): 3340, 3275 (NH), 1602 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 2.38 (s, 3H, CH_3), 6.35 (s,1H, H-4), 7.03 (d, 2H, *J* = 8.4 Hz, ArH), 7.20 (m, 1H, pyridyl H), 7.66 (d, 2H, *J* = 8.4 Hz, ArH), 7.75 (m, 2H, Pyridyl), 8. 50 (m, 1H, pyridyl H), 9.15 (brs, 1H, NH), 12.42 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6): 20, 90, 121, 124, 126, 129, 133.5, 137, 137.5, 139, 145, 149, 155; Anal. Calcd. for $C_{15}H_{14}N_4$ (250): C, 71.98; H, 5.64; N, 22.38. Found C, 71.89; H, 5.37; N, 22.50.

*3-(3-Pyridylamino)-5-(*p-*chlorophenyl)-2*H-*pyrazole* (**4c**): M.p. 230°C, yield 72%; IR (KBr): 3323, 3273 (NH), 1601 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 6.45 (s, 1H, H-4), 7.10 (m, 1H, pyridyl H), 7.30 (d, 2H, *J* = 8.0 Hz, ArH), 7.40–7.50 (m, 3H, two ArH and one pyridyl), 8.15 (m, 1H, pyridyl H), 8.55 (m, 1H, pyridyl H), 9.30 (brs, 1H, NH), 12.45 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6): 91, 122, 125, 127, 129, 135, 136, 138, 139, 145, 149, 155.5; Anal. Calcd. for $C_{14}H_{11}N_4Cl$ (270.5): C, 62.11; H, 4.10; N, 20.70. Found C, 62.15; H, 4.20; N, 20.75.

*3-(3-Aminopyridyl)-5-(*p-*methoxyphenyl)-2*H-*pyrazole* (**4d**): Mp 200°C, yield 70%; IR (KBr): 3340, 3275 (NH), 1602 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 3.79 (s, 3H, OCH_3), 6.30 (s, 1H, H-4), 7.00 (d, 2H, *J* = 8.4 Hz, Ar H), 7.26 (m, 1H, pyridyl H), 7.65 (d, 2H, *J* = 9.0 Hz ArH), 7.95 (m, 1H, pyridyl H), 8.10–8.15 (m, 1H, pyridyl H), 8.65 (m, 1H, pyridyl H), 9.00 (brs, 1H, NH), 12.41 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6): 55.5, 90.5, 114.5, 120, 122, 123, 126, 137, 139, 140, 142, 151, 159; Anal. Cald. for $C_{15}H_{14}N_4O$ (266): C, 67.65; H, 5.30; N, 21.04. Found C, 67.69; H, 5.34; N, 21.10.

General procedure for **6a–g**

Ketene *N,N*-aminal 5 (5 mmol) was dissolved in 30 ml of ethanol. Hydrazine (6 mmol) was added and the reaction mixture was refluxed for 10 h (monitored by TLC). The solvent was removed under reduced pressure and the residue was diluted with water (100 ml) and extracted with chloroform (2 × 50 ml). The organic layer was washed with water (100 ml), dried (Na_2SO_4), and evaporated to give the crude pyrazoles which were purified by column chromatography on silica gel using hexane/ethyl acetate (20:1) as eluent.

*3-(2-Chloroanilino)-3-phenyl-2*H-*pyrazoles* (**6e**): M.p. 250°C, yield 60%; IR (KBr): 3340, 3275 (NH), 1602 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 6.50 (s, 1H, H-4), 6.55–6.65 (m, 2H), 6.80 (m, 1H), 7.08 (m, 1H), 7.22–7.33 (m, 3H), 7.40–7.49 (m, 2H, ArH), 9.00 (brs, 1H, NH), 12.46 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6): 102.9, 120.5, 127.0, 127.5, 128.5, 129, 130, 135.5, 133, 136, 137.5, 150, 151.5; Anal. Calcd. for $C_{15}H_{12}ClN_3$ (255.5): C, 66.79; H, 4.48; N, 15.58. Found C, 66.69; H, 4.40; N, 15.30.

*3-(2-Chloroanilino)-5-(*p-*methylphenyl)-2*H-*pyrazoles* (**6f**): M.p. 200°C, yield 65%; IR (KBr): 3340, 3275 (NH), 1602 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 2.35 (s, 3H, CH_3), 6.35 (s, 1H, H-4), 7.00–7.05 (m, 3H), 7.10 (m, 1H), 7.15 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 9.20 (brs, 1H, NH), 12.51 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6): 21.4, 102.5, 126.9, 127.5, 128.5, 129.9, 130, 130.5, 132.3, 133.5, 136.9,137.9, 150, 151.5; Anal. Cald. for $C_{16}H_{14}ClN_3$ (283.5): C, 67.72; H, 4.98; N, 14.81. Found C, 67.69; H, 4.90; N, 14.91.

*3-(2-Chloroanilino)-5-(*p-*methoxyphenyl)-2*H-*pyrazoles* (**6g**): M.p. 220°C, yield 62%; IR (KBr): 3340, 3275 (NH), 1602 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 3.75 (s, 3H, OCH_3), 6.47 (s, 1H, H-4), 6.45 (m, 1H), 6.56 (m, 1H, 6.85 (d, 2H, *J* = 8.4 Hz, ArH), 7.01 (m, 1H), 7.35 (d, 2H, *J* = 8.4 Hz, ArH), 9.10 (brs, 1H, NH), 12.56 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6): 56.5, 102.7, 126.9, 127.5, 129.9, 130, 130.5, 132, 133, 133.5, 136.9, 150, 151.5, 162.5; Anal. Calcd. for $C_{16}H_{14}ClN_3O$ (299.5): C, 64.11; H, 4.71; N, 14.02. Found C, 64.15; H, 4.75; N, 13.81.

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