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STUDIES WITH MALONONITRILE DERIVATIVES: SYNTHESIS AND REACTIVITY OF 4-BENZYLPYRAZOLE-3,5-DIAMINE, 4-BENZYLISOXAZOLE-3,5-DIAMINE AND THIAZOLIDIN-3-PHENYLPROPANENITRILE

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Abstract – Benzylmalononitrile **6** reacts with hydrazines, and hydroxylamine hydrochloride to yield the 4-benzylpyrazole-3,5-diamines **7** and 4-benzylisoxazole-3,5-diamine **9**, respectively. Pyrazole-3,5-diamines **7** could be readily reacted with α,β-unsaturated nitriles to yield pyrazolo[1,5-*a*]pyrimidines **20**. Benzylmalononitrile, also reacted with thioglycolic acid to yield tautomeric mixture of 2-(4-hydroxythiazol-2-yl)-3-phenylpropanenitrile **29** and 2-(4-oxothiazolidin-2-yl)-3-phenylpropanenitrile **30** that coupled with benzene diazonium chloride to yield 2-(4-oxo-5-(phenylhydrazono)-thiazolidin-2-ylidene)-3-phenylpropanenitrile **31**.

INTRODUCTION

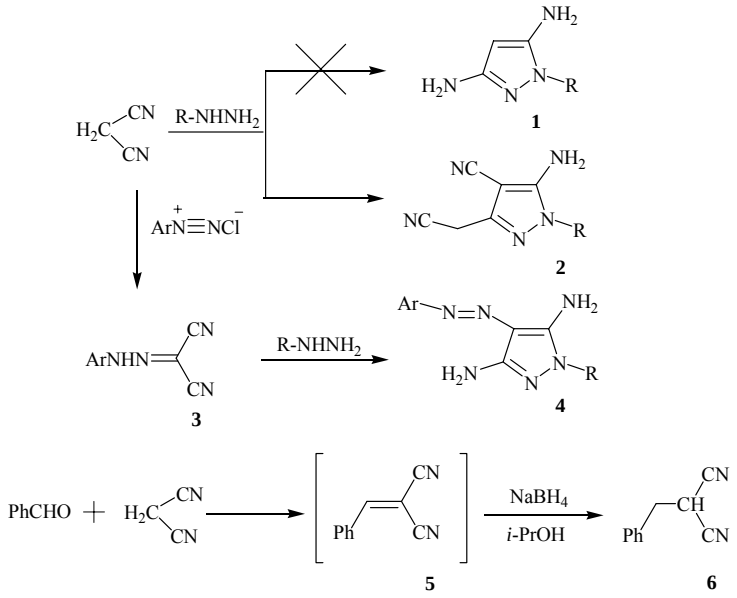
Since reported economical preparation of malononitrile,[1] the chemistry of this unique molecule has received considerable attention. It is now more than fourty years when one of us started investigations on its potential utility for synthesis of functionally substituted heteroaromatics.[2,3] Over this long period Elnagdi *et al.* could develop synthetic approaches to a diversity of polyfunctional heteroaromatics including aminopyrans,[4] thiopyrans,[5] diaminopyrazoles,[6] aminopyrazolo[1,5-*a*]pyrimidines,[7] pyranopyrazoles,[8] pyridines,[9] quinolines[10] and diversity of other heteroaromatics.[11,12] It has been shown that despite the reported formation of pyrazole-3,5-diamine **1** *via* reacting malononitrile with hydrazines,[13] the pyrazolylcarbonitrile **2** was the really formed product.[14] In contrast, Elnagdi and

Abdulla[2] have shown that 2-arylhydrazonomesoxalonitrile **3** which is prepared *via* coupling malononitrile with aromatic diazonium salts, reacts with hydrazines to yield 4-arylazopyrazole-3,5-diamine **4** that has in recent years deserved several patents due to its observed potential antibacterial and anticancer activities (Scheme 1).[15,16] Moreover, a patent in 2005 has also claimed these compounds as potential hair dyes.[17] In the light of this, we were again attracted to synthesis of the diaminopyrazoles. Although Elguero *et al.*[18] and Soto *et al.*[19] have sometime ago reported the synthesis of 4-substituted pyrazole-3,5-diamines *via* reacting alkylmalononitrile with hydrazines and reported some of their chemistry, the chemistry of these pyrazole derivatives did not attract further attention perhaps as monoalkyl malononitriles are not readily accessible. A recent paper,[20] however, has reported that mixing aldehydes or ketones with malononitrile and reducing the most likely formed arylidenemalononitrile **5** with sodium borohydride affords arylmethylenemalononitrile **6** (Scheme 1). This synthesis appeared in our eyes an easy way to monosubstituted malononitriles that can subsequently be utilized for the synthesis of a variety of heteroaromatics by adopting our established synthetic methodologies.

