Preparation of Polyfunctionally Substituted Pyridine-2(1H)-Thione Derivatives as Precursors to Bicycles and Polycycles

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Abstract

Reaction of acetylacetone with 1 mole of dimethylformamide dimethyl acetal (DMFDMA) affords enamine 2a which reacts with cyanothioacetamide to give pyridinethione 3a. Pyridinethione 3a reacts with methyl iodide, halogenated compounds, aromatic aldehyde and malononitrile/elemental sulfur to yield compounds 7-10 respectively. Reactions of thioether 7 in ethanolic K2CO3, 1 mole DMFDMA and 4-(dimethylamino)benzaldehyde give compounds 11, 13, 14 respectively. Enaminone 12 can be prepared by reaction of compound 11 with DMFDMA. We have demonstrated some reactions in order to show the potential usefulness of the prepared compounds for the preparation of new bipyridyl compounds 15, 16, 18, bicyclic compounds 17 and uncommon tricyclic compounds 20, 21, 22 and 23 respectively using DMFDMA.

Keywords
Acetyl Acetone, DMFDMA, Malononitrile Dimmer, Bipyridyl, 5-Acetylpyridinethione

1. Introduction

Formamide acetals are useful reagents in organic synthesis; [1] [2] their main application has been used for functional group transformations [3], but they may also be regarded as one-carbon synthons in the construction of carbon skeletons. One type of reaction, which is potentially valuable for the future purpose, is the reaction of N,N’-dimethylformamide dimethyl acetal (DMFDMA) with 1,3-dicarbonyl compounds 1 to give enamines 2 [2] [4] (Figure 1).

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We have reported that enamines 2 were used as precursors in the synthesis of pentasubstituted pyridines 3-6 [5]-[8] (Figure 2).

The treatment of acetyacetone (1a) with dimethyl formamide dimethylacetal (DMFDMA) in dry DMF under nitrogen and stirring over night afforded the corresponding enamine 2a which on treatment with cyanothioacetamide and sodium hydride in dry DMF (in situ) afforded pyridine-2(1H)-thione (3a) [6], when the enamine 2a was treated with cyanothioacetamide in ethanol and pepridine as a base afforded the pyridine-2(1H)-thione (5a) [7] [12] (Figure 3).

2. Results and Discussion

In conjunction of this work, we report here the reaction of acetylacetone 1a with one mole of N,N'-dimetylformamide dimethyl acetal (DMFDMA) in dry dioxane gave the corresponding enamine 2a. The treatment of this enamine (in situ) with cyanothioacetamide in ethanol in the presence of sodium ethoxide under reflux gave 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a with a very good yield [7], Scheme 1.

We have found that the prepared compound 3a included three functional groups which are thioamido group, cyano group and acetyl group. These functional groups can be used for the preparation of bicyclic or polycyclic compounds of biological interest. Thus, some illustrative reactions designed to demonstrate the potential usefulness of 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a for further heterocyclic synthesis. Therefore, the reaction of 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a with methyl iodide in alcoholic sodium hydroxide afforded the corresponding thioether derivative 7, which in turn is a good intermediate for the preparation of further heterocyclic compounds of biological interest. The structure of the isolated compound 7 is confirmed by spectral analysis. The IR spectrum shows the disappearance of (NH) group. Also, the 1H NMR spectrum shows the disappearance of the thioamide proton and the appearance of a singlet signal corresponding to (SCH3) at δH = 2.63 ppm. Also, the mass spectrum shows the molecular ion peak at m/e 206 which corresponding to the molecular formula (C10H10N2OS). The reaction of 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a with ethyl chloroacetate or chloroacetamides in ethanolic sodium ethoxide afforded the corresponding 5-acetyl-3-amino-6-methylthieno[2,3-b]pyridine derivatives 8a-c in a good yield. The structure of the isolated compounds is confirmed by elemental and spectral analysis. The IR spectrum shows the disappearance of cyano group and appearance of amino group at νmax = 3427, 3328 cm⁻¹ in compound 8a as example beside the other functional groups. Also, the mass spectra show the molecular ion peaks fit to all compounds 8a-c. The presence of acetyl group in 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a is useful for the preparation of fused heterocyclic compounds. So that the reaction of compound 3a with aldehydes like 4-(dimethylamino) benzaldehyde and 4-methylbenzaldehyde in ethanolic sodium hydroxide afforded the corresponding chalcones 9a,b. The structure of the isolated chalcones is confirmed by elemental analysis as well as spectral analysis. The mass spectra show the molecular ion peak at m/e 323 which corresponding to the molecular formula (C18H17N3OS). Also, the 1H NMR spectra of these compounds 9a,b show the disappearance of the signal corresponding to the methyl of acetyl group and the appearance of two doublets signals corresponding to the two protons of double bond of chalcone. Finally, 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a was treated with malononitrile and sulfur element (Gewald’s reaction) in ethanol in the presence of triethylamine as a base to afford 5-(5-amino-4-cyanothiophen-3-yl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 10 in a good yield, Scheme 1. The IR spectrum of compound 10 shows the appearance of amino group at νmax = 3435, 3350 cm⁻¹ beside the other
Different polysubstituted pyridines have been prepared.

