Proceedings of Basic and Applied Sciences
ISSN 1857-8179 (paper). ISSN 1857-8187 (online). http://www.anglisticum.mk
Proceedings of the 1st International Conference on New Horizons in Basic and Applied Science, Hurghada – Egypt, Vol 1(1), 2013.

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

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Received November 13, 2013; Revised November 14, 2013; Accepted November 15, 2013

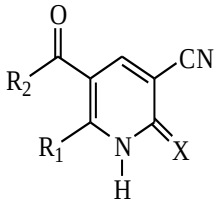
Abstract: *Reaction of acetylacetone with 1 mole of dimethylformamide dimethyl acetal (DMFDMA) affords enamine 2a which react with cyanothioacetamide to give pyridinethione 3a. Pyridinethione 3a reacts with methyl iodide, halogenated compounds, aromatic aldehyde and malononitrile / elemental sulfur to yiled compounds 7-10 respectively. Reactions of thioether (7) in ethanolic K_2CO_3, 1 mole DMFDMA and 4-(dimethylamino) benzaldehyde gave compounds (11, 13, 14) respectively. Enaminone (12) can be prepared by reaction of compound (11) with DMFDMA. Also, compounds (13) and (14) can be obtained by reaction of compounds (3a) and (9a) with 2 mole of DMFDMA and methyl iodide respectively. Reactions of enaminone (9) with hydrazine hydrate and cyanothioacetamide gave compounds (11) and (12) respectively. Malononitrile dimmer when reacted with chalcones (9a), (14) and enaminone (12), (13) gave bipyridyl (15), (16) and (19a,b) respectively. Bipyridyl (15) can be converted to (16) by methylation using methyl iodide. Reactions of thienopyridine (8) with DMFDMA and sodium nitrite in acetic acid gave tricyclic compounds (20) and (21) respectively. Finally, reactions of (21a) with malononitrile / elemental sulfur and DMFDMA gave compounds (22) and (23) respectively.*

Keywords: *Acetyl acetone; DMFDMA; Malononitrile dimmer; Bipyridyl; 5-Acetylpyridinethione.*

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].

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



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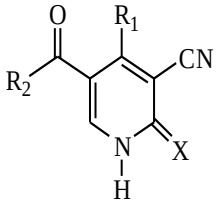

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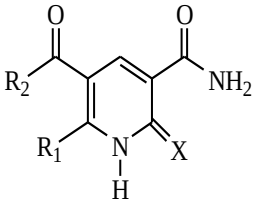

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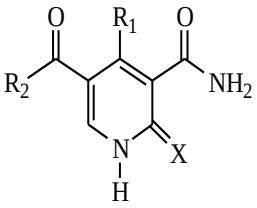

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X = O, S, $C(CN)_2$

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**. Treatment of the lasted compound with cyanothioacetamide in ethanol in the presence of sodium ethoxide gave 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile **3a** [7], scheme 1.

We have found that the prepared compound **3a** contains three functional groups which are thioamido group, nitrile 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 conformed by spectral analysis. The IR spectrum shows the disappearance of (NH) group. Also, the ^{1}H NMR spectrum shows the disappearance of the thioamide proton and the appearance of a singlet signal corresponding to (SCH_3) at δ_H = 2.63 ppm. Also, the mass spectrum shows the molecular ion peak at m/e 206. 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 conformed by elemental and spectral analysis. The IR spectrum shows the disappearance of cyano group and appearance of amino group at υ_{max} = 3427 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**. Also, the ^{1}H NMR spectra show signals fit to the structure of 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 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile **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 conformed by elemental analysis as well as spectral analysis. The mass spectra show the molecular ion peak fit to all compounds **9a,b**. As an example compound **9a** shows the molecular ion peak at m/e 323 which corresponding to the molecular formula ($C_{18}H_{17}N_3OS$).

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 proton 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 υ_{max} = 3435 cm^{-1} beside the other functional groups**.** Also, ^1H NMR spectrum of compound **10** shows singlet signal at δ_H = 2.45 ppm corresponding to methyl group and singlet signal at δ_H = 6.95 ppm corresponding to amino group and singlet signal at δ_H = 7.07 ppm corresponding to CH thiophene ring and singlet signal at δ_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 heterocyclic compounds.