RESULTS AND DISCUSSIONS

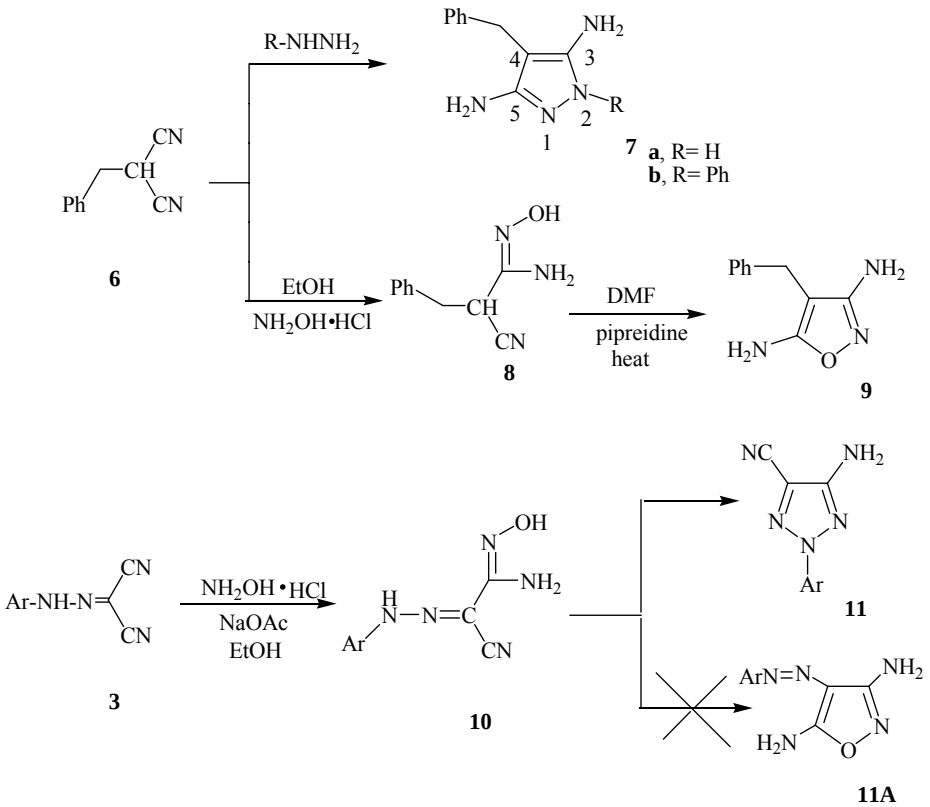
Mixing benzaldehyde, malononitrile and $NaBH_4$ in *iso*propanol has afforded **6** in 85 % yield. Compound **6** reacted smoothly with hydrazine hydrate and with phenylhydrazine to yield the pyrazole-3,5-diamines **7a** and **7b** respectively. On the other hand, reacting **6** with hydroxylamine hydrochloride in ethanolic solution containing sodium acetate resulted in the formation of amidooxime **8**. This could be successfully cyclized into the isoxazole-3,5-diamine **9** in 66 % yield upon refluxing in *N*,*N*-dimethylformamide containing a few drops of piperidine (Scheme 2).

Clearly initially nitrogen lone pair in hydrazine and hydroxylamine adds to the electrophilic activated nitrile. In case of reaction with hydrazine intermediately formed amidrazone could not be isolated yielding the aromatic diaminopyrazole. Aromatisity is deriving force for cyclization. Incase of reaction with hydroxyl amine the reaction stopped at amidoxime as energy in cyclization step is higher than that with hydrazine. Only upon reflux in DMF energy barrier for cyclization could be overcomed. Elguero *et al.*[18] and Soto *et al.*[19] had in the past conducted a similar work and the formed 3,5-diaminoisoxazole was sole 3,5-diaminoisoxazole. Recently trials to synthesize 4-arylazoisoxazole-3,5-diamines have failed, where the reaction of 2-arylhydrazonomesoxalonitrile **3** and hydroxylamine resulted only in the formation of amidooxime **10** which on attempted cyclization afforded 1,2,3-triazole **11**[21] (Scheme 2). We obtained ^{13}C NMR data very close to those reported by Elguero *et al.*[18] and Soto *et al*.[19] For example, in our hands the diaminopyrazole **7** revealed C-4 at δ = 87.79 ppm for **7a** and at δ = 90.25 ppm for **7b**, which are the expected positions for pyrazole C-4 shielded by two amino functions.



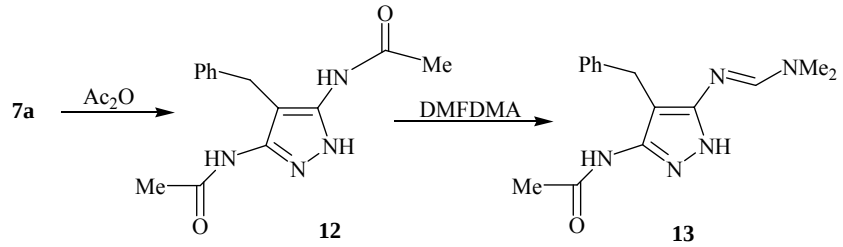
Scheme 1

Elguero's reported C-4 at δ = 89.9 ppm. The ^{13}C NMR of isoxazole **9** revealed a pattern very close to those of the pyrazolediamine **7a** for C-4, benzyl protons, C-3 and C-5 which appeared at δ = 142, δ = 164 ppm and δ = 166 ppm respectively. These are somewhat lower field than that for pyrazoles which is in accordance with increased deshielding of these carbons on replacing the nitrogen by an oxygen.



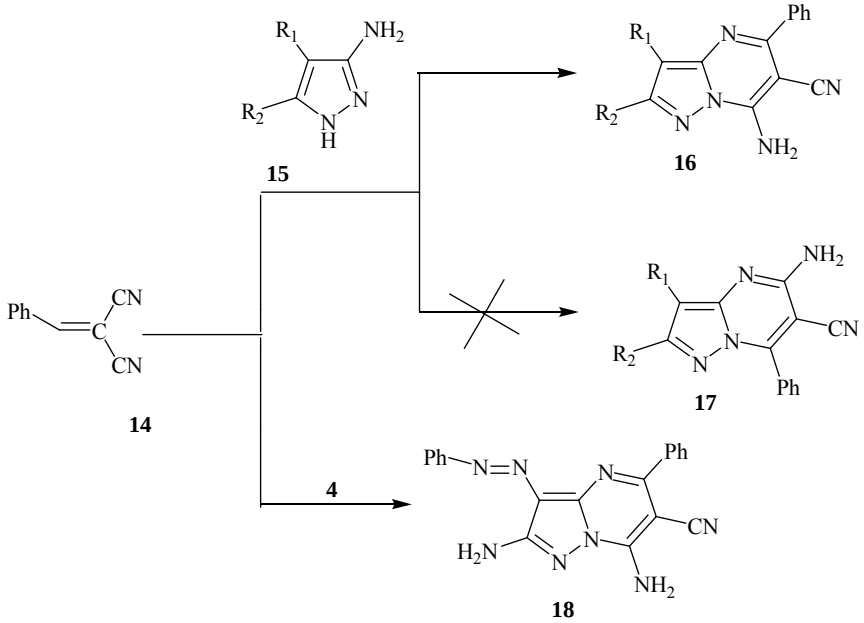
Scheme 2

When refluxed in acetic anhydride, compound **7a** afforded a diacetyl derivative for which structure **12** could be assigned based on ^{1}H NMR that revealed only one low field NH signal and amide signals at δ = 9.84 ppm and δ = 10.04 ppm. Refluxing this diacetyl derivative with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) afforded **13** *via* condensation of the amino function with the reagent and subsequent deacylation (cf. Scheme 3).