Tetrasubstituted pyridinethione have been prepared.

Scheme 1. Synthesis of pyridine (1H)-thione derivative 3a and its reactions with MeI, α-chloroketones, aldehydes and malononitrile.

Functional groups. Also, $^1$H NMR spectrum of compound 10 shows singlet signal at $\delta_{H} = 2.45$ ppm corresponding to methyl group and singlet signal at $\delta_{H} = 6.95$ ppm corresponding to amino group and singlet signal at $\delta_{H} = 7.07$ ppm corresponding to CH thiophene ring and singlet signal at $\delta_{H} = 7.2$ ppm corresponding to CH pyridine ring.

5-Acetyl-6-methyl-2-(methylthio)nicotinonitrile 7 can be used as intermediate for further preparation of hetero-
rocyclic compounds. So that compound 7 was treated with potassium carbonate in ethanol to afford 5-acetyl-2-ethoxy-6-methylnicotinonitrile 11. This compound was formed by nucleophilic substitution of SMe by OEt group. The structure of the isolated compound is confirmed by elemental and spectral analyses. The mass spectrum shows the molecular ion peak at m/e 204 corresponding to the molecular formula (C_{11}H_{10}N_{6}O_{2}). Also, the \(^1\)H NMR spectrum shows the disappearance of SMe signal and appearance of two signals; a triplet at \(\delta_{\text{H}} = 1.43\) ppm and a quartet at \(\delta_{\text{H}} = 4.54\) ppm corresponding to the OEt moiety, in addition to the rest of signals corresponding to the other protons in the molecule. Compound 11 was reacted with N,N'-dimethylformamide dimethyl acetal (DMFDMA) in dry xylene to give the corresponding enamine 12 in a good yield. The mass spectrum of compound 12 shows the molecular ion peak at m/e 259 which corresponding to the molecular formula (C_{12}H_{11}N_{2}O_{2}). Also, the \(^1\)H NMR spectrum of compound 12 shows the disappearance of the singlet signal which is related to the methyl of acetyl group and the appearance of two singlet signals at \(\delta_{\text{H}} = 2.68\) and 3.04 ppm corresponding to the two methyl groups of NMe\(_2\) moiety. Consequently the \(^1\)H NMR spectrum shows the appearance of two doublets at \(\delta_{\text{H}} = 6.25\) ppm and 7.87 ppm corresponding to the two protons of the enamine double bond.

Enamine 13 can be prepared in a good yield by reaction of 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a with two moles of N,N'-dimethylformamide dimethylelacetal (DMFDMA) in dry xylene or by the reaction of 5-acetyl-6-methyl-2-(methylthio)nicotinonitrile 7 with one mole of N,N'-dimethylformamide dimethylelacetal (DMFDMA) in dry xylene. The structure of the isolated compound is confirmed by elemental and spectral analysis. Whereas the mass spectrum shows the molecular ion peak at m/e 261 which corresponding to the molecular formula (C_{11}H_{13}N_{3}O_{2}). Also, the \(^1\)H NMR spectrum of it shows the disappearance of the singlet signal which is related to the methyl of acetyl group and appearance of two singlet signals at \(\delta_{\text{H}} = 2.62\) and 2.64 ppm corresponding to the two methyl groups of NMe\(_2\) moiety. Consequently, the \(^1\)H NMR spectrum shows the appearance of two doublets at \(\delta_{\text{H}} = 5.28\) ppm and 7.75 ppm corresponding to the two protons of double bond of enamine.

Chalcone 14 can either be prepared by the reaction of compound 7 with (4-(dimethylamino)benzaldehyde) in ethanolic sodium hydroxide or by treatment of compound 9a with methyl iodide in ethanolic sodium hydroxide. The mass spectrum of compound 14 shows the molecular ion peak at m/e 337 corresponding to the molecular formula (C_{12}H_{10}N_{2}O_{2}). Also, the \(^1\)H NMR spectrum of compound 14 shows singlet signal at \(\delta_{\text{H}} = 2.62\) ppm corresponding to methyl group and singlet signal at \(\delta_{\text{H}} = 2.66\) ppm corresponding to SCH\(_3\) and two singlet signal at \(\delta_{\text{H}} = 2.9, 3.04\) ppm corresponding to NMe\(_2\) moiety and appearance of some signals of other protons in molecule.

For preparation of bipyridyl derivatives, we have carried out the reaction of chalcones 5-(3-(4-(dimethylamino)phenyl)acryloyl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 9a and 5-(3-(4-(dimethylamino)phenyl)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile 14 with malononitrile dimmer [9] in acetic acid and ammonium acetate afforded the corresponding bipyridyl derivatives 6-(dicyanomethylene)-4-(4-(dimethylamino)phenyl)-2'-methyl-6'-thioxo-1',1',6,6'-tetrahydro-[2,3'-bipyridine]-5,5'-dicarbonitrile 15 and 6-(dicyanomethylene)-4-(4-(dimethylamino)phenyl)-2'-methyl-6'- (methylthio)-1,6-dihydro-[2,3'-bipyridine]-5,5'-dicarbonitrile 16 respectively. The reaction proceeds by Michael addition followed by cyclization through condensation as shown in Scheme 2.

