Enamines in Heterocyclic Synthesis: A Route to 4-Substituted Pyrazoles and Condensed Pyrazoles

Huwaida M. E. Hassaneen, Hamdi M. Hassaneen, and Mohamed H. Elnagdi

Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt

Reprint requests to H. M. E. Hassaneen. E-mail: huwaidah@hotmail.com

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The reaction of nitrile imines, generated *in situ*, from hydrazonoyl halides **3a – e** with enamines **2a – c** affords pyrazoles **8a – g**. These pyrazoles have been used to prepare condensed pyrazoles.

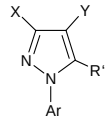
Key words: Enamines, Hydrazonoyl Halides, Pyrazoles, Dimethylformamide Dimethylacetal

Introduction

The significant biological and medicinal activities of pyrazoles and condensed pyrazole derivatives [1 – 4] has stimulated considerable recent interest in synthesis and chemical reactivity of functionally substituted pyrazoles [5 – 7]. 4-Amino-pyrazole-3-carboxylic esters **1a**, now used as intermediates for the synthesis of Sildenafil (Viagra) and Allopurinol, are prepared from acylpyruvates *via* a multistage synthetic approach [8 – 12]. 3,4-Diacylpyrazoles **1b** are obtainable either from reaction of enaminones with acyl hydrazonoyl halides [13] or from reaction of the latter with β-diketones [14]. To our knowledge no general efficient simple synthesis of 3-acyl-4-amino- or 3-acyl-4-nitropyrazoles **1c,d** has been reported although these derivatives could be interesting intermediates for the synthesis of biologically interesting condensed pyrazoles. In the present paper we report such a route. Moreover, extension of synthetic methodology described earlier by one of us [13] for the synthesis of 3,4-diacylpyrazoles to enable synthesis of (methylamino)pyrazolo[3,4-*d*]pyridazines will be reported.

Results and Discussion

In conjunction with our interest in exploring the potential utility of functionally substituted enamines [13, 15 – 18], we report here a convenient synthesis of different 3,4-substituted-1-arylpyrazoles from enamines **2a – c** and hydrazonoyl halides **3a – e**, and the conversion of the formed pyrazoles into condensed pyrazoles needed for biological evaluation. The required enamines **2a – c** were prepared *via* reacting dimethylformamide dimethylacetal with nitromethane,



1a: X=ROCO, Y= NH_2
b: X=Y= RCO
c: X=RCO, Y=NH_2
d: X=RCO,Y=NO_2

N-acetonyl-phthalimide (**4**) and 4-nitrotoluene. These products have been prepared earlier utilizing the same reaction conditions [19 – 21]. Although addition of nitrile imines to polymer-supported arylenamines [22] and enaminones [23] has been reported earlier, to our knowledge addition of hydrazonoyl halides to enamines **2a – c** has not yet been investigated.

2a – c reacted with hydrazonoyl halides **3a – e** in presence of triethylamine to yield products of condensation *via* dimethylamine hydrochloride elimination. It is believed that **3a – e** initially generate nitrile imines **5a – e** *in situ* and these then undergo 1,3-dipolar cycloaddition to **2a – c** yielding intermediate cycloadducts that aromatize *via* dimethylamine elimination. Two isomeric structures are possible for the cycloadducts (**6** and **7**).

Aromatization of **6** would afford **8** while **7** would yield **9** (Scheme 1). ^{1}H NMR as will as chemical behavior of the formed pyrazoles indicated that they are the 4-substituted derivates **8**. Thus, ^{1}H NMR spectra of reaction products showed pyrazole H-5 at $\delta \approx$ 8.60 ppm which is very close to that predicted for **8a – g**. If the reaction product is isomeric **9** simulated spectra predict pyrazole ring H-4 at $\delta \approx 6.5$ ppm [24]. Moreover, reduction of **8a** in a trial to obtain the 4-aminopyrazole **10** has afforded **12**. It is believed