Scheme 3

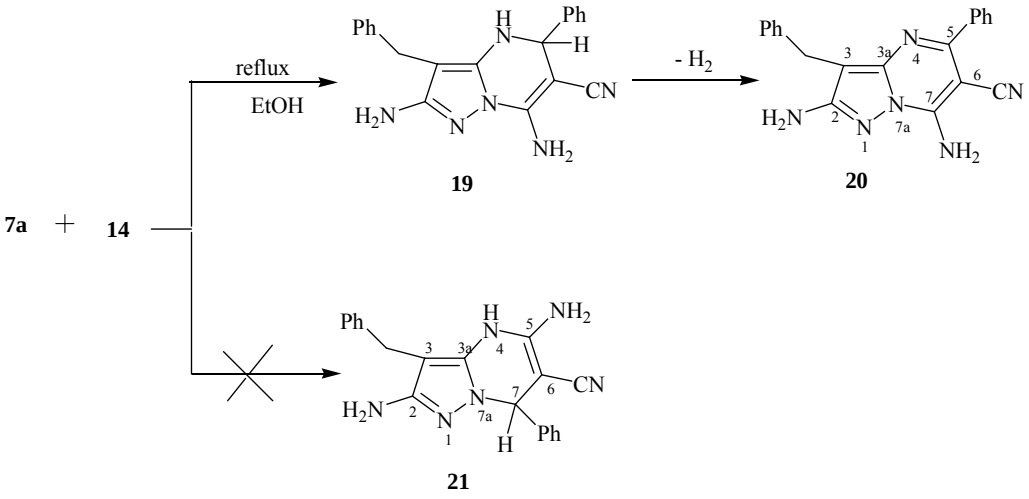
Elnagdi *et al.*[22] have reported that the addition of benzylidenemalononitrile **14** to 3(5*H*-1*H*)pyrazoleamine **15** afforded the 7-aminopyrazolo[1,5-*a*]pyrimidines **16**, not as previously stated the 5-aminoisomer **17** based on HMBC-N[15] NMR (Scheme 4).



Scheme 4

Although Soto *et al.*[19] have reported that, the reaction of arylidenemalononitrile **14** with **4** affords **18**, no convening evidence for an observed regio orientation has been offered (Scheme 4). In this investigation we have found that reacting **7a** with **14** affords a mixture of two products **19** and **20** of molecular masses 342 and 340 respectively. It is most likely that compound **19** of molecular weight (342) was autooxidised on long standing at room temperature into the other product **20** of molecular formula (340). Accordingly,

it was assumed that these products are the 2,7-diamino-3-benzyl-5-phenyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **19** and the 2,7-diamino-3-benzyl-5-phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **20** (Scheme 5).