The compound 16 can also be obtained by the reaction of 6-(dicyanomethylene)-4-(4-(dimethylamino)phenyl)-2'-methyl-6'-thioxo-1',1',6,6'-tetrahydro-[2,3'-bipyridine]-5,5'-dicarbonitrile 15 with methyl iodide in alcoholic sodium hydroxide Scheme 2.

The structure of the isolated compounds 15 and 16 is established by elemental and spectral analysis. Whereas the mass spectra of these compounds show the molecular ion peaks at m/e 435 corresponding to the molecular formula (C_{23}H_{17}N_{7}S), and at m/e 449 corresponding to the molecular formula (C_{25}H_{19}N_{7}S) for 15 and 16 respectively. The IR spectra of both compounds 15 and 16 show the disappearance of the carbonyl group and the appearance of NH group. Also, the \(^1\)H NMR spectra of these compounds show signals fit to structures 15 and 16.

For further preparation of heterocyclic compounds [10], we carried out the following reactions. The reaction of enamine 13 with excess hydrazine hydrate in ethanol afforded 6-methyl-5-(1H-pyrazol-3-yl)-1H-pyrazolo[3, 4-b]pyridin-3-amine 17 in a good yield as shown in Scheme 3. The IR spectrum of compound 17 shows the disappearance of the cyan group and the appearance of NH\(_2\) and NH groups at \(\nu_{\text{amide}}\) at 3405 cm\(^{-1}\), 3329 cm\(^{-1}\) and 3136 cm\(^{-1}\) respectively. Also, the mass spectrum of compound 17 shows the molecular ion peak at m/e 214 corresponding to the molecular formula (C_{15}H_{18}N_{2}). Also, the \(^1\)H NMR spectrum of compound 17 shows signals fit to the structure.
Scheme 2. Reactions of tetrasubstituted pyridine 7 with DMF DMA, alcoholic K2CO3 and p-N, N-dimethylaminobenzaldehyde.
Also, the enamine 13 is treated with cyanothioacetamide in acetic acid and ammonium acetate afforded 2'-methyl-6'-(methylthio)-6-thioxo-1,6-dihydro-[2,3'-bipyridine]-5,5'-dicarbonitrile 18. The reaction is started by Michael addition of cyanothioacetamide on the double bond followed by elimination of dimethylamine (HNMe₂) and cyclization with the carbonyl group. The structure of the isolated compound 18 is confirmed by elemental and spectral analysis. The IR spectrum of compound 18 shows the disappearance of carbonyl group and appearance of NH group at $\nu_{\text{max}}$ at 3428 cm$^{-1}$. The mass spectrum of compound 18 shows the molecular ion peak at $m/e$ 298 corresponding to the molecular formula (C₁₄H₁₀N₄S₂). Also, the $^1$H NMR spectrum of compound 18 shows the disappearance of protons of NMe₂ moiety and appearance of NH proton beside the other protons.

Another type of bipyridyl derivatives 19a,b can be prepared by the reaction of the enamines 12 and 13 with malononitrile dimer in acetic acid and ammonium acetate. This reaction proceeds by Michael addition of malononitrile dimer, followed by elimination of dimethylamine (HNMe₂) and cyclization through condensation of amino group with carbonyl group as shown in Scheme 3. The mass spectrum of compound 19a shows the molecular ion peak at $m/e$ 328 corresponding to the molecular formula (C₁₈H₁₂N₆O), and compound 19b shows the molecular ion peak at $m/e$ 330 corresponding to the molecular formula (C₁₇H₁₀N₆S). The IR spectra of the compounds 19a,b shows the disappearance of the carbonyl group and the appearance of NH group beside the other groups. Also, the $^1$H NMR spectra of compounds 19a,b show the disappearance of protons of NMe₂ moiety and appearance of NH proton beside the other protons.

The tricyclic heterocyclic compounds are biologically interest compounds. They are examples of uncommon ring system [11] [12]. Therefore we are interested for the preparation of this type of heterocyclic compound.
Thus 5-acetyl-3-amino-6-methyl-N-(p-tolyl)benzof[b]thiophene-2-carboxamide 8b is reacted with N,N'-dimethylformamide dimethyl acetal (DMFDMA) in dry dioxane afforded 8-acetyl-7-methyl-3-(p-tolyl)pyrido [3',2',4,5] thieno[3,2-d]pyrimidin-4(3H)-one 20. The IR spectrum of compound 20 shows the disappearance of (NH₃) and (NH) groups. The mass spectrum of compound 20 shows the molecular ion peak at m/e 349 which corresponding to the molecular formula (C₁₉H₁₅N₃O₂S). Also, the ¹H NMR spectrum of compound 20 shows the appearance of two singlet signals at δ_H = 8.43 ppm, and 8.52 ppm corresponding to two protons of pyrimidinone and pyridine rings respectively beside other signals for other protons.

