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Enamines in heterocyclic synthesis: Route to aminopyrazolopyrimidines and arylpyrazolopyrimidiens derivatives

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Abstract: An easy preparation of enaminonitrile derivatives, obtained by using a mixture of triethyl orthoformate and piperidine in DMF solution, and their transformation into new substituted azolopyrimidines is described. The one-step transformation was carried out under microwave irradiation and by classical heating methods. The use of microwave irradiation led to high conversion and shorter reaction times.

Keywords: Pyrazolopyrimidines, Enamines, Aminopyrazole, Microwave Irradiation

1. Introduction

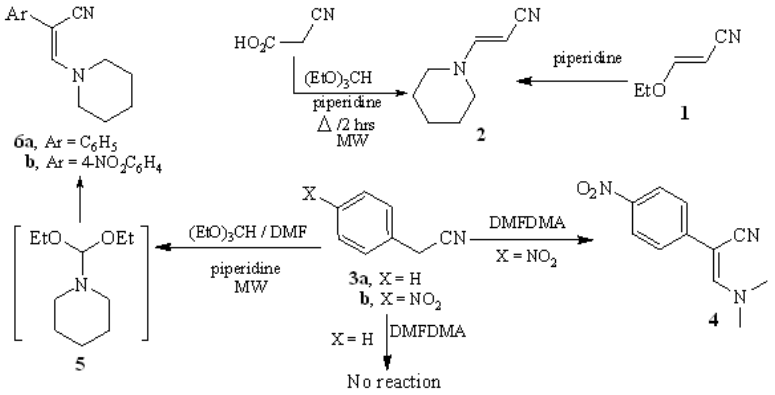
Pyrazolopyrimidines attracted organic chemists very much due to their biological and chemotherapeutic importance [1-7]. Pyrazolopyrimidines and related fused heterocycles are of interest as potential bioactive molecules. They are known to exhibit pharmacological activities such as antimicrobial, antioxidant [8] and agrochemical importance. Moreover they are promising as new classes of dyes for D2T2 printing and as potential hair dyes [9, 10].

Microwave heating has been employed as a frequent resource for improvement of classical reactions. The major benefits of performing reactions under microwave condition are: significant rate enhancements and higher product yields as compared to reactions which run under conventional heating. A key advantage of modern, scientific microwave apparatus is their ability to control reaction conditions precisely, by monitoring temperature/pressure, reaction times and ease of isolation of the products after easy work-up [11, 12]. In conjunction to our interest in the chemistry of enaminonitriles [13-17], we report here results of our work aimed at developing efficient environmentally friendly syntheses for several targeted pyrazolopyrimidines utilizing enamines 2,4 and 6a,b as starting materials. In our chemical reactivity studies described here, we principally employed the intermediate 6b due to their easy preparation and good yield of reactions.

2. Results and Discussions

The enamine 2 could be prepared either *via* heating cyanoacetic acid, piperidine and triethyl orthoformate in a microwave oven or as has been described recently [6, 7] *via* heating a mixture of triethyl orthoformate, piperidine and cyanoacetic acid under reflux for two hours. A synthesis of 2 *via* heating 3-ethoxyacrylonitrile (1) and piperidine in a microwave oven for five minutes was also achieved. This reaction required 12 hours reflux for completion [7] (Scheme 1).

