Brand new quantitative solid-state synthesis of N-pyrazolyl azomethines

Ehab Abdel-Latif[a], Gerd Kaupp[b] and Mohamed A. Metwally[a]*

[a]*University of Mansoura, Faculty of Science, Chemistry Department, Egypt*

[b]*University of Oldenburg, Faculty 5, Organische Chemie I, Germany*

Fifteen preparatively useful azomethines 3 and 5 have been quantitatively (100% yield at 100% conversion) obtained as hydrates by ball-milling together 4-aminoantipyrine 1 and 3-amino-4,6-dimethylpyrazolopyridine 4 with solid benzaldehydes 2 without passing through liquid phases. Unlike (acid catalysed) azomethine syntheses in solution, the solid–solid condensations proceed "waste free" in the absence of any auxiliaries or microwave irradiation. The product yields are quantitative in all cases and the products do not require purifying workup.

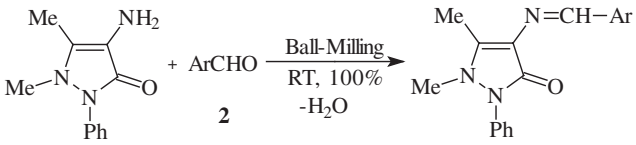
Keywords: azomethines, aminoantipyrine, condensation, solid-state reactions, ball mill, ninhydrin, indenopyridazine

Azomethines are important building blocks in enantio-selective oxidations (chiral oxaziridines),[1] cycloadditions[2] and cyclisations.[3] Previously, the derivatisation of primary amine functions by their reaction with carbonyl compounds in solution required strong acid catalysis and removal of the water of reaction from the equilibrium with production of much dangerous wastes. It is, therefore, of high interest that many of these reactions can be performed wasteless by the gas–solid or solid–solid technology which provides 100% yield of the product. The recent observation that gaseous carbonyl compounds condense quantitatively with carbonyl reagents such as 2,4-dinitrophenylhydrazine, without acid catalysts,[4] suggests improvements in azomethines syntheses using solid-to-solid reactions. Thus, we report on the quantitative preparation of eight azomethines of type **3** by ball milling together stoichiometric amounts of aminoantipyrine **1** and solid benzaldehydes **2** in the 2.0 mmol range (Scheme 1). The water of reaction in all of these condensations was easily removed from the product crystals by heating at 80 °C under vacuum to obtain 100% yield. No further workup was necessary, as the products were pure. Although some of the N-antipyrinyl azomethines **3** have been previously prepared in solution reactions but no quantitative yield was obtained.

Solid-state reactions profit from higher reactivity as the reagents are not solvated. It is, thus, more common to work at room temperature or to cool down below eutectic temperatures than to heat up. However, reactions will freeze out at very low temperatures, and there may also be a requirement for heating in order to overcome activation barriers. Many solid anilines and benzaldehydes condense quantitatively at room temperature to give azomethines.[5] However, the combination of 3-amino-4,6-dimethylpyrazolo[3,4-*b*]pyridine (**4**) with various solid benzaldehydes **2** require heating and the ball mill has to be run at 60 °C in order to reach the reaction (30 min). The aldehydes **2** and the pyrazolopyridinylamine **4** do not melt upon ball-milling of stoichiometric mixtures but provide the solid azomethine products **5** and in pure form. Therefore, no purifying workup is required in the absence of solid supports, microwave or catalyst or solvent and the reactions are thus truly solvent free. The water of the reaction is simply removed by heating to 80 °C in a vacuum (Scheme 2). The chemical structure of **5a–g** was secured by IR, ^{1}H and ^{13}C NMR data and MS.