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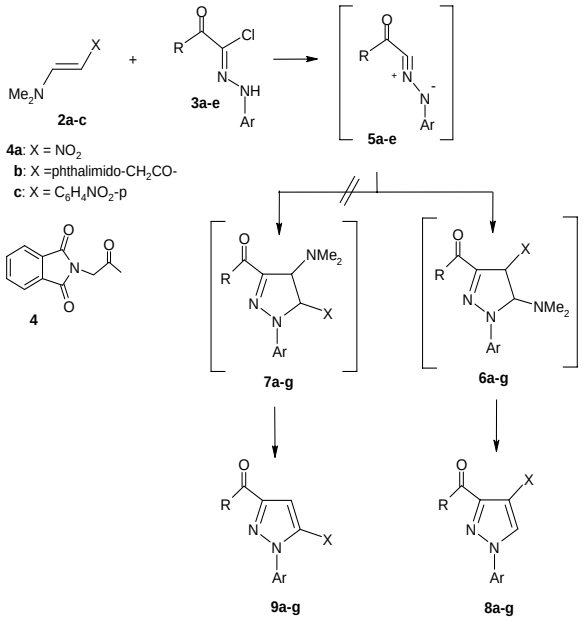


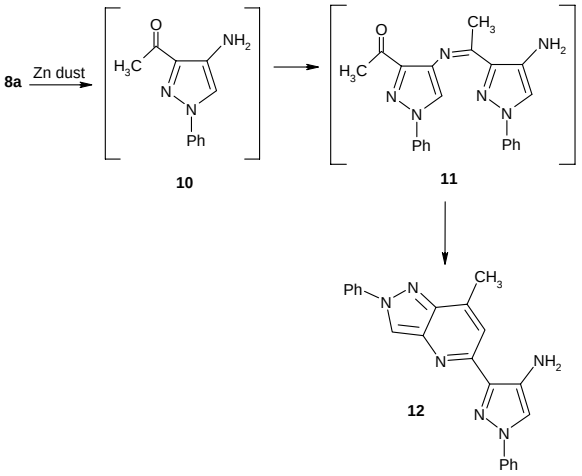
3,8,9 a: R=CH_3; X=NO_2; Ar = C_6H_5
b: R=EtO; X=NO_2; Ar = C_6H_5
c: R=CH_3;X=phthalimido-CH_2CO-; Ar = C_6H_4Cl-p
d: R=EtO;X=phthalimido-CH_2CO-; Ar = C_6H_4Cl-p
e: R= EtO; X= phthalimido-CH_2CO-; Ar = $C_6H_4CH_3$-p
f: R=CH_3; X=$C_6H_4NO_2$-p; Ar = C_6H_4Cl-p
g: R=EtO; X=$C_6H_4NO_2$-p; Ar = C_6H_4Cl-p

Scheme 1.

that **8a** initially yields intermediate **10** which undergoes self-condensation to **11** that cylises further into **12** (Scheme 2). Very similar condensation of 5-aminopyrazoles on attempted C-4 acylation has been observed [25].

On the other hand reaction of **8d** with hydrazine hydrate afforded the (methylamino)pyrazolopyridazine **13** in excellent yield. Acetylation of **13** with acetic anhydride afforded (acetylmethylamino)pyrazolopyridazine whose ^{1}H NMR spectrum indicated that it exists at least in DMSO solution as a mixture of **14a** and isomeric tautomeric **14b** in 3:1 ratio (Scheme 3). Fixation of the cyclic hydrazide form **14b** is due to hydrogen bonding. Similarly, reaction of **8c** with hydrazine hydrate has afforded the pyrazolo [3,4-*d*]pyridazine **15**.

In conclusion, cycloaddition of functionally substituted enamines to nitrile imines is an excellent route to 3,4-difunctionally substituted pyrazoles that can be readily converted into a variety of biologically interesting condensed pyrazoles.



Scheme 2.

Experimental Section

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Pye Unicam SP-3000 IR spectrophotometer and Testscan Shimadzu FT-IR 8000 series. ^{1}H NMR spectra were recorded on Varian EM 390 spectrometers with $CDCl_3$ and [D_6]-DMSO as solvents and TMS as an internal standard; chemical shifts (δ) are reported in ppm. Mass spectra were measured on a GCMS-QP 1000-EX Shimadzu. Elemental analyses were carried out at the microanalytical center, University of Cairo, Giza, Egypt.

