Studies with Enaminonitriles : Synthesis and Chemical Reactivity of 2-Phenyl-3-Piperidin-1-yl Acrylonitrile under Microwave Heating

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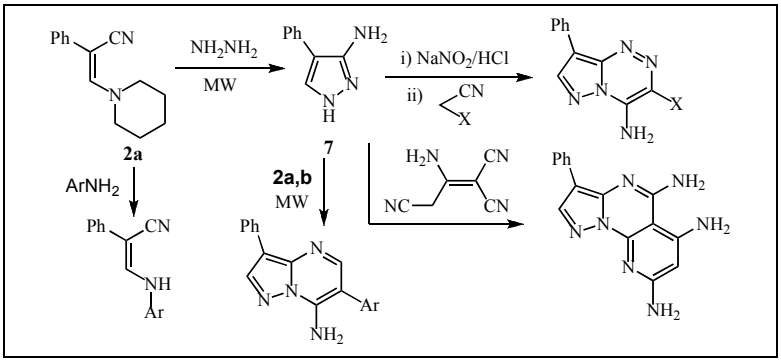

Benzyl cyanide reacts with triethylorthoformate and piperidine in DMF solution to yield the title compound **2**. This reacted with aromatic amines to yield either aminoacrylonitriles or quinoline depending on reaction conditions and substitution pattern on the aromatic amine. The reaction of compound **2** with hydrazine hydrate could only be effected in the microwave oven and resulted in the formation of aminopyrazole **7**. Diazotization of **7** and coupling with an active methylene reagent afforded pyrazolo[5,1-*c*]-[1,2,4]triazine derivatives.

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INTRODUCTION

Microwave (MW) heating has been employed for the rapid synthesis of a wide variety of organic molecules [1-4] wherein chemical reactions are accelerated because of selective absorption of MW energy by polar molecules, non-polar molecules being inert to the MW dielectric loss. The applications of microwave irradiation with the use of catalysts or mineral supported reagents, under solvent-free conditions, provide unique chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity and ease of manipulation. This solventless microwave methodology is exemplified by a concise synthesis of amino acrylonitriles, aminopyrazoles, pyrazolo[1,5-*a*]pyrimidines, and benzimidazoles.

RESULTS AND DISCUSSION

Enaminonitriles are versatile reagents and their chemistry is now receiving considerable attention as precursors to, otherwise not readily obtainable heteroaromatics [5-10]. The synthesis of compounds **2a,b** were achieved *via* reacting benzyl cyanide or 4-nitrobenzyl cyanide (**1a,b**) with triethylorthoformate and piperidine in refluxing dimethylformamide solution (readily available starting materials instead of using dimethylformamide dimethylacetal (DMFDMA) an expensive and carcinogenic material) (Scheme 1).

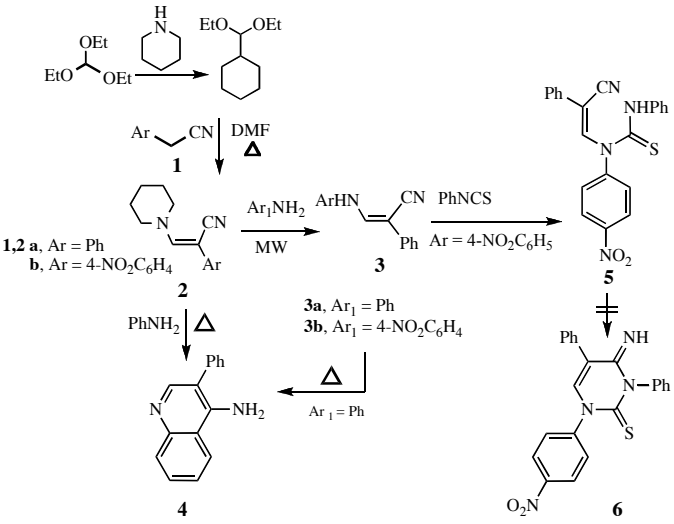
In the present article, we report results of our work aimed at exploring the synthetic potential of **2**. It has been found that **2a** reacts with aniline, when both reagents were heated in a domestic microwave oven for two minutes in absence of solvent to yield the aniline derivative **3a**. On the other hand reacting **2a** with aniline in refluxing dioxane for ten hours afforded the aminoquinoline **4** in good yield. Compound **3a** was converted into **4** on long reflux in dioxane solution. On the other hand **2a** reacted with 4-nitroaniline to yield **3b**. Trials to effect cyclization of the later into a quinoline derivative failed due to the effect of an electron attracting substituent on aryl moiety (Scheme 1).