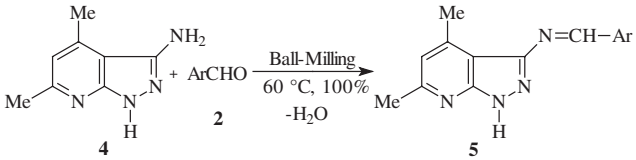
While previous quantitative and waste-free reactions of amines have been concentrated on reactions with aldehydes and ketones it is also possible to react with ninhydrin. Thus, aminoantipyrine **1** condensed quantitatively with ninhydrin **6** at room temperature in the solid-state (Scheme 3) to give the product **7** in 100% yield. The structure of **7** was established by its NMR and MS spectral data.

* Correspondent. E-mail: mamegs@mans.edu.eg



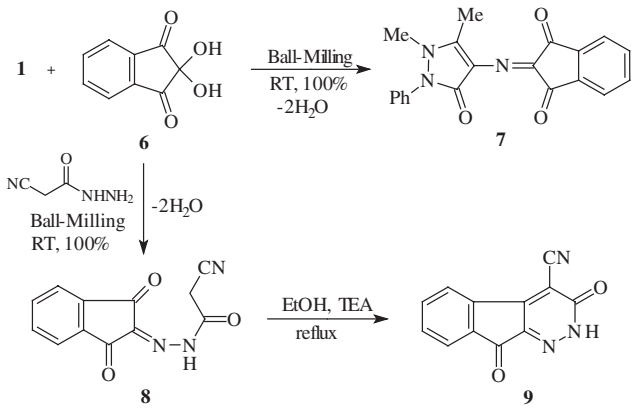
a; Ar = 2-$O_2NC_6H_4$ b; Ar = 3-$O_2NC_6H_4$
c; Ar = 4-$O_2NC_6H_4$ d; Ar = 4-ClC_6H_4
e; Ar = 4-HOC_6H_4 f; Ar = 4-$Me_2NC_6H_4$
g; Ar = 3-MeO-4-HOC_6H_3 h; Ar = 2,4-$(MeO)_2$-6-HOC_6H_2

Scheme 1 Quantitative solid–solid of antipyrinyl azomethines.



a; Ar = 2-$O_2NC_6H_4$ b; Ar = 3-$O_2NC_6H_4$
c; Ar = 4-$O_2NC_6H_4$ d; Ar = 4-ClC_6H_4
e; Ar = 4-HOC_6H_4 f; Ar = 4-$Me_2NC_6H_4$
g; Ar = 3-MeO-4-HOC_6H_3

Scheme 2 Quantitative solid–solid synthesis of dimethylpyrazolo[3,4-*b*]pyridinyl azomethines.



Scheme 3 Quantitative solid–solid reaction of ninhydrin with aminoantipyrine and cyanoacetohydrazide.

The previous solid-state cascades[6-9] prompt us to explore the reaction of ninhydrin with cyanoacetohydrazide in the solid-state. The ball-milling reaction of ninhydrin with cyanoaceto-hydrazide at room temperature afforded only the corresponding azomethine **8** in a quantitative yield. The water of reaction did not significantly hydrolize the "amide" moiety of **8** and it was

easily removed by heating to 80 °C in a vacuum. Azomethine **8** underwent cyclisation by reflux in ethanol containing drops of triethylamine to give the corresponding indeno[2, 1-*c*]pyridazine derivative **9**. The chemical structures of **8** and **9** were supported by the ^{1}H NMR, ^{13}C NMR and MS spectral data.

These reactions may appear common and simple; from the point of view of sustainable chemistry, however, it is extremely useful to perform them in stoichiometric 1:1 reactant ratio without production of wastes in order to avoid the necessity for workup with solvent.

Experimental

Melting points were determined with a Gallenkamp melting point apparatus (capillary method) and are uncorrected. Elemental analyses were carried out at the Microanalytical Unit of the Faculty of Science, Cairo University and all compounds gave satisfactory elemental analyses. IR spectra (KBr) were recorded with a Mattson 5000 FTIR spectrometer (not all frequencies are reported). The ^{1}H NMR and ^{13}C NMR spectra were acquired using a Bruker WP 300 spectrometer at 300 MHz (^{1}H) or 75.5 MHz (^{13}C; in broad band mode). Mass spectra were obtained at a Finnigan MAT 212 instrument by electron impact at 70 eV.