For further reaction of 5-acetyl-3-amino-6-methyl-N-substituted[b]thiophene-2-carboxamide 8b,c it reacted with nitrous acid in acetic acid afforded the tricyclic compounds 21a,b in a good yield as shown in Scheme 4. The structures of the compounds 21a,b are established by elemental and spectral analysis. Whereas the IR spectra of both compounds 21a,b show the disappearance of the bands corresponding to (NH₃) and (NH) groups.

The mass spectrum of the compound 21a as an example shows the molecular ion peak at m/e 350 corresponding to molecular formula (C₁₈H₁₄N₄O₂S).

Also, the ¹H NMR spectra of compounds 21a,b show the disappearance of the signals which corresponding to (NH₃) and (NH) groups beside the appearance the other signals for other groups.

We have found that the prepared tricyclic compounds 20 and 21a,b contain acetyl group which is very important for the preparation of new heterocyclic compounds. So that the reaction of 21a with malononitrile and sulphur element in ethanol and triethylamine (Geweld reaction) afforded 2-amino-4-(7-methyl-4-oxo-3-(p-tolyl)-3,4-dihydropyrido[3',2',4,5]thieno[3,2-d][1,2,3]triazin-8-yl)thiophene-3-carbonitrile 22. The IR spectrum of compound 22 shows the disappearance of the carbonyl group of acetyl moiety and the appearance of amino and cyano groups at ν_max at 3427 cm⁻¹ and 2208 cm⁻¹ respectively. Also, the mass spectrum of this compound 22 shows the molecular ion peak at m/e 430 which corresponding to the molecular formula (C₂₁H₁₄N₆O₂S₂).

Scheme 4. Reactions of thienopyridine derivatives (8b,c) with DMFDMA and sodium nitrile in acetic.
Also, the compound 21a is treated with N,N-dimethylformamide dimethyl acetal (DMFDMA) in dry xylene afforded the corresponding enamine 8-(3-dimethylamino)acryloyl)-7-methyl-3-(p-tolyl)pyrido[3',2':4,5] thieno[3,2-d][1,2,3]triazin-4(3H)-one 23 in a good yield. Scheme 4. The mass spectrum of compound 23 shows the molecular ion peak at m/e 405 corresponding to molecular formula (C_{21}H_{19}N_{5}O_{2}S). Also, the ¹H NMR spectrum of compound 23 shows the disappearance of the methyl of acetyl moiety and appearance instead of it two singlet signals at δ_H = 3.63 ppm and 3.67 ppm corresponding to (NMe₂) moiety. Also, it shows the appearance of two doublet signals at δ_H = 5.42 ppm and 7.82 ppm respectively corresponding to the double bond protons of enaminoic moiety beside signals for other protons.

3. Experimental

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 17,100 FTIR spectrometer as KBr disks. NMR spectra were recorded on a Varian Gemini (400 MHz) spectrometer for solutions in CDCl₃ or DMSO-d₆, with tetramethylsilane (TMS) as an internal standard unless otherwise. Mass spectra were obtained on Finnigan 4500 (low resolution) spectrometers using electron impact (EI) at Micro-analytical Center Cairo University Giza Egypt.

**Preparation of 5-acetyl-3-cyano-6-methylpyridine-2(1H)-thione (3a):**

A mixture of acetylacetone (1a) (1.0 g, 10 mmol), dry dioxane (10 mL) and N,N-dimethylformamide dimethyl acetal (1.19 g, 10 mmol) was added under dry condition at room for 24 h. In a second flask, a mixture of dry ethanol (15 mL), and sodium metal (0.46 g, 20 mmol) was stirred for 10 min. Then cyanothioacetal (1.19 g, 10 mmol) was added to the mixture. The mixture was left for further 10 min. The contents of the second flask were transferred into the first flask, and the resulting mixture was stirred for further 1 h, followed by converting stirring into reflux for 4 h. After cooling, the mixture was poured onto acidified ice/cold water. The product was recovered by filtration and recrystallised from ethanol as orange crystals (77%), Mp. 232 − 233°, similar to be published before [7] and mixed Mp.

**Preparation of 5-acetyl-6-methyl-2-(methylthio)nicotinonitrile (7):**

Mixture of 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a (1.92 g, 10 mmol) in ethanol as solvent and sodium hydroxide (0.4 g, 10 mmol) with stirring for 1 hr., and added methyl iodide (0.62 ml, 10 mmol) with stirring until precipitate formed. The product was recovered by filtration and recrystallised from ethanol as white crystals (1.52 g, 74%), Mp. 140°C - 142°C; ¹H-NMR (CDCl₃): δ = 2.54 (3H, s, CH₃ py.), 2.63 (3H, s, SCH₂), 2.73 (3H, s, CH₃CO), 8.07 (1H, s, CH py.); IR (KBr) ν 2227 (CN), 1685 cm⁻¹(C=O); MS (EI): m/z 206 M⁺; Anal. Calcd for C_{10}H_{10}N_{2}O₃S (206.27): C, 58.23; H, 4.89; N, 13.58. Found: C, 58.03; H, 4.73; N, 13.41.

