SHORT PAPER

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A novel and facile synthesis of pyrazolo [3,4-*b*]pyridines†

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Pyrazolo[3,4-*b*]pyridines have been obtained by the condensation of 5-amino-4-cyanopyrazole, readily available by the reaction of dithioacetals with substituted hydrazines, with β-ketoesters or β-diketone in the presence of tin(IV) chloride at reflux temperature in dry toluene.

Keywords: fused pyrazoles, fused pyridines, tin(IV) chloride

In recent years various pharmacological activities have been reported for polyfunctional substituted pyrazolo[3,4-*b*]pyridine derivatives as good vasodilators, hypotensive, hypoglycemic, anti-inflammatory, analgesic and antipyretic agents.[1] And their potential pharmacological activities have generated much interest in improving the methods for their synthesis in good yields.[2]

It has been reported that the metal ions may promote formation of a carbon–carbon bond between the cyano group of nitriles and the intercarbonyl methylene group of β-dicarbonyl compounds.[3] This reaction has been explored to obtain pyridines and quinolines.[4] Here, we explore further the synthetic scope and synthetic utility of this reaction and report a novel approach to the synthesis of pyrazolo[3,4-*b*]pyridines that involves annulation of a pyridine ring onto a preformed pyrazole ring.

The condensation of 5-amino-3-methylthio-1-phenyl-1*H*-pyrazole-4-carbonitrile (**2**), which can readily be prepared by the reaction of the dithioacetal **1** with phenylhydrazine,[5] with β-ketoesters or β-diketones was carried out in the presence of tin(IV) chloride at the temperature of refluxing toluene for 3–6 h (Scheme 1). The reaction mixture was then treated with a saturated aqueous solution of Na_2CO_3, and the resulting suspension was extracted with ethyl acetate and the extract concentrated to dryness. The residue was recrystallised to give 6-alkyl-4-amino-3-methylthio-1-phenyl-5-(substituted carbonyl)pyrazolo[3,4-*b*]pyridines **3** in yields between 46 and 64%.

The method was extended the synthesis of a pyrazolo[3,4-*b*]pyridinone. The reaction of **2** with diethyl malonate in refluxing temperature of dry toluene with the presence of tin(IV) chloride gave ethyl 4-amino-3-methylthio-6-oxo-1-phenyl-6*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (**4**), but in low yield (20%).

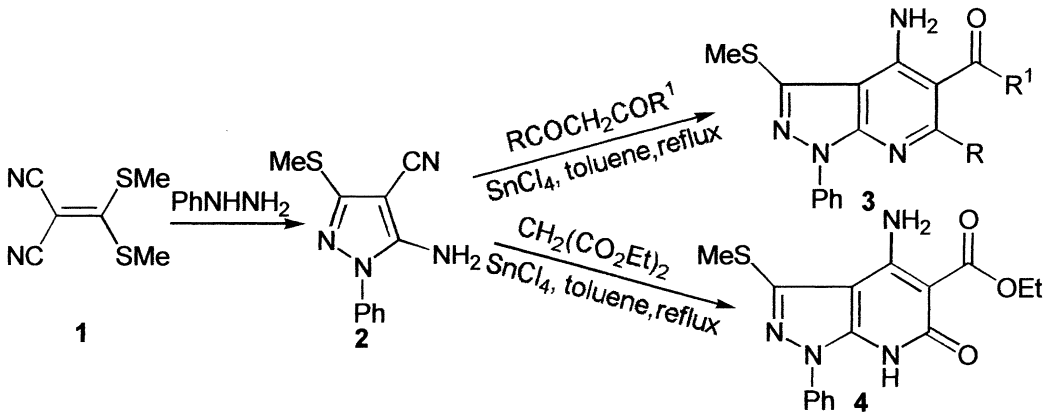
Since different substituted 5-amino-4-cyanopyrazoles can easily be prepared by the reaction of dithioacetals or other N,S-acetals with substituted hydrazines[6], this method for the synthesis of pyrazolo[3,4-*b*]pyridines enjoys a number of advantages, in that it is carried out under comparatively mild conditions, the starting materials are easily available, and different substituted pyrazolo[3,4-*b*]pyridines are readily synthesised.

Experimental

Proton NMR spectra were obtained at 200 MHz using a Bruker AC-P 200 spectrometer. Infrared spectra were recorded on a Shimadu-435 spectrometer. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental analyser. Melting points were taken on a Yanaco MP-500 apparatus.