General procedure for the preparation of antipyrinyl azomethines **3**: A mixture of 4-aminoantipyrine 1 (0.406 g, 2.00 mmol) and the solid aldehyde 2 (2.00 mmol) was ball-milled at room temperature for 1h. The solid powders were dried at 80 °C in a vacuum to give pure 3 with 100% yield and did not require purifying workup.

4-(2-Nitrobenzylideneamino)-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (**3a**): M.p. 211–212 °C; IR (KBr): 3074, 2934, 1651, 1592, 1569, 1521, 1487, 1455, 1415, 1386, 1357, 1306, 1131, 1072, 973, 945, 857, 771, 705; ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 7.20–7.60 (m, 7H, Ar–H), 7.80, (d, 1H, Ar–H), 8.10 (d, 1H, Ar–H), 10.00 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): δ 10.02, 35.51, 118.17, 124.05, 124.66 (2C), 127.14, 128.96, 129.21 (2C), 129.76, 131.92, 132.29, 134.48, 149.13, 151.36, 152.45, 160.17; MS *m/z* (%): 336 (65), 319 (20), 291 (20), 244 (10), 215 (12), 202 (92), 188 (20), 172 (15), 121 (20), 104 (24), 83 (30), 77 (40), 56 (100). Found: C, 64.35; H, 4.71; N, 16.61%. $C_{18}H_{16}N_4O_3$ (336.34) requires C, 64.28; H, 4.79; N, 16.66%.

4-(3-Nitrobenzylideneamino)-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (**3b**): M.p. 218–219 °C; IR (KBr): 3074, 2948, 1651, 1594, 1569, 1523, 1491, 1458, 1416, 1383, 1348, 1310, 1137, 1093, 956, 868, 816, 772, 736, 700; ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 7.25–7.60 (m, 6H, Ar–H), 8.10 (d, 1H, Ar–H), 8.25 (d, 1H, Ar–H), 8.75 (s, 1H, Ar–H), 9.80 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): δ 10.04, 35.45, 117.65, 121.46, 124.10, 124.74 (2C), 127.27, 129.25 (2C), 129.40, 133.76, 134.45, 139.77, 148.73, 152.29, 153.47, 160.39; MS *m/z* (%): 336 (90), 244 (15), 188 (34), 121 (38), 56 (100). Found: C, 64.38; H, 4.83; N, 16.72%. $C_{18}H_{16}N_4O_3$ (336.34) requires C, 64.28; H, 4.79; N, 16.66%.

4-(4-Nitrobenzylideneamino)-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (**3c**): M.p. 252–253 °C; IR (KBr): 3072, 2943, 1642, 1573, 1554, 1516, 1497, 1340, 1110, 949, 855, 754, 700; ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 7.20–7.50 (m, 5H, Ar–H), 8.00 (d, 2H, Ar–H), 8.25 (d, 2H, Ar–H), 9.80 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): δ 10.03, 35.40, 117.85, 123.82 (2C), 124.89 (2C), 127.44, 128.05 (2C), 129.32 (2C), 134.37, 143.75, 148.37, 152.35, 153.43, 160.22; MS *m/z* (%): 336 (100), 244 (22), 188 (50), 121 (50), 56 (90). Found: C, 64.22; H, 4.73; N, 16.70%. $C_{18}H_{16}N_4O_3$ (336.34) requires C, 64.28; H, 4.79; N, 16.66%.