**General procedure for the preparation of compounds 8a-c**

In dry flask, a mixture 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a (1.92 g, 10 mmol) and α-chloro compounds (10 mmol) in ethanol and sodium ethoxide (20 mmol) was left under reflux for two hours. The mixture was left for cooling and poured onto ice cold water. The solid product was recovered by filtration and recrystallised from the proper solvent.

**Ethyl 5-acetyl-3-amino-6-methylthieno[2,3-b]pyridine-2-carboxylate (8a):** Obtained using ethyl 2-chloroacacetate (1.06ml, 10 mmol). The product was recrystallised from acetic acid as yellow crystals (2.16 g, 77.7%), Mp. 220°C - 222°C; ¹H-NMR (DMSO): δ = 1.25 (3H, t, CH₃ ethyl), 2.6 (3H, s, CH₃ py.), 2.66 (3H, s, CH₃CO), 4.25 (2H, q, CH₂ ethyl), 7.29 (2H, s, NH₂), 8.95 (1H, s, CH py.); IR (KBr) ν 3393, 1679 cm⁻¹ (C=O); MS (EI): m/z 339 M⁺; Anal. Calcd for C_{13}H_{14}N₂O₃S (339.42): C, 56.10; H, 5.07; N, 10.06. Found: C, 56.03; H, 4.73; N, 13.41.

**5-Acetyl-3-amino-6-methyl-N-(p-tolyl)thieno[2,3-b]pyridine-2-carboxamide (8b):** Obtained using 2-chloro-N-(p-tolyl)acetamide (1.83 g, 10 mmol). The product was recrystallised from ethanol as yellow crystals (2.7 g, 79%), Mp. 218°C - 220°C; ¹H-NMR (DMSO) δ = 2.26 (3H, s, CH₃ Ar), 2.64 (3H, s, CH₃ py.), 2.73 (3H, s, CH₃CO), 7.12 (2H, d, Ar), 7.47 (2H, s, NH₂), 7.55 (2H, d, Ar), 9.04 (1H, s, CH py.), 9.4 (1H, s, NH); IR (KBr) ν 3428, 3312 (NH₂, NH), 1685 cm⁻¹ (C=O); MS (EI): m/z 339 M⁺; Anal. Calcd for C_{13}H_{14}N₂O₃S (339.42): C, 63.70; H, 5.05; N, 12.38. Found: C, 63.56; H, 4.93; N, 12.15.

**5-Acetyl-3-amino-6-methyl-N-(4-methoxyphenyl)thieno[2,3-b]pyridine-2-carboxamide (8c):** Obtained using 2-chloro-N-(4-methoxyphenyl)acetamide (1.99 g, 10 mmol). The product was recrystallised from ethanol as yellow crystals (2.8 g, 79%), Mp. 240°C - 242°C; ¹H-NMR (DMSO) δ = 2.65 (3H, s, CH₃ py.), 2.73 (3H, s, CH₃CO), 3.76 (3H, s, CH₃O), 6.9 (2H, d, Ar), 7.45 (2H, s, NH₂), 7.56 (2H, d, Ar), 9.04 (1H, s, CH
A mixture of 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a (1.92 g, 10 mmol) in ethanol and potassium carbonate was left under reflux for 3 hr. after cooling the mixture was poured onto ice cold water. The product was recovered and recrystallised from EtOH/H₂O (1:1) as yellow crystals (2.1 g, 80.4%); Mp. and mixed Mp. 100°C - 102°C. 1H-NMR (CDCl₃) δ = 2.62, 2.64 (6H, 2s, NMe₂), 2.9 (3H, s, CH₃ py.), 3.15 (3H, s, CH₃), 5.28 (1H, d, trans CH), 6.28 (1H, d, cis CH), 7.75 (1H, d, trans CH), 8.07 (1H, s, CH py.), 10.15 (1H, d, cis CH); IR (KBr) ν 2227 (CN), 2231 (CN), 1659 cm⁻¹ (C=O); MS (EI): m/z 294 M⁺; Anal. Calcd for C₁₂H₈N₄S₂ (272.35): C, 52.92; H, 2.96; N, 13.54.

5-Acetyl-2-ethoxy-6-methylnicotinonitrile (11)

In dry flask, a mixture of 5-acetyl-6-methyl-2-(methylthio)nicotinonitrile 7 (2.06 g, 10 mmol) in dry xylene as solvent and potassium carbonate was left under reflux for 3 hr. after cooling the mixture was poured onto ice cold water. The product was recovered and recrystallised from EtOH/H₂O (1:1) as yellow crystals (1.9 g, 76.8%), Mp. 100°C - 102°C. 1H-NMR (CDCl₃) δ = 1.43 (3H, t, CH₃ ethyl), 2.66 (3H, s, CH₃), 3.04 (3H, s, CH₃CO), 4.54 (2H, q, CH₂ ethyl), 7.95 (1H, s, CH py.); IR (KBr) ν 2228 (CN), 1688 cm⁻¹ (C=O); MS (EI): m/z 223 (M⁺); Anal. Calcd for C₁₂H₁₀N₂O₂ (204.23): C, 64.69; H, 5.92; N, 13.72; Found: C, 64.51; H, 5.83; N, 13.54.

