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Study on Pyrazolo-4-Carboxaldehyde: Synthesis of Fused Pyrazole, Isoxazole, Pyrimidine and Pyridine-[2, 3-d]-Pyrazoline Derivatives

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4-Carboxaldehyde-5-chloro-3-methyl-1-phenylpyrazoline has been used to synthesize several heterocyclic compounds via condensation substitution, elimination and cycloaddition reactions.

INTRODUCTION

In spite of the literatures reported on the chemistry of pyrazole nucleus[1–5], no attention has been paid to the chemistry of 4-carboxaldehyde-5-chlorophenylpyrazoline[6] (1), although it should be an excellent starting material for synthesis of many fused heteropyrazolo derivatives. Several pyridines, pyrazolines and pyrimidines are well known to be active as herbicides[7], this paper presents a report on the synthesis of different heterocylic compounds which may have potential herbicidal activity.

RESULTS AND DISCUSSION

The aldehydic compound (1) reacted with α-cyanoacetamide, α-cyanothioacetamide and cyanoacetohydrazide afforded the condensation products (2, 3 and 4), respectively. The elemental analysis and IR spectra proved the acyclic structure for these orange/yellow products. There are strong absorptions at 1725, 2210 and 3500–3300 cm^{-1} for carbonyl, nitrile and amino groups, respectively. Refluxing each of 2, 3 or 4 in pyridine resulted in the proposed cyclic structures (5, 6 and 7) as a reddish product. The elemental analysis, IR and ^{1}H-NMR spectra confirmed the cyclic structures (5, 6 and 7). The ^{1}H-NMR spectrum for the compound (6) shows a singlet at 1.2 ppm for methyl and a singlet at 8.2 ppm for the pyridine proton[8] in position 4 and at 3.5 ppm for NH proton[9], besides the multiplets of the aromatic protons. It needs to be pointed out that the activation exerted by the nitrile group on the pyridine ring renders it available to substitution by a bromine atom, which increases its utility as starting material. In fact, on bromination the reddish compound (6) turned to a pale brownish compound (8).

The reactivity of the aldehydic group prompted to investigate the condensation reactions with hydrazine derivatives (hydrazine hydrate, phenylhydrazine) and hydroxylamine hydrochloride. Actually the basic catalyst used, the refluxing time as well as the attacking reagents play a

role in the nature of the condensation products whether it cyclized or acyclic one. The piperidine resulted in a yellow precipitate after 30 minutes using hydrazine hydrate this precipitate increases by the time. The elemental analysis ^{1}H-NMR and mass spectra m/z (234) indicated the cyclic structure (11) which is obtained as the hydrochloride salt. The filtrate on dilution with water afforded a yellow fine precipitate which was proven as acyclic structure (9). The compounds (9, 10) were obtained using triethylamine as a catalyst even under long refluxing time, whereas using the piperidine gave a very negligible yield of compound (12). Fusion of (8, 9) in pyridine for 5 hrs. afforded the compounds (11, 12). Reaction of hydroxylamine hydrochloride with compound (1) did not proceed in triethylamine. However, the use of catalytic amounts of piperidine and/or sodium hydroxide produced the same isoxazoline compound (13). Formation of the pyrimidine nucleus upon several α, β-unsaturated ketonic systems[10,11] has been described, in different media[12–14]. However hydrochloric acid failed to produce the desired pyrimidine, whereas using 3 N of alcoholic sodium hydroxide afforded the expected pyrimidines (14, 15). The structure was established through spectral data.

EXPERIMENTAL

All melting points are uncorrected. Elemental analysis, IR spectra (KBr, cm^{-1}) were recorded on Perkin Elmer Infrared 127B spectrophotometer. ^{1}H-NMR spectra were obtained on EM 360 90 MHz in $CDCl_3$ using TMS as internal standard in Microanalytical center, Cairo University. Mass spectra (MAT 311 A, 70 eV) were carried out at Dusiburg University, Germany. All the reactions were followed by TLC.

5-Chloro-3-methyl-4-(cyanoacetamido)-1-phenylpyrazoline(2–4): Equimolar amounts 0.01 mol of (1) and α-cyanoacetamide, α-cyanothioacetamide or cyanoacetohydrazide, respectively were dissolved in ethanol (40 ml), catalytic amount of triethylamine was added (1 ml), after reflux for 4–6 hrs, filtered, concentrated, dilute with cold water, the orange precipitate collected by filtration in quantitative yield, then crystallised from DMF–H_2O mixture.

Compound (2): Orange, m.pt.: 172°C, IR: 1725 (C=O), 2210 (CN), 3500–3300 cm^{-1} (NH_2). ^{1}H–NMR: 1.3 (s, 3H, CH_3), 2.8 (s, 1H, CH), 5.8 (s, 2H, NH_2), 7.3–6.8 (m, 5H, Ar). Anal. found for $C_{14}H_{11}N_4OCl$ (286.5). C 58.60; H 3.79; N 19.40. Calcd. C 58.64; H 3.48; N 19.55.