Compound **3b** reacted readily with phenylisothiocyanate to yield the thiourea derivative **5**. Trials to cyclize the later into pyrimidine **6** failed. When refluxed in acetic acid compound **5** afforded only **3b**.

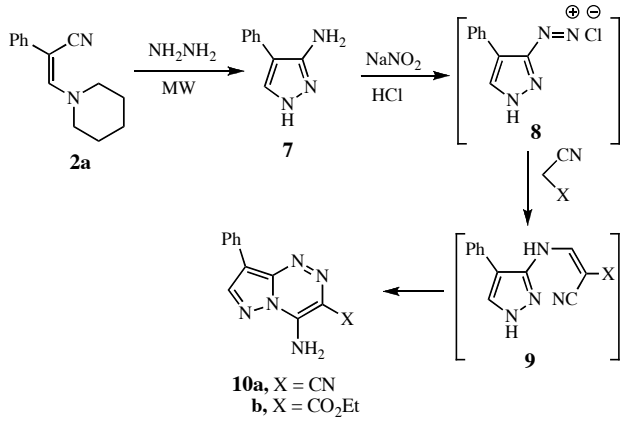
Compound **2** failed to react with hydrazine hydrate in refluxing DMF under a variety of conditions. However, when heated with hydrazine hydrate in presence of acetic acid in a microwave oven for two minutes the amino pyrazole **7** was formed in almost quantitative yield.

This could be readily diazotized and the resulting diazonium salt **8** coupled with ethyl cyanoacetate and with malononitrile to yield the amino pyrazolo[5,1-*c*]-triazine **10a,b** respectively. Intermediates **9** are postulated although they could not be isolated (Scheme 2).

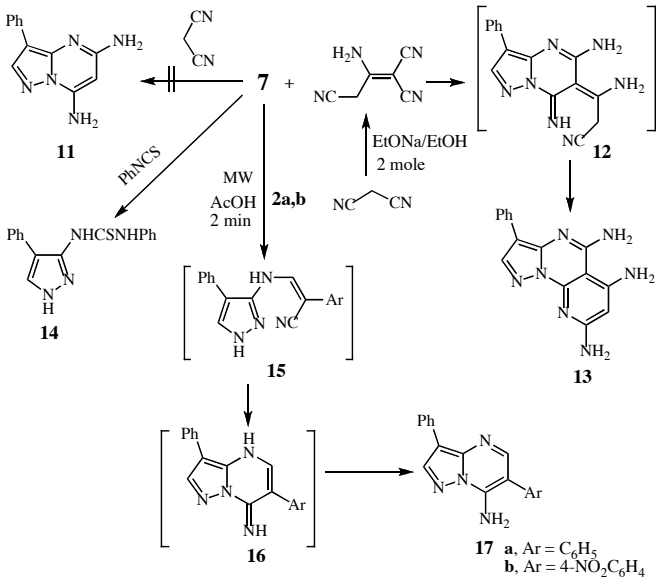
Scheme 1



Scheme 2



Scheme 3



Compound **7** reacts with malononitrile in ethanol sodium ethoxide to afford product **13** and not **11**. The chemical analysis of compound **13** showed that this compound is a 2:1 adduct with m/z = 291. Two moles of malononitrile condensed together to afford malononitrile dimer *(in situ)* which reacts with aminopyrazole to yield intermediate **12** (not isolated) which undergoes cyclization to the final product **13**. To confirm the formation of **13**, malononitrile dimer was first prepared and then reacted with aminopyrazole to yield the same product **13** (m.p. mixed m.p. and TLC) (Scheme 3).

In recent years, urea and thiourea [11-13] have emerged as structurally novel anticonvulsant agents. Thus compound **7** reacted with phenylisothiocyanate to yield the thiourea **14**. Finally the enaminonitriles **2a,b** were reacted with amniopyrazole **7**, in the microwave oven for two minutes, to produced pyrazolo[1,5-*a*]pyrimidine derivatives **17a,b** in excellent yields (Scheme 3).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr pellets with Satellite 2000 spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Bruker AC-300 spectrometer in DMSO-d_6 and $CDCl_3$ as solvents and TMS as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured at 70 eV using Shimadzu GCMS-QP 1000 EX spectrometer. Microanalytical Data were obtained from the Microanalytical Centre at Cairo University. Microwave experiments were conducted in a domestic microwave oven SJO 390W.