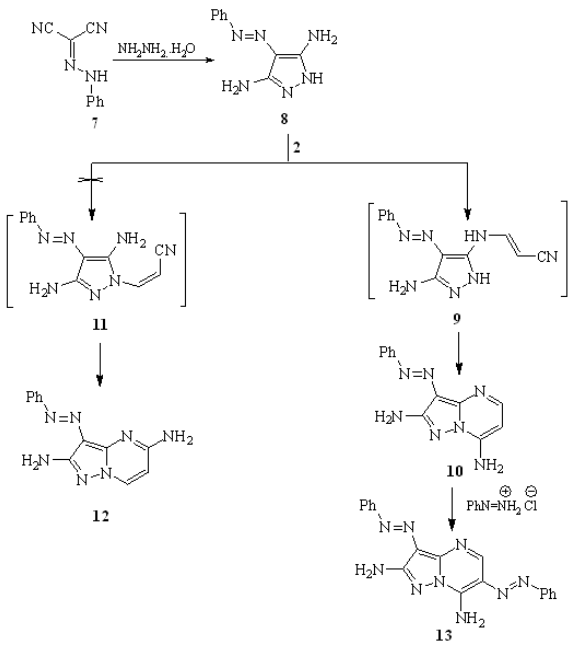
The enaminonitrile 4 could be easily obtained via reacting *p*-nitrobenzylcyanide (3b) and dimethylformamide dimethylacetal (DMF-DMA) in refluxing dioxane. Trials to condense benzyl cyanide (3a) with DMFDMA failed. Compounds 6a,b could be readily obtained by refluxing a mixture of 3a, b, triethyl orthoformate and piperidine in DMF solution for 72 h to produce 6a, or 24 h to obtain 6b. We believe that the in *situ*-generated amidoacetal 1-(diethoxymethyl) piperidine (5) is initially formed and then these react with 3a,b to yield the enaminonitriles 6a,b [13]. This condensation could be effected by microwave heating, 20 minutes for 6a and 10 minutes for 6b, and the products were found identical in all details (melting point and TLC analysis, NMR) to the compounds obtained from the other method.



Scheme 1.

The yellow 4-(phenylazo)pyrazole-3,5-diamine (8) was prepared by heating 2-(phenylazo) mesoxalonitrile (7) and hydrazine hydrate in dioxan in a microwave oven or by conventional heating [18] (Scheme 2).

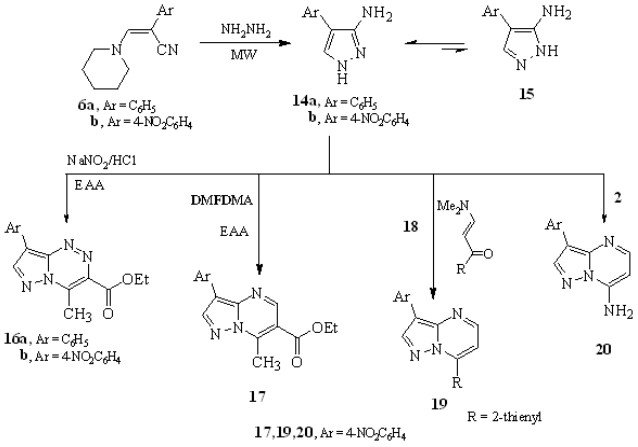
Compound 8 condensed with 2 *via* piperidine elimination upon reflux in pyridine solution or upon heating in a microwave oven to yield a product that may be formulated as 9-12. Thus initial condensation with the exocyclic amino function would afford 9 which can then cyclizes into 10. Alternately, 11 may be initially formed which then cyclises into 12. Acyclic structures 9 and 11 were readily ruled out based on the absence of a CN band in the IR spectrum and the presence of two amino functions according to the ^{1}H NMR spectrum.



Scheme 2.

Structure 10 is preferred over 12 based on the appearance of NH_2 singlet at δ = 8.0 ppm. Isomeric 12 should show this function at higher field [19, 20]. Compound 10 could be coupled with benzenediazonium chloride to yield 13.

Enamine 6b was readily converted into aminopyrazole 14b on reflux with hydrazine hydrate in DMF solution for 3 h or on heating in microwave oven for 5 minutes also in DMF. However, 6a did not react under similar conditions. However, in microwave and in the presence of acetic acid the aminopyrazole 14a was formed (Scheme 3) [21].



Scheme 3.

Compounds 14a,b reacted with sodium nitrite to afford a diazonium salt that coupled with ethyl acetoacetate to yield 16a,b , while the reaction of 14b with DMF-DMA followed by ethyl acetoacetate yields 17. Reaction of 14b with enaminone 18 [21] and enaminonitrile 2 afforded pyrazolopyrimidine 19 and 20, respectively, (Scheme 3). The structures of these compounds were established based on their elemental analysis and spectral data (*cf.* Experimental Section).