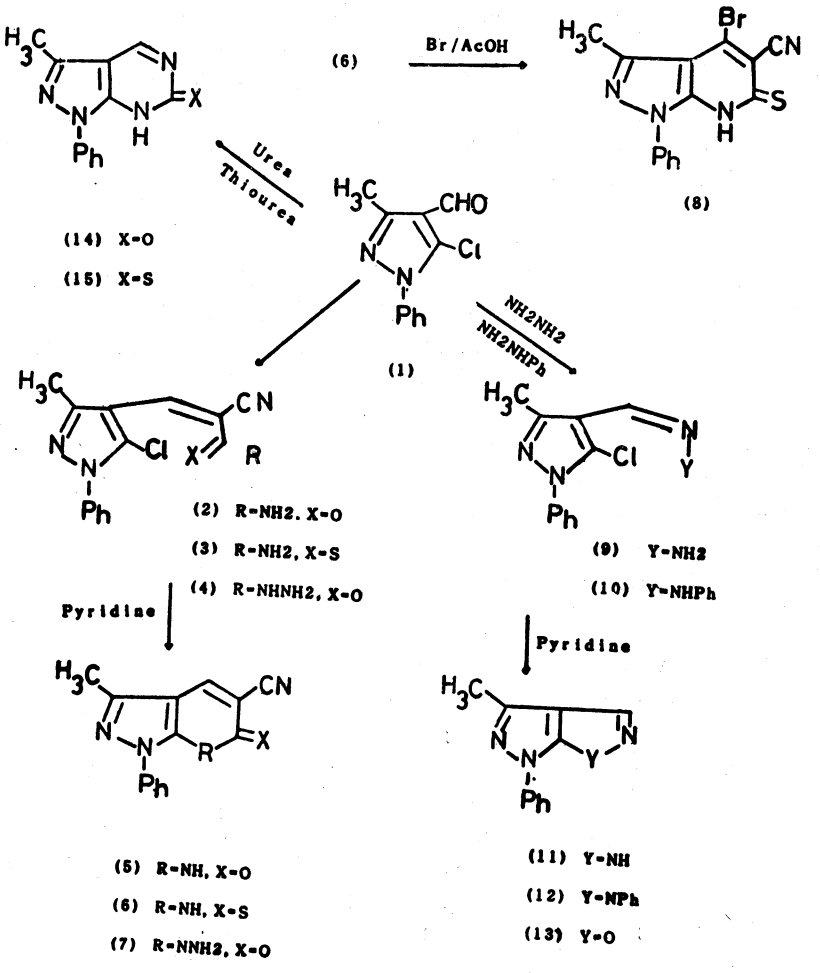
Compound (3): Orange, m.pt. 180°C, IR : 1200–1190 (C=S), 2220 (CN), 3500–3300 cm^{-1} (NH_2). Anal. found for $C_{14}H_{11}N_4SCl$ (302.5). C 55.51; H 3.58; N 18.48, Calcd. C 55.60; H 3.64; N 18.51.

Compound (4): Yellowish, m.pt.: 205°C, IR : 1720 (C=O), 2225 (CN), 3500–3300 cm^{-1} (NH, NH_2). Anal. found for $C_{14}H_{12}N_5OCl$ (301.5). C 55.65; H 3.82; N 23.17. Calcd. C 55.72; H 3.98; N 32.22.

5-Cyano-3-methyl-1-phenylpyrazolo-(2, 3-d)-pyridin-6-one (5–7) : The acyclic compounds (2–4) were fused in 15 ml of pyridine, refluxed for 2 hrs at 120–40°C, cooled, evaporated in vacuum till dryness then extracted with ethanol whereby an brownish/red precipitates crystalised on addition of few drops of water, recrystalised from dilute ethanol.

Compound (5): Brownish, m. pt. : 190°C. IR : 1710 (C=O), 2220 (CN), 3340 cm^{-1} (NH). ^1H-NMR : 1.2 (s, 3H, CH_3); 3.5 (s, 1H, NH); 8.2 (s, 1H, pyridine); 7.0–7.5 ppm (m, 5H, Ar). Anal. found for $C_{14}H_{10}N_4O$ (250) : C 67.12; H 3.95; N 22.28. Calcd. C 67.20; H 4.00; N 22.40.

Compound (6): Reddish brown, m. pt. : 195°C. IR 1200–1190 (C=S), 2221 (CN), 3500–3300 cm^{-1} (NH). Anal. found for $C_{14}H_{10}N_4S$ (266). C 63.09; H 3.62; N 20.83. Cald. C 63.16; H 3.76; N 21.05.



Compound (7): Yellowish, m.pt : 238°C. IR : 1710 (C=O), 2220 (CN),

3400–3300 cm^{-1} (NH_2). Anal. found for $C_{14}H_{11}N_5O$ (265). C 63.28; H 4.06; N 26.31. Calcd. C 63.40; H 4.15; N 26.42.

