SYNTHESIS OF SOME NOVEL BIS(PYRAZOLE), BIS(PYRIDINE) AND BIS(PYRAZOLO[5,1-c]-1,2,4-TRIAZINE DERIVATIVES

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Abstract – Treatment of N,N'-(ethane-1,2-diyl)bis(cyanoacetamide) (1) with hydrazonoyl chlorides 2a,b afforded bis(aminopyrazoles) 5a,b. Heating of compound 1 with arylmethylene propanedinitrile 9a-c afforded bis(pyridine) derivatives 13a-c. Also, compound 1 coupled smoothly with the arenediazonium salt generated from 3-chloroaniline or 5-amino-4-methyl-3-phenylpyrazole (16) to afford the corresponding hydrazones 15 or bis(pyrazolo[5,1-c]-1,2,4-triazine-3-carboxamide) 19. Refluxing of compound 1 with N,N-dimethylformamide dimethyl acetal (DMF-DMA) in xylene afforded bis(2-cyano-3-(dimethylamino)acrylamide) (20) which reacted with hydrazine hydrate to afford the novel bis(cyanoopyrazole) 23.

Recently, bis(heterocycles) have received grate deal of attention, not only for being model compounds for main chain polymers,1-6 but also because many biologically active natural and synthetic products have molecular symmetry.7 On the other hand, the synthesis of combinatorial libraries of heterocyclic compounds permits the testing of the biological properties of a vast array of compounds. Routes to novel skeletons, which could be synthesized using combinatorial methods, are presently a major research objective. In continuation of our recent work aiming at the synthesis of bis(heterocyclic) systems,8-12 it was found that compound 1, is versatile and readily accessible building block for the synthesis of several new bis(pyrazole)-, bis(pyridine)- and bis(pyrazolo[5,1-c]-1,2,4-triazine) derivatives of expected biological potency.

Treatment of compound 113 with hydrazonoyl chloride 2a14 in ethanolic sodium ethoxide solution at rt furnished a single product for which the two possible structures 5a and 8a can be envisaged (Scheme 1). However, elemental analyses and spectral data were in complete accordance with the bis(aminopyrazole)
structure 5a. The IR spectrum of 5a showed absorption bands at 3439, 3315, 3261, 1675 and 1639 cm\(^{-1}\) due to amino, amide-NH and two carbonyl groups, respectively. Its \(^1\)H NMR spectrum showed signals at \(\delta \) 2.49, 3.37 and two D\(_2\)O-exchangeable signals at \(\delta \) 6.83 and 9.65 due to CH\(_3\), NCH\(_2\), amino and imino protons, respectively in addition to an aromatic multiplet in the region \(\delta \) 7.53-7.62. Prompted by the foregoing results and to generalize this finding I also studied the reaction of the acetamide 1 with other hydrazonoyl chloride 2b\(^{15}\) under the same experimental conditions and obtained the respective aminopyrazole derivative 5b.

![Scheme 1]

Treatment of compound 1 with arylmethylenepropanedinitrile 9a-c\(^{16}\) furnished 1, 1’-(ethane-1,2-diyl)-bis(6-amino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) 13a-c (Scheme 2). The IR spectrum of compound 13a, taken as a typical example of the prepared series, revealed absorption bands at 1631, 2206, 3317 and 3392 cm\(^{-1}\) corresponding to carbonyl group, nitrile function and amino group, respectively. Its \(^1\)H NMR spectrum showed signals at \(\delta \) 3.13 and D\(_2\)O-exchangeable signals at \(\delta \) 4.18 due
to NCH₂ and NH₂ protons, respectively, in addition to an aromatic multiplet in the region δ 7.44-7.53. Compounds 13a-c are assumed to be formed via an initial Michael type adducts 10 followed by an intramolecular cyclization and dehydrogenation to the final products 13a-c (Scheme 2).

Scheme 2

Compound 1 coupled smoothly with the diazonium salt 14 generated from 3-chloroaniline in pyridine to afford N,N'-(ethane-1,2-diyl)bis[2-(N''-(4-chlorophenylhydrazonoyl)-2-cyanoacetamide] (15) (Scheme 3). The IR spectrum of 15 showed absorption bands at 1651 and 2222 cm⁻¹ corresponding to carbonyl group and nitrile function, respectively. Its ¹H NMR spectrum showed signal at δ 3.39 due to NCH₂ and two D₂O-exchangeable signals at δ 8.65 and 14.39 due to two NH protons, in addition to an aromatic multiplet in the region δ 7.10-7.88.

