Studies on Enaminonitriles: a New Synthesis of 1,3-Substituted Pyrazole-4-carbonitrile

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3-Diethylaminoacrylonitrile (1) reacts with hydrazonyl halides (2a-d) to yield 1,3-disubstituted pyrazole-4-carbonitriles 5a-d. The acetyl 1-p-chlorophenylpyrazole-4-carbonitrile (5a) condensed with hydrazine hydrate to yield the bishydrazone 10 and with dimethylformamide dimethacetal to yield 1-aryl-3-(3-dimethylamino)acryloyl pyrazole-4-carbonitrile (11). This enamine reacts with hydrazine hydrate to yield the pyrazolylpyrazole (12) and with naphthoquinone to yield the 3-naphthofuranoyl pyrazole 13. The pyrazolyl pyridine derivative 14 was obtained upon treatment of 11 with acetylacetone in the presence of ammonium acetate. Compound 11 was coupled with p-chlorobenzene diazonium chloride to yield the hydrazone 16 that was coupled further with p-chlorobenzene diazonium chloride to yield the formazane 18.


Introduction.

Functionally substituted enamines are versatile reagents and their chemistry has received in the last fifteen years considerable attention [1-4]. In our previous work aimed at exploring synthetic potentialities of enaminones [5-12] we have reported 1,3-dipolar cycloaddition of nitrileimines to enaminones to yield pyrazoles [13,14]. This reaction was then utilized to prepare several novel pyrazoles and tetrazines [15].

In conjunction of this work we investigated the reaction of enaminonitriles with nitrileimines. We have found that 3-diethylaminoacrylonitrile 1, the preparation of which has been described in the literature [16], reacts readily with nitrileimines, generated in situ from hydrazonyl halides 2a-e and triethylamine, to yield products of addition across the double bond affording cycloadducts that subsequently aromatized via diethylamine elimination to yield pyrazoles. Two structures seemed possible for these pyrazoles (cf. 5 and 6) depending on regioorientation of the cycloaddition. Thus cycloadduct 3 would afford 5 while cycloadduct 4 would yield 6.

1H NMR and 13C NMR enabled assignment of structure 5 for these reaction products. Thus 1H NMR, taking 5a as a typical example, showed pyrazole ring proton signal at $\delta$ 9.42 ppm, which can only be interpreted for pyrazole H-5. Pyrazole H-4 should appear at a much higher field. Simulated spectra for both structures proposed H-4 in compound 6 to appear at $\delta$ 7.35 ppm while H-5 in compound 5 at 8.17 ppm. 13C NMR adds further evidence. Thus taking again 5a as typical example pyrazole C-4 appeared at $\delta$ 92.9 ppm. If the reaction product was 6 again the carbon should appear at much lower field. Spectral simulation for 5 and 6 showed C-4 in 5 to expected at $\delta$ 98.33 ppm while in isomeric 6 this carbon would be expected at $\delta$ 108.69 ppm. In an attempt to convert 5a into amino pyrazolo[3,4-c]pyrimidine 9 via intermediate 8a, only the bishydrazone 10 was obtained. Condensation with phenylhydrazine afforded only the phenylhydrazine 8b, which could not be further cyclised.

Compound 5a condensed with dimethylformamide dimethacetal to yield the trans enaminone 11 as 1H NMR revealed trans olefinic protons at $\delta$ 5.86 and $\delta$ 7.71.
ppm as two doublets with $J = 16$ Hz. The enaminone $11$ reacted readily with hydrazine hydrate to yield the pyrazolopyrazole $12$. Typical for the recently reported behavior of enaminones, Compound $11$ reacted with naphthoquinone to yield naphthofuranpyrazole $13$. Reaction of $11$ with acetylacetone in refluxing acetic acid and in presence of ammonium acetate has afforded a pyrazolopyridine derivative that may be formulated.
as 14 or isomeric 15. Structure 14 is assigned for the product based on presence of pyridyl ring protons as doublets at $\delta$ 8.36 and $\delta$ 9.56 ppm with $J = 8$ Hz. If the reaction product is 15 one would expect [17,18] pyridyl ring protons to have much smaller coupling constant ($J = 3-4$ Hz).

Similar to reported behavior of enamiones [19] compound 11 also coupled with benzenediazonium chloride to yield the arylhydrazono derivative 16 that could be cyclised into pyrazolylcinnoline 17 on heating with concentrated sulphuric acid. Further coupling with 16 gave the coupling product 18. Attempts to convert 5b into a pyrazolopyridazine derivative via reaction with hydrazine hydrate afforded only hydrazide 19.