4-(4-Chlorobenzylideneamino)-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (**3d**): M.p. 242–243 °C, lit.[10] 244 °C; IR (KBr): 3060, 2937, 1651, 1594, 1572, 1495, 1455, 1379, 1301, 1134, 1087, 1008, 836, 768; ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 7.20–7.50 (m, 7H, Ar–H), 7.80 (d, 2H, Ar–H), 9.75 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): δ 10.10, 35.75, 118.23, 124.49 (2C), 126.99, 128.71 (2C), 128.88 (2C), 129.17 (2C), 134.64, 135.90, 136.33, 151.94, 155.53, 160.68; MS *m/z* (%): 325 (100), 326 (40), 327 (80), 233 (35), 216 (20), 205 (15), 188 (65), 162 (15), 121 (62), 77 (18), 56 (98). Found: C, 66.24; H, 4.89; N, 12.94%. $C_{18}H_{16}ClN_3O$ (325.79) requires C, 66.36; H, 4.95; N, 12.90%.

4-(4-Hydroxybenzylideneamino)-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (**3e**): M.p. 226–227 °C, lit.[11] 228–230 °C; IR (KBr): 3071, 2949, 1656, 1611, 1581, 1511, 1455, 1425, 1379, 1313, 1276, 1233, 1159, 1100, 1025, 968, 833, 764, 702; ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 2.50 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 6.90 (d, 2H, Ar–H), 7.25–7.80 (m, 7H, Ar–H), 9.50 (s, 1H, N=CH), 9.75 (s, 1H exchangeable by D_2O, OH); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 8.00, 33.91, 113.71 (2C), 115.89, 122.27 (2C), 124.66, 127.13 (2C), 127.22 (2C), 130.09, 133.00, 149.75, 153.64, 157.93, 158.41; MS *m/z* (%): 307 (26), 198 (23), 121 (30), 56 (100). Found: C, 70.46; H, 5.64; N, 13.75%. $C_{18}H_{17}N_3O_2$ (307.35) requires C, 70.34; H, 5.58; N, 13.67%.

4-(4-Dimethylaminobenzylideneamino)-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (**3f**): M.p. 215–216 °C, lit.[10] 210°C; IR (KBr): 2893, 1651, 1611, 1581, 1527, 1489, 1408, 1371, 1311, 1291, 1230, 1176, 1135, 1071, 973, 946, 819, 774, 701; ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 3.00 (s, 6H, $2CH_3$), 3.10 (s, 3H, CH_3), 6.70 (d, 2H, Ar–H), 7.20–7.50 (m, 5H, Ar–H), 7.75 (d, 2H, Ar–H), 9.60 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): δ 10.20, 36.13, 40.16 (2C), 110.93, 111.64 (2C), 123.98 (2C), 125.74, 126.45 (2C), 129.01 (2C), 129.53, 135.06, 150.94, 152.04, 157.90, 161.22; MS *m/z* (%): 334 (42), 224 (15), 121 (25), 56 (100). Found: C, 71.71; H, 6.69; N, 16.81%. $C_{20}H_{22}N_4O$ (334.41) requires C, 71.83; H, 6.63; N, 16.75%.

4-(4-Hydroxy-3-methoxybenzylideneamino)-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (**3g**): M.p. 217–218 °C; IR (KBr): 33229, 2935, 1646, 1591, 1511, 1456, 1429, 1283, 1153, 1030, 761, 701; ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 6.10 (s, 1H exchangeable by D_2O, OH), 6.90 (d, 1H, Ar–H), 7.20–7.60 (m, 7H, Ar–H), 9.65 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): δ 10.28, 35.90, 55.98, 108.70, 114.39, 122.94, 123.40, 124.34 (2C), 126.86, 129.13 (2C), 130.17, 134.77, 146.92, 148.40, 151.21, 157.55, 160.89; MS *m/z* (%): 337 (35), 228 (18), 189 (20), 121 (52), 56 (100). Found: C, 67.51; H, 5.76; N, 12.54%. $C_{19}H_{19}N_3O_3$ (337.37) requires C, 67.64; H, 5.68; N, 12.46%.