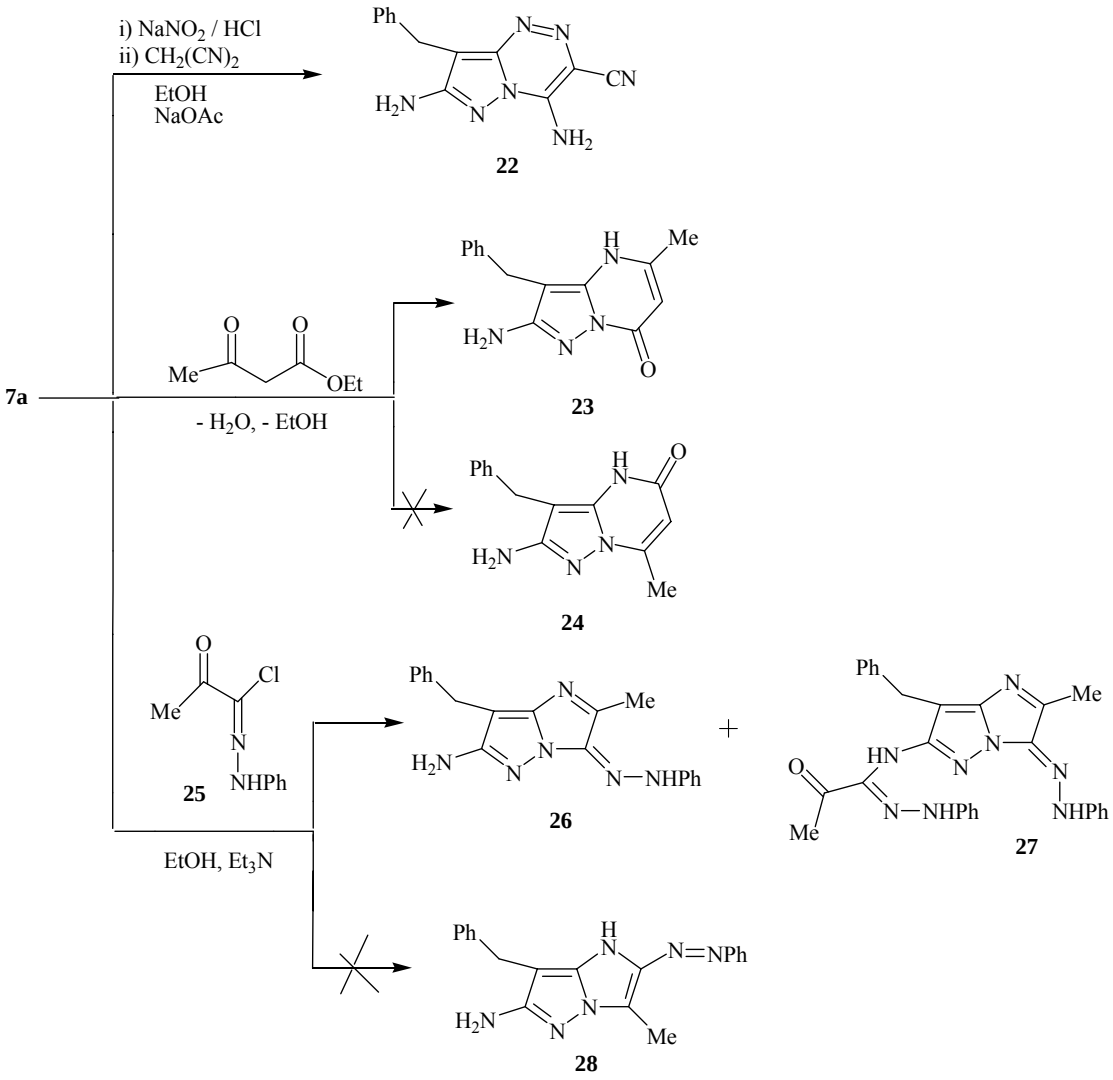


Scheme 5

To provide a conclusive evidence for these structure assignments, ^{15}N NMR and ^{15}N HMBC of **20** were run and inspected. ^{15}N NMR of **20** revealed six nitrogen signals at δ = 272, 236, 225, 186, 80, 52 ppm respectively. The signals at δ = 80 and δ = 52 ppm were attributed to the aminofunctions at C-2 and C-7 respectively. The aminofunction at δ = 52 ppm revealed a crosspeak peak at δ = 225 ppm for N-7a. It was thus concluded that the product of molecular formula (340) is compound **20**. If it was the 5-amino isomer formed *via* **21**, this amino function should have a cross peak with N-4 at δ = 272.[23]

Treatment of **7a** with sodium nitrite in the presence of hydrochloric acid afforded a diazonium salt that easily coupled with malononitrile to yield 2,7-diamino-3-benzylpyrazolo[5,1-*c*][1,2,4]triazine-6-carbonitrile **22** (Scheme 6). Reacting **7a** with ethyl acetoacetate afforded a product of condensation *via* water and ethanol elimination. This can be formulated as **23** or its isomeric form **24**. Structure **23** was readily established based on NOE difference experiment which indicated that NH and CH_3 protons are sterically proximal. Thus irradiating NH signal at δ = 12.09 ppm enhanced CH_3 signal at δ = 2.31 ppm and vise versa. Compound **7a** was reacted with 1-chloro-1-(2-phenylhydrazono)propan-2-one **25** in ethanolic triethylamine to yield a mixture of two products **26** and **27** of molecular formula $C_{19}H_{18}N_6$ (330.39) and $C_{28}H_{26}N_8O$ (490.22). The one of two products corresponds to the reaction of **7a** with one molecule of **25**, *via* hydrochloric acid and water elimination and the other formed from condensation of **7a** with two molecules of **25**, with elimination of two molecules of hydrochloric acid and one molecule of water. These were assigned to structures **26** and **27** respectively, however, we could not get an accurate elemental ' N ' analysis as for compound **27**. Structure **28** for the monocondensation product was excluded

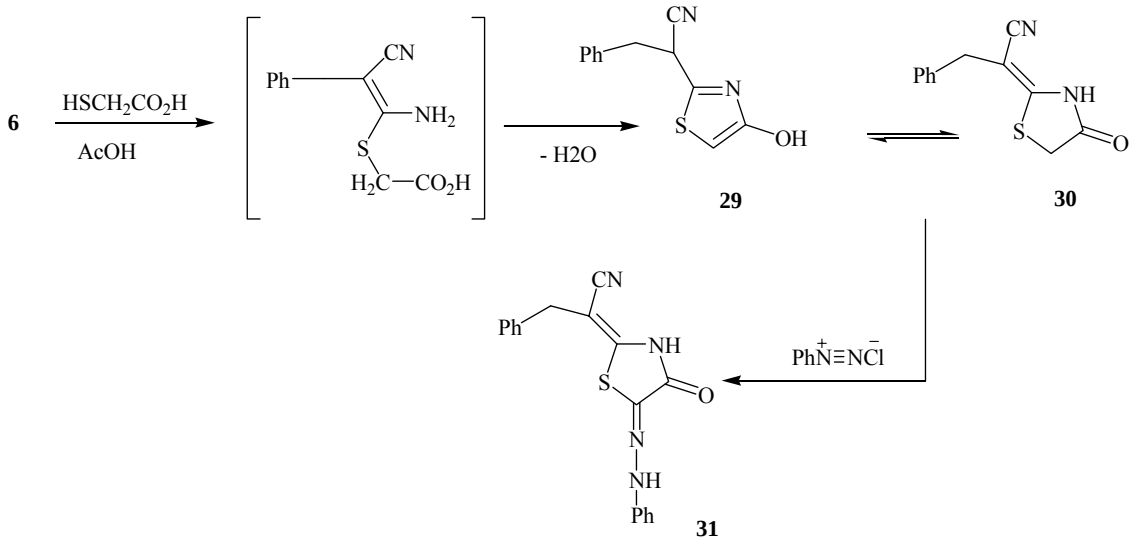
based on NOE that revealed special proximity of NH proton and aryl protons as in the case with **23** (Scheme 6).



Scheme 6

Benzylmalononitrile **6** could be also used for the synthesis of thiazolidin-4-ones *via* reaction of **6** with thioglycolic acid utilizing a procedure similar to that reported originally by Elnagdi *et al.*[11] for converting malononitrile into 2-(4-hydroxythiazol-2-yl)-3-phenylpropanenitrile. Thus refluxing **6** with thioglycolic acid in acetic acid afforded a product of addition and water elimination. The ^{1}H NMR, ^{13}C NMR and IR indicated that this product is a mixture of two of the tautomeric products **29** and **30**. IR revealed two signals corresponding to OH and CO groups and in ^{13}C-NMR an amide carbonyl carbon appeared at δ = 175.69 ppm. As indicated in (Scheme 7) initially sulphur lone pair adds to alectron deficient cyanocarbon. Formed adduct again cyclized *via* addition of formed amino group to carboxylic acid group and subsequent cyclization. These tautomeric products were coupled readily with benzene diazonium chloride to yield **31** (Scheme 7).

In conclusion the recently obtainable benzylmalononitrile is an interesting precursor to diaminoazoles, substituted thiazolidinones and products similar to these reported here which are expected to have potential biological activity of these unique diaminoazoles.



