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SYNTHESIS OF 1*H*-PYRAZOLO [4', 3':5, 6] PYRIMIDO [2, 1-*a*]-ISOINDOL-4(10*H*)-ONES. DERIVATIVES OF A NEW RING SYSTEM

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Abstract –Several derivatives of the new pyrazolo[4',3':5,6]pyrimido[2,1-*a*]-isoindolone ring system (**4**) have been prepared through heterocyclization of 2-chloromethylbenzoyl chloride (**1**) with appropriately substituted 5-amino-1*H*-pyrozole-4-carbonitriles **(2)**. The reaction intermediate inden-2-yl-1-phenyl-pyrazole-4-carbonitrile **(3)**, on subjection to acid or base, underwent hydrolysis and cyclocondensation simultaneously to afford the tetracyclic compound (**4)**.

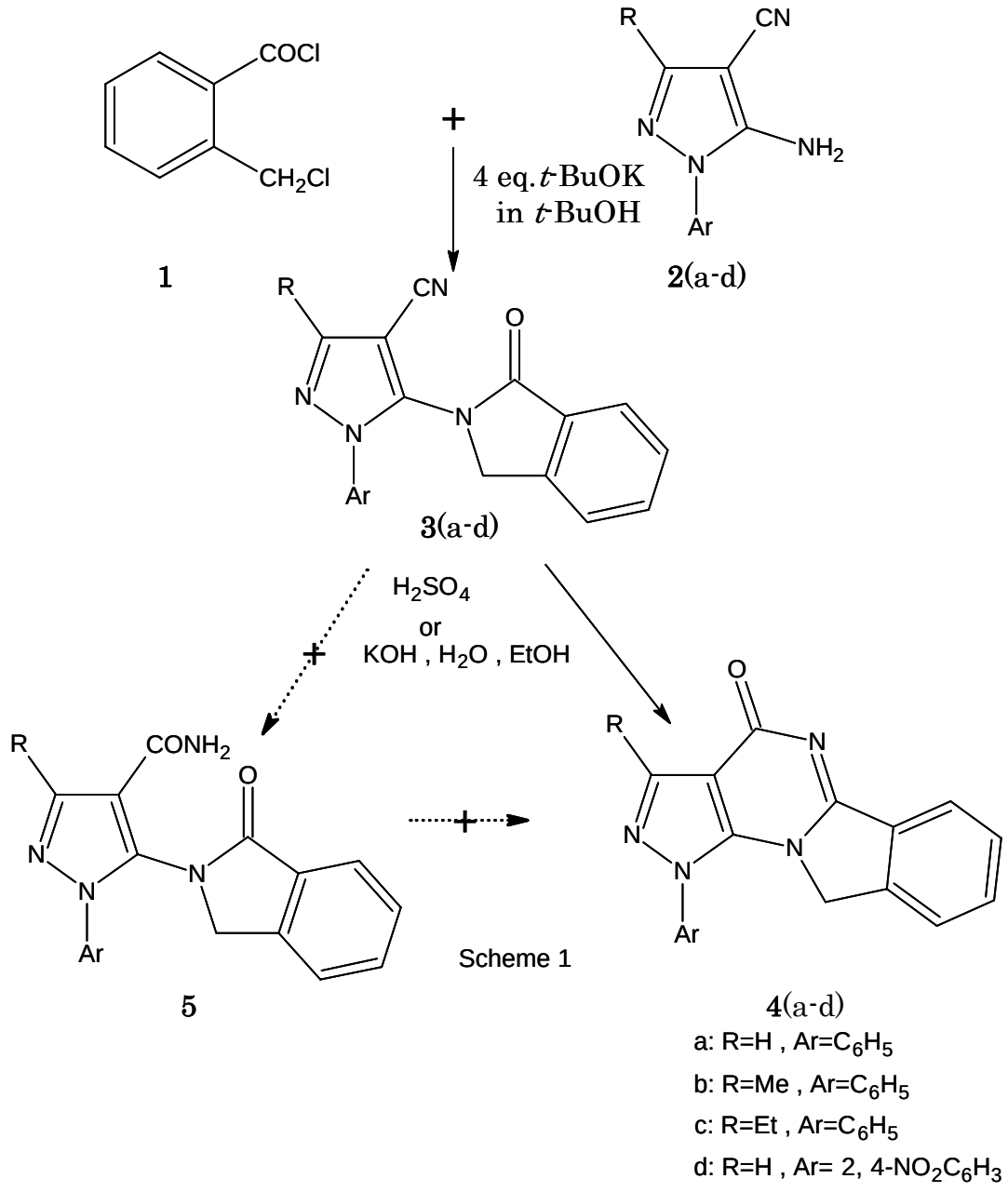
INTRODUCTION

The preparation of novel polycyclic *N*-heterocyclic compounds and the exploration of their synthetic pathways have recently received much attention in our group.[1] In connection with these studies, in a previous paper,[2] we reported a new synthetic route to new tetracyclic isoindolo[2,1-*a*]quinazoline derivatives through heterocyclization of 2-aminobenzonitrile with 2-chloromethylbenzoyl chloride and we gave an account of the synthetic pathways to these compounds. As an extension of this work we now report our investigations for the synthesis of 1*H*-pyrazolo[4',3':5,6]pyrimido[2,1-*a*]isoindol-4(10*H*)ones, members of a new heterocyclic ring system.

RESULTS AND DISCUSSION

The synthetic utility of 2-chloromethylbenzoyl chloride (**1)**, as a reactive bifunctional reagent in producing polycyclic *N*-heterocycles is well known.[3-9] In our hands, we reacted this reagent with 5-amino-1*H*-pyrazole-4-carbonitriles (**2**a-d) in the presence of four equivalents of potassium *t*-butoxide in