3. Experimental

3.1. General

All melting points are uncorrected. IR spectra were recorded in KBr with a Bruker Vector 22 spectrophotometer. The 1H NMR (300 MHz) and 13C NMR (75.4 MHz) spectra were recorded on a Varian Mercury 300 MHz spectrometer in [D6]DMSO as solvent and with TMS as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra

were measured at 70 eV using a Shimadzu GCMS-QP-1000 EX mass spectrometer. Microanalyses were performed on a Leco CHN-932 by the Microanalysis Unit of Cairo University. Microwave experiments were conducted in a CEM MARS oven. Compounds 2 and 8 were provided by Prof. Elnagdi, while compounds 14a and 18 were prepared as previously reported by us [20, 21].

3.2. 3-Dimethylamino-2-(4-Nitrophenyl) Acrylonitrile (4)

A mixture of 3b (0.01 mol, 1.62 g) and DMF-DMA (0.012 mol) in dioxane (15 mL) was refluxed for 3 h then cooled and poured onto water. The green solid product formed was collected by filtration and crystallized from ethanol to give 4. Yield 70 %; m. p. 178-180 oC. - IR (KBr): = 2222 (CN), 1610 (C=C) cm-1. - 1H NMR (300 MHz,): δ = 3.27 (s, 3H, CH3), 3.33 (s, 3H, CH3), 7.50 (d, 2H, J = 9 Hz, Ar-H), 7.80 (s, 1H, olefinic-H), 8.12 (d, 2 H, J = 9 Hz, Ar-H). - 13C NMR (75.4 MHz,): δ = 43.64 (2 CH3), 97.27 (C=CH), 122.54 (CN), 123.36, 132.40, 144.45, 145.75, 150.50 (C=CH). - MS (EI, 70 eV): m/z(%) = 217 (100) [M]+. - C11H11N3O2 (217.22): calcd. C 60.82, H 5.10, N 19.34; found C 60.85, H 5.03, N 19.30.

3.3. General Procedure for the Preparation of Compounds 6a, b

Method A. To a mixture of benzyl cyanide 3a or 4-nitrobenzyl cyanide 3b (0.3 mol), triethyl orthoformate (0.32 mol), and piperidine (0.3 mol) DMF (40 mL) was added and the solution was refluxed for 72 h. The reaction mixture was then cooled and poured onto water. The solid product formed, was collected by filtration and crystallized from ethanol, (6a: 70%; 6b: 65%).

Method B. Under Microwave Irradiation. In a round bottom flask of 100 mL equipped with a condenser, benzyl cyanide 3a or 4-nitrobenzyl cyanide 3b (0.3 mol), triethyl orthoformate (0.32 mol), piperidine (0.3 mol) and DMF (40 mL) was added and the mixture was heated at reflux during 20 min (for 6a) and 10 min (for 6b) under microwave irradiation (at a constant power of 400 W). After cooling to r. t., the reaction mixture was poured onto water to give a solid, which was identical in all respects with that obtained from the above reactions (TLC, m. p., NMR), (6a: 85%; 6b: 77%).

3.3.1. 2-Phenyl-3-(Piperidin-1-Yl)-Acrylonitrile (6a)

Yield: 85 %; - m. p. 116-117 ºC. - IR (KBr): ν = 2190 (CN), 1616 (C=C) cm^{-1}. - ^{1}H NMR (300 MHz,): δ = 1.60 (s, 6 H, 3 CH_2), 3.63 (s, 4H, 2 CH_2), 7.16 (s, 1H, olefinic-H), 7.26-7.45 (m, 5H, Ar-H)- ^{13}C NMR (75.4 MHz,): δ = 24.36, 26.41, 51.96, 75.41 (C=CH), 121.59 (CN), 124.48, 125.51, 129.14, 137.27, 149.29 (C=*C*H). - MS (EI, 70 eV): *m/*(%)= 212 (42) $[M]^+$. - $C_{14}H_{16}N_2$ (212.29): calcd. C 79.21, H 7.60, N 13.20; found C 79.29, H 7.67, N 13.17.

