A facile synthesis of 4,5-dihydropyrazolo[4,3-*c*]quinolines with Vilsmeier reagent

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4,5-Dihydropyrazolo[4,3-*c*]quinolines have been synthesised in moderate to good yields from dihydroquinolin-4-ones using the Vilsmeier reagent, under conventional and microwave irradiation conditions.

Keywords: Vilesmeier–Haack reagent, fused pyrazoles, quinolines, microwave heating

Pyrazoloquinolines are important compounds since they are isosteric with other biologically active 5,6,6-ring systems.[1] They have attracted considerable attention in recent years due to the discovery of their potential uses as analgesic, antipyretic, anti-inflammatory, antifertility agents and as gastric H^+/K^+- ATP ase inhibitors.[2]

The halomethyleniminium salts[3] generated under Vilsmeier-Haack conditions are capable of producing iminium species from numerous aromatic compounds,[4] alkene derivatives,[5] carbonyl compounds,[6] and, in addition, oxygen and nitrogen nucleophiles.[7] The Vilsmeier cyclisation of iminium species provides access to a large number of heterocyclic systems.[8] Earlier reports from our laboratory have described the synthesis of pyran, quinoline, pyrrole, pyridine, quinazolinone, oxazole, imidazole and pyrazole derivatives using the Vilsmeier reagent.[9]

In continuation of our interest in exploiting the cyclisation potential of this versatile reagent, we have developed a simple route to the synthesis of dihydropyrazoloquinoline derivatives from dihydroquinolone hydrazones,[10] as delineated in Scheme 1.

When **2a** was treated with Vilsmeier reagent and refluxed at 90 °C for 6–8 h, formylation and cyclisation occured to give the dihydropyrazoloquinoline **3a** in 45 % yield. Other substituted dihydroquinolone hydrazones similarly underwent cyclisation smoothly. The yields and melting points of the products are given in Table 1. The same reaction carried out under microwave irradiation led to high yields of products after three minutes of irradiation. A comparison of conventional and microwave methods is tabulated below.

In conclusion: this paper describes a new and convenient method for the synthesis of dihydropyrazoloquinolines using the Vilsmeier reagent under reflux and microwave conditions, yielding moderate to good yields of the products **3**. Microwave irradiation enables synthesis of the products in high yields within a short period of time.

Table 1 Reaction products of dihydroquinolone dinitrophenylhydrazones with Vilsmeier reagent

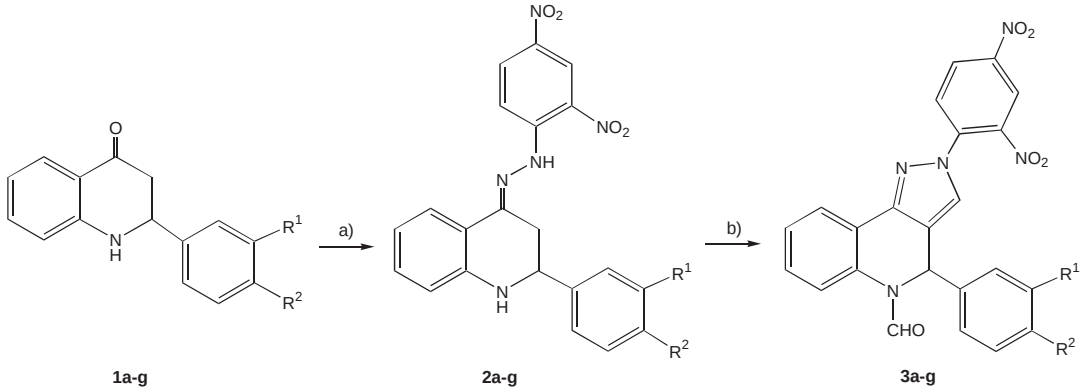
Entry	R_1	R_2	Product[a]	Method A Yield/%[b]	Method B Yield/%[b]	M.p./°C
2a	H	CH_3	**3a**	45	55	224
2b	H	H	**3b**	35	50	220
2c	H	Cl	**3c**	40	70	240
2d	Cl	H	**3d**	45	62	245
2e	NO_2	H	**3e**	40	52	215
2f	OCH_3	OCH_3	**3f**	60	85	185
2g	H	OCH_3	**3g**	55	80	190

[a]See Experimental section. [b] Isolated yield using conventional (A) and microwave irradiation (B) respectively.