ISSN 1857-8179 (paper). ISSN 1857-8187 (online). http://www.anglisticum.mk
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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 conformed by elemental and spectral analyses. The mass spectrum shows the molecular ion peak at m/e 204 corresponding to the molecular formula ($C_{11}H_{12}N_2O_2$). Also, the ^{1}H NMR spectrum shows the disappearance of SMe signal and appearance of two signals; a triplet at δ_H = 1.43 ppm and a quartet at δ_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'*-dimetylformamide dimethyl acetal (DMFDMA) in dry xylene to give the corresponding enamine **12** in a good yield. The mass spectrum of compound **11** shows the molecular ion peak at m/e 259 which corresponding to the molecular formula ($C_{14}H_{17}N_3O_2$). 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 δ_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 δ_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'*-dimetylformamide dimethylacetal (DMFDMA) in dry xylene or by reaction of 5-acetyl-6-methyl-2-(methylthio)nicotinonitrile **7** with one mole of *N,N'*-dimetylformamide dimethylacetal (DMFDMA) in dry xylene. The structure of the isolated compound is conformed by elemental and spectral analysis. Where as the mass spectrum shows the molecular ion peak at m/e 261 which corresponding to the molecular formula ($C_{13}H_{15}N_3OS$). 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 δ_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 δ_H = 5.28 ppm and 7.75 ppm corresponding to the two protons of double bond of enamine.

Chalcone **14** can be prepared by either 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 ($C_{19}H_{19}N_3OS$). Also, the ^{1}H NMR spectrum of compound **14** shows singlet signal at δ_H = 2.62 ppm corresponding to methyl group and singlet signal at δ_H = 2.66 ppm corresponding to SCH_3 and two singlet signal at δ_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-arbonitrile **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 conformed by elemental and spectral analysis. Where as the mass spectra of these compounds show the molecular ion peaks at m/e 435 corresponding to the molecular formula ($C_{24}H_{17}N_7S$), and at m/e 449 corresponding to the molecular formula ($C_{25}H_{19}N_7S$) for **15** and **16** respectively. The IR spectra of both compounds **15** and **2.14** 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 cyano group and the appearance of NH_2 and NH groups at υ_{max} 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 ($C_{10}H_{10}N_6$).

Also, the ^1H NMR spectrum of compound **17** shows signals fit to the structure. 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 Micheal addition of cyanothioacatamide on the double bond followed by elimination of dimethylamine ($HNMe_2$) and cyclization with the carbonyl group.

The structure of the isolated compound **18** is conformed by elemental and spectral analysis. The IR spectrum of compound **18** shows the disappearance of carbonyl group and appearance of NH group at υ_{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 ($C_{14}H_{10}N_4S_2$). Also, the ^1H NMR spectrum of compound **18** shows the disappearance of protons of NMe_2 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 dimmer in acetic acid and ammonium acetate. This reaction proceeds by Michael addition of malononitrile dimmer, followed by elimination of dimethylamine ($HNMe_2$) 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 ($C_{18}H_{12}N_6O$), and compound **19b** shows the molecular ion peak at m/e 330 corresponding to the molecular formula ($C_{17}H_{10}N_6S$).

The IR spectra of the compounds **19 a, b** show the disappearance of the carbonyl group and the appearance of NH group beside the other groups. Also, the ^1H NMR spectra of compounds **19a,b** show the disappearance of protons of NMe_2 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)benzo[b]thiophene-2-carboxamide **8b** is reacted with *N,N'*-dimetylformamide 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 (NH_2) and (NH) groups. The mass spectrum of compound **20** shows the molecular ion peak at m/e 349 which corresponding to the molecular formula ($C_{19}H_{15}N_3O_2S$). Also, **the** ^{1}H 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, under cooling, afforded the tricyclic compounds **21a,b** in a good yield as shown in scheme 4. The structures of the compounds **21a,b** are conformed by elemental and spectral analysis. Where as the IR spectrum of both compounds **21a,b** show the disappearance of the bands corresponding to (NH_2) 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 ($C_{18}H_{14}N_4O_2S$).

Also, the ^{1}HNMR spectra of compounds **21a,b** shows the disappearance of the signals which corresponding to (NH_2) 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 υ_{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 ($C_{21}H_{14}N_6OS_2$). Also, the compound **21a** is treated with *N*,*N'*-dimetylformamide 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 ($C_{21}H_{19}N_5O_2S$). Also, the ^{1}H NMR spectrum of compound **22** 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 (NMe_2) 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 enaminone moiety beside signals for other protons.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 17100 FTIR spectrometer as KBr disks. NMR spectra were recorded on Bruker AC300 spectrometer at 400 MHz for solutions in $CDCl_3$ or DMSO with tetramethylsilane (TMS) as an internal standard unless otherwise recorded at Department of Chemistry, College of Science, Sultan Qaboos University, P.O. Box 36, Al-Khod23, Oman. 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-6-methyl-2-(methylthio) nicotinonitrile