3.3.2. 2-(4-Nitrophenyl)-3-(Piperidin-1-yl)-Acrylonitrile (6b)

Yield: 77%; - m. p. 130-132 ºC. - IR (KBr): ν = 2206, (CN), 1618 (C=C), 1595, 1330 (NO_2) cm^{-1}. - ^{1}H NMR (300 MHz,): δ = 1.75 (m, 6H, 3 CH_2); 3.70 (m, 4 H, 2 CH_2); 7.10 (s, 1H, olefinic-H); 7.45 (d, 2 H, *J* = 10 Hz, Ar-H), 8.08 (d, 2 H, *J* = 10 Hz, Ar-H). - MS (EI, 70 eV): *m/z*(%) = 257 (42) $[M]^+$. - $C_{14}H_{15}N_3O_2$ (257.29): calcd. C 65.35, H 5.88, N 16.33; found C 65.15, H 5.70, N 16.44.

3.4. 3-(2-Phenyldiazenyl) Pyrazolo [1,5-a] Pyrimidine -2,7-Diamine (10)

Method A. A mixture of 8 (0.01 mol, 2.02 g), enaminonitrile 2 (0.01 mol, 1.36 g) in pyridine (25 mL) was refluxed for 3 h. The reaction mixture was then acidified with concentrated hydrochloric acid and refluxed for ten min. The reaction mixture was then poured onto water, and the solid formed was collected by filtration and crystallized from ethanol, yield 65%.

Method B. A mixture of 8 (0.01 mol, 2.02 g) and 2 (0.01 mol, 1.36 g) in DMF (10 mL) was heated in a microwave oven for five min then left to cool. The solid formed was collected and identified as 10 (m. p, mixed m. p. and TLC). Yield 80 %; m. p. 185-187 ºC. - IR (KBr): ν = 3340 (NH_2), cm^{-1}. - ^{1}H NMR (300 MHz): δ = 6.65 (d, 1 H, *J* = 8 Hz, 6-H), 7.20-7.35 (m, 5H, Ar-H), 8.0 (s, 2H, NH_2), 8.10 (d, 1 H, *J* = 8 Hz, H-5), 11.81 (s, 2H, NH_2). - MS (EI, 70 eV): *m/z*(%) = 253 (56) $[M]^+$. - $C_{12}H_{11}N_7$ (253.26): calcd. C 56.91; H 4.38; N 38.71; found C 56.80, H 4.42, N 38.77.

3.5. 3,6-Di(2-phenyldiazenyl)Pyrazolo[1,5-a]Pyrimidine -2,7-Diamine (13)

A cold solution of benzenediazonium chloride (0.01 mol) was prepared by adding a solution of sodium nitrite (0.01 mol in 2 mL of H_2O) to a cold solution of the aniline in concentrated hydrochloric acid with stirring. The resulting solution of the benzenediazonium chloride was added to a cold solution of 10 in ethanol (50 mL) containing sodium acetate (5 g). The reaction mixture was stirred at room temperature for 30 min. The solid product formed was collected by filtration, washed with water and crystallized from ethanol. Yield 81%; m. p. 162-163 ºC. - IR (KBr): ν = 3360 (NH_2), cm^{-1}. . - ^{1}H NMR (300 MHz): δ = 7.35 (s, 1H, 5-H), 7.51 (t, 6H, *J* = 9 Hz, Ar-H), 7.61 (s, 2H, NH_2), 7.83 (d, 4 H, *J* = 9Hz, Ar-H), 12.60 (s, 2H, NH_2). - MS (EI, 70 eV): *m/z*(%) = 357 (44) $[M]^+$. - $C_{18}H_{15}N_9$ (357.37): calcd. C 60.50, H 4.23, N 35.27; found C 60.60, H, 4.30, N 35.30.

3.6. 4-(4-Nitrophenyl)-1H-Pyrazol-3-Amine (14b)

Method A. A mixture of 6b (0.01 mol, 2.57 g) and hydrazine hydrate (0.01 mol) in DMF (15 mL) was refluxed for 3 h. The reaction mixture was left to cool to room temperature, and the solid formed was collected by filtration and crystallized from ethanol yield (60%).