**EXPERIMENTAL**

The melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using a FTIR unit Bruker-vector 22 spectrophotometer. The $^1$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ and CDCl$_3$ as solvent at 200 or 300 MHz on a Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in $\delta$ units (ppm). Mass spectra were measured on a Shimadzu GMMS - QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the microanalytical center, Cairo University.

General Procedure for Preparation of 5a-d.

A mixture of enamionitrile 1 (10 mmol), hydrazon halide 2a-d (10 mmol), Et$_3$N (10 mmol) in ethanol (20 ml) was refluxed for 4 h. The solvent was evaporated under vacuo and the crude product was collected and crystallized from ethanol.

3-Acetyl-1-(4-chlorophenyl)-1H-pyrazole-4-carbonitrile (5a).

This compound was obtained in 72 % yield, mp: 207 °C; IR (KBr): $\nu$ 2238 (CN), 1688 cm$^{-1}$ (CO); MS (EI): m/z (%) = 245/247 (M$^+$); $^1$H NMR (DMSO-d$_6$): $\delta$ = 2.57 (s, 3H, CH$_3$), 7.62-7.93 (m, 4H, Ar-H), 9.42 ppm (s, 1H, pyrazole H); $^{13}$C NMR (DMSO-d$_6$): $\delta$ = 26.5 (CH$_3$), 92.9 (C-4 pyrazole), 112.6 (CN), 121.5, 129.9, 133.1, 136.9, (CH aromatic), 137.5 (C-5 pyrazole), 151.2 (C-3 pyrazole -1H), 191.6 (CO) ppm.


1-(4-Chlorophenyl)-4-cyano-1H-pyrazole-3-carboxylic Acid (5d).

This compound was obtained in 55 % yield, mp: 236-238 °C; IR (KBr): $\nu$ 3300 (NH), 2241.1 cm$^{-1}$ (CN); MS (EI): m/z (%) = 322/324 (M$^+$); $^1$H NMR (DMSO-d$_6$): $\delta$ = 7.15-8.09 (m, 9H, Ar H), 9.491 (s, 1H, pyrazole H), 10.46 (s, 1H, NH, D$_2$O exchage). **Anal.** Calcd. for C$_9$H$_7$ClN$_2$O (322.76): C, 63.26; H, 3.44; N, 17.36. Found: C, 63.23; H, 3.45; N, 17.38.

General Procedure for Preparation of Compounds 8b and 10.

A mixture of 3-acetyl-1-(4-chloro-phenyl)-1H-pyrazole-4-carbonitrile 5a (10 mmol) and phenylhydrazine and/or hydrazine hydrate (10 mmol) is refluxed in DMF for 2 hrs. The reaction mixture is then poured on water. The crude product was collected and crystallized from an ethanol/DMF mixture.

1-(4-Chlorophenyl)-3-[1-(phenylhydrazono)-ethyl]-1H-pyrazole-4-carbonitrile (8b).

This compound was obtained in 79 % yield, mp: 190 °C; IR (KBr): $\nu$ 3348.4 (NH), 2232.2 (CN); MS (EI): m/z (%) = 335/337 (M$^+$); $^1$H NMR (DMSO-d$_6$): $\delta$ = 2.28 (s, 3H, CH$_3$), 6.72-7.84 (m, 9H, Ar H), 9.26(s, 1H, pyrazole H), 9.61 (s, 1H, NH); $^{13}$C NMR (DMSO-d$_6$): $\nu$ = 12.06 (CH$_3$), 90.1 (C-4 pyrazole), 113.2 (C-3 pyrazole), 114.7 (CN), 119.7, 120.5, 128.9, 131.8, 133.8, 136.4 (CH aromatic), 137.2 (C-5 pyrazole), 145.3 (CH aromatic), 153.8 (C=N). **Anal.** Calcd. for C$_{18}$H$_{14}$N$_4$ClO (335.80): C, 64.38; H, 4.20; N, 20.86. Found: C, 64.41; H, 4.23; N, 20.83.

Preparation of 1-[1-(4-Chlorophenyl)-3-cyano-1H-pyrazol-4-yl)-3-dimethylamino-acryloyl]-1H-pyrazole-4-carbonitrile (10).

This compound was obtained in 70 % yield, mp: 320 °C; IR (KBr): $\nu$ = 2230.3 (CN); MS (EI): m/z (%) = 487/348 (M$^+$); $^1$H NMR (DMSO-d$_6$): $\delta$ = 2.5 (s, 6H, 2CH$_3$), 7.90 – 8.12 (m, 8H, Ar H), 9.70 (s, 2H, CH pyrazole). **Anal.** Calcd. for C$_{21}$H$_{16}$N$_4$O$_2$ (487.35): C, 59.15; H, 3.31; N, 22.99. Found: C, 59.20; H, 3.28; N, 22.89.