Scheme 3
In a similar manner, compound 1 coupled smoothly with the diazonium salt 17 generated from 5-amino-4-methyl-3-phenylpyrazole (16) in pyridine, at room temperature to afford a single product identified as \(N,N'-(\text{ethane-1,2-diyl})\text{bis}(4\text{-imino-8-methyl-7-phenyl-1,4-dihydropyrazolo}[5,1-c]-1,2,4-triazine-3-carboxamide})\) (19) (Scheme 4).

![Scheme 4](image)

The IR spectrum of 19 revealed the absence of a band corresponding to nitrile function. Its \(^1\text{H NMR}\) spectrum showed signals at \(\delta 2.48, 3.59\) due to \(\text{CH}_3\) and \(\text{NCH}_2\) protons, and three \(\text{D}_2\text{O}\)-exchangeable signals at \(\delta 9.01, 9.12\) and 9.2 due to three \(\text{NH}\) protons, in addition to aromatic multiplet in the region 7.30-7.89.

Treatment of compound 1 with \(N,N'\)-dimethylformamide-dimethylacetal (DMF-DMA) in refluxing xylene afforded \(N,N'-(\text{ethane-1,2-diyl})\text{bis}[2\text{-cyano-3-(dimethylamino)acrylamide}]\) (20). The \(^1\text{H NMR}\) spectrum of compound 20 showed signals at \(\delta 3.19, 3.22, 3.33, 7.19\) and 7.68 due to \(N,N'\)-dimethylamino, \(\text{NCH}_2\), \(\text{C}^=\text{CH}-\text{N}\) and amide-\(\text{NH}\) protons, respectively. When compound 20 was treated with hydrazine hydrate in refluxing EtOH, the novel \(3,3'-(\text{ethane-1,2-diyl})\text{bis}(\text{azanediyl})\text{bis}(1H\text{-pyrazole-4-carbonitrile})\) (23) was produced (Scheme 5). The IR spectrum of the isolated product showed absorption bands at 3314 and 2217 cm\(^{-1}\) characteristic for \(\text{NH}\) and nitrile function, respectively. Its \(^1\text{H NMR}\) spectrum showed signals at \(\delta 3.35, 8.40, 10.2\) and 11.0 corresponding to \(\text{NCH}_2\), \(\text{CH}\) and two \(\text{D}_2\text{O}\)-exchangeable signals corresponding to two \(\text{NH}\) protons. The foregoing spectral data supported the proposed structure 23 and ruled out the other possible pyrazole structure 24 (Scheme 5).

In conclusion, the reactivity of \(N,N'-(\text{ethane-1,2-diyl})\text{bis(cyanoacetamide})\) (1) was investigated as a versatile and readily accessible building block for the synthesis of new \(\text{bis(heterocycles)}\) of biological and pharmaceutical importance.
EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer.

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{CN} & \quad \text{NH} \\
\text{O} & \quad \text{Me}_2\text{N} \\
\text{CN} & \quad \text{HN} \\
\text{H}_2\text{N} & \quad \text{NH}_2\text{N} \\
\text{O} & \quad \text{HN} \\
\text{CN} & \quad \text{NMe}_2 \\
\text{HN} & \quad \text{H}_2\text{N} \\
\text{O} & \quad \text{HN} \\
\text{NH} & \quad \text{CN} \\
\text{NMe}_2 & \quad \text{Me}_2\text{N} \\
\text{H}_2\text{N} & \quad \text{NH}_2\text{N} \\
\text{O} & \quad \text{HN} \\
\text{CN} & \quad \text{NMe}_2 \\
\text{HN} & \quad \text{H}_2\text{N} \\
\text{O} & \quad \text{HN} \\
\text{NH} & \quad \text{CN} \\
\text{NMe}_2 & \quad \text{Me}_2\text{N} \\
\text{H}_2\text{N} & \quad \text{NH}_2\text{N} \\
\text{O} & \quad \text{HN} \\
\text{CN} & \quad \text{NMe}_2 \\
\text{HN} & \quad \text{H}_2\text{N} \\
\text{O} & \quad \text{HN} \\
\text{NH} & \quad \text{CN} \\
\text{NMe}_2 & \quad \text{Me}_2\text{N} \\
\text{H}_2\text{N} & \quad \text{NH}_2\text{N} \\
\text{O} & \quad \text{HN} \\
\text{CN} & \quad \text{NMe}_2 \\
\text{HN} & \quad \text{H}_2\text{N} \\
\text{O} & \quad \text{HN} \\
\text{NH} & \quad \text{CN} \\
\text{NMe}_2 & \quad \text{Me}_2\text{N} \\
\text{H}_2\text{N} & \quad \text{NH}_2\text{N} \\
\text{O} & \quad \text{HN} \\
\text{CN} & \quad \text{NMe}_2 \\
\text{HN} & \quad \text{H}_2\text{N} \\
\text{O} & \quad \text{HN} \\
\text{NH} & \quad \text{CN} \\
\text{NMe}_2 & \quad \text{Me}_2\text{N} \\
\text{H}_2\text{N} & \quad \text{NH}_2\text{N} \\
\end{align*}
\]