Scheme 7

EXPERIMENTAL

All melting points are uncorrected and were determined with Sanyo (Gallaenkamp) instrument. Infrared spectra were recorded in KBr and were determined on a Perkin-Elmer 2000 FT–IR system.^{1}H NMR spectra were determined on a Bruker DPX at 400 MHz and ^{13}C NMR were determined on Bruker DPX at 600 MHz spectrometer in $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard; chemical shifts are reported in δ (ppm). Mass spectra were measured on VG Autospec Q MS 30 and MS 9 (AEI) spectrometers, with EI 70 EV. Elemental analyses were measured by means of LEOCHNS-932 Elemental Analyzer.

Synthesis of compound 2-Benzyl-malononitrile 6

A solution of malononitrile (0.66 g, 0.01 mol) and benzaldehyde (1.00 mL, 0.01 mol) in *i*-PrOH (5 mL) was cooled to 0 ^{o}C. Sodium borohydride (0.756 g, 0.02 mol) was added and the reaction mixture was stirred (followed by TIC test using EtOAc : petroleum ether 1 : 1 until completion). If any intermediate was present or aldehyde is remaining, more sodium borohydride (up to 0.6 equivalent) was added. The reaction was carefully quenched with ice-H_2O and 1M HCl solution, extracted with CH_2Cl_2, filtered, and concentrated. The crude product was recrystallized from 60-80 traction was used as petroleum ether to give colorless crystals; yield 85 %; mp 88-90 ºC. *Anal*. Calcd for $C_{10}H_8N_2$ (156.19): C, 76.90; H, 5.16; N, 17.94. Found: C, 76.88; H, 5.16; N, 18.13. IR (KBr): υ_{max} = 2257 (CN), 2189 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 3.31 (d, 2H, CH_2, J = 8 Hz), 3.93 (t, 1H, CH, J = 8 Hz), 7.34-7.46 (m, 5H,

Ar-H); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 133.40, 129.73, 129.61, 129.24, 112.72, 37.03, 25.43. MS: *m/z* (%) 156 (M^+, 30), 91 (100), 65 (20).

General procedures for preparation of compounds (7a and 7b)

Equimolecular amounts of **6a,b** (0.01 mol) and hydrazine hydrate (0.5 g, 0.01 mol) or phenylhydrazine (1.08 g, 0.01 mol) in EtOH (20 mL) were refluxed for 5-10 h (monitored by TLC using EtOAc: petroleum ether 1 : 1). The reaction mixture was cooled and poured onto ice-water. The solid, so formed, was collected by filtration and recrystallized from EtOH.

4-Benzyl-1*H*-pyrazole-3,5-diamine (7a)

White product; yield 80 %; mp 149-150 ºC. *Anal*. Calcd for $C_{10}H_{12}N_4$ (188.10): C, 63.81; H, 6.43; N, 29.76. Found: C, 63.77; H, 6.43; N, 29.62. IR (KBr): υ_{max} = 3416, 3311 (NH_2), 3369, 3193 (NH_2), 3138 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 3.50 (s, 2H, CH_2), 4.26 (br, 4H, amino-H, D_2O exchangeable, 7.12-7.23 (m, 5H, Ar-H), 9.91 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 143.53, 129.30, 129.20, 126.22, 86.7, 80.20, 27.94. MS: *m/z* (%) 188 (M^+, 100), 172 (25), 145 (30), 130 (15), 111 (80), 91 (15), 77 (10).

4-Benzyl-1-phenyl-1*H*-pyrazole-3,5-diamine (7b)

Brown product; yield 75 %; mp 133-135 ºC. *Anal*. Calcd for $C_{16}H_{16}N_4$ (264.33): C, 72.70; H, 6.10; N, 21.20. Found: C, 72.57; H, 6.10; N, 21.31. IR (KBr): υ_{max} = 3422, 3265 (NH_2), 3335, 3157 (NH_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 3.62 (s, 2H, CH_2), 4.54 (br, 2H, NH_2, D_2O exchangeable), 5.01 (br, 2H, NH_2, D_2O exchangeable, 7.09-7.56 (m, 10H, Ar-H); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 154.15, 143.89, 141.88, 140.21, 128.73, 128.19, 127.94, 125.36, 123.69, 120.87, 90.25, 26.78. MS: *m/z* (%) 264 (M^+, 100), 246 (30), 221 (15), 187 (70), 155 (10), 19 (90), 77 (40).

Synthesis of 3-cyano-*N'*-hydroxy-4-phenylbutanamidine (8)

A mixture of **6a** (1.56 g, 0.01 mol), hydroxylamine hydrochloride (0.69 g, 0.01 mol), and sodium acetate (1.5 g) in EtOH (20 mL) was refluxed for 4 h. After cooling the mixture was poured onto ice-water. The solid, so formed, was collected by filtration and recrystallized from petroleum ether to give white crystals; yield 90 %; mp. 160-162 ºC *Anal*. Calcd for $C_{10}H_{11}N_3O$ (189.22): C, 63.48; H, 5.86; N, 22.21. Found: C, 63.44; H, 5.80; N, 22.39. IR (KBr): υ_{max} = 3446 (OH), 3352, 3195 (NH_2), 2256 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 3.21 (d, 2H, CH_2, J = 8 Hz), 3.62 (t, 1H, CH, J = 8 Hz), 5.87 (br, 2H, NH_2, D_2O exchangeable), 7.24-7.33 (m, 5H, Ar-H), 9.42 (br, 1H, OH, D_2O exchangeable); ^{13}C NMR (600 MHz, DMSO-d6): δ, ppm = 148.75, 138.03, 130.14, 129.52, 127.97, 119.73, 36.76, 36.54. MS: *m/z* (%) 189 (M^+, 25), 130 (30), 91 (100).

Synthesis of 4-benzylisoxazole-3,5-diamine (9)

A mixture of compound **8** (1.89 g, 0.01 mol), and *N*,*N*-dimethylformamide (DMF) (10 mL) was treated with a few drops of piperidine. The reaction mixture was refluxed for 6-8 h. (monitored by TLC using

EtOAc : petroleum ether 1 : 1), cooled and then poured onto ice-water. The solid, so formed, was collected by filtration and recrystallized from petroleum ether to give colorless crystals; yield 66 %; mp 70-72 ºC. *Anal*. Calcd for $C_{10}H_{11}N_3O$ (189.22): C, 63.48; H, 5.86; N, 22.21. Found: C, 63.60; H, 5.87; N, 22.19. IR (KBr): υ_{max} = 3367, 3301 (NH_2), 3343, 3184 (NH_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 3.47 (s, 2H, CH_2), 4.98 (br, 2H, NH_2, D_2O exchangeable), 6.07 (br, 2H, NH_2, D_2O exchangeable), 7.14-7.31 (m, 5H, Ar-H); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 166.36, 164.86, 142.18, 135.19, 131.25, 129.27, 81.07, 26.41. MS: *m/z* (%) 189 (M^+, 25), 155 (10), 130 (15), 117 (25), 91 (100), 65 (15).