Mixture of 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a (1.92g, 10 mmol) in ethanol as solvent and sodium hydroxide (0.4g, 10 mmol) with stirring for 1hr.,and add methyl iodide (0.63 ml, 10 mmol) with stirring until precipitate formed . The product was recovered by filtration and recrystallised from ethanol as white crystals (1.52g, 74%), Mp. 140-142 oC; 1H-NMR (CDCl3): δ = 2.54 (3H, s, CH3 py.), 2.63 (3H, s, SCH3), 2.77 (3H, s, CH3CO), 8.07 (1H, s, CH py.); IR (KBr) υ 2227 (CN), 1685 cm-1 (C=O); MS (EI)+: m/z 206 M+; Anal. Calcd for C10H10N2OS (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 (1.92g, 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-chloroacetate (1.06ml, 10 mmol). The product was recrystallised from acetic acid as yellow crystals (2.16g, 77.7%), Mp. 220-222 oC; 1H-NMR (DMSO): δ = 1.25 (3H, t, CH3 ethyl), 4.25 (2H, q, CH2 ethyl), 2.6 (3H, s, CH3 py.), 2.66 (3H, s, CH3CO), 7.29 (2H, s, NH2), 8.95 (1H, s, CH py.); IR (KBr) υ 3427, 3328 (NH2), 1679 cm-1 (C=O); MS (EI)+: m/z 278 M+; Anal. Calcd for C13H14N2O3S (278.33): C, 56.10; H, 5.07; N, 10.06, Found: C, 55.96; H, 4.94; N, 9.97.

5-Acetyl-3-amino-6-methyl-N-(p-tolyl)thieno[2,3-b]pyridine-2-carboxamiden(8b): Obtained using 2-chloro-N-(p-tolyl)acetamide (1.83g, 10 mmol). The product was recrystallised from ethanol as yellow crystals (2.7g, 79%), Mp. 218-220 oC; 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), 7.55 (2H, d, Ar) 7.47 (2H, s, NH2), 9.04 (1H, s, CH py.), 9.4 (1H, s, NH); IR (KBr) υ 3428 , 3312 (NH2, NH), 1685 cm-1 (C=O); MS (EI)+: m/z 339 M+; Anal. Calcd for C18H17N3O2S (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-N-(4-methoxyphenyl)-6-methylthieno[2,3-b]pyridine-2-carboxamide(8c): Obtained using 2-chloro-N-(4-methoxyphenyl)acetamide (1.99g, 10 mmol). The product was recrystallised from ethanol as yellow crystals (2.8g, 79%), Mp. 240-242 oC; 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), 7.56 (2H, d, Ar) 7.45

(2H, s, NH2), 9.04 (1H, s, CH py.), 9.4 (1H, s, NH); IR (KBr) υ 3428,3310, 3251 (NH2, NH), 1680 cm-1 (C=O); MS (EI)+: m/z 355 M+; Anal. Calcd for C18H17N3O3S (355.42): C, 60.83; H, 4.82; N, 11.82, Found: C, 60.76; H, 4.73; N, 11.69.

General procedure for the preparation of compounds 9a,b

A mixture of 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a (1.92g, 10 mmol) in ethanol as solvent in presence of sodium hydroxide (0.4g, 10 mmol) with aromatic aldehydes (10 mmol) with stirring for 2hr. then poured onto ice, cold water and acidified with conc. Hydrochloric acid until the precipitate was formed. The solid product was recovered by filtration and recrystallised from ethanol.

5-(3-(4-(Dimethylamino)phenyl)acryloyl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (9a):

Obtained using 4-(dimethylamino)benzaldehyde (1.49g, 10 mmol). Mp. 140-142 oC as yellow crystals (2.45g, 76%); 1H-NMR (CDCl3) δ = 2.65 (3H, s, CH3), 2.79 (6H, s, NMe2), 6.70 (2H, d, Ar), 7.74 (2H, d, Ar), 7.06 (1H, d, CH chalcone), 7.85 (1H, d, CH chalcone), 8.07 (1H, s, CH py.), 13.2 (1H, br., NH); IR (KBr) υ 3437 (NH), 2225 (CN), 1685 cm-1 (C=O); MS (EI)+: m/z 323 M+; Anal. Calcd for C18H17N3OS (323.42): C, 66.85; H, 5.30; N, 12.99, Found: C, 65.4; H, 5.17; N, 12.86.