Scheme 5

\(^1\text{H}\) spectra were run at 300 MHz and \(^{13}\text{C}\) spectra were run at 75.46 MHz in deuterated dimethyl sulfoxide (DMSO-\(d_6\)). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. \(N, N'\)-((Ethane-1,2-diyl)bis[cyanocacetamide] (1),\(^{13}\) hydrazonoyl halides 2\(_a\),\(^{14}\) 2\(_b\),\(^{15}\) arylmethylenepropanedinitrile 9\(_a\)-c\(^{16}\) and 5-amino-4-methyl-3-phenyl-pyrazole (16)\(^{17}\) were prepared following the literature procedure.

**Reaction of** \(N, N'\)-((Ethane-1,2-diyl)bis(cyanocacetamide)(1) **with hydrazonoyl halides.**

**General procedure:**

Compound 1 (0.194 g, 1 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (46 mg, 2 mmol) and absolute EtOH (20 mL)] with stirring. After stirring the resulting
solution for 15 min., the appropriate hydrazonoyl halide 2a,b (2 mmol) was added portionwise and the reaction mixture was stirred further for 12 h at rt. The solid product that formed was filtered off, washed with water and dried. Recrystallization from the proper solvent afforded the corresponding bis(pyrazole) derivatives 5a,b.

\[ N,N^\prime-(\text{Ethane-1,2-diyl})\text{bis}(3\text{-acetyl-5-amino-1-phenyl-1H-pyrazole-4-carboxamide})(5a). \]
Yield (53%), mp > 300 °C (DMF); IR (KBr) ν 1639 (C=O), 1675 (C=O), 3261 and 3315 (NH2), 3439 (NH) cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)) δ 2.49 (s, 6H, 2CH\(_3\)), 3.37 (s, 4H, 2NCH\(_2\)), 6.83 (s, 4H, D\(_2\)O-exchangeable 2NH\(_2\)), 7.53-7.62 (m, 10H, Ar-H), 9.65 (s, 2H, D\(_2\)O-exchangeable 2NH); MS m/z (%) 271 (6.91), 258 (1.47), 257 (M\(^+\)/2, 2.64). Anal. Calcd for C\(_{26}\)H\(_{26}\)N\(_8\)O\(_4\): C, 60.69; H, 5.09; N, 21.78. Found: C, 60.61; H, 5.02; N, 21.72%.

\[ N, N^\prime-(\text{Ethane-1,2-diyl})\text{bis}(5\text{-amino-1,3-diphenyl-1H-pyrazole-4-carboxamide}) (5b). \]
Yield (66%), mp > 300 °C (DMF); IR (KBr) ν 1632 (C=O), 3055 (NH), 3314 and 3422 (NH\(_2\)) cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)) δ 3.20 (s, 4H, 2NCH\(_2\)), 6.29 (s, 4H, D\(_2\)O-exchangeable 2NH\(_2\)), 7.18-7.62 (m, 20H, Ar-H), 9.57 (s, 2H, D\(_2\)O-exchangeable 2NH). Anal. Calcd for C\(_{34}\)H\(_{30}\)N\(_8\)O\(_2\): C, 70.09; H, 5.19; N, 19.23. Found: C, 70.01; H, 5.24; N, 19.25%.

