Vilsmeier–Haack reaction on hydrazones: a convenient synthesis of 4-formylpyrazoles

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Vilsmeier–Haack reaction has been found to be an excellent method for the formylation of a variety of hydrazones to yield the corresponding 4-formylpyrazoles.

Keywords: Vilsmeier–Haack reaction, formylation, hydrazones, 4-formylpyrazoles

Pyrazole derivatives have attracted a great deal of attention on account of their antibacterial[1], antifungal[2] and anti-inflammatory[3] properties. Keeping in mind the biological significance of thiazole derivatives, we report here, the synthesis of some new 4-formylpyrazole derivatives incorporating a thiazole ring.

The Vilsmeier–Haack reaction is a common method for the synthesis of 4-formylpyrazoles.[4] Besides this, the reaction has been extensively used to bring about formylation of reactive aromatic and heteroaromatic substrates.[5-9] A wide variety of carbonyl compounds[10], activated methyl and methylene groups[11] efficiently react with Vilsmeier–Haack reagent to yield the corresponding iminium salts. The utilty of this reagent also explores the intramolecular cyclisation of azides by iminium species.[12, 13] It has been found in the present investigation that Vilsmeier–Haack reaction on hydrazones provides 4-formylpyrazoles containing thiazole ring in excellent yields.

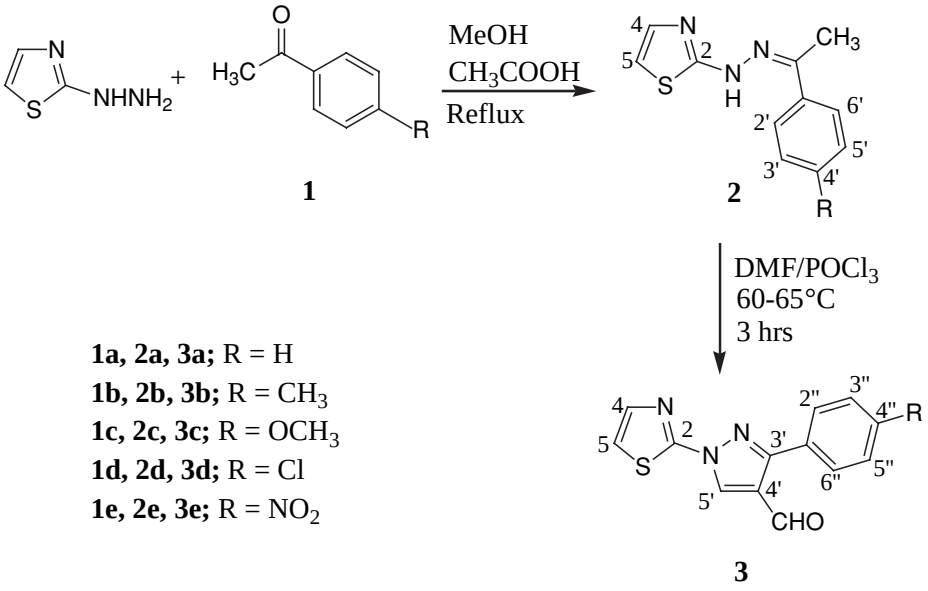
Result and discussion

Condensation of an equimolar amount of a methanolic solution of 2-hydrazinothiazole[14] with acetophenone or 4-substituted acetophenones in presence of a catalytic amount of glacial acetic acid[15] provided the corresponding hydrazones **2** in excellent yields. Hydrazone **2** on stirring with the Vilsmeier–Haack reagent prepared from DMF-$POCl_3$ at 60–65 °C gave the corresponding 4-formylpyrazoles (**3**) (Scheme 1).

A plausible mechanism for the formation of 4-formylpyrazoles is outlined in Scheme 2.

Initial electrophilic attack of Vilsmeier–Haack reagent **4** on hydrazone **2** yielded the intermediate **5** which subsequently loses a molecule of HCl to provide intermediate **6**. Then the nucleophilic attack by NH group initiates the cyclisation and the resulting pyrazoline immediately loses Me_2NH to give the more stable pyrazole derivatives **7**. The pyrazole **7** reacts with another mole of Vilsmeier–Haack reagent **4** in an electrophilic substitution process giving an iminium salt **8**, which is hydrolysed to the corresponding 4-formylpyrazole **3**. The intermediacy of the pyrazole 7 is supported by an earlier report[16] which indicates the formation of 1-phenyl-3-diethoxyphosphonylpyrazole (**10**) on reaction of phosphonyl hydrazone 9 with the Vilsmeier–Haack reagent (DMF/$POCl_3$) in equimolar ratio and another mole of the Vilsmeier–Haack reagent (DMF/$POCl_3$) reacts further with product 10 to afford 4-formylpyrazole (**11**) (Scheme 3).