General procedure for preparation of compounds 2a,b. To a mixture of benzyl cyanide **1a** or 4-nitrobenzyl cyanide **1b** (0.5 mmoles), triethyl orthoformate (0.6 m moles), and piperidine (0.5 mmoles) DMF (50 ml) was added and the solution was refluxed for 72 hours. The reaction mixture was then cooled and poured onto water. The solid product formed, was collected by filtration and crystallized from ethanol.

2-Phenyl-3-piperidin-1-yl-acrylonitrile (2a). This compound was obtained as yellowish white needles in 70% yield (EtOH-H_2O), mp 115-116°; ir (potassium bromide): 2190 (CN), 1616 (C=C) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.75 (m, 6H, $3CH_2$), 3.75 (m, 4H, $2CH_2$), 6.95 (s, 1H olefinic-H), 7.20-7.45 (m, 5 H, Ar-H). ^{13}C nmr (deuteriochloroform): δ 149.2, 137.2, 129.1, 125.5, 124.4, 121.5, 75.4, 51.9, 26.4, 24.3; ms: m/z 212 (M^+). *Anal.* Calcd. for $C_{14}H_{16}N_2$ (212.29): C, 79.21; H, 7.60; N, 13.20. Found: C, 79.29; H, 7.67; N,13.17.

2-(4-Nitrophenyl)-3-piperidin-1-yl-acrylonitrile (2b). This compound was obtained as pale yellow needles in 70% yield; mp 130-131°; ir (potassium bromide): 2206, (CN), 1618 (C=C), 1595, 1330 (NO_2) cm^{-1}; ^{1}H nmr (deuterio-chloroform): δ 1.75 (m, 6H, $3CH_2$); 3.70 (m, 4H, $2CH_2$); 7.10 (s, 1H, olefinic-H); 7.45 (d, 2H, *J* = 10 Hz, Ar-H), 8.08 (d, 2H, *J* = 10 Hz, Ar-H); ms: m/z 257 (M^+). *Anal.* Calcd. for $C_{14}H_{15}N_3O_2$ (257.29): C, 65.35; H, 5.88; N, 16.33.Found : C, 65.15 ; H, 5.70; N, 16.44.

General procedure for preparation of 2-phenyl-3-(substituted amino) acrylonitrile 3a,b. A mixture of **2a** (0.2 mmoles) and aniline or 4-nitro aniline (0.1 mmole), were heated in a domestic microwave oven for three minutes, in absence of solvent, the resulting product treated with ethanol, and the solid collected by filtration, then crystallized from ethanol, to afford **3a,b**.

2-Phenyl-3-(phenylamino)acrylonitrile (3a). This compound was obtained as pale yellow needles in 85% yield; mp 165-166°; ir (potassium bromide): 2210 (CN); 3360 (NH) cm^{-1}; ^{1}Hnmr (dimethylsulfoxide-d_6): δ 6.96-7.30 (m, 10H, Ar-H); 6.50 (s, 1H, NH); 7.40 (s, 1H, olefinic-H); ms: m/z 220 (M^+). *Anal.* Calcd. for $C_{15}H_{12}N_2$ (220.28) C, 81.79; H, 5.49; N, 12.72. Found: C, 81.88; H, 5.51; N, 12.80.

3-(4-nitrophenyl amino)-2-phenyl acrylonitrile (3b). This compound was obtained as yellow needles in 80% yield; mp 160°; ir (potassium bromide): 2190 (CN); 3330 (NH), 1590, 1320 (NO_2) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 6.40 (s, 1H, NH); 6.90-7.30 (m, 5H, Ar-H); 7.45 (s, 1H, olefinic-H); 7.85 (d, 2H, *J* = 10Hz, Ar-H); 8.25 (d, 2H, *J* = 10Hz, Ar-H); ms: m/z = 265 (M^+) *Anal.* Calcd. for $C_{15}H_{11}N_3O_2$ (265.27) C, 67.92; H, 4.18; N, 15.84; Found C, 69.74; H, 4.88; N, 16.04.