**Synthesis of 1,1'-\(\text{Ethane-1,2-diyl}\)\text{bis}[6-amino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile] 13a-c.**

General procedure:

To a solution of the appropriate arylmethylenepropanedinitrile 9a-c (2 mmol) in EtOH (20 mL) was added compound 1 (0.194 g, 1 mmol), and few drops of piperidine and the reaction mixture was heated under reflux for 2 h. The solid product that formed was collected by filtration, washed with EtOH and then crystallized from a proper solvent to afford the corresponding bis(pyridine) derivatives 13a-c.

\[ 1,1'-(\text{Ethane-1,2-diyl})\text{bis}(6\text{-amino-4-phenyl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile})(13a). \]
Yield (70%), mp > 300 °C (DMF); IR (KBr) ν 3392 and 3317 (NH\(_2\)), 2206 (C≡N), 1631 (C=O) cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)) δ 3.13 (s, 4H, 2NCH\(_2\)), 4.18 (s, 4H, D\(_2\)O-exchangeable 2NH\(_2\)), 7.44-7.53 (m, 10H, Ar-H); \(^13\)C NMR (DMSO-\(d_6\)) δ 43.92, 76.92, 83.28, 117.15, 117.49, 127.79, 128.40, 129.72, 135.34, 158.02, 159.33, 160.39. Anal. Calcd for C\(_{28}\)H\(_{18}\)N\(_8\)O\(_2\): C, 67.46; H, 3.64; N, 22.48. Found: C, 67.41; H, 3.60; N, 22.51%.

\[ 1,1'-(\text{Ethane-1,2-diyl})\text{bis}(6\text{-amino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile}) (13b). \]
Yield (72%), mp > 300 °C (DMF); IR (KBr) ν 3332 and 3179 (NH\(_2\)), 2214 (C≡N), 1651 (C=O) cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)) δ 3.02 (s, 4H, 2NCH\(_2\)), 3.83 (s, 6H, 2OCH\(_3\)), 4.21 (s, 4H, D\(_2\)O-exchangeable 2NH\(_2\)), 7.06 (d, 4H, ArH’s, J = 8.7 Hz), 7.4 (d, 4H, ArH’s, J = 8.7 Hz). Anal. Calcd for C\(_{30}\)H\(_{22}\)N\(_8\)O\(_4\): C, 64.51; H, 3.97; N, 20.06. Found: C, 64.57; H, 3.92; N, 20.10%.

\[ 1,1'-(\text{Ethane-1,2-diyl})\text{bis}(6\text{-amino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile}) (13c). \]
(13c). Yield (77%), mp > 300 °C (DMF); IR (KBr) ν 3333 and 3179 (NH₂), 2214 (C≡N), 1636 (C=O) cm⁻¹; ¹H NMR (DMSO-d₆) δ 3.01 (s, 4H, 2NCH₂), 4.17 (s, 4H, D₂O-exchangeable 2 NH₂), 7.48 (d, 4H, ArH’s, J = 8.4 Hz), 7.62 (d, 4H, ArH’s, J = 8.4 Hz); ¹³C NMR (DMSO-d₆) δ 43.92, 76.93, 89.16, 117.03, 117.39, 128.59, 129.80, 134.19, 134.57, 157.97, 158.09, 160.28. Anal. Calcd for C₂₈H₁₆N₈Cl₂O₂: C, 59.27; H, 2.84; N, 19.75. Found: 59.32; H, 2.80; N, 19.70%.

Synthesis of N,N’-(ethane-1,2-diyl)bis[2-(N”-(4-chlorophenylhydrazonoyl)-2-cyanoacetamide] (15) and N,N’-(ethane-1,2-diyl)bis(4-imino-8-methyl-7-phenyl-1,4-dihydropyrazolo[5,1-c]-1,2,4-triazine-3-carboxamide)(19).

General procedure.
To a cold solution of the compound 1 (0.194 g, 1 mmol) in pyridine (20 mL) was added the appropriate diazonium salt generated from 3-chloroaniline or 5-amino-4-methyl-3-phenylpyrazole (16) [prepared by diazotizing the appropriate amine (2 mmol) in hydrochloric acid (6M, 1.2 mL) with sodium nitrite solution (0.138 g, 2 mmol) in water (1.0 mL)]. The addition was carried out portionwise with stirring at 0-5 °C over a period of 30 min. After complete addition, the reaction mixture was stirred for further 4 h, then kept in an ice chest for 12 h, and finally diluted with water. The precipitated solid was collected by filtration, washed with water, dried and finally recrystallized from a proper solvent to afford the corresponding products 15 and 19, respectively.