Compounds 3 were characterised using spectral data and microanalysis. The IR spectra of the pyrazolylthiazoles 3 in the functional group region, showed a strong band at 1685 cm^{-1} due to C=O stretch of the $C_{4'}$–CHO group. Besides this two characteristic weak bands also observed at 2736 and 2833 cm^{-1} due to Fermi resonance between C–H stretch and C–H bending vibration of the aldehyde group. While their ^{1}H NMR spectra showed two sharp singlets at δ10.07 and δ8.95 due to aldehyde proton of $C_{4'}$–CHO group and $C_{5'}$–H of the pyrazole ring respectively. The deshielding of about 1ppm of $C_{5'}$–H relative to its usual position at δ7.61[17] may well be due to anisotropic effect of the contiguous $C_{4'}$–CHO group. Besides



Scheme 1

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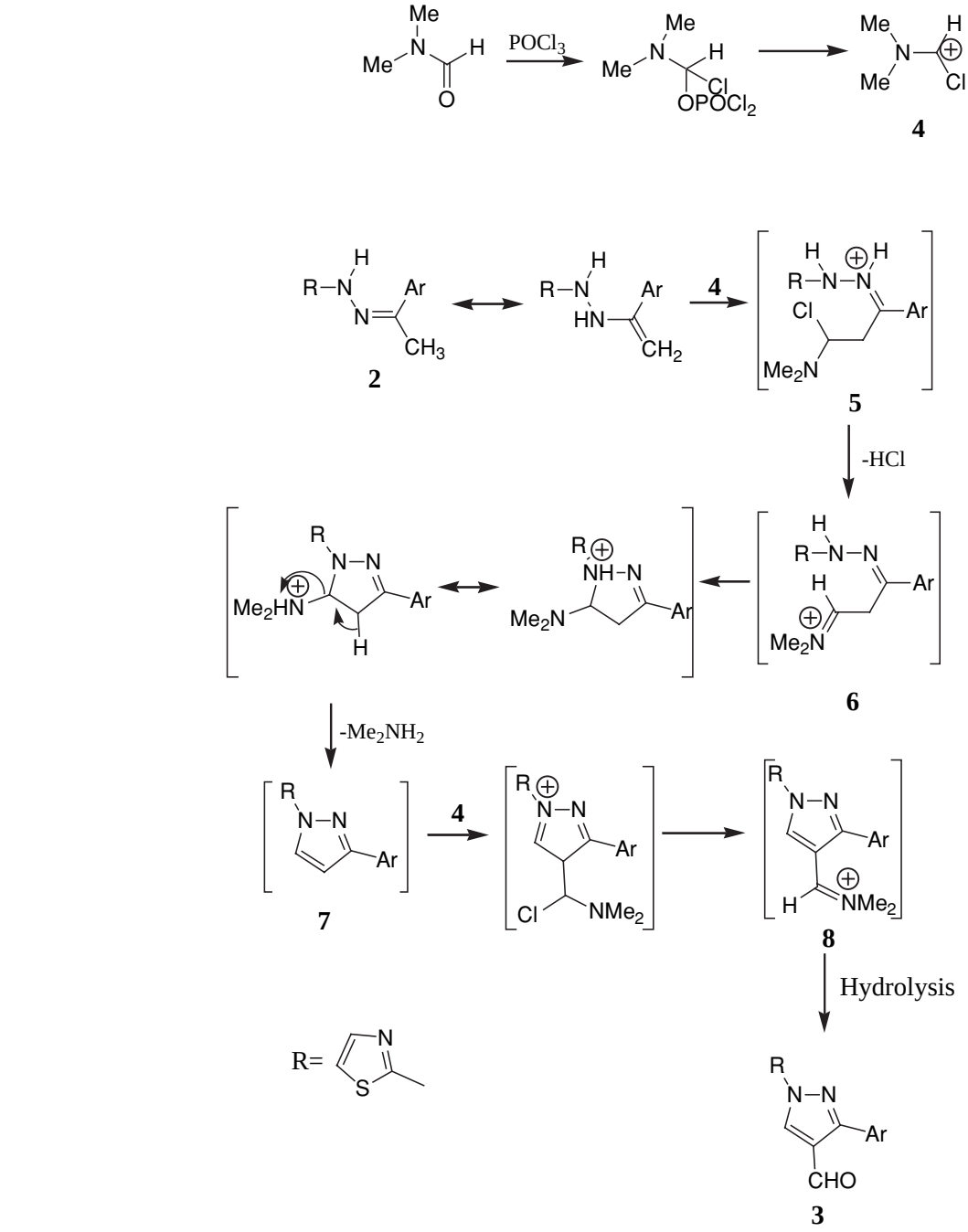
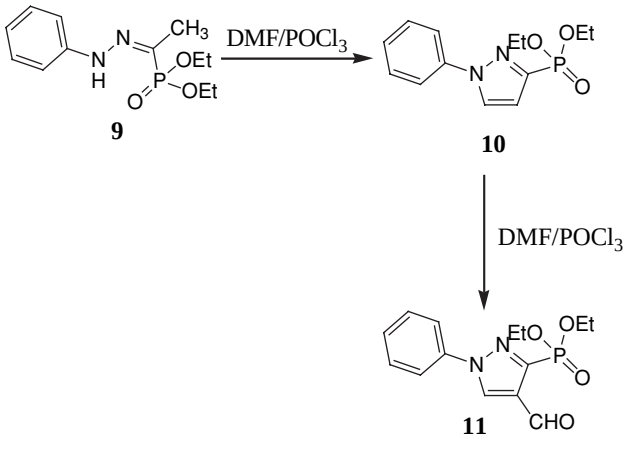