Experimental

Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2mm thickness (Machery-Nagel, Germany). IR spectra were taken as KBr pellets on a Perkin Elmer RXI FT-IR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6 solutions with TMS as internal standard. Column chromatography was performed on silica gel (60–120 mesh, SRL, India). The 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **1a–g** used as substrates in this investigation were prepared from the corresponding 2-aminochalcones following a reported method,[10] and the dihydroquinolone dinitrophenylhydrazones **2a–g** were prepared by standard procedure.[11]

Synthesis of dihydropyrazoloquinoline 3a under conventional conditions; typical procedure: Method A: Dihydroquinolone hydrazone **2a** (1.25 g, 3 mmol) was dissolved in DMF (10 ml) and cooled to 0 °C. $POCl_3$ (2.5 ml, 24 mmol) was added dropwise with stirring over a period of 20–30 min. The reaction mixture was stirred for 1h at room temperature and then stirred at 90 °C for 6–8 h. After completion of the reaction, the mixture was cooled and poured onto crushed ice and neutralised with sodium hydroxide. The crude solid was filtered off and purified by column chromatography using silica gel (60–120 mesh), eluting with petroleum ether : ethyl acetate (75:25), to afford **3a** as a pale yellow solid (0.60g, 45%). The same procedure was followed to prepare other compounds in the series.



Scheme 1 Conditions: (a) 2,4-DNPH/H_2SO_4/MeOH; (b) DMF/$POCl_3$, 6–8 h, 90°C, *or* MW, 3 min.

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Synthesis of dihydropyrazoloquinoline 3f under microwave irradiation; typical procedure: Method B: The dinitrophenylhydrazone **2f** (1.39 g, 3 mmol) was dissolved in excess of DMF (10 ml) in a RB flask fitted with a calcium chloride guard tube and cooled in ice. To the stirred solution $POCl_3$ (2.24 ml, 24 mmol) was added dropwise and the mixture was subjected to microwave irradiation for 3 minutes with 70 % power with pulse rate of 30 sec. After the completion of the reaction (monitored by TLC), the reaction mixture was poured onto crushed ice and neutralised with sodium hydroxide and the purification procedure of Method A was followed to afford **3f** as an orange solid (1.28g, 85 %). The same procedure was followed for the rest of the compounds in the series.

2-(2,4-Dinitrophenyl)-5-formyl-4,5-dihydro-4-(4-methylphenyl)-2H-pyrazolo[4,3-c]quinoline (**3a**): solid, m.p. 224 °C. ^{1}H NMR: δ 8.92 (d, 1H, *J* = 2.5 Hz), 8.86 (s, 1H, *N*-CHO), 8.76 (s, 1H), 8.68 (dd, 1H, *J* = 8.9, 2.5 Hz), 8.23 (d, 1H, *J* = 8.9 Hz), 7.74 (d, 1H, *J* = 7.38 Hz), 7.66 (d, 1H, *J* = 7.9 Hz), 7.47 (t, 1H, *J* = 7.5 Hz), 7.37 (t, 1H, *J* = 7.38 Hz), 7.1 (m, 4H), 7.04 (s, 1H), 2.20 (s, 3H, CH_3). ^{13}C NMR: δ 162.5, 146.9, 145.45, 142.55, 137.0, 136.5, 135.9, 135.5, 130.5, 129.2, 128.85, 128.3, 126.2, 126.1, 125.6, 123.1, 121.3, 120.8, 120.2, 119.4, 48.1, 20.6. IR 1684 cm^{-1}. MS: *m/z* 455 (M^+). Anal: calc. for $C_{24}H_{17}N_5O_5$: C, 63.29; H, 3.76; N, 15.38. Found: C, 63.12; H, 3.78; N, 15.29 %.