General procedure for the preparation of **8a – g**

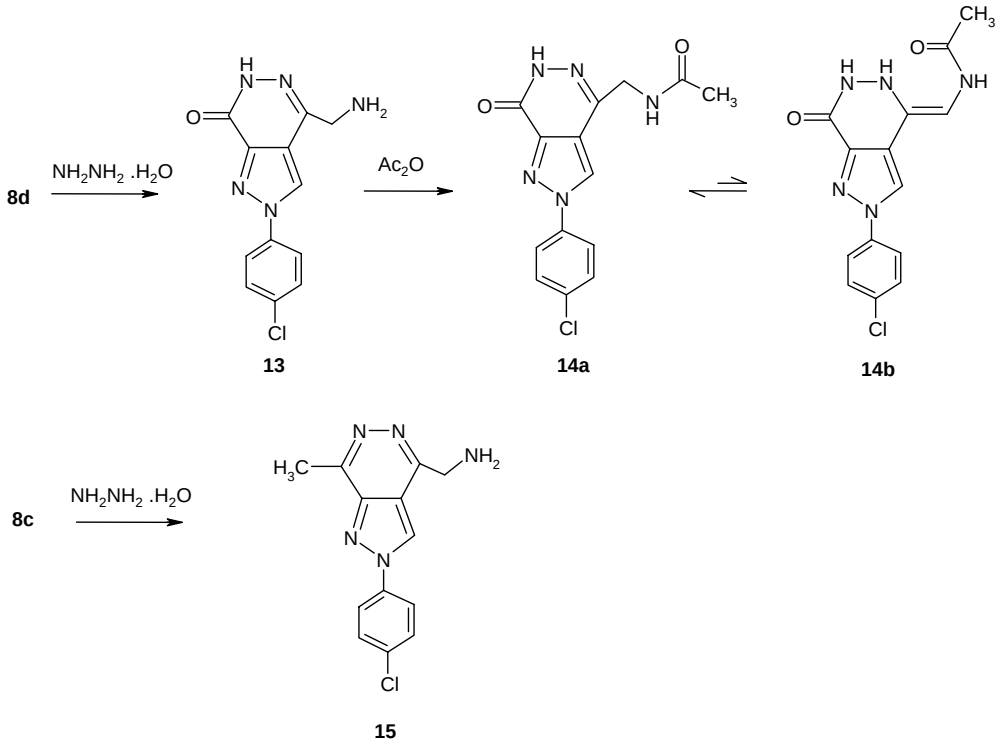
A mixture of enamine derivatives **2a – c** (0.01 mol), hydrazonoyl halides **3a – e** (0.01 mmol), triethylamine (1.01 g, 0.01 mol) in chloroform (30 ml) was refluxed for 4 h. The solvent was evaporated under vacuo and the crude product was collected and crystallized from ethanol.

*3-Acetyl-4-nitro-1-phenylpyrazole (***8a***)*

Yellow crystals, 70% yield, m.p. 135 – 136 °C. – IR (KBr): ν 1699 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68 (s, 3H, CH_3CO), 7.46 – 7.77 (m, 5H, arom-H), 8.67 (s, 1H, pyrazole-5-H). – MS (EI, 70 eV): *m/z* (%) = 231 (31.5) [M^+], other major fragments: 216 (34), 142 (11), 104 (71), 77 (100), 51 (68). – $C_{11}H_9N_3O_3$ (231.2): calcd. C 57.14, H 3.92, N 18.18; found C 57.20, H 3.89, N 18.16.

*3-Ethoxycarbonyl-4-nitro-1-phenylpyrazole (***8b***)*

Yellow crystals, 72% yield, m.p. 150 – 151 °C. – IR (KBr): ν 1726 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 – 1.63 (t, 3H, J = 7 Hz, CH_3), 4.41 – 4.55 (q, 2H, J = 7 Hz, CH_2), 7.43 – 7.74 (m, 5H, arom-H), 8.62 (s, 1H,



Scheme 3.

pyrazole-5-H). – MS (EI, 70 eV): *m/z* (%) = 261 (53.0) [M^+], other major fragments: 233 (51), 216 (34), 149 (22), 129 (21), 116 (24), 104 (65), 77 (92), 75 (100), 51 (47). – $C_{12}H_{11}N_3O_4$ (261.2): calcd. C 55.17, H 4.24, N 16.09; found C 55.20, H 4.19, N 16.11.

*2-(2-[3-Acetyl-1-(4-chlorophenyl)pyrazol-4-yl]-2-oxo-ethyl)isoindoline-1,3-dione (***8c***)*

Yellow crystals, 75% yield, m.p. 152 °C. – IR (KBr): ν 1774 (C=O), 1717 (C=O), 1693 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.77$ (s, 3H, CH_3CO), 5.22 (s, 2H, CH_2-olefinic), 7.26 – 7.91 (m, 8H, arom-H), 8.50 (s, 1H, pyrazole-5-H). – MS (EI, 70 eV): *m/z* (%) = 408 (8.0) [M^+], other major fragments: 247 (100), 77 (7), 51 (4). – $C_{21}H_{14}N_3O_4Cl$ (407.82): calcd. C 61.84, H 3.45, N 10.30; found C 61.87, H 3.43, N 10.25.