4-(2-Hydroxy-4,6-dimethoxybenzylideneamino)-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (**3h**): M.p. 189–190 °C; IR (KBr): 3189, 2935, 1650, 1594, 1490, 1457, 1405, 1344, 1219, 1156, 1112, 1044, 837, 764; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 3.80 (s, 6H, $2OCH_3$), 5.90 (s, 1H, Ar–H), 6.10 (s, 1H, Ar–H), 7.10–7.50 (m, 5H, Ar–H), 10.00 (s, 1H, N=CH), 14.55 (s, 1H exchangeable by D_2O, OH); ^{13}C NMR ($CDCl_3$): δ 10.22, 35.90, 55.35, 55.50, 89.85, 93.37, 103.83, 116.87, 124.24 (2C), 126.87, 129.11 (2C), 134.59, 148.73, 156.63, 160.44, 161.02, 164.28, 164.62; MS *m/z* (%): 367 (22), 275 (38), 121 (55), 56 (100). Found: C, 65.55; H, 5.83; N, 11.54%. $C_{20}H_{21}N_3O_4$ (367.40) requires C, 65.38; H, 5.76; N, 11.44%.

General procedure for the preparation of dimethylpyrazolo[3,4-b]-pyridinyl azomethines **5**: 3-Aminopyrazolopyridine **4** (0.324 g, 2.00 mmol) and the solid aldehyde **2** (2.00 mmol) were ball-milled at 60 °C for 30 min. The solid powders were dried at 80 °C in a vacumm to give a quantitative yield of pure **5**.

N-(2-Nitrobenzylidene)-4,6-dimethyl-1H-pyrazolo[3,4-b]pyridin-3-amine (**5a**): M.p. 246–247 °C; IR (KBr): 3161, 3096, 2923, 1603, 1568, 1522, 1441, 1372, 1345, 1304, 1199, 1163, 1032, 975, 857, 830, 790, 742, 701; ^{1}H NMR (CF_3COOD): δ 2.90 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 7.30 (s, 1H, pyridine-H), 7.70–8.20 (m, 4H, Ar–H), 10.10 (s, 1H, N=CH); ^{13}C NMR (CF_3COOD): δ 19.55, 20.13, 107.56, 120.12, 126.27, 131.14, 131.82, 137.18, 138.44, 142.30, 148.15, 150.78, 158.73, 161.83, 194.23; MS *m/z* (%): 295 (20), 249 (18), 162 (32), 133 (15), 40 (100). Found: C, 61.17; H, 4.37; N, 23.80%. $C_{15}H_{13}N_5O_2$ (295.30) requires C, 61.01; H, 4.44; N, 23.72%.

N-(3-Nitrobenzylidene)-4,6-dimethyl-1H-pyrazolo[3,4-b]pyridin-3-amine (**5b**): M.p. 231–232 °C; IR (KBr): 3143, 3093, 2919, 1608, 1531, 1440, 1376, 1356, 1298, 1268, 1205, 1153, 1083, 837, 735, 677; ^{1}H NMR (CF_3COOD): δ 2.90 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 7.30 (s, 1H, pyridine-H), 7.80 (s, 1H, Ar–H), 8.30–8.80 (m, 3H, Ar–H), 10.05 (s, 1H, N=CH); ^{13}C NMR (CF_3COOD): δ 19.31, 19.65, 107.49, 120.14, 125.10, 130.11, 130.99, 136.65, 136.76, 142.52, 147.93, 148.78, 159.59, 162.49, 195.50; MS *m/z* (%): 295 (100), 249 (42), 173 (48), 147 (45), 119 (28). Found: C, 60.89; H, 4.36; N, 23.63%. $C_{15}H_{13}N_5O_2$ (295.30) requires C, 61.01; H, 4.44; N, 23.72%.