5-(3-Dimethylamino)acryloyl)-2-ethoxy-6-methylnicotinonitrile (12)

In dry flask a mixture of 5-acetyl-6-methyl-2-(methylthio)nicotinonitrile 7 (2.06 g, 10 mmol) in dry xylene as solvent and N,N'-dimethylformamide dimethyl acetal (DMFDMA) (1.32 ml, 10 mmol) was left under reflux for 2 hr., cool and poured in dry backer and the solvent was evaporated. The product was recovered and recrystallised from EtOH/H₂O (1:1) as yellow crystals (2 g, 76.6%), Mp. 100°C - 102°C; (B) In dry flask a mixture of 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a (1.92 g, 10 mmol) in dry xylene as solvent and N,N'-dimethylformamide dimethyl acetal (DMFDMA) (2.64 ml, 20 mmol) was left under reflux for 2 hr., cool and poured in dry backer and the solvent was evaporated. The product was recovered and recrystallised from EtOH/H₂O (1:1) as yellow crystals (2.1 g, 80.4%), Mp. and mixed Mp. 100°C - 102°C; 1H-NMR (CDCl₃) δ = 2.62, 2.64 (6H, 2s, NMe₂), 2.9 (3H, s, CH₃ py.), 3.15 (3H, s, CH₃), 5.28 (1H, d, trans CH), 6.28 (1H, d, cis CH), 7.75 (1H, d, trans CH), 8.07 (1H, s, CH py.), 10.15 (1H, d, cis CH); IR (KBr) ν 2227 (CN), 2231 (CN), 1659 cm⁻¹ (C=O); MS (EI): m/z 294 M⁺; Anal. Calcd for C₁₂H₁₀N₂O₂ (204.23): C, 64.69; H, 5.92; N, 13.72; Found: C, 64.51; H, 5.83; N, 13.54.
In dry flask, a mixture of 5-(3-(dimethylamino)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile 9a (3.23 g, 10 mmol) and malononitrile dimer (1.32 g, 10 mmol) in acetic acid and ammonium acetate was left under reflux for four hours, cool. The solid product was recovered by filtration and recrystallised from ethanol as yellowish crystals (1.6 g, 75%), mp. 260°C (172); 1H-NMR (DMSO) δ = 2.61 (3H, s, CH3), 2.65 (3H, s, SCH3), 2.99, 3.01 (6H, 2s, NMe2), 6.83 (2H, d, Ar), 7.30 (1H, s, CH py.), 7.70 (1H, s, CH py.), 7.93 (2H, d, Ar), 10.3 (1H, br, NH); IR (KBr) ν = 3428 (NH), 2267 cm−1; MS (EI) +: m/z = 298 M+; Anal. Calcd for C10H9N5S (298.39): C, 56.35; H, 4.71; N, 39.23, Found: C, 55.85; H, 4.56; N, 39.16.

6-(Dicyanomethylene)-4-(3-(dimethylamino)phenyl)-2'-methyl-6'-thioxo-1,1',6,6'-tetracyclo-[2,3'-bipyridine]-5,5' dicarbonitrile (15)

In dry flask, a mixture of 5-(3-(dimethylamino)acryloyl)-6-methyl-2-thiooxy-1,2-dihydropyridine-3-carbonitrile 9a (3.23 g, 10 mmol) and malononitrile dimer (1.32 g, 10 mmol) in acetic acid and ammonium acetate was left under reflux for three hours. The mixture was left for cooling and poured onto ice, cold water. The product was recovered by filtration and recrystallised from ethanol as yellow crystals (2.61 g, 10 mmol) with 4-(dimethylamino)benzaldehyde (1.49 g, 10 mmol) with stirring for 2 hr., until precipitate formed and dialute with water. The product was recovered by filtration and purified by recrystallised from ethanol as yellow crystals (2.5 g, 74%), mp. 160°C - 162°C; (B) mixture of 5-acetyl-6-methyl-2-(methylthio)nicotinonitrile 7 (2.06 g, 10 mmol) in ethanol as solvent in presence of sodium hydroxide (0.4 g, 10 mmol) and methyl iodide (0.62 ml, 10 mmol) with stirring until precipitate was formed. The product was recovered by filtration and was purified by recrystallised from ethanol as yellow crystals (2.4 g, 71%), Mp. 160°C - 162°C; 1H-NMR (CDCl3) δ = 2.62 (3H, s, CH3), 2.66 (3H, s, SCH3), 2.9, 3.04 (6H, 2s, NMe2), 6.83 (2H, d, Ar), 7.46 (2H, d, Ar), 6.67 (1H, d, CH), 7.38 (1H, d, CH), 7.85 (1H, s, CH py.). IR (KBr) ν = 2217 (CN), 1648 cm−1 (C=O); MS (EI) +: m/z = 337 M+; Anal. Calcd for C10H10N6 (337.45): C, 67.63; H, 5.68; N, 12.45, Found: C, 67.49; H, 5.62; N, 12.48.