Method B. A mixture of enaminonitrile 6b (0.01 mol, 2.57 g) and hydrazine hydrate (0.01 mol) in DMF (10 mL) was heated in a microwave oven for five min. The same work up as mentioned above.

Yield 85 %; m. p. 184-186 ºC.-IR (KBr): = 3340 (NH_2), 3280 (NH), 1565, 1360 (NO_2) cm^{-1}. - ^{1}H NMR (300 MHz): δ

= 7.69 (d, 2H, *J* = 9 Hz, Ar-H), 7.82 (s, 2H, NH_2), 8.15 (s, 1H, NH), 8.22 (d, 2 H, *J* = 9 Hz, Ar-H), 8.32 (s, 1H, pyrazole-H). - MS (EI, 70 eV): *m/z*(%) = 204 (55) $[M]^+$.- $C_9H_8N_4O_2$ (204.19): calcd. C 52.94, H 3.95, N 27.44; found C 52.90, H 4.05, N 27.40.

3.7. Ethyl 4-Methyl-8-Substituted Pyrazolo [5,1-C][1,2,4] -Triazine-3-Carboxylate (16a,B)

A cold solution of pyrazolediazonium chloride (0.01 mol) was prepared by adding a solution of sodium nitrite (0.01 mol in 2 mL of H_2O) to a cold solution of the aminopyrazoles 14a or 14b in concentrated hydrochloric acid with stirring. The resulting solution of the pyrazolediazonium chloride was added to a cold solution of ethyl acetoacetate in ethanol (50 mL) containing sodium acetate (5 g). The reaction mixture was stirred at room temperature for 30 min. The solid product formed was collected by filtration, washed with water and crystallized from ethanol to afford 16a, b.

3.7.1. Ethyl 4-Methyl-8-Phenyl Pyrazolo [5,1-C][1,2,4] Triazine-3-Carboxylate (16a)

Yield 78%; m. p. 202-203 ºC. - IR (KBr): ν = 1690 (CO) cm^{-1}. - ^1H NMR (300 MHz): δ = 1.15 (t, 3 H, *J* = 7.5 Hz, CH_3), 2.30 (s, 3H, CH_3), 4.10 (q, 2 H, *J* = 7.5 Hz, CH_2), 7.20-7.45 (m, 5H, Ar-H), 8.25 (s, 1H, H-7). - MS (EI, 70 eV): *m/z* (%) = 282 (98) $[M]^+$.- $C_{15}H_{14}N_4O_2$ (282.30): calcd. C 63.82, H 5.00, N 19.85; found C 63.70, H 4.90, N 19.90.

3.7.2. Ethyl-4-Methyl-8-(4-Nitrophenyl) Pyrazolo [5,1-C] [1,2,4]Triazine-3-Carboxylate (16b)

Yield 68%; m. p. 223-225 ºC., IR (KBr): ν = 1705 (CO) 1560, 1367 (NO_2) cm^{-1}- ^1H NMR (300 MHz): δ = 1.18 (t, 3H, *J* = 7.5 Hz, CH_3), 2.32 (s, 3H, CH_3), 4.20 (q, 2 H, *J* = 7.5 Hz, CH_2), 7.20 (d, 2H, *J* = 10 Hz, Ar-H), 8.18 (d, 2H, *J* = 10Hz, Ar-H), 8.32 (s, 1H, H-7).- MS (EI, 70 eV): *m/z*(%) = 327 (90) $[M]^+$. -$C_{15}H_{13}N_5O_4$ (327.29): calcd. C 55.05, H 4.00, N 21.40; found C 54.95, H 4.10, N 21.20.