t-butanol at reflux temperature to afford the corresponding 5-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-1*H*-pyrazole-4-carbonitriles (**3**a-d) . These products were respectively cyclised to the corresponding 1*H*-pyrazolo[4,3:5,6]pyrimido[2,1-*a*]isoindol-4(10*H*)-ones (**4**) either on subjection to acid or base at elevated temperatures. A tentative mechanism to explain the formation of this heterocyclic ring system (Scheme 1) primarily involves the formation of the intermediate (**3**) through cyclocondensation of 2-chloromethylbenzoyl chloride with the amino moiety of the pyrazole ring (**2**) followed by hydrolysis of the cyano group into amide with subsequent cyclocondesation to the novel tetracyclic compound (**4**). It is worth noting that in this multi-step synthesis the key intermediate (**5**) was not isolated. It seems likely that hydrolysis of the cyano group into amide and ring closure step occurs simultaneously. All our effort to isolate this intermediate was not successful.



Scheme 1

Table 1 Physical, Spectral, and Microanalytical Data of 5-(1-Oxo-1,3-dihydro-2*H*-isoindol-2-yl)-1*H*-pyrazole-4-carbonitriles **(3a-d)**

Entry	Yield (%)	mp (^{o}C)	Spectral data
3a	69	156-158	^{1}H NMR: δ ($CDCl_3$), 4.66 (s, 2H, CH_2), 7.43-8.04 (m,10H, Aromatic rings);IR (KBr, disc), v, CN, 2212 cm^{-1}; MS m/z, M^+ 300; Anal. Calcd for $C_{18}H_{12}N_4O$: C, 71.99; H, 4.03; N, 18.66. Found: C, 72.05; H, 4.01 N, 18.62.
3b	83	138-140	^{1}H NMR: δ ($CDCl_3$), 2.48 (s, 3H, Me), 4.62 (s, 2H, CH_2), 7.41-7.86 (m, 9H, Aromatic rings); IR (KBr, disc), v , CN, 2210 cm^{-1}, MS m/z, M^+ 314; Anal. Calcd for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.54; H, 4.44 N, 17.85.
3c	85	60-62	^{1}H NMR: δ ($CDCl_3$), 2.47 (t, 3H, j=7.8 Hz, Me), 3.97 (q, 2H, j=7.8 Hz, CH_2), 4.57 (s, 2H, CH_2), 7.42-7.86 (m, 9H, Aromatic rings); IR (KBr, disc), v , CN, 2148 cm^{-1}; MS m/z, M^+ 328; Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.12; H, 4.96 N, 17.04.
3d	65	272-274	^{1}H NMR: δ ($CDCl_3$), 5.25 (s, 2H, CH_2),7.36-8.82 (m, 8H, Aromatic rings); IR (KBr, disc), v , CN, 2217 cm^{-1} ; MS m/z, M^+ 390; Anal. Calcd for $C_{18}H_{10}N_6O_5$: C, 55.39; H, 2.58; N, 21.53. Found: C, 55.35; H, 2.56 N, 21.56.

