Diazotization and Coupling Reactions of Ethyl 3-amino-1H-pyrazole-4-carboxylate; Synthesis of some Pyrazoloazines

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ABSTRACT. Pyrazoloazines are extremely useful in agriculture and medicine. The main objective of this article is to synthesize some new pyrazoloazines. Ethyl 3-amino-1H-pyrazole-4-carboxylate undergoes diazotization, couples with activated methylene compounds and cyclizes to form pyrazolo[5,1-c][1,2,4]triazine derivatives. The title compound also reacts with α-substituted cinnamionitriles to produce pyrazolo[1,5-a]pyrimidine derivatives. Structures of newly synthesized compounds are established via chemical and spectral methods.

Some pyrazoloazines are found to be useful in agricultural applications as herbicides and plant growth regulators¹, and in medicinal applications as antibiotics², antileishmanics and cardiotonics³, central nervous system agents⁴, anxiolytics⁵, treatment of inflammation⁶, antidepressants and antiulceratives⁷, and its antihypertensive and antitripanosomal activities⁸. Due to these agricultural and medicinal activities, it is desirable to synthesize novel heterocyclic compounds containing the pyrazole ring fused to either pyrimidine or 1,2,4-triazine rings.

The title compound (1) was prepared according to literature⁹ and used as a starting material to synthesize the desirable azoloazines.

Compound 1 was diazotized with hydrochloric acid and sodium nitrite then coupled with either phenolic compounds or some activated methylene nitriles. Thus, when the diazotized derivative of 1 was coupled with each of 2-naphthol or 8-hydroxyquinoline, it yielded the corresponding aryazole derivatives 2a,b, respectively (Scheme I). The IR spectra of compounds 2a,b displayed absorption bands near 3300 cm⁻¹ (NH), 3280-2980 (broad OH) and 1710 (C=O). The ¹H-NMR spectrum...
Treatment of the produced diazonium salt with some activated methylene compounds, namely malononitrile, ethyl cyanoacetate and benzyllacetonitrile, yielded the corresponding azo derivatives 3a-c, respectively (Scheme 1). The IR spectra of 3a-c displayed absorption bands near 3400 cm⁻¹ (NH), 1720 and 1670 (C=O). The ¹H-NMR spectrum (DMSO-d₆) of compound 3b, as an example, showed signals at δ 1.32 ppm (t, 2H, CH₃), 1.39 (q, 2H, CH₂), 4.30 (q, 2H, CH₂), 5.60 (s, 1H, pyrazole H-5), 8.30 (s, 1H, pyrazole 1H-11), 8.74 (s, 1H, NH, D₂O exchangeable) and 9.56 (s, 1H, NH, D₂O exchangeable). The mass spectrum of 3a showed the molecular ion peak at m/z 222 (59.5%).

The mass spectrum of 3c showed the molecular ion peak at m/z 311 (86.8%).

Heating under reflux compounds 3a-c with aqueous alcoholic potassium hydroxide solution led to the formation of the cyclised products ethyl 4-amin-3-substituted-pyrazolo[5,1-c][1,2,4]triazine-8-carboxylates (4a-c), respectively (Scheme 1).

Formation of 4 from 3 most probably took place via Michael-type addition of the pyrazole NH on the cyano group. The IR spectra of compounds 4a-c revealed the absence of any absorption bands in the cyano region, as well as the appearance of the expected N1H and CO bands. It seems that 3a underwent partial hydrolysis to convert the cyano group into amide group.

The mass spectrum of 4b showed the molecular ion peak at m/z 280 (47.0%).

Furthermore, compound 1 behaved differently towards some a-substituted cyanonitriles (5a,b & 6a,b), when a solution of 1 was heated under reflux with 5 or 6 in pyridine. Thus, when compound 1 was treated with a solution of each of the co-cyanonitriles 5b in pyridine, ethyl 7-amino-5-aryl-6-cyanopyrazolo[1,5-a]pyrimidine-5-carboxylates (7a,b), rather than the isomeric compounds 8a,b, was produced.

Formation of 7 from 1 may proceed via firstly Michael addition of the amino group of 1 onto the ethylenic double bond of 5, secondly, addition of the pyrazole hydrogen atom onto the cyano group of the intermediate and finally autoxidation (Scheme 2).

Elemental analyses and IR data are in agreement with the proposed structures 7(8), experimental. The H-NMR spectrum (DMSO-d₆) of 7a(8a), as an example, showed...
signals at δ 1.31 ppm (t, 3H, CH₃), 4.27 (q, 2H, CH₂), 7.60 (m, 3H, aromatic protons), 7.86 (m, 2H, aromatic protons), 8.61 (s, 1H, CH pyrazole) and 9.17 (bs, 2H, NH, D,O exchangeable). The NH signal appeared at δ 9.17 ppm, which favours the enaminonitrile moiety in structure 7b.