Scheme 2



Scheme 3

these, the two protons of the thiazole ring, *i.e.* C_4–H and C_5–H appeared as a pair of two doublets in the region δ7.62–7.64 (J=3.7 Hz) and δ7.23–7.26 (J=3.7 Hz) respectively. The shielding of C_5–H relative to C_4–H is presumably due to greater (σ+π) net charge[18] on C_5–H relative to C_4–H.

Experimental

Melting points were taken in a sulfuric acid bath and are uncorrected. The IR (KBr) and ^{1}H NMR spectra were recorded on Buck Scientific IR M-500 and Bruker (300MHz) spectrometers, respectively. Mass spectra were measured on a Varian MAT CH-7 instrument at 70V.

Synthesis of 4-substituted acetophenonethiazol-2-ylhydrazones (**2a-e**) *General procedure*: A mixture of 2-hydrazinothiazole (1.5mmol) and substituted acetophenone (1.5mmol) in methanol (20ml) containing acetic acid (1ml) was refluxed for 15 min. Addition of water (10ml) with cooling gave the corresponding hydrazone which was crystallised from aqueous methanol.

2a: M.p. 157–159 °C (Lit[14] 158–160 °C); yield 80%; IR (KBr): 3156cm^{-1} (N–H stretch), 1635cm^{-1} (>C=N stretch); ^{1}H NMR (300MHz, $CDCl_3$): δ2.29 (s, 3H, C*H*$_3$–C=N–), 6.69–6.71 (d, 1H, *J*=3.6Hz, C$_5$–*H*), 7.27–7.29 (d, 1H, *J*=3.6Hz, C$_4$–*H*), 7.33–7.44 (m, 3H, C$_{3'}$–*H*, C$_{4'}$–*H* and C$_{5'}$–*H*), 7.76–7.81 (m, 2H, C$_{2'}$–*H* and C$_{6'}$–*H*), 9.50 (bs, 1H, N–*H* exchangeable with D_2O).

2b: M.p. 178–179 °C; yield 80.9%; IR (KBr): 3156cm^{-1} (N–H stretch), 1625cm^{-1} (>C=N stretch); ^{1}H NMR (300MHz, $CDCl_3$): δ2.26 (s, 3H, C*H*$_3$–C=N–), 2.32 (s, 3H, C$_{4'}$–C*H*$_3$), 6.67–6.69 (d, 1H, *J*=3.6Hz, C$_5$–*H*), 7.18–7.21 (d, 2H, *J*=8.1Hz, C$_{3'}$–*H*, and C$_{5'}$–*H*), 7.25–7.27 (d, 1H, *J*=3.6Hz, C$_4$–*H*), 7.67–7.69 (d, 2H, *J*=8.1Hz, C$_{2'}$–*H* and C$_{6'}$–*H*), 9.50 (bs, 1H, N–*H* exchangeable with D_2O).