Synthesis of *N*-(1-acetyl-5-amino-4-benzyl-*1H*-pyrazol-3-yl)acetamide (12)

A mixture of compound **7a** (1.88 g, 0.01 mol) and acetic anhydride (20 ml) was refluxed for 2 h. The reaction mixture was evaporated under reduced pressure in vacuum yielding a crude product. The crude product formed was recrystallized from petroleum ether to give a white product; yield 80 %; mp 197-199 ºC. *Anal*. Calcd for $C_{14}H_{16}N_4O_2$ (272.31): C, 61.75; H, 5.92; N, 20.57. Found: C, 61.64; H, 5.93; N, 20.42. IR (KBr): υ_{max} = 3263 (NH), 3062 (NH), 3028 (NH), 1742 (CO), 1675 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 1.88 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 3.61 (s, 2H, CH_2), 7.05-7.24 (m, 5H, Ar-H), 9.84 (br, 1H, NH, D_2O exchangeable), 10.04 (br, 2H, NH, D_2O exchangeable); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 170.16, 170.10, 148.37, 139.64, 136.58, 129.08, 129.02, 126.82, 116.15, 29.20, 23.48, 23.39. MS: *m/z* (%) 272 (M^+, 100), 229 (85), 186 (45), 127 (35), 90 (25).

Synthesis of *N*-(4-benzyl-5-((dimethylamino)methyleneamino)-1*H*-pyrazol-3-yl)acetamide (13)

A mixture of compound **12** (2.72 g, 0.01 mol) and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) (1.19 g, 0.01 mol) in xylene (20 mL)) was refluxed for 6 h. The reaction mixture was evaporated under reduced pressure in vacuum yielding a crude product, which was recrystallized from toluene to give a faint yellow product; yield 60 %; mp 148-150 ºC. *Anal*. Calcd for $C_{15}H_{19}N_5O$ (285.35): C, 63.14; H, 6.71; N, 24.54. Found: C, 62.94; H, 6.60; N, 24.72. IR (KBr): υ_{max} = 3263 (NH), 3295 (NH), 3062 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 1.62 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 7.05-7.21 (m, 5H, Ar-H), 7.76 (s, 1H, CH), 9.47 (br, 1H, NH, D_2O exchangeable), 11.6 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 170.39, 155.25, 142.73, 141.35, 129.07, 129.00, 126.45, 102.05, 79.88, 39.53, 34.57, 23.46. MS: *m/z* (%) 285 (M^+, 100), 272 (30), 225 (30), 187 (30), 172 (30), 91 (40), 77 (10).

Synthesis of compounds (19 and 20)

Equimolecular amounts of **7a** (1.88 g, 0.01 mol) and benzylidenemalononitrile (1.54 g, 0.01 mol) in EtOH (20 mL) were refluxed for 5-7 h (monitored by TLC using EtOAc : petroleum ether 1 : 1). The reaction mixture was evaporated under reduced pressure in vacuum yielding a crude product. This crude product contains two compounds which were separated by a long column chromatography using a mixture of petroleum ether and EtOAc (1:1) as an eluent. Compound **19** was separated at R_f = 0.54, while

compound **20** was separated at $R_f = 0.32$.

2,7-Diamino-3-benzyl-5-phenyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine-6-carbonitrile (19)

The solid, so formed after evaporation of the eluent, was recrystallized from petroleum ether to give a faint brown product; yield 35 %; mp 179-180 ºC. *Anal*. Calcd for $C_{20}H_{18}N_6$ (342.40): C, 70.16; H, 5.30; N, 24.54. Found: C, 70.07; H, 5.33; N, 24.13. IR (KBr): υ_{max} = 3440, 3332 (NH_2), 3381, 3329 (NH_2), 3203 (NH), 2172 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 3.56 (s, 2H, CH_2), 5.02-5.11 (br, 3H, CH, NH_2, D_2O exchangeable), 6.43 (br, 2H, NH_2, D_2O exchangeable), 7.13 (br, 1H, NH, D_2O exchangeable), 7.20-7.34 (m, 10H, Ar-H); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 158.35, 148.68, 145.17, 144.24, 141.98, 129.23, 128.93, 128.85, 128.30, 126.84, 126.41, 121.89, 88.19, 55.12, 54.01, 26.75. MS: *m/z* (%) 342 (M^+, 80), 264 (35), 186 (40), 111 (80), 91 (100).

2,7-Diamino-3-benzyl-5-phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile (20)

The solid, so formed after evaporation of the eluent, was recrystallized from petroleum ether (60-80) to give a faint yellow product; yield 55 %; mp 214-216 ºC. *Anal*. Calcd for $C_{20}H_{16}N_6$ (340.14): C, 70.57; H, 4.74; N, 24.69. Found: C, 70.33; H, 4.73; N, 24.40. IR (KBr): υ_{max} = 3443, 3352 (NH_2), 3417, 3300 (NH_2), 2212 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 3.89 (s, 2H, CH_2), 5.78 (br, 2H, NH_2, D_2O exchangeable), 7.11-7.79 (m, 10H, Ar-H), 8.13 (br, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 161.08, 158.56, 149.71, 146.50, 142.06, 138.88, 131.03, 130.29, 129.48, 129.23, 129.18, 126.71, 118.34, 96.45, 70.93, 27.44. MS: *m/z* (%) 340 (M^+, 100), 324 (15), 297 (30), 263 (80), 195 (10), 153 (10), 127 (10), 104 (20), 77 (10).