It seems that the proton NMR data are valuable in preferring 7 over 8. Thus in structure 7 the amino group should be affected by the both inductive and mesomeric effects of the cyano group (a structure which is known to show the chemical shift of the amino group at low field).

Had we had structure 8 for the reaction product, the amino group should be affected by the electron withdrawal effect of the cyano group by inductive effect only. To some extent, similar work was reported by the research group, which I am a member of⁶. In this publication structures 9 and 10 similar to 7 and 8 were reported and showed that the amino group in 9 appeared at lower field than 10.

Moreover, an indirect chemical proof supporting the above structure 7 for the reaction product was performed. Acylation of compound 1 with acetic anhydride or chloroacetyl chloride gave, in each case, a monoaclylated compound 11 with two different exchangeable NH protons. Thus, the presence of two different exchangeable protons in ¹H-NMR spectra of both 11a,b indicates that the acylation took place at the amino group and this in turn indicates that the amino group is more active towards electrophiles than the pyrazole NH group. That the reaction of 1 with some electrophiles starts at the amino group is in favor of structure 7.

On the other hand, heating compound 1 under reflux in pyridine with each of the ethyl α-cyanoacetamates (6a,b) led to the formation of the corresponding ethyl 5-aryl-6-cyano-7-oxo-4H,7H-pyrazolo[1,5-a]pyrimidine-3-carboxylates (13a,b), respectively, rather than structure 1.

Structure 13 was preferred over structure 14 on the basis of IR and mass spectra. Thus, the IR spectrum of the reaction product displayed absorption bands at 2230 cm⁻¹ (CN). Had we had structure 14 for the reaction product, it would not display any absorption at this region.

The mass spectrum of compound 13b showed the molecular ion peak at m/z 342 (100%) and 344 (34.2%).

**EXPERIMENTAL**

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ¹H-NMR spectra were obtained with a Varian ¹H-Gemini 200 spectrometer with chemical shifts are expressed in δ (ppm) using TMS as the internal reference. Mass spectra were recorded on GC-MS QP 1000 EX mass spectrometer operating at 70 eV. The elemental analyses were performed by the Microanalytical Data Center, Cairo University, Egypt.

**Ethyl 3-amino-1H-pyrazole-4-carboxylate 1**

Was prepared as previously described⁷.

**Ethyl 3-arylamino-1H-pyrazole-4-carboxylate 2a,b**
A solution of 1 (0.775 g, 0.005 mol) in concentrated hydrochloric acid (5 ml) was cooled at 0°C and a cooled solution of sodium nitrite (0.8 g, 0.008 mol) in water (4 ml) was gradually added (15 min). The diazotized solution was coupled with 0.005 mol of both 2-naphthol (0.720 g) and 8-hydroxyquinoline (0.725 g) in ethanol containing two pellets of potassium hydroxide, kept at 0-5°C for 2 hours and diluted with water whereupon precipitation took place. The solid that precipitated in each case were collected and crystallized from dilute DMF.

**Ethyl 3-[2-hydroxynaphth-1-yloxyl]-1H-pyrazole-4-carboxylate 2a:** Yield, 1.15 g (74.2%); m.p. 215°C; IR: 3417 cm⁻¹ (N-H), 3170-2990 (broad O-H) and 1710 (CO). ¹H-NMR (DMSO-d₆): δ 1.32 ppm (t, 3H, C₆H₄), 4.20 (q, 2H, C₆H₄), 6.71-8.60 (m, 7H, 6 aromatic protons, pyrazole 1H), 13.47 (s, 1H, N=N exchangeable) and 14.15 (s, 1H, OH, D,O exchangeable).

**Analysis:** C₆H₄N₂O₂ (310.309)

Required: C, 61.93; H, 4.54; N, 18.95%.
Found: C, 62.0; H, 4.5; N, 18.1%.

**Ethyl 3-[8-hydroxyquinolin-5-ylaxol]-1H-pyrazole-4-carboxylate 2b:** Yield 1.20 g (77.4%); m.p. 206°C; IR: 3300 cm⁻¹ (N-H), 3200-2980 (broad O-H) and 1708 (CO). ¹H-NMR (DMSO-d₆): δ 1.35 ppm (t, 3H, C₆H₄), 4.28 (q, 2H, C₆H₄), 7.34-8.91 (m, 6H, 5 aromatic protons, pyrazole 1H), 12.55 (s, 1H, N=N exchangeable) and 13.95 (s, 1H, OH, D,O exchangeable).

**Analysis:** C₆H₄N₂O₂ (311.296)

Required: C, 57.87; H, 4.21; N, 22.49%.
Found: C, 57.9; H, 4.2; N, 22.4%.