*2-(2-[3-Ethoxycarbonyl-1-(4-chlorophenyl)pyrazol-4-yl]-2-oxoethyl)isoindoline-1,3-dione (***8d***)*

Pale yellow crystals, 73% yield, m.p. 182 °C. – IR (KBr): ν 1724 (C=O), 1708 (C=O), 1679 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): $\delta = 1.25 - 1.33$ (t, 3H, $J = 7$ Hz, CH_3), 4.27 – 4.31 (q, 2H, $J = 7$ Hz, CH_2), 5.12 (s, 2H, CH_2-olefinic), 7.35 – 7.94 (m, 8H, arom-H), 9.53 (s, 1H, pyrazole-5-H). – MS (EI, 70 eV): *m/z* (%) = 438 (12.6) [M^+], other major fragments: 277 (100), 249 (81), 77 (12), 51 (6). – $C_{22}H_{16}N_3O_5Cl$ (437.85): calcd. C 60.34, H 3.68, N 9.60; found C 60.30, H 3.70, N 9.55.

*2-(2-[3-Ethoxycarbonyl-1-(4-methylphenyl)pyrazol-4-yl]-2-oxoethyl)isoindoline-1,3-dione (***8e***)*

Yellow crystals, 73% yield, m. p. 182 °C. – IR (KBr): ν 1775 (C=O), 1724 (C=O), 1689 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.43 - 1.50$ (t, 3H, $J = 7$ Hz, CH_3), 2.40 (s, 3H, CH_3), 4.46 – 4.56 (q, 2H, $J = 7$ Hz, CH_2), 5.19 (s, 2H, CH_2-olefinic), 7.26 – 7.90 (m, 8H, arom-H), 8.44 (s, 1H, pyrazole-5-H). – MS (EI, 70 eV): *m/z* (%) = 417 (12.0) [M^+], other major fragments: 257 (100), 229 (67), 91 (24), 77 (13), 51 (5). – $C_{23}H_{19}N_3O_5$ (417.38): calcd. C 66.18, H 4.58, N 10.07; found C 66.13, H 4.57, N 10.03.

*3-Acetyl-1-(4-chlorophenyl)-4-(4-nitrophenyl)pyrazole (***8f***)*

Dark yellow crystals, 66% yield, m.p. 242 °C. – IR (KBr): ν 1690 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.72$ (s, 3H, CH_3CO), 7.26 – 7.91 (m, 8H, arom-H), 8.05 (s, 1H, pyrazole-5-H). – MS (EI, 70 eV): *m/z* (%) = 342 (68.5) [M^+], other major fragments: 326 (100), 75 (18), 51 (7). – $C_{17}H_{12}N_3O_3Cl$ (341.77): calcd. C 59.74, H 3.53, N 12.29; found C 59.69, H 3.50, N 12.27.

*3-Ethoxycarbonyl-1-(4-chlorophenyl)-4-(4-nitrophenyl)pyrazole (**8g**)*

Dark yellow crystals, 69% yield, m.p. 177 °C. – IR (KBr): ν 1719 (C=O) cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35-1.40$ (t, 3H, $J = 7$ Hz, CH_3), 4.34–4.45 (q, 2H, $J = 7$ Hz, CH_2), 7.26–7.90 (m, 8H, arom-H), 8.04 (s, 1H, pyrazole-5-H). – MS (EI, 70 eV): *m/z* (%) = 372 (100) [M^+], other major fragments: 299 (66), 75 (32), 51 (12). – $C_{18}H_{14}N_3O_4Cl$ (371.79): calcd. C 58.15, H 3.79, N 11.30; found C 58.11, H 3.77, N 11.23.

*3-(7-Methyl-2-phenyl-2H-pyrazolo[4,3-e]pyridin-5-yl)-1-phenyl-1H-pyrazol-4-yl-amine (**12**)*

A suspension of nitro compound **8a** (1.16 g, 0.005 mol) and Zn dust (0.01 mol) in methanol (3 ml) was stirred with hydrazinium monoformate (2 ml) at 20 °C. The reaction mixture was filtered through celite. The organic layer was evaporated and the residue was triturated with chloroform where it solidified. The crude product was collected to give **12**, (0.59 g, 51%), m.p. 310 °C. – IR (KBr): ν 3298, 3363 (NH_2) cm^{-1}. – Insoluble in common ^1H NMR solvents. – MS (EI, 70 eV): *m/z* (%) = 366 (30.3) [M^+], other major fragments: 313 (23), 230 (23), 171 (10), 137 (11), 121 (12), 114 (56), 73 (10), 55 (100). – $C_{22}H_{18}N_6$ (366.38): calcd. C 72.12, H 4.94, N 22.94; found C 72.07, H 4.90, N 22.92.