N,N’-(Ethane-1,2-diyl)bis[2-(N”-(4-chlorophenylhydrazonoyl)-2-cyanoacetamide] (15). Yield (66%), mp 270 °C (DMF); IR (KBr) ν 3356 (NH), 3074 (NH), 2222 (C≡N), 1651 (C=O) cm⁻¹; ¹H NMR (DMSO-d₆) δ 3.39 (s, 4H, 2NCH₂), 7.10-7.88 (m, 8H, Ar-H), 8.65 (s, 2H, D₂O-exchangeable 2NH), 14.39 (s, 2H, D₂O-exchangeable 2NH); MS m/z (%) 473 (14.1), 472 (30.6), 470 (M⁺-1, 30.5), 248 (14.5), 112 (8.4), 111 (64.5). Anal. Calcd for C₂₀H₁₆Cl₂N₈O₂: C, 50.97; H, 3.42; N, 23.78. Found: C, 50.93; H, 3.47; N, 23.72.%

N,N’-(Ethane-1,2-diyl)bis(4-imino-8-methyl-7-phenyl-1,4-dihydropyrazolo[5,1-c]-1,2,4-triazine-3-carboxamide)(19). Yield (62%), mp 283 °C (DMF); IR (KBr) ν 3306 (NH), 3209 (NH), 1659 (C=O) cm⁻¹; ¹H NMR (DMSO-d₆) δ 2.48 (s, 6H, 2CH₃), 3.59 (s, 4H, 2NCH₂), 7.30 (m, 2H), 7.47 (m, 4H), 7.89 (d, 4H), 9.01 (s, 2H, D₂O-exchangeable 2NH), 9.12 (s, 2H, D₂O-exchangeable 2NH), 9.20 (s, 2H, D₂O-exchangeable 2NH). Anal. Calcd for C₂₈H₂₆N₁₂O₂: C, 59.78; H, 4.66; N, 29.88. Found: C, 59.72; H, 4.63; N, 29.83%.

Reaction of N,N’-(ethane-1,2-diyl)bis(cyanoacetamide) (1) with DMF-DMA.
A mixture of the compound 1 (1.94 g, 10 mmol) and N,N-dimethylformamide dimethyl acetal (DMF-DMA) (2.66 ml, 20 mmol) in dry xylene (30 mL) was refluxed for 3 h, then left to cool to rt. The yellow precipitated product was filtered off, washed with petroleum ether and dried. Crystallization from EtOH/ DMF gave N,N’-(ethane-1,2-diyl)bis[2-cyano-3-(dimethylamino)acrylamide] (20) in 54 % yield,
mp 224 °C; IR (KBr) ν 3348 (NH), 2195 (C≡N), 1655 (C=O) cm⁻¹; ¹H NMR (DMSO-d₆) δ 3.19 (s, 6H, 2CH₃), 3.22 (s, 6H, 2CH₃), 3.33 (s, 4H, 2NCH₂), 7.19 (s, 2H, 2CH), 7.68 (s, 2H, D₂O-exchangeable 2NH); ¹³C NMR (DMSO-d₆) δ 37.90, 46.69, 69.90, 119.49, 155.86, 164.81.

Anal. Calcd for C₁₄H₂₀N₆O₂: C, 55.25; H, 6.62; N, 27.61. Found: C, 55.20; H, 6.67; N, 27.57%.

**Reaction of N,N'-((ethane-1,2-diyl)bis[2-cyano-3-(dimethylamino)acrylamide] (20) with hydrazine hydrate.**

To a solution of the compound 20 (0.30 g, 1 mmol) in EtOH (20 mL), hydrazine hydrate (80%, 0.2 mL, 2 mmol) was added and the reaction mixture was refluxed for 4 h, then left to cool. The solid product so formed was filtered off, washed with EtOH and dried. Recrystallized from DMF afforded 3,3'-(ethane-1,2-diylbis(azanediyl)bis[1H-pyrazole-4-carbonitrile] (23), yield (66%), mp > 300 °C; IR (KBr) ν 3314 (NH), 2217 (C≡N) cm⁻¹; ¹H NMR (DMSO-d₆) δ 3.35 (s, 4H, 2NCH₂), 8.40 (s, 2H, 2CH), 10.2 (s, 2H, D₂O-exchangeable 2NH), 11.0 (s, 2H, D₂O-exchangeable 2NH). Anal. Calcd for C₁₀H₁₀N₈: C, 49.58; H, 4.16; N, 46.26. Found: C, 49.52; H, 4.20; N, 46.21%.

**REFERENCES**