Synthesis of 4,7-diamino-8-benzylpyrazolo[5,1-*c*][1,2,4]triazine-3-carbonitrile (22)

A solution of malononitrile (0.66 g, 0.01 mol) in EtOH (50 mL) was treated with sodium acetate (5 g). The diazonium salt was then added gradually, with stirring, to the mixture. These diazonium salts was prepared from compound **7a** (1.88 g, 0.01 mol) dissolved in acetic acid (5 mL), concentrated hydrochloric acid (2.5 mL), and sodium nitrite (0.69 g, 0.01 mol) according to the standard literature procedures. After complete addition of the diazonium salt, the reaction mixture was kept at rt for 1 h. The resulting solid product was filtered. The solid, so formed, was collected by filtration and recrystallized from EtOH to give a yellow product; yield 80 %; mp 237-239 ºC. *Anal*. Calcd for $C_{13}H_{11}N_7$ (265.28): C, 58.86; H, 4.18; N, 36.96. Found: C, 58.91; H, 4.14; N, 37.08. IR (KBr): υ_{max} = 3314, 3162 (NH_2), 3235, 3159 (NH), 2225 (CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 4.21 (s, 2H, CH_2), 7.17-7.32 (m, 7H, Ar-H, NH_2, D_2O exchangeable), 9.28 (br, 1H, NH_2, D_2O exchangeable); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 146.06, 145.61, 143.15, 140.21, 128.41, 128.36, 126.11, 115.99, 112.46, 104.30, 28.20. MS: *m/z* (%) 265 (M^+, 40), 250 (60), 222 (30), 170 (20), 129 (30), 84 (100), 66 (20).

Synthesis of compound 2-amino-3-benzyl-5-methylpyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one (23)

Equimolecular amounts of **7a** (1.88 g, 0.01 mol) and EtOAc (1.30 g, 0.01 mol) in ethanol (20 mL) were

refluxed for 5-10 h (monitored by TLC using EtOAc : petroleum ether 1 : 1). The reaction mixture was cooled and poured onto ice-water. The solid, so formed, was collected by filtration and crystallized from EtOH, to give a white crystals, yield 85 %; mp 255-256 ºC. *Anal*. Calcd for $C_{14}H_{14}N_4O$ (254.29): C, 66.13; H, 5.55; N, 22.03. Found: C, 66.33; H, 5.55; N, 21.98. IR (KBr): υ_{max} = 3338, 3266 (NH_2), 3173 (NH), 1681 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 2.31 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 5.56 (br, 2H, NH_2, D_2O exchangeable, 7.16-7.30 (m, 5H, Ar-H), 7.68 (s, 1H, CH), 12.09 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 156.76, 150.78, 143.55, 141.21, 139.26, 128.75, 128.62, 126.44, 101.70, 95.22, 27.88, 19.08. MS: *m/z* (%) 254 (M^+, 15), 239 (100), 211 (20), 162 (50), 128 (15), 91 (25).

Synthesis of compounds (26 and 27)

Equimolecular amounts of **7a** (1.88 g, 0.01 mol) and **25** (1.96 g, 0.01 mol) in EtOH (20 mL) was treated with a few drops of Et_3N. and the whole mixture was refluxed for 5-7 h (monitored by TLC using EtOAc: petroleum ether 1 : 1). The reaction mixture was evaporated under reduced pressure in vacuum yielding a crude product. The crude was washed with petroleum ether to extract the compound **27** as a red product. The residue was crystallized from toluene to yield compound **26** as a red product also.

1-(7-Benzyl-2-methyl-3H-imidazo[1,2-*b*]pyrazol-3-ylidene)-2-phenylhydrazine (26)

Compound **26** was formed in 55 % yield; mp166-168 ºC. *Anal*. Calcd for $C_{19}H_{18}N_6$ (330.39): C, 69.07; H, 5.49; N, 25.44. Found: C, 68.87; H, 5.70; N, 25.65. IR (KBr): υ_{max} = 3328, 3292 (NH_2), 3228 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 2.50 (s, 3H, CH_3), 3.82 (s, 2H, CH_2), 5.67 (br, 2H, NH_2 D_2O exchangeable), 6.95-7.36 (m, 10H, Ar-H), 10.06 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 166.54, 160.11, 152.25, 142.67, 139.99, 131.50, 129.49, 128.31, 128.19, 125.99, 122.02, 113.57, 96.93, 26.69, 14.78. MS: *m/z* (%) 330 (M^+, 25), 274 (95), 236 (20), 278 (70), 160 (40), 147 (25), 105 (45), 77 (60).

***N*-(7-Benzyl-2-methyl-3-(2-phenylhydrazono)-3*H*-imidazo[1,2-*b*]pyrazol-6-yl)-2-oxo-*N*'-(phenyl-amino)propanamidine (27)**

Compound **27** was formed in 35 % yield; mp 181-183 ºC. *Anal*. Calcd for $C_{28}H_{26}N_8O$ (490.57): C, 68.55; H, 5.34; N, 22.84. Found: C, 68.76; H, 5.52; N, 20.43. IR (KBr): υ_{max} = 3436 (NH), 3336 (NH), 3252 (NH), 1654 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm = 2.60 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 6.70-7.40 (m, 16H, Ar-H, NH, D_2O exchangeable), 9.11 (br, 1H, NH, D_2O exchangeable), 9.71 (br, 1H, NH D_2O exchangeable); MS: *m/z* (%) 490 (M^+, 15), 474 (25), 434 (20), 398 (30), 274 (100), 178 (30), 77 (70).

Synthesis of 2-(4-hydroxythiazol-2-yl)-3-phenylpropanenitrile (29) and 2-(4-oxothiazolidin-2-ylidene)-3-phenylpropanenitrile (30)

Equimolecular amounts of **6a** (1.56 g, 0.01 mol) and thioglycolic acid (0.92 g, 0.01 mol) in acetic acid (20 mL) were refluxed for 5 h. The reaction mixture was cooled and poured onto ice-water. The solid, so

formed, was collected by filtration and recrystallized from EtOH, to give a brown product; yield 75 %; mp 180-182 ºC. *Anal*. Calcd for $C_{12}H_{10}N_2OS$ (230.05): C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.38; H, 4.59; N, 12.19; S, 13.84. The mixture of two tautomers give IR (KBr): υ_{max} = 3443 (OH), 3174 (NH), 2244 (CN), 2202 (CN), 1720 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 3.08 (d, 2H, CH_2, J = 8 Hz), 3.45 (s, 2H, CH_2), 3.91 (s, 2H, CH_2), 4.69 (t, 1H, CH, , J = 8 Hz), 7.26-7.41 (m, 11H, Ar-H, CH), 9.29 (br, 1H, OH, D_2O exchangeable), 11.85 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 175.69, 175.18, 154.34, 139.32, 138.02, 129.98, 129.63, 129.19, 128.04, 127.87, 127.70, 120.48, 120.44, 81.81, 57.47, 45.23, 35.75, 34.41, 34.35, 32.33. MS: *m/z* (%) 230 (M^+, 70), 196 (10), 161 (45), 129 (20), 101 (100), 83 (85), 73 (40).