6-Methyl-2-thioxo-5-(3-(p-tolyl)acryloyl)-1,2-dihydropyridine-3-carbonitrile (9b):

Obtained using 4-methylbenzaldehyde (1.2g, 10 mmol). Mp. = 240-242 oC as yellow crystals (2.2g, 74.8%); 1H-NMR (DMSO) δ = 2.31 (3H, s, CH3 Ar), 2.58 (3H, s, CH3 py.), 7.24 (2H, d, Ar), 7.69 (2H, d, Ar), 7.49 (1H, d, CH chalcone), 7.6 (1H, d, CH chalcone), 8.58 (1H, s, CH py.), 13 (1H, br., NH); IR (KBr) υ 3434 (NH), 2231 (CN), 1659 cm-1 (C=O); MS (EI)+: m/z 294 M+; Anal. Calcd for C17H14N2OS (294.38): C, 69.36; H, 4.79; N, 9.52, Found: C, 69.19; H, 4.81; N, 9.45.

5-(5-Amino-4-cyanothiophen-3-yl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (10)

In dry flask a mixture 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 3a (1.92g, 10 mmol), malononitrile (0.66g, 10 mmol) and sulfur (0.32g, 10 mmol) in ethanol and few drops of triethylamine as base was left under reflux for three hours. The mixture was left for cooling then poured onto ice cold water. The product obtained was recrystallised from a mixture of ethanol/DMF (3:1) as brown crystals (1.9g, 69.8%), Mp. >300 oC; 1H-NMR (DMSO) δ = 2.45 (3H, s, CH3), 6.95 (2H, s, NH2), 7.07 (1H, s, CH thiophene), 7.2 (1H, s, CH py.); IR (KBr) υ 3435, 3350 (NH2), 3250 (NH), 2210 cm-1 (CN); Anal. Calcd for C12H8N4S2 (272.35): C, 52.92; H, 2.96; N, 20.57, Found: C, 52.85; H, 2.92; N, 20.15.

***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 ethanol and potassium carbonate was left under reflux for 3hr. after cooling the mixture was poured onto ice cold water. The product was recovered and recrystallised from EtOH/H_2O (1:1) as yellowish crystals (1.6g, 78%), Mp. 78-80 ^oC; ^1H-NMR ($CDCl_3$) δ = 1.43 (3H, t, CH_3 ethyl), 4.54 (2H, q, CH_2 ethyl), 2.66 (3H, s, CH_3), 3.04 (3H, s, CH_3CO), 7.85 (1H, s, CH py.); IR (KBr) υ 2228 (CN), 1688 cm^{-1} (C=O); MS $(EI)^+$: *m/z* 204 M^+; Anal. Calcd for $C_{11}H_{12}N_2O_2$ (204.23): C, 64.69; H, 5.92; N, 13.72, Found: C, 64.51; H, 5.83; N, 1

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

In dry flask a mixture of 5-acetyl-2-ethoxy-6-methylnicotinonitrile **11** (2.04 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 2hr., cool and the solvent was evaporated. The product was recovered and recrystallised from EtOH/H_2O (1:1) as yellow crystals (1.9g, 73.3%), Mp. 68-70 ^oC ; ^{1}H-NMR ($CDCl_3$) δ = 1.3 (3H, t, CH_3 ethyl), 4.58 (2H, q, CH_2 ethyl), 2.62 (3H, s, CH_3), 2.68, 3.04 (6H, 2s, NMe_2), 6.25 (1H, d, CH), 7.87 (1H, d, CH), 8.2 (1H, s, CH py.); IR (KBr) υ 2230 (CN), 1684 cm^{-1} (C=O); MS $(EI)^+$: *m/z* 259 M^+; Anal. Calcd for $C_{14}H_{17}N_3O_2$ (259.31): C, 64.85; H, 6.61; N, 16.20, Found: C, 64.56; H, 6.47; N, 16.11.