3-Phenyl quinoline-4-amine (4). A solution of (**2a**, 1 mmole) and the aniline (1 mmole) in dioxane (30 ml) was refluxed for 10 hrs. A similar solution with compound **3a** (1 mmole) in the place of aniline was refluxed for 8 hours. The solvent was reduced under vacuum. The solid formed was collected by filtration and crystallized from ethanol. This compound was obtained as yellow solid in 85% yield; mp 135-136°; ir (potassium bromide): 3360-3290 (NH_2) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 6.14 (s, 2H, NH_2); 7.10-7.80 (m, 9H, Ar-H); 8.33 (s, 1H, quinoline-H-2); ms: m/z 220 (M^+). *Anal.* Calcd. for $C_{15}H_{12}N_2$ (220.28) C, 81.79; H, 5.49; N, 12.72. Found: C, 81.95; H, 5.44; N, 12.65.

1-(2-Cyano-2-phenylvinyl)-1-(4-nitrophenyl)-3-phenyl thiourea (5). A solution of (0.2 mmoles) (**3b**) and phenyl isothiocyanate (0.1 mmole) was dissolved in dry acetone (20 ml) was refluxed for 3 hours. The reaction mixture was allowed to cool and the solid so formed was collected by filtration and crystallized from ethanol/DMF (2:1) to afford (**5**). This compound was obtained as a dark yellow solid in 70% yield; mp 250°C; ir (potassium bromide): 1681 (C=S); 2208 (CN); 3301, 3251,(NH) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.25-7.37 (m, 10H, Ar-H); 7.52 (d, 2H, *J* = 10 Hz, Ar-H); 8.17 (d, 2H, *J* = 10 Hz, Ar-H); 8.23 (s, 1H, CH); 10.25 (s, 1H, NH), ms: m/z 400 (M^+, 70%). *Anal.* Calcd. For $C_{22}H_{16}N_4O_2S$ (400.46). C, 65.99; H, 4.03; N, 13.99; S, 8.01. Found. C, 66.10; H, 3.86; N, 14.14; S, 8.21.

3-Amino-4-phenyl-1*H*-pyrazole (7). A mixture of (**2a**, 1 mmole), hydrazine hydrate (0.5 mmoles) and a few drops from acetic acid were heated in a domestic microwave oven at full power for two minutes. A solid formed, which was treated with ethanol, collected by filtration, was crystallized from ethanol. This compound was obtained as pale yellow needles in 95% yield; mp 175-176° (lit. mp 173-173.5°) [14]; ir (potassium bromide): 3340 (NH_2) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): 6.10 (s, 2H, NH_2); 7.05 (s, 1H, pyrazole-H), 7.20-7.50 (m, 5H, Ar-H), 7.65 (s, 1H, NH), ms: m/z 159 (M^+). *Anal.* Calcd. For $C_9H_9N_3$ (159.19): C, 67,90; H, 5.70; N, 26.40. Found. C, 67.80; H, 5.82; N, 26.50.

General procedure for preparation of pyrazolo[1,5-*c*]-[1,2,4]triazine derivatives (10a,b). A cold solution of pyrazole diazonium chloride was prepared by adding a solution of sodium nitrite (10 mmoles in a small amount of water) to a cold solution of aminopyrazole (**7**) in hydrochloric acid with stirring .The resulting solution was added slowly into a cold solution of malononitrile or ethyl cyanoacetate in ethanol (40 ml)/sodium acetate (5g). The mixture was stirred at r.t for 1 hr, the semisolid so formed, was washed with cold water then dissolved in acetic acid (15 ml), and refluxed for three hours, The mixture was allowed to cool, then it was poured onto ice-cold water, the solid so formed was collected by filtration, and crystallized from ethanol to afford **10a,b** respectively.

4-Amino-8-phenylpyrazolo[5,1-*c*][1,2,4]triazine-3-carbonitrile (10a). This compound was obtained as yellow solid in 70% yield; mp 290°; ir (potassium bromide): 2227 (CN); 3310 (NH_2).cm^{-1}; ms: m/z =235 (M^+, 100%); (M^{+1}, 81%). *Anal.* Calcd. For $C_{12}H_8N_6$ (236.24) C, 61.01; H, 3.41; N, 35.57. Found. C, 61.35; H, 3.54; N, 35.70.

Ethyl 4-amino-8-phenyl pyrazolo[5,1-*c*][1,2,4]triazine-3-carboxylate (10b). This compound was obtained in yellow solid 70%yield; mp 220°; ir (potassium bromide): 1675 (C=O); 3391, 3264, (NH_2) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 1.38 (t, 3H, *J* = 7.5 Hz, CH_3); 4.44 (q, 2H, CH_2); 7.29-7.51 (m, 5H, Ar-H); 8.24 (s, 2H, NH_2); 8.92 (s, 1H, H-6), ms: m/z 283 (M^+). *Anal.* Calcd. For $C_{14}H_{13}N_5O_2$ (283.29): C, 59.36; H, 4.63; N, 24.72. Found. C, 59.52; H, 5.05; N, 25.09.