**Coupling of 1 with active methylene compounds:**

Preparation of 3a-c

The same experimental procedure described above for the synthesis of 2a,b has been followed up except for using the diazotized solution which coupled with active methylene compounds such as malononitrile, ethyl cyanoacetate and benzoyl acetonitrile in ethanol containing catalytic amount of sodium acetate, kept at 0°C for one hour and diluted with water whereby the solid product that precipitated in each case was filtered off, dried and crystallized from the proper solvent (cf. Table 1).

**Ethyl 4-amino-3-substitutedpyrazol[5,1-c][1,2,4]triazine-8-carboxylates 4a-c**

To an aqueous ethanolic potassium hydroxide prepared by dissolving potassium hydroxide (0.3 g, 0.005 mol) in ethanol containing few drops of water, each of 3a-c (0.005 mol) was added and the solution was refluxed for 10 hours. The reaction mixture was then cooled, poured onto ice water acidified by hydrochloric acid, whereby, the solid that formed was filtered off, dried and crystallized from the proper solvent (cf. Table 1).

**Ethyl 7-amino-5-aryl-6-cyanopyrazolo[1,5-a]pyrimidine-3-carboxylate 7a,b**

A mixture of 1 (0.005 mol) and some 6-cyanoaminonitriles 5a,b was heated in pyridine under reflux for 24 hours. The reaction mixture was cooled and acidified with dilute hydrochloric acid, whereby, the solid that precipitated was filtered off, dried and crystallized from ethanoll.

**Ethyl 7-amino-5-phenyl-6-cyanopyrazolo[1,5-a]pyrimidine-3-carboxylate 7a:** Yield: 1.18 g (77.12%); m.p. 250°C; IR: 3425 cm⁻¹ (N-H), 2243 (CN) and 1718 (CO). ¹H-NMR (DMSO-d₆): δ 2.13 ppm (t, 2H, CH₂), 4.27 (q, 2H, CH₂), 7.60 (m, 3H, aromatic protons), 7.86 (m, 2H, aromatic protons), 8.61 (s, 1H, pyrazole H₃), and 9.17 (bs, 2H, NH, D,O exchangeable). Mass spectrum at m/z 307 (42.6%).

**Analysis:** C₁₆H₁₂N₈O₂ (307.260)

Required: C, 62.55; H, 4.26; N, 22.79%.
Found: C, 62.4; H, 4.2; N, 22.8%.

**Ethyl 7-amino-5-[4-chlorophenyl]-6-cyanopyrazolo[1,5-a]pyrimidine-3-carboxylate 7b:**

Yield: 1.42 g (83.13%); m.p. 262°C; IR: 3307 cm⁻¹ (N-H), 2208 (CN) and 1697 (CO).

**Analysis:** C₁₆H₁₀ClN₈O₂ (341.775).

Required: C, 56.23; H, 3.53; Cl, 10.37; N, 20.49%.
Found: C, 56.2; H, 3.6; Cl, 10.4; N, 20.5%.

**Ethyl 3-(N-acetylamino)-2H-pyrazole-4-carboxylate 11a:** A solution of 1 (0.005 mol) in glacial acetic acid (5 ml) was treated with acetic anhydride (0.01 mol) and heated under reflux for 3 hours. The reaction mixture was diluted with cold water. The precipitate, that formed, was collected by filtration, dried and crystallized from ethanoll to yield 0.76 g (77.55%) of 11a, m.p. 214°C; IR: 3342 cm⁻¹ (N-H), 3249 (N-N), 1701 (CO) and 1681 (CO).

¹H-NMR (DMSO-d₆): δ 1.26 ppm (t, 3H, CH₂), 2.13 (s, 3H, CH₃), 4.21 (q, 2H, CH₂), 7.86 (s, 1H, pyrazole H₃), 9.50 (s, 1H, NH, D,O exchangeable) and 13.21 (s, 1H, NH, D,O exchangeable).

**Analysis:** C₁₆H₁₂N₄O₂ (197.19).
Table 1. Characterization Data of 3a-c and 4a-c

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<th>Comp. No.</th>
<th>M.p. (C) (Solvent)</th>
<th>Yield (%)</th>
<th>Molecular Formula (M.Wt)</th>
<th>Analysis (Req found)</th>
<th>IR (cm⁻¹)</th>
<th>Selected bands</th>
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<td></td>
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<td></td>
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<td>%C</td>
<td>%H</td>
<td>%N</td>
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<td>3a*</td>
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<td>3b**</td>
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<td>C₁₁H₁₄N₂O₂ (311.29)</td>
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<td>57.9</td>
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*H-NMR (DMSO-d₆): δ 1.33 ppm (t, 3H, CH₃), 4.25 (q, 2H, CH₂), 7.96 (s, 1H, pyrazole H₁), 8.65 (s, 1H, NH, D₂O exchangeable) and 10.89 (s, 1H, NH, D₂O exchangeable); mass spectrum at m/z 232 [M⁺](59.3%).