5-Cholro-3-methyl-4-(methylhydrazino)-1-phenylpyrazolines (9, 10):

To ethanolic solution of (1) (0.01 mol, 40 ml) an excess of hydrazine hydrate or phenylhydrazine (0.015 mol) was added in the presence of few drops of triethylamine, refluxed for 10–12 hrs. filtered, concentrated, cooled then filtered the yellowish fine products, recrystallised from methanol.

Compound (9): Yellowish, m. pt. : 178°C. IR : 1635 (C=C), 3500–3300 cm^{-1} (NH_2). Anal. found for $C_{11}H_{11}N_4Cl$ (234.5), C 56.17; H 4.52; N 23.16. Calcd. C 56.29; H 4.70; N 23.88.

Compound (10): Yellowish, m.pt. : 150°C. IR : 1640 (C=C), 3450–3300 cm^{-1} (NH). ^{1}H-NMR : 1.3 (s, 3H, CH_3), 2.7 (s, 1H, CH), 5.2 (s, 1H, NH), 7.3–78 (m, 10H, Ar). Anal. found for $C_{17}H_{15}N_4Cl$ (310.5). C 65.53; H 4.72; N 17.85. Calcd. C 65.70; H 4.83; N 18.04.

3-Methyl-1 phenylpyrazolo-[2, 3-d]-pyrazoline and/or isoxazoline derivatives (11–13): The hydrazino compounds (9, 10), (3 g) and 15 ml of pyridine was refluxed for 4–6 hrs. evaporated till dryness, extracted with ethanol, cooled, then filtered the products, washed with water, crystallised from methanol.

Compound (11): Pale yellowish, m.pt. : 235°C. IR : 1560 (C=N), 1620 (C=C), 3470–3300 cm^{-1} (NH). ^{1}H-NMR : 1.3 (s, 3H, CH_3), 3.6 (s, 1H, CH), 6.7–7.8 (m, 5H, Ar). Anal. found for $C_{11}H_{10}N_4$ (198). C 66.48; H 4.83; N 28.19. Calcd. C 66.67; H 5.05; N 28.28.

Compound (12): Brownish, m. pt. : 135°C. IR : 1556 (C=N), 1620 cm^{-1} (C=C). Anal. found for $C_{17}H_{14}N_4$ (274). C 74.23; H 5.04; N 20.15. Calcd. C 74.45; H 5.11; N 20.44.

Compound (13): This compound was prepared using either piperidine or KOH and was identified as: Yellowish, m. pt. ; 95°C. IR : 1540 (C=N), 1620 cm^{-1} (C=C). Anal. found for $C_{11}H_9N_4O$ (213). C 61.72; H 4.17; N 26.12. Calcd. C 61.97; H 4.23; N 26.30.

3-Methyl-1-phenylpyrazolo-[2, 3-d]-1, 4-di (H)-pyrimidine-6-one derivatives (14, 15): Alcoholic solution of compound (1), (0.01 mol) and (0.02 mol) of urea or thiourea in presence of 3 N NaOH was refluxed for 15 hrs. on water bath, filtered, cooled, a precipitate was separated off upon addition of water/HCl, collected by filtration, washed with water, crystallised from ethanol.

Compound (14): Brownish, m. pt.: 180°C. IR: 1550 (C=N), 1620 (C=C), 1720 (C=O), 3500–3300 cm^{-1} (NH). ^{1}H-NMR : 1.2 (s, 3H, CH_3), 3.4 (s, 1H, NH), 7.3–7.6 (m, 5H, Ar), 8.4 (s, 1H, H-4-pyrimidine). Anal. found for $C_{12}H_{10}N_4O$ (226). C 63.54; H 4.23; N 24.56. Calcd. C 63.72; H 4.42; N 24.79.

Compound (15): Pale yellowish brown, m.pt. : 120°C. IR : 1200–1190

(C=S), 1540 (C=N), 3500–3300 cm^{-1} (NH). Anal. found for $C_{12}H_{10}N_4S$ (242). C 59.38; H 4.04; N 23.10. Calcd. 59.50; H 4.13; N 23.14.

3-Methyl-1-phenylpyrazolo-[2, 3-d]-4-bromo-5-cyano-1H-pyridin-6-thione (8): Compound (6) was dissolved in acetic acid (3g, 20 ml) and a solution of bromine/acetic acid (2 ml/10 ml) was added dropwise at 50°C with stirring, cooled, add water then decant, the residue was washed several time with water, then extracted with methanol as a pale brownish crystals. m.pt. : 112°C. IR : 1200–1190 (C=S), 1550 (C=N), 2220 (CN), 3500–3300 cm^{-1} (NH). ^{1}H-NMR : 1.2 (s, 3H, CH_3), 3.4 (1H, NH), 7.2–7.6 (m, 5H, Ar). Anal. found for $C_{14}H_9N_4SBr$ (345). C 48.54; H 2.47; N 16.18. Calcd. C 48.70; H 2.61; N 16.23.

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