*4-Aminomethyl-2-(4-chlorophenyl)-2,6-dihydropyrazolo[3,4-d]pyridazin-7-one (**13**)*

A mixture of **8d** (4.38 g, 0.01 mol) and hydrazine hydrate (5 ml, 85%) was refluxed for 5 min. The reaction mixture was left to cool and the solid product was collected and crystallized from dimethylformamide to give **13**, (3.50 g, 80%), m.p. 299 °C. – IR (KBr): ν 3337, 3289 (NH_2), 3199 (NH), 1665 (C=O) cm^{-1} – ^1H NMR (300 MHz, [D_6]-DMSO): $\delta =$ 2.50 (s, 2H, CH_2-olefinic), 3.23 (br, 3H, NH, NH_2), 7.64–8.08 (m, 4H, arom-H), 9.41 (s, 1H, pyrazole-3-H). – MS (EI, 70 eV): *m/z* (%) = 276 (55.9) [M^+], 247 (100), 230 (50), 111 (57), 75 (38), 51 (19). – $C_{12}H_{10}N_5OCl$ (275.72): calcd. C 52.27, H 3.65, N 25.40; found C 52.30, H 3.62, N 25.35.

*N-[2-(4-Chlorophenyl)-7-oxo-6,7-dihydro-2H-pyrazolo[3,4-d]pyridazin-4-ylmethyl]acetamide (**14**)*

A solution of **13** (2.76 g, 0.01 mol) in acetic anhydride (20 ml) was refluxed for 3 h. The reaction mixture was cooled and the solid that separated was collected and crystallized from dimethylformamide to give **14**, (2.15 g, 78%), m.p. 260 °C. – IR (KBr): ν 3296 (NH), 3121 (NH), 1709 (C=O) 1691 (C=O) cm^{-1}. – ^1H NMR (300 MHz, [D_6]-DMSO) of **14a**: $\delta = 1.91$ (s, 3H, CH_3CO), 2.61 (s, 2H, CH_2-olefinic), 3.30 (br, 2H, 2NH), 7.70–8.07 (m, 4H, arom-H), 9.20 (s, 1H, pyrazole-H-3) and ^1H NMR (300 MHz, [D_6]-DMSO) of **14b**: $\delta = 1.88$ (s, 3H, CH_3CO), 3.30 (br, 3H, 3NH), 4.44–4.46 (d, 2H, CH-olefinic), 7.70–8.07 (m, 4H, arom-H), 9.42 (s, 1H, pyrazole-3-H). – MS (EI, 70 eV): *m/z* (%) = 318 (48.2) [M^+], other major fragments: 274 (100), 75 (6), 51 (3). – $C_{14}H_{12}N_5O_2Cl$ (317.75): calcd. C 52.91, H 3.80, N 22.04; found C 52.90, H 3.77, N 22.10.

*4-Aminomethyl-2-(4-chlorophenyl)-7-methyl-2,6-dihydropyrazolo[3,4-d]pyridazine (**15**)*

A mixture of **8c** (4.07 g, 0.01 mol) and hydrazine hydrate (5 ml, 85%) was refluxed for 5 min. The reaction mixture was left to cool and the solid product was collected and crystallized from dimethylformamide to give **15**, (3.26 g, 80%), m.p. 174 °C. – IR (KBr): ν 3337, 3289 (NH_2) cm^{-1}. – ^1H NMR (300 MHz, [D_6]-DMSO): $\delta = 1.62$ (s, 3H, CH_3CO); 2.50 (s, 2H, CH_2-olefinic), 3.92 (br, 2H, NH_2), 7.42–8.15 (m, 4H, arom-H), 9.60 (s, 1H, pyrazole-3-H). – MS (EI, 70 eV): *m/z* (%) = 274 (7.7) [M^+], other major fragments: 243 (55), 162 (87), 104 (100), 75 (62), 51 (56). – $C_{13}H_{12}N_5Cl$ (273.75): calcd. C 57.04, H 4.41, N 25.58; found C 57.09, H 4.39, N 25.50.

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