2c: M.p. 180–181 °C; yield 78.6%; IR (KBr): 3156cm^{-1} (N–H stretch), 1630cm^{-1} (>C=N stretch); ^{1}H NMR (300MHz, $CDCl_3$): δ2.20 (s, 3H, C*H*$_3$–C=N–), 3.84 (s, 3H, C$_{4'}$–OC*H*$_3$), 6.66–6.68 (d, 1H, *J*=3.6Hz, C$_5$–*H*), 6.91–6.94 (d, 2H, *J*=8.2Hz, C$_{3'}$–*H*, and C$_{5'}$–*H*), 7.25–7.27 (d, 1H, *J*=3.6Hz, C$_4$–*H*), 7.73–7.76 (d, 2H, *J*=8.2Hz, C$_{2'}$–*H* and C$_{6'}$–*H*), 9.50 (bs, 1H, N–*H* exchangeable with D_2O).

2d: M.p. 170–171 °C; yield 78.4%; IR (KBr): 3154cm^{-1} (N–H stretch), 1625cm^{-1} (>C=N stretch); ^{1}H NMR (300MHz, $CDCl_3$): δ2.25 (s, 3H, C*H*$_3$–C=N–), 6.69–6.71 (d, 1H, *J*=3.6Hz, C$_5$–*H*), 7.27–7.29 (d, 1H, *J*=3.6Hz, C$_4$–*H*), 7.34–7.37 (d, 2H, *J*=8.1Hz, C$_{3'}$–*H*, and C$_{5'}$–*H*), 7.70–7.73 (d, 2H, *J*=8.1Hz, C$_{2'}$–*H* and C$_{6'}$–*H*), 9.30 (bs, 1H, N–*H* exchangeable with D_2O).

2e: M.p. 220–221 °C; yield 81.4%; IR (KBr): 3154cm^{-1} (N–H stretch), 1625cm^{-1} (>C=N stretch), 1556cm^{-1} (NO_2 asym. stretch), 1373cm^{-1} (NO_2 sym. stretch); ^{1}H NMR (300MHz, $CDCl_3$): δ2.32 (s, 3H, C*H*$_3$–C=N–), 6.75–6.77 (d, 1H, *J*=3.6Hz, C$_5$–*H*), 7.30–7.32 (d, 1H, *J*=3.6Hz, C$_4$–*H*), 7.92–7.95 (d, 2H, *J*=8.6Hz, C$_{3'}$–*H*, and C$_{5'}$–*H*), 8.23–8.26 (d, 2H, *J*=8.6Hz, C$_{2'}$–*H* and C$_{6'}$–*H*), 9.50 (bs, 1H, N–*H* exchangeable with D_2O).

Synthesis of 2-(3-aryl-4-formylpyrazol-1-yl)thiazoles (**3a–e**)

General procedure: To the Vilsmeier–Haack reagent prepared from DMF (10ml) and $POCl_3$ (1.1ml, 12mmol), hydrazone 2 (4mmol) was added and the reaction mixture stirred at 60–65 °C for 3h and then poured into ice-cold water. The solid that separated on neutralisation with $NaHCO_3$ was filtered, washed with water and crystallised from ethanol.

3a: M.p. 110–111 °C; yield 68.7%; IR (KBr): 2833 and 2775cm^{-1} (C–H stretch, Fermi resonance), 1688cm^{-1} (>C=O stretch of CHO group); ^{1}H NMR (300MHz, $CDCl_3$): δ7.23–7.26 (d, 1H, *J*=3.6Hz, C$_5$–*H*), 7.48–7.55 (m, 3H, C$_{3''}$–*H*, C$_{4''}$–*H* and C$_{5'''}$–*H*), 7.62–7.64 (d, 1H, *J*=3.6Hz, C$_4$–*H*), 7.81–7.86 (m, 2H, C$_{2''}$–*H* and C$_{6''}$–*H*), 8.95 (s, 1H, C$_5$–*H*), 10.07 (s, 1H, C$_{4'}$–C*H*O); MS: *m*/*z* 255 (M$^+$, 100%), Anal. Found: C, 61.10; H, 3.50; N, 16.53%. Calcd for $C_{13}H_9N_3SO$: C, 61.17; H, 3.53; N, 16.47%.