6-(Dicyanomethylene)-4-(3-(dimethylamino)phenyl)-2'-methyl-6'-thioxo-1,1',6,6'-tetracyclo-[2,3'-bipyridine]-5,5' dicarbonitrile (15)

In dry flask, a mixture of 5-(3-(dimethylamino)acryloyl)-6-methyl-2-thiooxy-1,2-dihydropyridine-3-carbonitrile 9a (3.23 g, 10 mmol) and malononitrile dimer (1.32 g, 10 mmol) in acetic acid and ammonium acetate was left under reflux for four hours. The solid product was recovered by filtration and was purified by recrystallisation from ethanol as brown crystals (3.37 g, 10 mmol) and malononitrile dimer (1.32 g, 10 mmol) in acetic acid and ammonium acetate was left under reflux for four hours, cool. T he solid product was recovered by filtration and recrystallised from ethanol as brown crystals (3.25 g, 77.1%), mp. 170°C - 172°C; 1H-NMR (DMSO) δ = 2.49 (3H, s, CH3), 2.65 (3H, s, SCH3), 7.71 (1H, d, CH py.), 8 (1H, d, CH py.), 8.14 (1H, s, CH py.), 12.25 (1H, br, NH); IR (KBr) ν = 3428 (NH), 2221 cm−1 (CN); MS (EI) +: m/z = 298 M+; Anal. Calcd for C10H10N6S2 (298.39): C, 56.35; H, 3.38; N, 18.78, Found: C, 56.12; H, 3.24; N, 18.58.
**General procedure for the preparation of compounds 19a,b**

In dry flask, a mixture of 5-(3-(dimethylamino)acryloyl)-2-ethoxy-6-methylnicotinonitrile 12 (2.59 g, 10 mmol) or 5-(3-(dimethylamino)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile 13 (2.61 g, 10 mmol) and malononitrile dimmer (1.32 g, 10 mmol) in acetic acid and ammonium acetate was heated under reflux for four hours. The solid product was recovered by filtration and recrystallised from ethanol.

6-(Dicyanomethylene)-6'-ethoxy-2'-methyl-1,6-dihydro-[2,3'-bipyridine]-5,5'-dicarbonitrile (19a):

Obtained using 5-(3-(dimethylamino)acryloyl)-2-ethoxy-6-methylnicotinonitrile 12. Mp. 200°C - 202°C as brown crystals (2.4 g, 73.1%); 1H-NMR (DMSO) δ = 1.39 (3H, t, CH3), 2.62 (3H, s, CH3), 4.50 (2H, q, CH2), 7.58 (1H, d, CH py.), 8.48 (1H, d, CH py.), 8.7 (1H, s, CH py.), 11.3 (1H, br, NH); IR (KBr) ν 3330 (NH), 2218 cm⁻¹ (CN); MS (EI)⁺: m/z 328 M⁺; Anal. Calcd for C18H12N6O (328.34): C, 65.85; H, 3.68; N, 25.60, Found: C, 65.19; H, 3.94; N, 25.78.

6-(Dicyanomethylene)-2'-methyl-6'-[(methylthio)-1,6-dihydro-[2,3'-bipyridine]-5,5'-dicarbonitrile (19b):

Obtained using 5-(3-(dimethylamino)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile 13. Mp. 190°C - 192°C as brown crystals (2.3 g, 69.7%); 1H-NMR (DMSO) δ = 2.58 (3H, s, CH3), 2.64 (3H, s, CH3), 6.5 (1H, d, CH py.), 8.2 (1H, d, CH py.), 8.69 (1H, s, CH py.), 11.31 (1H, br, NH); IR (KBr) ν 3340 (NH), 2212 cm⁻¹ (CN); MS (EI)⁺: m/z 330 M⁺; Anal. Calcd for C18H16N6S (330.37): C, 61.80; H, 3.05; N, 15.24; Found: C, 61.63; H, 2.89; N, 25.27.

8-Acetyl-7-methyl-3-(p-toly]-pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (20)

A mixture of 5-acetyl-3-aminomethyl-N-(p-tolyl)thieno[2,3-b]pyridine-2-carboxamide 8b (3.39 g, 10 mmol) in dry dioxane and DMFDMA (1.32 ml, 10 mmol) with stirring for 12 hrs. The product was recovered by filtration and recrystallised from acetic acid as gray crystals (2.6 g, 74.5%); 1H-NMR (DMSO) δ = 2.26 (3H, s, CH3 Ar), 2.68 (3H, s, CH3 py.), 2.69 (3H, s, CH3CO), 7.16 (2H, d, Ar), 7.52 (2H, d, Ar), 8.43 (1H, s, CH pyrimidinone), 8.52 (1H, s, CH py.), IR (KBr) ν 1691, 1649 cm⁻¹ (2C=O); MS (EI)⁺: m/z 349 M⁺; Anal. Calcd for C19H14N6O (349.31): C, 63.27; H, 3.96; N, 25.78, Found: C, 63.19; H, 3.96; N, 25.78.