Table 2 Physical, Spectral, and Microanalytical Data of 1*H*-Pyrazolo[4',3':5,6]pyrimido[2,1-*a*]isoindol-4(10*H*)-ones **(4a-d)**

Entry	Yield (%)	mp (^{o}C)	Spectral data
4a	81	182-184	^{1}H NMR: δ (DMSO-d_6), 4.16 (s, 2H, CH_2), 6.90-8.41 (m, 10H, Aromatic rings); MS m/z, M^+ 300; Anal. Calcd for $C_{18}H_{12}N_4O$: C, 71.99; H, 4.03; N, 18.66. Found: C, 71.96; H, 3.99 N, 18.67.
4b	74	258-260	^{1}H NMR: δ (DMSO-d_6), 1.29 (s, 3H, CH_3), 4.86 (s, 2H, CH_2), 7.70-8.07 (m, 9H, Aromatic rings); MS m/z, M^+ 314; Anal. Calcd for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.57; H, 4.53 N, 17.76.
4c	79	270-272	^{1}H NMR: δ (DMSO-d_6), 1.29 (t, 3H, j=8.0 Hz, CH_3), 2.92 (q, 2H, j=8.0 Hz, CH_2), 4.79 (s, 2H, CH_2), 7.65-8.03 (m, 9H, Aromatic rings); MS m/z, M^+ 328; Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.10; H, 4.93; N, 17.05.
4d	61	350(decomp)	^{1}H NMR: δ (DMSO-d_6), 4.56 (s, 2H, CH_2), 7.27-9.04 (m, 8H, Aromatic rings); MS m/z, M^+ 390; Anal. Calcd for $C_{18}H_{10}N_6O_5$: C, 55.39; H, 2.58; N, 21.53. Found: C, 55.43; H, 2.54 N, 21.51.

The structure of the novel compounds (**4**a-d) was deduced from their spectral data. The MS of these compounds displayed molecular ion peaks at the appropriate m/z values.

The ^{1}H NMR spectrum of **4**a exhibited one single sharp line readily recognizable as arising from CH_2 of the isoindole ring protons (δ = 4.16 ppm). The aromatic hydrogens give rise to charactristic signals in the aromatic region of the spectrum (δ = 6.90-8.41 ppm). The IR spectrum was devoid of the CN absorption band at 2212 cm^{-1} of the precurser, which shows the inclusion of nitrile moiety in cyclocondensation process.

In conclusion, we have developed a method for preparing in moderate to good yields of tetracyclic pyrazolo[4′,3′:5,6]pyrimido[2,1-*a*]isoindoles.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The MS were scanned on a Varian CH-7 instrument at 70 ev. Elemental analysis was performed on a Thermofinnigan Flash EA microanalyzer.

General Procedure for the Preparation of 5-(1-Oxo-1,3-dihydro-2*H*-isoindol-2-yl)-1*H*-pyrazole-4-carbonitriles (3a-d).

To a solution of the 5-amino-1*H*-pyrazole-4-carbonitriles **(2a-d)** (5 mmol) and potassium *t*-butoxide (20 mmol) in *t*-butanol (40 mL), 2-chloromethylbenzoyl chloride **(1)** (1.13 g, 6 mmol) was added. The reaction mixture was heated under reflux for 5.0 h. After the completion of the reaction, the mixture was cooled to rt and water was added. The precipitate was collected and recrystallised from *n*-hexane-toluene to give compounds **(3a-d)** in 69, 83, 85 and 65% yield, respectively (see Table 1).

General Procedure for the Preparation of 1*H*-pyrazolo[4′,3′:5,6]pyrimido[2,1-*a*]isoindol-4(10*H*)-one (4a and 4d).

5-(1-Oxo-1,3-dihydro-2*H*-isoindol-2-yl)-1*H*-pyrazole-4-carbonitriles **(3a or 3d)** (5 mmol) was dissolved in EtOH (20 mL)-H_2O (10 mL) containing KOH (0.37 g, 6 mmol). The mixture was refluxed for 12 h. The reaction mixture was cooled to rt and neutralized by 1M HCl. The crude product was collected and washed with water and chloroform respectively, then recrystallized from ethanol to give compounds **(4a**) and (**4d)** in 81 and 61% yield, respectively (see Table 2).

General Procedure for the Preparation of 1*H*-Pyrazolo[4′,3′:5,6]pyrimido[2,1-*a*]isoindol-4(10*H*)-one (4b and 4c).

5-(1-Oxo-1,3-dihydro-2*H*-isoindol-2-yl)-1*H*-pyrazole-4-carbonitriles **(3b or 3c)** (5 mmol) was dissolved in conc. H_2SO_4 (15 mL). The mixture was stirred at 180 °C for 4 h, then cooled and neutralized by potassium hydroxide. The precipitate was collected and washed with water and methanol respectively, then recrystallized from ethanol to give compounds (**4b)** and **(4c**) in 74 and 79% yield respectively (see Table 2).

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