**H-NMR (DMSO-d₆): δ 1.39 ppm (t, 3H, CH₃), 1.39 (t, 3H, CH₃), 4.30 (q, 2H, CH₂), 4.43 (q, 2H, CH₂), 8.30 (s, 1H, pyrazole H₂), 7.48-8.27 (m, 6H, 5 aromatic protons, pyrazole H₃). 8.89 (s, 1H, NH, D₂O exchangeable) and 11.05 (s, 1H, NH, D₂O exchangeable); mass spectrum at m/z 311 [M⁺](86.8%).

***H-NMR (DMSO-d₆): δ 1.35 ppm (t, 3H, CH₃), 4.14 ppm (t, 3H, CH₃), 1.39 (t, 3H, CH₃), 4.30 (q, 2H, CH₂), 4.49 (q, 2H, CH₂), 8.09 ppm (t, 3H, NH, D₂O exchangeable) and 7.89 ppm (s, 1H, pyrazole H₁); mass spectrum at m/z 280(100%).

#¹¹H-NMR (DMSO-d₆): δ 1.25 ppm (t, 3H, CH₃), 1.38 ppm (t, 3H, CH₃), 2.65 ppm (2H, CH₂), 2.11 ppm, NH D₂O exchangeable) and 3.35 ppm (q, 2H, CH₂, CH₂), 2.07 ppm (s, 1H, NH, D₂O exchangeable) and 7.60-8.22 ppm (m, 6H, 5 aromatic protons, pyrazole H₁).

Required: C, 48.72; H, 5.62; N, 21.30%

Found: C, 48.8; H, 5.6; N, 21.2%.

**Ethyl 3-(N-chloroacetamido)-2H-pyrazole-4-carboxylate** (11a): A mixture of 1 (0.005 mol) and an equimolecular amount of chloroacetyl chloride in anhydrous dioxane (15 ml) were heated under reflux for 3 hours. The reaction mixture was cooled and then neutralized by adding a solution of sodium acetate (2H₂O). The solid so formed was filtered off, washed with water, dried and crystallized from dilute dioxane to yield 0.83 g (72.17%) of 11a; m.p. 213°C; IR: 3319 cm⁻¹ (NH), 3220 (NH), 1699 (CO) and 1685 (CO); ¹¹H-NMR (DMSO-d₆): δ 1.26 ppm (t, 3H, CH₃), 4.21-4.32 (m, 4H, 2CH₂), 8.09 ppm (s, 1H, pyrazole H₅), 10.24 ppm (s, 1H, NH, D₂O exchangeable) and 10.35 ppm (s, 1H, NH, D₂O exchangeable); mass spectrum at m/z 231 (39.4%).

Analysis: C₈H₁₀ClN₄O₂ (231.63)

Required: C, 41.48; H, 4.4; Cl, 15.3; N, 18.14%

Found: C, 41.5; H, 4.4; Cl, 15.3; N, 18.1%

**Ethyl 5-aryl-cyano-7-oxo-4H,7H-pyrazolo[1,5-a]pyrimidine-3-carboxylates (13a,b)**

A mixture of 0.005 mol of 1 and some 7-cyanoenaminates 6a,b was heated in pyridine under reflux for 24 hours.
The reaction mixture was cooled and acidified with dilute hydrochloric acid, whereby, the solid that precipitated was filtered off, dried and crystallized from dilute dioxane.

Ethyl 6-cyano-7-oxo-5-phenyl-4H,7H-pyrazolo[1,5-alpyrimidine-3-carboxylate 13a: Yield, 1.08 g (70.58%), m.p. 250°C. IR: 3425 cm⁻¹ (NH), 2237 (CN) and 1718-1689 (2CO).

Analysis: C₁₆H₁₂N₄O₃ (308.29)
Required: C, 62.33; H, 3.92; N, 18.17%
Found: C, 62.4; H, 4.0; N, 18.1%

Ethyl 5-[4-chlorophenyl-6-cyano-7-oxo-4H,7H-pyrazolo|1,5-alpyrimidine-3-carboxylate 13b: Yield, 1.34 g (78.45%), m.p. 322°C. IR: 3317 cm⁻¹ (NH), 2230 (CN) and 1725-1686 (2CO); mass spectrum at m/z 342 (100.0%) and 344 (34.2%).

Analysis: C₁₆H₁₁ClN₄O₃ (342.73)
Required: C, 56.07; H, 3.23; Cl, 10.34, N, 16.36%
Found: C, 56.1; H, 3.3; Cl, 10.4; N, 16.3%

REFERENCES