General procedure for the preparation of 4-amino-6-alkyl-3-methylthio-1-phenyl-5-(substituted carbonyl)-1H-pyrazolo[3,4-b]pyridines (**3**): 5-Amino-3-methylthio-1-phenyl-1*H*-pyrazole-4-carbonitrile (**2**) (0.92 g, 4 mmol) and $SnCl_4$ (0.92 ml, 8 mmol) were added to a stirred solution of a β-ketoester (4.3 mmol) in dry toluene (15 ml), and then the reaction mixture was heated under reflux for 5 hours. After cooling to room temperature, saturated aqueous Na_2CO_3 (50 ml) was added to the reaction mixture. The suspension was extracted with ethyl acetate (3 × 25 ml) and the combined extracts were dried ($MgSO_4$). After removal of solvent, the residue was recrystallized from ethanol.

Methyl 4-amino-6-methyl-3-methylthio-1-phenyl-1H-pyrazolo [3,4-b]pyridine-5-carboxylate (**3a**): yield 53%, white needles, m.p.



Scheme 1

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

135.5–136.5 °C; ^{1}H NMR: 2.67 (s, 3H, SCH_3), 2.75 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 7.24–8.23 (m, 5H, C_6H_5), 7.3 (br, 2H, NH_2); MS: *m*/*z* = 328 (M^+, 100), 295 (22), 268 (23), 77 (26); Anal. Calcd. for $C_{16}H_{16}N_4O_2S$: C, 58.52; H, 4.91; N, 17.06. Found: C, 58.56; H, 4.94; N, 17.07.

Ethyl 4-amino-6-methyl-3-methylthio-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (**3b**): yield 64%, white crystals, m.p. 118–119 °C; ^{1}H NMR: 1.40 (t, 3H, CH_3), 2.67 (s, 3H, SCH_3), 2.80 (s, 3H, CH_3), 4.37 (q, 2H, OCH_2), 7.24–8.20 (m, 5H, C_6H_5), 7.3 (br, 2H, NH_2); Anal. Calcd. For $C_{17}H_{18}N_4O_2S$: C, 59.63; H, 5.30; N, 16.36. Found: C, 59.68; H, 5.25; N, 16.46.

5-Acetyl-4-amino-6-methyl-3-methylthio-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**3c**): yield: 46%, yellow crystals, m.p. 101–102.5 ºC; ^{1}H NMR: 2.60 (s, 3H, $COCH_3$), 2.68 (s, 3H, SCH_3), 2.77 (s, 3H, CH_3), 7.23–8.21 (m, 5H, C_6H_5), 5.4 (br, 2H, NH_2); Anal. Calcd. For $C_{16}H_{16}N_4OS$: C, 61.52; H, 5.16; N, 17.93. Found: C, 61.66; H, 5.13; N, 17.64.

Methyl 4-amino-6-ethyl-3-methylthio-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (**3d**): yield: 54%, white crystals, m.p. 121–122 ºC; ^{1}H NMR: 1.31 (t, 3H, CH_3), 2.69 (s, 3H, SCH_3), 3.18 (q, 2H, CH_2), 3.91 (s, 3H, OCH_3), 7.23–8.21 (m, 5H, C_6H_5), 7.3 (br, 2H, NH_2); Anal. Calcd. For $C_{17}H_{18}N_4O_2S$: C, 59.63; H, 5.30; N, 16.36. Found: C, 59.73; H, 5.38; N, 16.37.

Procedure for the preparation of ethyl 4-amino-1,7-dihydro-3-methylthio-6-oxo-1-phenyl-6H-pyrazolo[3,4-b]pyridine-5-carboxylate (**4**): 5-Amino-3-methylthio-1-phenyl-1*H*-pyrazole-4-carbonitrile (**2**) (0.58 g, 2.5 mmol) and $SnCl_4$ (0.58 ml, 5 mmol) were added to a stirred solution of diethyl malonate (0.40g, 2.5 mmol) in dry toluene (15 ml). Then the reaction mixture was refluxed for 6 hours. After cooling to room temperature, a saturated aqueous solution of Na_2CO_3 (35 ml) was added to the reaction mixture. The suspension was extracted with ethyl acetate (3 × 15 ml) and the combined extracts were dried ($MgSO_4$). After removal of solvent, the residue was recrystallised from ethanol, providing the desired ester **4**: yield: 20%, white crystals, m.p. 190–192°C; ^{1}H NMR ($CDCl_3$, ppm): 1.43 (t, 3H, CH_3), 2.67 (s, 3H, SCH_3), 4.44 (q, 2H, OCH_2), 7.24–8.12 (m, 5H, C_6H_5), 7.0 (br, 2H, NH_2), 11.0 (br, 1H, NH); MS: *m*/*z* = 344 (M^+, 87), 298 (52), 283 (100), 77 (51); Anal. Calcd. for $C_{16}H_{16}N_4O_3S$: C, 55.80; H, 4.68; N, 16.27. Found: C, 56.05, H, 4.70; N, 16.30.

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