N-(4-Nitrobenzylidene)-4,6-dimethyl-1H-pyrazolo[3,4-b]pyridin-3-amine (**5c**): M.p. >280 °C; IR (KBr): 3089, 2920, 1597, 1381, 1338, 1302, 1288, 1198, 1158, 1105, 851, 830, 776, 748, 694; ^{1}H NMR (CF_3COOD): δ 2.90 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 7.30 (s, 1H, pyridine-H), 8.25 (d, 2H, Ar–H), 8.50 (d, 2H, Ar–H), 10.15 (s, 1H, N=CH); ^{13}C NMR (CF_3COOD): δ 19.88, 20.30, 107.70, 120.19, 124.87 (2C), 131.28, 131.99 (2C), 140.00, 142.86, 148.06, 152.17, 159.44, 196.20; MS *m/z* (%): 295 (100), 249 (50), 162 (30), 147 (40), 119 (25). Found: C, 61.13; H, 4.49; N, 23.68%. $C_{15}H_{13}N_5O_2$ (295.30) requires C, 61.01; H, 4.44; N, 23.72%.

N-(4-Chlorobenzylidene)-4,6-dimethyl-1H-pyrazolo[3,4-b] pyridin-3-amine **(5d)**: M.p. >280 °C; IR (KBr): 3090, 3041, 2921, 1609, 1594, 1504, 1491, 1439, 1407, 1296, 1198, 1155, 1087, 1014, 975, 835, 822, 781; ^{1}H NMR (CF_3COOD): δ 2.90 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 7.30 (s, 1H, pyridine-H), 7.60 (d, 2H, Ar–H), 7.95 (d, 2H, Ar–H), 9.90 (s, 1H, N=CH); ^{13}C NMR (CF_3COOD): δ 21.46, 21.76, 108.13, 122.24, 131.99 (2C), 132.34, 134.24 (2C), 135.62, 144.89, 146.36, 150.42, 161.65, 199.10; MS *m/z* (%): 286 (100), 284 (35), 249 (18), 173 (10), 147 (52), 119 (18), 89 (20), 78 (15). Found: C, 63.16; H, 4.69; N, 19.59%. $C_{15}H_{13}ClN_4$ (284.74) requires C, 63.27; H, 4.60; N, 19.68%.

N-(4-Hydroxybenzylidene)-4,6-dimethyl-1H-pyrazolo[3,4-b] pyridin-3-amine **(5e)**: M.p. >280 °C; IR (KBr): 3146, 3083, 3004, 2942, 1592, 1516, 1442, 1376, 1281, 1196, 1159, 1089, 834; ^{1}H NMR (CF_3COOD): δ 2.80 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 7.00 (d, 2H, Ar–H), 7.30 (s, 1H, pyridine-H), 7.60 (d, 2H, Ar–H), 9.70 (s, 1H, N=CH); ^{13}C NMR (CF_3COOD): δ 21.54, 21.71, 108.87, 121.59 (2C), 122.39, 124.16, 136.73 (2C), 141.86, 143.46, 158.65, 161.89, 171.19, 198.70; MS *m/z* (%): 266 (100), 249 (10), 147 (30), 133 (10). Found: C, 67.82; H, 5.41; N, 21.11%. $C_{15}H_{14}N_4O$ (266.30) requires C, 67.65; H, 5.30; N, 21.04%.

N-(4-Dimethylaminobenzylidene)-4,6-dimethyl-1H-pyrazolo[3,4-b]pyridin-3-amine **(5f)**: M.p. 263–264 °C; IR (KBr): 3159, 3101, 2923, 1616, 1582, 1548, 1436, 1372, 1294, 1176, 1139, 1123, 827, 806; ^{1}H NMR (CF_3COOD): δ 2.80 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.40 (s, 6H, $2CH_3$), 7.25 (s, 1H, pyridine-H), 7.80 (d, 2H, Ar–H), 8.20 (d, 2H, Ar–H), 9.90 (s, 1H, N=CH); ^{13}C NMR (CF_3COOD): δ 21.69, 22.04, 49.79 (2C), 109.87, 119.79, 122.56, 123.85 (2C), 135.73 (2C), 140.03, 144.90, 149.56, 150.33, 162.00, 197.92; MS *m/z* (%): 293 (100), 278 (18), 249 (15), 147 (52). Found: C, 69.48; H, 6.44; N, 23.93%. $C_{17}H_{19}N_5$ (293.37) requires C, 69.60; H, 6.53; N, 23.87%.