2-(2,4-Dinitrophenyl)-5-formyl-4,5-dihydro-4-phenyl-2H-pyrazolo[4,3-c]quinoline (**3b**): solid, m.p. 220 °C. ^{1}H NMR: δ 8.90 (d, 1H, *J* = 2.4 Hz), 8.82 (s, 1H, N-CHO), 8.72 (s, 1H), 8.60 (dd, 1H, *J* = 8.8, 2.4 Hz), 8.21 (d, 1H, *J* = 8.79 Hz), 7.71 (d, 1H, *J* = 7.24 Hz), 7.62 (d, 1H, *J* = 7.24 Hz), 7.42 (t, 1H, *J* = 7.4 Hz), 7.33 (t, 1H, *J* = 7.38 Hz), 7.1–7.0 (m, 5H), 6.98 (s, 1H), ^{13}C NMR: δ 162.4, 147.0, 146.5, 143.3, 138.7, 137.0, 136.3, 135.0, 131.2, 129.1, 128.4, 127.2, 126.1, 126.0, 125.5, 124.1,123.0, 120.8, 120.0, 119.8, 48.9. IR: 1685 cm^{-1}. MS: *m/z* 441 (M^+); Anal: calc. for $C_{23}H_{15}N_5O_5$: C, 62.58; H, 3.43; N, 15.87. Found: C, 62.52; H, 3.41; N, 15.79 %.

4-(4-Chlorophenyl)-2-(2,4-dinitrophenyl)-5-formyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline (**3c**): solid, m.p. 240 °C. ^{1}H NMR: δ 8.92 (d, 1H, *J* = 2.4 Hz), 8.87 (s, 1H, N-CHO), 8.70 (s, 1H), 8.68 (dd, 1H, *J* = 9.0, 2.4 Hz), 8.25 (d, 1H, *J* = 8.8 Hz), 7.76 (d, 1H, *J* = 7.84 Hz), 7.68 (d, 1H, *J* = 7.84 Hz), 7.37 (t, 1H, *J* = 8.36 Hz), 7.25 (t, 1H, *J* = 8.76 Hz), 7.23–7.17 (m, 4H), 7.10 (s, 1H). ^{13}C NMR: δ 162.5, 146.8, 145.5, 142.6, 138.5, 135.9, 135.2, 132.4, 130.6, 129.12 129.1, 128.6, 128.2, 126.2, 125.7, 125.5, 123.1, 121.3, 120.8, 118.8, 47.8. IR: 1682 cm^{-1}. MS: *m/z* 474 (100%, M-H)$^+$, 475 (84%, M^+). Anal: calc. for $C_{23}H_{14}ClN_5O_5$: C, 58.05; H, 2.97; N, 14.72. Found: C, 58.12; H, 2.98; N, 14.69 %.

4-(3-Chlorophenyl)-2-(2,4-dinitrophenyl)-5-formyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline (**3d**): solid, m.p. 245 °C. ^{1}H NMR: δ 9.0 (d, 1H, *J* = 2.3 Hz), 8.91 (s, 1H, N-CHO), 8.8 (s, 1H), 8.71 (dd, 1H, *J* = 8.9, 2.3 Hz), 8.32 (d, 1H, *J* = 8.9 Hz), 7.92 (d, 1H, *J* = 7.8 Hz), 7.64 (d, 1H, *J* = 7.8 Hz), 7.42 (t, 1H, *J* = 8.24 Hz), 7.31 (t, 1H, *J* = 8.26 Hz), 7.28–7.14 (m, 4H), 7.0 (s, 1H), ^{13}C NMR: δ 162.7, 146.7, 145.55, 142.6, 142.0, 135.9, 135.3, 133.4, 130.6, 129.3, 128.1, 127.7, 126.3, 126.2, 125.85, 124.9, 123.1, 121.3, 120.8, 120.0, 119.2, 118.55, 47.9. IR: 1684 cm^{-1}. MS: *m/z* 474 (M-H)$^+$. Anal: calc. for $C_{23}H_{14}ClN_5O_5$: C, 58.05; H, 2.97; N, 14.72. Found: C, 57.98; H, 2.91; N, 14.60 %.