3-Phenylpyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidine-5,6,8-triamine (13). To a solution of aminopyrazole (**7**, 1 mmol) and malononitrile (0.5 mmol) in DMF (25 ml) piperidine (1 ml) was added and then the mixture was refluxed for three hours, the reaction mixture was allowed to cool, then poured onto ice. The solid so formed, was collected by filtration and crystallized from ethanol to afford (**13**). This compound was obtained as brown solid in 70% yield mp 226°C; ir (potassium bromide): 1610 (C=C); 3450, 3320 (NH_2) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.18-7.44 (m, 6H, Ar-H, H-7), 7.55, (s, 2H, NH_2), 7.89, (s, 2H, NH_2), 8.16 (s, 2H, NH_2), 8.68 (s, 1H, pyrazole–H-2), ms: m/z 291 (M^+, 100%). *Anal.* Calcd. For $C_{15}H_{13}N_7$ (291.28) C, 61.84; H, 4.50; N, 33.66. Found C, 61.50; H, 4.39; N, 33.30.

1-Phenyl-3-(4-phenyl-1*H*-pyrazol-5-yl)thiourea (14). A solution of aminopyrazole (**7**, 1 mmol) and phenylisothiocyante (0.5 mmol) in dry acetone (25 ml) was refluxed for three hours and the reaction mixture was allowed to cool. A solid formed was collected by filtration and crystallized from ethanol to afford (**14**). This compound was obtained as pale yellow needles in 75% yield; mp 142-143°; ir (potassium bromide): 1675, (C=S), 3310, 3256, (NH)cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.32-7.53 (m, 10H, Ar-H), 7.90 (s, 1H NH), 8.20 (s, 1H NH), 8.56 (s, 1H, pyrazole-H); 9.42 (s, 1H NH), ms: m/z 294 (M^+, 100%). *Anal.* Calcd. For $C_{16}H_{14}N_4S$ (294.37) C, 65.28; H, 4.79; N, 19.03; S, 10.89. Found. C, 65.42; H, 5.04; N, 19.25; S, 10.68.

General procedure for preparation of pyrazolo[1,5-*a*]-pyrimidine derivative (17a,b). A mixture of aminopyrazole (**7**, 1 mmol) and enaminonitrile (**2a, b**, 1.3 mmol) was heated in a domestic microwave oven for two minutes. The resulting products were treated with ethanol and the solids were collected by filtration, crystallized from ethanol and identified as **17a,b**, respectively.

3,6-Diphenylpyrazolo[1,5-*a*]pyrimidine-7-amine (17a). This compound was obtained as yellow solid in 80% yield; mp 220-222°C; (lit. mp 222-224°C) [15], ir (potassium bromide): 3340, (NH_2).cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 4.50 (brs, 2H, NH_2), 6.92 (s, 1H, H-5), 7.13-7.50 (m, 10H, Ar-H), 7.77 (s,

1H, H-2); ^{13}C nmr (deuteriochloroform): δ 104.4 (C-6), 108.4 (C-3), 124.6, 125.7, 127.4, 128.5, 128.8, 129.2, 133.8, 135.9, 142.3 (C-2), 145.6 (C-3a), 146.2 (C-7), 151.1 (C-5); ms: m/z 286. (M^+, 100%). *Anal*. Calcd. For $C_{18}H_{14}N_4$, (286.34) C, 75.51; H, 4.93; N, 19.57. Found C, 75.24; H, 5.05; N, 19.71.

6-(4-Nitrophenyl)-3-phenylpyrazolo[1,5-*a*]pyrimidin-7-amine (17b). This compound was obtained as yellow solid in 85% yield; mp 196°; ir (potassium bromide): 3360-3290 (NH_2), 1565, 1360 (NO_2) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 4.60 (bs, 2H, NH_2), 6.90 (s, 1H, H-5), 7.08-7.26 (m, 5H, Ar-H), 7.36 (d, 2H, Ar-H); 750 (d, 2H, Ar-H); 7.75 (s, 1H, H-2), ms: m/z 331 (M^+). *Anal*. Calcd. For $C_{18}H_{13}N_5O_2$ (331.34) C, 65.25; H, 3.95; N, 21.14. Found: C, 65.50; H, 4.10; N, 21.61.

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