N-(4-Hydroxy-3-methoxybenzylidene)-4,6-dimethyl-1H-pyrazolo [3,4-b]pyridin-3-amine **(5g)**: M.p. 214–215 °C; IR (KBr): 3175, 3019, 2938, 1592, 1511, 1429, 1376, 1288, 1266, 1203, 1147, 1083, 1033, 981, 866, 831, 784, 726; ^{1}H NMR (CF_3COOD): δ 3.00 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 7.20 (d, 1H, Ar–H), 7.40 (s, 1H, pyridine-H), 7.70 (s, 1H, Ar–H), 7.90 (d, 1H, Ar–H), 9.75 (s, 1H, N=CH); ^{13}C NMR (CF_3COOD): δ 19.75, 20.10, 56.13, 107.92, 111.15, 115.62, 120.58, 122.41, 130.75, 148.57, 153.80, 156.89, 158.24, 162.64, 169.57, 196.92; MS *m/z* (%): 296 (100), 280 (12), 147 (20), 119 (15). Found: C, 64.92; H, 5.50; N, 18.83%. $C_{16}H_{16}N_4O_2$ (296.32) requires C, 64.85; H, 5.44; N, 18.91%.

Synthesis of 2-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-ylimino)-2H-indene-1,3-dione **(7)**: A mixture of 4-aminoantipyrine **1** (0.406 g, 2.00 mmol) and the ninhydrin **6** (0.356 g, 2.00 mmol) was ball-milled at room temperature for 1 h. The solid powder was dried at 80 °C in a vacuum to give pure **7** with 100% yield and did not require purifying workup.

M.p. 205–206 °C; IR (KBr): 3049, 2931, 1692, 1593, 1475, 1412, 1385, 1326, 1214, 1159, 1119, 1053, 1018, 991, 775, 751, 697; ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 2.55 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 7.30–8.00 (m, 7H, Ar–H); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 9.31, 33.51, 118.62, 121.45 (2C), 122.13, 124.74 (2C), 126.64 (2C), 127.68 (2C), 132.35, 133.16, 133.88 (2C), 150.02, 153.31, 166.55, 182.23, 182.74; MS *m/z* (%): 345 (30), 327 (100), 298 (20), 132 (15), 104 (40), 77 (25), 56 (48). Found: C, 69.43; H, 4.47; N, 12.27%. $C_{20}H_{15}N_3O_3$ (345.35) requires C, 69.56; H, 4.38; N, 12.17%.

Synthesis of 2-cyano-N'-(1,3-dioxo-1H-inden-2(3H)-ylidene) acetohydrazide **(8)**: A mixture of ninhydrin **6** (0.356 g, 2.00 mmol) and cyanoacetohydrazide (0.198 g, 2.00 mmol) was ball-milled at room temperature for 1 h. The solid powder was dried at 80 °C in a vacumm to give pure **8** with 100% yield and did not require purifying workup.

M.p. 162–163 °C; IR (KBr): 3321, 3228, 3117, 2961, 2921, 2257, 1758, 1723, 1667, 1600, 1567, 1494, 1398, 1297, 1270, 1181, 1117, 983, 942, 823, 739, 687, 612, 546; ^{1}H NMR ($CDCl_3$/CF_3COOH): δ 4.15 (s, 2H, CH_2), 8.00–8.30 (m, 4H, Ar–H), 12.70 (s, 1H, NH); ^{13}C NMR ($CDCl_3$/CF_3COOH): δ 23.98, 124.88 (2C), 126.31, 136.22, 138.06 (2C), 139.99, 141.60, 166.92, 185.78, 186.52; MS *m/z* (%): 241 (20), 223 (52), 173 (100), 145 (95), 104 (65), 76 (36). Found: C, 59.84; H, 3.02; N, 17.50%. $C_{12}H_7N_3O_3$ (241.20) requires C, 59.75; H, 2.93; N, 17.42%.