Synthesis of 2-[4-oxo-5-(phenylhydrazono)-thiazolidin-2-ylidene]-3-phenylpropionitrile (31)

A solution of a mixture of two of the tautomiric products **29** and **30** (2.30 g, 0.01 mol) in EtOH (50 mL) was treated with sodium acetate (5 g). Benzenediazonium chloride was then added gradually, with stirring, to the mixture; the diazonium salt was prepared from aniline (0.93 g, 0.01 mol), concentrated hydrochloric acid (2.5 mL) according to standard literature procedures, and sodium nitrite (0.69 g, 0.01 mol). After complete addition of the diazonium salt, the reaction mixture was kept at rt for 1 h. The solid, so formed, was collected by filtration and recrystallized from EtOH, to give red product; yield 80 %; mp 236-237 ºC. *Anal*. Calcd for $C_{18}H_{14}N_4OS$ (334.4): C, 64.65; H, 4.22; N, 16.75; S, 9.59. Found: C, 64.65; H, 4.36; N, 16.88; S, 9.44. IR (KBr): υ_{max} = 3272 (NH), 3237 (NH), 2205 (CN), 1710 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm = 3.81 (s, 2H, CH_2), 7.01-7.43 (m, 11H, Ar-H, NH, D_2O exchangeable), 8.18 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (600 MHz, DMSO-d_6): δ, ppm = 165.45, 133.12, 129.97, 129.84, 129.74, 128.68, 128.50, 126.50, 123.49, 118.50, 117.51, 114.39, 114.30, 35.11. MS: *m/z* (%) 234 (M^+, 90), 207 (25), 181 (15), 90 (100).

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REFERENCES

1. F. Freeman, *Chem. Rev.*, 1969, **69**, 591.
2. M. H. Elnagdi and S. O. Abdoula, *J. Prakt. Chem*, 1973, **315**, 1009.
3. M. H. Elnagdi, *Tetrahedron*, 1974, **30**, 2791.
4. M. H. Elnagdi, H. A. El-fahham, and G. E. H. Elgemeie, *Heterocycles*,1983, **20,** 519.
5. G. E. H. Elgemeie, M. M. M. Sallam, S. M. Sherif, and M. H. Elnagdi, *Heterocycles*, 1985, **23**, 3107.

6. M. H. Elnagdi, E. M. Kandeel, and M. R. H. Elmoghayer, *Z. Naturforsch.*, 1977, **32b**, 307.
7. M. H. Elnagdi, M. R. H. Elmoghayer, and G. E. H. Elgemeie, *Advanced in Heterocyclic Chemistry*, 1987, **41**, 319.
8. S. Abdou, H. M. Fahmy, K. U. Sadek, and M. H. Elnagdi, *Heterocycles*, 1981, **16**, 2177.
9. Z. E. Kandeel, E. A. Hafez, M. A. Sleim, F. A. Abdellatif, and M. H. Elnagdi, *Heteroatom Chem.*, 1995, **6**, 305.
10. F. Al-Omran, M. M. Abdel Khalik, A. A. ElKhair, and M. H. Elnagdi, *J. Chem. Res (s)*, 1998, 294 *Ibid. (m)* 1201.
11. M. H. Elnagdi, M. R. H. Elmoghayer, A. E. F. G. Hammam, and S. A. Khallaf, *J. Heterocycl. Chem.*, 1979, **15**, 1541.
12. M. R. H. Elmoghayer, M. K. Ibraheim, A. Elghandour, and M. H. Elnagdi, *Synthesis*, 1981, 635.
13. H. Reimlinger, M. A. Reiren, and R. Merenyi, *Chem. Ber.*, 1970, **103**, 3252.
14. E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.*, 1959, **81**, 2452.
15. V. Kryštof, P. Cankar, I. Fryšová, J. Slouka, G. Kontopidis, P. Dzubák, M. Hajdúch, J. Srovnal, W. F. de Azevedo, M. Orság, M. Paprskárová, J. Rolcık, A. Látr, P. M. Fischer, and M. Strnad, *J. Med. Chem.*, 2006, **49**, 9500.
16. M. A. Chafeev, T. S. Daynard, Z. Zhang, S. Wang, G. B. Cheopiuk, S. V. Sviridov, U. S. patent 7105503 *Kinetek Pharmaceuticals*, (*Chem. Abstr.,* 2006, **144**, 9080A).
17. L. Gerard, U. S. patent 6890326, May 10, 2005, (*Chem. Abstr.,* 2005, **142**, 4270A).
18. A. Echevarria, J. Elguero, G. Yranzo, E. Diez-Barra, A. de la Hoz, A. Moreno, and M. Garcia-Martin, *J. Chem. Soc.,* 1993, **18**, 2229.
19. J. Vaquero, L. Fuentes, J. C. Del Castillo, M. Perez, J. L. Garcia, and J. L. Soto, *Synthesis*, 1987, **1**, 33.
20. J. C. Dunham, A. D. Richardson, and R. E. Sammelson, *Synthesis*, 2006, **4**, 680.
21. H. M. Al-Matar and S. M. Riyadh, *J. Heterocycl. Chem.*, submitted for publication.
22. H. F. Anwar, D. H. Fleita, H. Kolshorn, H. Meier, and M. H. Elnagdi, *Arkivoc*, 2006, **xv**, 133.
23. R. M. Silverstein, F. X. Webster, and D. J. Kiemle, 'Spectrometric Identification of Organic Compounds', 7 ed, Wiley & Sons. Inc., Hoboken, NJ, USA, p. 317.