2-(2,4-Dinitrophenyl)-5-formyl-4,5-dihydro-4-(3-nitrophenyl)-5H-pyrazolo[4,3-c]quinoline (**3e**): solid, m.p. 215 °C. ^{1}H NMR: δ 8.94 (d, 1H, *J* = 2.5 Hz), 8.84 (s, 1H, N–CHO), 8.79 (s, 1H), 8.70 (dd, 1H, *J* = 9.0, 2.4 Hz), 8.43 (d, 1H, *J* = 9.0 Hz), 8.01 (d, 1H, *J* = 7.5 Hz), 7.92 (d, 1H, *J* = 7.5 Hz), 7.51 (t, 1H, *J* = 8.4 Hz), 7.42 (t, 1H, *J* = 8.46 Hz), 7.3–7.10 (m, 4H), 6.98 (s, 1H), ^{13}C NMR: δ 162.8, 147.8, 146.9, 145.9, 143.5, 142.65, 136.9, 135.5, 134.6, 132.65, 130.2, 129.3, 128.4, 127.8, 126.3, 125.3, 125.0, 124.1, 123.2, 121.1, 120.0, 118.5, 48.1. IR: 1690 cm^{-1}. MS: *m/z* 485 (M-H)$^+$; Anal: calc. for $C_{23}H_{14}N_6O_7$: C, 56.79; H, 2.90; N, 17.28. Found: C, 56.62; H, 2.81; N, 17.19 %.

4-(3,4-Dimethoxyphenyl)-2-(2,4-dinitrophenyl)-5-formyl-2,4-dihydro-5H-pyrazolo[4,3-c]quinoline (**3f**): solid, m.p. 185 °C. ^{1}H NMR: δ 8.89 (d, 1H, *J* = 2.4 Hz), 8.83 (s, 1H, N-CHO), 8.72 (s, 1H), 8.65 (dd, 1H, *J* = 8.7 and 2.4 Hz), 8.62 (d, 1H, *J* = 8.7 Hz), 7.74 (d, 1H, *J* = 7.8 Hz), 7.64 (d, 1H, *J* = 8.3 Hz), 7.45 (t, 1H, *J* = 7.82 Hz), 7.34 (t, 1H, *J* = 7.32 Hz), 7.0 (s, 1H), 6.81(s, 1H), 6.80 (d, 1H, *J* = 8.2 Hz), 6.60 (d, 1H, *J* = 8.3 Hz), 3.65 (s, 6H). ^{13}C NMR: δ 162.4, 148.7, 148.3, 147.0, 145.5, 142.65, 136.0, 135.6, 131.9, 128.8, 128.2, 126.1, 125.8, 123.0, 122.6, 121.3, 120.3, 119.6, 118.2, 111.6, 110.2, 110.1, 55.4, 48.0. IR: 1680 cm^{-1}. MS: *m/z* 500 (M-H)$^+$. Anal: calc. for $C_{25}H_{19}N_5O_7$: C, 59.88; H, 3.82; N, 13.97. Found: C, 59.82; H, 3.79; N, 13.89 %.

2-(2,4-Dinitrophenyl)-4-(4-methoxyphenyl)-5-formyl-4,5-dihydro-5H-pyrazolo[4,3-c]quinoline (**3g**): solid, m.p. 190 °C. ^{1}H NMR: δ 8.85 (d, 1H, *J* = 2.86 Hz), 8.79 (s, 1H, N-CHO), 8.68 (s, 1H), 8.61 (dd, 1H, *J* = 9.0, 2.86 Hz), 8.17 (d, 1H, *J* = 9.0 Hz), 7.7 (d, 1H, *J* = 7.45 Hz), 7.5 (d, 1H, *J* = 8.02 Hz), 7.4 (t, 1H, *J* = 7.46 Hz), 7.3 (t, 1H, *J* = 7.45 Hz), 7.08 (d, 2H, *J* = 8.59 Hz) 6.98 (s, 1H), 6.82 (d, 2H, *J* = 8.59 Hz), 3.64 (s, 3H). ^{13}C NMR: δ 162.8, 159.2, 147.4, 145.9, 143.0, 136.4, 135.8, 132.0, 131.05, 129.1, 128.6, 128.0, 126.65, 126.1, 123.6, 121.8, 121.3, 120.7, 120.0, 114.5, 55.6, 48.4. IR: 1690 cm^{-1}. MS: *m/z* 470 (M-H)$^+$. Anal: calc. for $C_{24}H_{17}N_5O_6$: C, 61.15; H, 3.63; N, 14.86. Found: C, 60.92; H, 3.71; N, 14.19 %.

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