3,9-Dioxo-3,9-Dihydro-2H-indeno[2,1-c]pyridazine-4-carbonitrile **(9)**: A solution of **8** (0.481, 2.00 mmol) was refluxed in ethanol containing drops of triethylamine for 2 h. The precipitate, which separated on cooling, was filtered, dried and recrystallised from ethanol to give yellowish brown crystals of **9** in 77% yield.

M.p. >280 °C; IR (KBr): 3492, 3140, 3094, 3023, 2842, 2249, 1728, 1687, 1622, 1590, 1577, 1368, 1249, 1179, 1152, 1109, 1089, 981, 916, 866, 767, 722, 682; ^{1}H NMR ($CDCl_3$/CF_3COOD): δ 7.90–8.10 (m, 3H, Ar–H), 8.50 (d, 1H, Ar–H); ^{1}H NMR (DMSO-d_6): δ 7.75–8.00 (m, 3H, Ar–H), 8.20 (d, 1H, Ar–H), 14.00 (s, 1H, NH); ^{13}C NMR ($CDCl_3$/CF_3COOD): δ 102.67, 110.98, 126.38, 126.82, 135.91, 136.28, 137.28, 138.06, 143.26, 148.47, 159.62, 184.48; ^{13}C NMR (DMSO-d_6): δ 100.05, 110.99, 123.01, 123.40, 132.90, 134.14, 134.85, 135.60, 139.29, 145.05, 155.62, 182.08; MS *m/z* (%): 223 (100), 195 (60), 167 (40), 139 (44). Found: C, 64.51; H, 2.22; N, 18.78%. $C_{12}H_5N_3O_2$ (223.19) requires C, 64.58; H, 2.26; N, 18.83%.

Received 1 December 2004; accepted 19 January 2005
Paper 04/2907

References

1 F. Toda and M. Ochi, *Enantiomer*, 1996, **1**, 85.
2 F. Toda and M. Imai, *J. Chem. Soc., Perkin Trans I*, 1994, 2673; M. J. Brown, *Heterocycles*, 1989, **29**, 2225; T. Wagner-Jauregg, *Synthesis*, 1976, 349; A. Robert, *Tetrahedron*, 1973, **29**, 463.
3 L. Strekowski, M.I. Cegla, D.B. Harden, S.L. Mokrocz and M.S. Mokrocz, *Tetrahedron Lett*., 1988, **29**, 4265.
4 G. Kaupp, U. Pogodda and J. Schmeyers, *Chem. Ber*., 1994, **127**, 2249.
5 J. Schmeyers, F. Toda, J. Boy and G. Kaupp, *J. Chem. Soc. Perkin Trans. 2*, 1998, 989.
6 G. Kaupp, M.R. Naimi-Jamal and J. Schmeyers, *Chem. Eur. J.*, 2002, **8**, 594.
7 G. Kaupp and M.R. Naimi-Jamal, *Eur. J. Org. Chem.*, 2002, 1368.
8 G. Kaupp, M.A. Metwally, F.A. Amer and E. Abdel-Latif; *Eur. J. Org. Chem*., 2003, 1545-1551.
9 G. Kaupp, M.R. Naimi-Jamal and J. Schmeyers, *Tetrahedron*, 2002, **59**, 3753.
10 H.A. Al-khamees, S.M. Bayomi, H.A. Khandil and K.E.H. El-Tahir, *Eur. J. Med. Chem. Chim. Ther*., 1990, **25**, 103.
11 F. Sparatore, G. Pirisino, M.C. Alamanni P. Manca-Dimich and M. Satta *Boll. Chem. Farm*., 1978, **117**, 638.