3b: M.p. 115–116 °C; yield 72.6%; IR (KBr): 2833 and 2736cm^{-1} (C–H stretch, Fermi resonance), 1691cm^{-1} (>C=O stretch of CHO group); ^{1}H NMR (300MHz, $CDCl_3$): δ2.40 (s, 3H, C$_{4''}$–C*H*$_3$), 7.21–7.23 (d, 1H, *J*=3.6Hz, C$_5$–*H*), 7.30–7.33 (d, 2H, *J*=8.0Hz, C$_{3''}$–*H*, and C$_{5'''}$–*H*), 7.61–7.63 (d, 1H, *J*=3.6Hz, C$_4$–*H*), 7.72–7.74 (d, 2H, *J*=8.0Hz, C$_{2''}$–*H* and C$_{6''}$–*H*), 8.90 (s, 1H, C$_{5'}$–*H*), 10.00 (s, 1H, C$_{4'}$–C*H*O); MS: *m*/*z* 269 (M$^+$, 100%), Anal. Found: C, 62.31; H, 4.21; N, 15.79%. Calcd for $C_{14}H_{11}N_3SO$: C, 62.45; H, 4.09; N, 15.61%.

3c: M.p. 127–128 °C; yield 70.4%; IR (KBr): 2833 and 2736cm^{-1} (C–H stretch, Fermi resonance), 1691cm^{-1} (>C=O stretch of CHO group); ^{1}H NMR (300MHz, $CDCl_3$): δ3.80 (s, 3H, C$_{4''}$–OC*H*$_3$), 7.00–7.04 (d, 2H, *J*=8.1Hz, C$_{3''}$–*H*, and C$_{5''}$–*H*), 7.26–7.28 (d, 1H, *J*=3.7Hz, C$_5$–*H*), 7.65–7.67 (d, 1H, *J*=3.7Hz, C$_4$–*H*), 7.80–7.84 (d, 2H, *J*=8.1Hz, C$_{2''}$–*H* and C$_{6''}$–*H*), 8.90 (s, 1H, C$_5$–*H*), 10.00 (s, 1H, C$_{4'}$–C*H*O); MS: *m*/*z* 285 (M$^+$, 100%), Anal. Found: C, 58.76; H, 4.02; N, 15.01%. Calcd for $C_{14}H_{11}N_3SO_2$: C, 58.95; H, 3.86; N, 14.74%.

3d: M.p. 160–161 °C; yield 70.8%; IR (KBr): 2830 and 2730cm^{-1} (C–H stretch, Fermi resonance), 1691cm^{-1} (>C=O stretch of CHO group); ^{1}H NMR (300MHz, $CDCl_3$): δ7.24–7.26 (d, 1H, *J*=3.6Hz, C$_5$–*H*), 7.46–7.49 (d, 2H, *J*=8.3Hz, C$_{3''}$–*H*, and C$_{5''}$–*H*), 7.63–7.65 (d, 1H, *J*=3.6Hz, C$_4$–*H*), 7.84–7.88 (d, 2H, *J*=8.3Hz, C$_{2''}$–*H* and C$_{6''}$–*H*), 8.90 (s, 1H, C$_5$–*H*), 10.00 (s, 1H, C$_{4'}$–C*H*O); MS: *m*/*z* 291 (M$^+$+2, 45.2%) / 289 (M$^+$, 100%), Anal. Found: C, 53.42; H, 2.93; N, 14.71%. Calcd for $C_{13}H_8N_3SOCl$: C, 53.61; H, 2.75; N, 14.43%.

3e: M.p. 200–201 °C; yield 71.2%; IR (KBr): 2846 and 2763cm^{-1} (C–H stretch, Fermi resonance), 1691cm^{-1} (>C=O stretch of CHO group), 1538cm^{-1} (NO_2 asym.stretch), 1345cm^{-1} (NO_2 sym.stretch); ^{1}H NMR (300MHz, $CDCl_3$): δ7.26–7.28 (d, 1H, *J*=3.6Hz, C$_5$–*H*), 7.65–7.67 (d, 1H, *J*=3.6Hz, C$_4$–*H*), 8.18–8.21 (d, 2H, *J*=8.7Hz, C$_{2''}$–*H*, and C$_{6''}$–*H*), 8.34–8.36 (d, 2H, *J*=8.7Hz, C$_{3''}$–*H* and C$_{5''}$–*H*), 8.90 (s, 1H, C$_5$–*H*), 10.00 (s, 1H, C$_{4'}$–C*H*O); MS: *m*/*z* 300 (M$^+$, 100%), Anal. Found: C, 52.35; H, 2.93; N, 18.45%. Calcd for $C_{13}H_8N_4SO_3$: C, 52.00; H, 2.67; N, 18.67%.

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