3.8. Ethyl-7-Methyl-3-(4-Nitrophenyl)Pyrazolo[1,5-A] Pyrimidine-6-Carboxylate (17)

A mixture of 14b (0.01 mol, 2.04 g), DMF-DMA (0.01 mol) and ethyl acetoaceate (0.01 mol) in pyridine (25 mL) was refluxed for 3 h. The reaction mixture was left to cool to room temperature and the solid formed was collected by filtration and crystallized from ethanol. Yield 69 %; m. p. 218-220 ºC.- IR (KBr): ν = 1708 (CO), 1570, 1355 (NO_2) cm^{-1}. - ^1H NMR (300 MHz): δ = 1.12 (t, 3H, *J* = 7.5 Hz, CH_3), 2.32 (s, 3H, CH_3), 4.18 (q, 2H, *J* = 7.5 Hz, CH_2), 7.45 (d, 2H, *J* = 9Hz, Ar-H), 7.92 (d, 2H, *J* = 9 Hz, Ar-H), 8.22 (s, 1H, 2-H), 8.52 (s, 1H, 5-H).-MS (EI, 70 eV): *m/z*(%) = 326 (64) $[M]^+$.-$C_{16}H_{14}N_4O_4$ (326.32): calcd. C 58.89, H 4.32, N 17.17; found C 58.80, H 4.35, N 17.25.

3.9. 3-(4-Nitro-Phenyl)-7-Thiophen-2-Yl-Pyrazolo[1,5-A] Pyrimidine (19)

A mixture of 14b (0.01 mol, 2.04 g) and enaminone 18 (0.01 mol, 1.81 g) in pyridine (25 mL) was refluxed for 3 h. The reaction mixture was left to cool to room temperature, and the solid formed was collected by filtration and crystallized from ethanol to afford 19. Yield 62%; m. p. 250-251 ºC. -IR (KBr): ν = 2985 (CH Ar), 1565, 1370 (NO_2), cm^{-1}. - ^1H NMR (300 MHz): δ = 7.0-7.31 (m, 3H, thiophene-H), 7.45 (d, 2H, *J* = 9Hz, Ar-H), 7.55 (d, 1H, *J* = 7Hz, 6-H), 8.23 (d, 2H, *J* = 9Hz, Ar-H), 8.66 (s, 1H, 2-H), 8.80 (d, 1H, *J* = 7Hz, 5-H).- MS (EI, 70 eV): *m/z*(%) = 322 (74) $[M]^+$.- $C_{16}H_{10}N_4O_2S$ (322.24): calcd. C 59.62, H 3.13, N 17.38, S 9.95; found C 59.50, H 3.20, N 17.35, S 10.0.

3.10. 3-(4-Nitrophenyl)-Pyrazolo [1,5-A]Pyrimidin-7-Ylamine (20)

A mixture of 14b (0.01 mol, 2.04 g) and enaminonitrile 2 (0.01 mol, 1.36 g) in pyridine (25 mL) was refluxed for 3 h. The reaction mixture was left to cool to room temperature, and the solid formed was collected by filtration and crystallized from ethanol to afford 20. Yield 77%; m. p. 160-162 ºC. - IR (KBr): ν = 3350 (NH_2) 1560, 1365 (NO_2) cm^{-1}. - ^1H NMR (300 MHz): δ = 6.59 (d, 1H, *J* = 7 Hz, 6-H), 7.15 (s, 2H, NH_2), 7.55 (d, 2 H, *J* = 10 Hz, Ar-H), 8.16 (d, 2H, *J* = 10 Hz, Ar-H), 8.33 (d, 1H, *J* = 7Hz, 5-H), 8.49 (s, 1H, 2-H) - ^{13}C NMR (75.4 MHz): δ = 95.9 (C-6), 102.2 (C-3), 122.36 (C-3`,5`),132.30 (C-2`,6`), 134.10 (C-3a), 135.20 (C-1`), 137.8 (C-2), 146.10 (C-4`), 148.7 (C-7), 155.5 (C-5). - MS (EI, 70 eV): *m/z*(%)=255 (80)$[M]^+$.-$C_{12}H_9N_5O_2$ (255.23): calcd. C 56.47, H 3.55, N 27.44; found C, 56.40, H 3.50, N 27.55.

4. Conclusion

In conclusion, *in situ* generation of less volatile amidoacetals from piperidine diethylacetal enables to apply drastic reaction conditions in the condensation of amide acetals with active methylene compounds, so that less reactive compounds can be applied to condensation reactions. This method implies use of less expensive chemicals and conversion of the methylene compounds to enamines enhances the reactivity toward electrophiles. Shorter reaction times and higher yields were obtained by microwave irradiation.

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