Preparation of 1-(4-Chlorophenyl)-3-[(E)-3-dimethylamino-acryloyl]-1H-pyrazole-4-carbonitrile (11).

A mixture of 5a and DMFDMA was refluxed in xylene for 3 hrs. The solvent was removed by evaporation under vacuo. The solid product was then crystallized from ethanol to give 5a in 75 % yield, mp: 190 °C; IR (KBr): $\nu$ = 3092, 3031 (CH olefinic, 2234 (CN), 1642 (CO); MS (EI): m/z (%) = 300/302 (M$^+$); $^1$H NMR (DMSO-d$_6$): $\delta$ = 2.92 (s, 6H, 2CH$_3$), 5.86 (d, 1H, olefinic H, J=16 Hz), 7.61-7.95 (m, 4H, Ar H), 7.71 (d, 1H, olefinic H, J=16 Hz), 9.34 (s, 1H, CH pyrazole); $^{13}$C NMR (DMSO-d$_6$): $\delta$ = 45.6 (CH$_3$), 93.2, 94.1 (C-4 pyrazole), 114.7 (CN), 119.7, 122.2, 130.6, 133.3 (C-5 pyrazole), 137.4, 137.4, 138.1, (C-3 pyrazole), 155.2 (N=C=O), 180.5 (CN).
Preparation of 1-(4-Chlorophenyl)-1H,1'H-[3,3]bipyrazoly1-4-carbonitrile (12).

A mixture of enamnine (11) with hydrazine hydroxid was refluxed in DMF (25 mL) for 3 h. The reaction mixture was then poured on water. The solid that formed was collected by filtration and crystallized from ethanol and DMF to give 12 in 78 % yield, mp: 310 °C; IR (KBr): v 3290-3131.6 (NH), 3030 (CH), 2239 (CN), 1705.7 (C=O); MS (EI): m/z (%) = 336/338 (M+).

A mixture of enamnine (11) and naphthoquinone was refluxed in acetic acid and left over night at room temperature. The reaction mixture is poured on water. The solid that formed was collected by filtration and crystallized from ethanol and DMF. This compound was obtained as brown crystals in 83 % yield, mp: 220-222 °C; IR (KBr): v 3448 (NH), 1711 (CO); MS (EI): m/z (%) = 521/523/525 (M+); 1H NMR (DMSO-d6): δ = 6.53-7.98 (m, 1H, pyrazole H), 9.14 (s, 1H, pyrazole H). This compound was obtained as brown crystals in 83 % yield, mp: 217 °C; IR (KBr): δ 3420 (NH), 2238 (CN), 1704 (CO), 1643 (CHO); MS (EI): m/z (%) = 411 (M+); 1H NMR (DMSO-d6): δ = 7.38-7.95 (m, 8H, Ar H), 7.79 (s, 1H, pyrazole H), 9.52 (s, 1H, CHO), 9.93 (s, 1H, NH, D2O exchange).

Preparation of 3-(6-Cinnoline-3-carbonyl)-1-(4-chlorophenyl)-1H-pyrazole-4-carboxylic Acid Amide (17).

Hydrazonal 16 was heated in H2SO4 for 15 minutes. The reaction mixture is poured on water. The solid that formed was collected by filtration and crystallized from ethanol. This compound was obtained as yellow a powders in a yield of 80%, mp: 265 °C; IR (KBr): v 3420.2, 3331.7 (NH), 1659.8, 1621 (CO); MS (EI): m/z (%) = 411/413 (M+); 1H NMR (DMSO-d6): δ = 7.41-8.13 (m, 7H, Ar H), 9.12 (s, 1H, pyrazole H), 9.14 (s, 1H, cinnoline H), 13.61 (s, 2H, NH).

Preparation of 3-[2-(4-Chlorophenylazo)-2-[4-chlorophenyl]-hydrazono][acyl]-1-(4-chloro-phenyl)-1H-pyrazole-4-carboxi-

Preparation of 1-(4-Chlorophenyl)-4-cyano-1H-pyrazole-3-carboxylic Acid Hydrazide (19).

A mixture of pyrazole ester 5b and hydrazine hydrate was refluxed in dimethylformamide (DMF) for 3 hr. The reaction mixture is poured on water. The solid that formed was collected by filtration and crystallized from an ethanol-DMF mixture. This compound was obtained as yellow powders in 85% yield, mp: 322 °C; IR (KBr): v 3290-3131.6 (NH2), 2244.8(CN), 1704.9 (CO); MS (EI): m/z (%) = 261/263 (M+); 1H NMR (DMSO-d6): δ = 5.96 (s, 2H, NH2), 7.66-7.96 (m, 4H, Ar H), 9.48 (s, 1H, pyrazole H), 11.190 (s, 1H, NH).

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REFERENCES AND NOTES

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