**General procedure for the preparation of compounds 21a,b**

A mixture of N-substituted-5-acetyl-3-aminomethyl-6-methylnicotinonitrile[2,3-b]pyridine-2-carboxamide 8b,c (10 mmol) in acetic acid and sodium nitrite (1.38 g, 20mmol) with stirring for 1 hr. the precipitate was formed and dilute with water. The product was recovered by filtration and recrystallised from ethanol.

8-Acetyl-7-methyl-3-(p-tolyl)pyrido[3',2':4,5]thieno[3,2-d]triazin-4(3H)-one (21a): Obtained using 5-acetyl-3-aminomethyl-N-(p-tolyl)thieno[2,3-b]pyridine-2-carboxamide 8b (3.39g, 10 mmol). Mp. 170°C - 172°C as gray crystals (3.5 g, 87.5%); 1H-NMR (DMSO) δ = 2.4 (3H, s, CH3 Ar), 2.74 (3H, s, CH3 py.), 2.77 (3H, s, CH3CO), 7.4 (2H, d, Ar), 7.5 (2H, d, Ar), 8.83 (1H, s, CH pyrimidinone), 8.84 (1H, s, CH py.), 9.17 (1H, s, CH py.), IR (KBr) ν 1691, 1649 cm⁻¹ (2C=O); MS (EI)⁺: m/z 349 M⁺; Anal. Calcd for C18H12N6O (349.31): C, 61.70; H, 4.33; N, 15.99, Found: C, 61.63; H, 3.94; N, 15.78.

8-Acetyl-3-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-d]triazin-4(3H)-one (21b): Obtained using 5-acetyl-3-aminomethyl-N-(4-methoxyphenyl)-6-methylnicotinonitrile[2,3-b]pyridine-2-carboxamide 8c (3.55 g, 10 mmol). Mp. = 220°C - 222°C as gray crystals (2.9 g, 79.4%); 1H-NMR (DMSO) δ = 2.74 (3H, s, CH3 py.), 2.81 (3H, s, CH3CO), 3.85 (3H, s, CH3O), 7.15 (2H, d, Ar), 7.61 (2H, d, Ar), 9.26 (1H, s, CH py.), IR (KBr) ν 1687 cm⁻¹ (2C=O); Anal. Calcd for C18H14N6O (366.40): C, 63.27; H, 3.96; N, 15.29; Found: C, 59.90; H, 3.85; N, 15.29; Found: C, 58.90; H, 3.76; N, 15.17.

2-Amino-4-(7-methyl-4-oxo-3-(p-tolyl)-3,4-dihydropyrido[3',2':4,5]thieno[3,2-d][1,2,3]triazin-8-yl)thiophene-3-carbonitrile (22):

In dry flask a mixture of 8-acetyl-7-methyl-3-(p-tolyl)pyrido[3',2':4,5]thieno[3,2-d][1,2,3]triazin-4(3H)-one 21a (3.5 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and elemental sulfur (0.32 g, 10mmol) in ethanol and few drops of triethylamine as base was heated under reflux for three hours. The mixture was left for cooling and poured onto ice cold water. The product was recovered by filtration and recrystallised from a mixture of ethanol/DMF (3:1) as brown crystals (3 g, 69.7%), Mp 260°C - 262°C; IR (KBr) ν 3427 (NH2), 2208 (CN), 1685 cm⁻¹ (C=O); MS (EI)⁺: m/z 430 M⁺; Anal. Calcd for C21H11N6OS2 (430.51): C, 58.59; H, 3.28; N, 19.52; Found: C, 58.43; H, 3.14; N, 19.36.

(3-(Dimethylamino)acryloyl)-7-methyl-3-(p-tolyl)pyrido[3',2':4,5]thieno[3,2-d][1,2,3]triazin-4(3H)-one (23):

In dry flask a mixture 8-acetyl-7-methyl-3-(p-tolyl)pyrido[3',2':4,5]thieno[3,2-d][1,2,3]triazin-4(3H)-one 21a (3.5 g, 10 mmol) and DMFDMA (1.32 ml, 10 mmol) in dry dioxane was left under reflux for two hours. The
mixture was left for cooling and evaporates the solvent. The product was recovered by filtration and recrystal-
ised from ethanol as brown crystals (2.9 g, 71.6%), Mp. 210°C - 212°C; 1H-NMR (DMSO) δ = 2.39 (3H, s, CH3 Ar), 2.66 (3H, s, CH3 py.), 3.63, 3.67 (6H, 2s, NMe2), 5.42 (1H, d, CH), 7.41 (2H, d, Ar), 7.54 (2H, d, Ar), 7.82 (1H, d, CH), 9.12 (1H, s, CH py.); IR (KBr) ν = 1693, 16.44 cm⁻¹ (2C=O); MS (EI⁺): m/z 405 M⁺; Anal. Calcd for C21H19N5O2S (405.48): C, 62.21; H, 4.72; N, 17.27, Found: C, 62.08; H, 4.59; N, 17.11.

4. Conclusion

From the biological importance of pyridine-2(1H)-thione derivatives, we have used it in order for the prepara-
tion of biologically important bipyridyls, bi- and uncommon tricyclic compounds.

References


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