***(E)-5-(3-(Dimethylamino)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile* (13)**

(A) 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 2hr., cool and poured in dry backer and the solvent was evaporated. The product was recovered and recrystallised from EtOH/H_2O (1:1) as yellow crystals (2g, 76.6%), Mp. 100-102 ^oC; **(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 2hr., cool and poured in dry backer and the solvent was evaporated. The product was recovered and recrystallised from EtOH/H_2O (1:1) as yellow crystals (2.1g, 80.4%), Mp. and mixed Mp. 100-102 ^oC; ^{1}H-NMR ($CDCl_3$) δ = 2.62, 2.64 (6H, 2s, NMe_2), 2.9 (3H, s, CH_3 py.), 3.15 (3H, s, SCH_3), 5.28 (1H, d, trans CH), 7.75 (1H, d, trans CH), 6.28 (1H, d, cis CH), 10.15 (1H, d, cis CH), 8.07 (1H, s, CH py.); IR (KBr) υ 2227 (CN), 1685 cm^{-1} (C=O); MS $(EI)^+$: *m/z* 261 M^+; Anal. Calcd for $C_{13}H_{15}N_3OS$ (261.35): C, 59.74; H, 5.79; N, 16.08, Found: C, 59.63; H, 5.45; N, 15.8.

***(E)-5-(3-(4-(Dimethylamino)phenyl)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile* (14)**

(A) Mixture of 5-(3-(4-(dimethylamino)phenyl)acryloyl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 9a (3.23g, 10 mmol) in ethanol as solvent and sodium hydroxide (0.4g, 10mmol) with stirring for 1hr., and add methyl iodide (10mmol) with stirring until precipitate was formed. The product was recovered by filtration and was purified by recrystallised from ethanol as yellow crystals (2.5g, 74%), Mp. 160-162 oC; (B) mixture of 5-acetyl-6-methyl-2-(methylthio)nicotinonitrile 7 (2.06g, 10 mmol) in ethanol as solvent in presence of sodium hydroxide (0.4g, 10 mmol) with 4-(dimethylamino)benzaldehyde (1.49g, 10 mmol) with stirring for 2hr., until precipitate formed and dilute with water. The product was recovered by filtration and purified by recrystallised from ethanol as yellow crystals (2.4g, 71%), Mp. and mixed Mp. 160-162 oC; 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) υ 2217 (CN), 1648 cm-1 (C=O); MS (EI)+: m/z 337 M+; Anal. Calcd for C19H19N3OS (337.45): C, 67.63; H, 5.68; N, 12.45, Found: C, 67.49; H, 5.62; N, 12.48.

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

In dry flask a mixture 5-(3-(4-(dimethylamino)phenyl)acryloyl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile 9a (3.23g, 10 mmol) and malononitrile dimmer (1.32g, 10 mmol) in acetic acid and presence of 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 recrystallisation from ethanol as brown crystals (3.25g, 74.7%), Mp. 260-262 oC; 1H-NMR (DMSO) δ = 2.38 (3H, s, CH3), 3.06 (6H, s, NMe2), 7.5 (1H, s, CH py.), 8.21 (1H, s, CH py.), 6.83 (2H, d, Ar), 7.93 (2H, d, Ar), 11.93 (1H, br, NH), 12.4 (1H, br, NH); IR (KBr) υ 3334, 3207 (2NH), 2206 cm-1 (CN); MS (EI)+: m/z 435 M+; Anal. Calcd for C24H17N7S (435.51): C, 66.19; H, 3.93; N, 22.51, Found: C, 66.06; H, 3.78; N, 22.3.

***6-(Dicyanomethylene)-4-(4-(dimethylamino)phenyl)-2'-methyl-6'-(methylthio)-1,6-dihydro-[2,3'-bipyridine]-5,5'-dicarbonitrile* (16)**

(A) In dry flask a mixture of 5-(3-(4-(dimethylamino)phenyl)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile **14** (3.37g, 10 mmol) and malononitrile dimmer (1.32g, 10 mmol) in acetic acid acid and ammonium acetate was left under reflux for four hours, cool. The solid product was recovered by filtration and recrystallised from acetic acid as brown crystals (3.4g, 76%), Mp. 220-222 ^{o}C; **(B)** mixture of 6-(dicyanomethylene)-4-(4-(dimethylamino)phenyl)-2'-methyl-6'-thioxo-1',5,6,6'-tetrahydro-[2,3'-bipyridine]-5,5'-dicarbonitrile (**15**) (4.35g, 10 mmol) in ethanol as solvent in presence of sodium hydroxide (0.4g, 10mmol) and methyl iodide (10 mmol) with stirring until precipitate formed . The product was recovered by filtration and recrystallised from acetic acid as brown crystals (3.2g, 71.5%), Mp. and mixed Mp. 220-222 ^{o}C; ^{1}H-NMR (DMSO) δ = 2.61 (3H, s, CH_3), 2.65 (3H, s, SCH_3), 2.99, 3.01 (6H, 2s, NMe_2), 7.09 (1H, s, CH py.), 8.66 (1H, s, CH py.), 6.82 (2H, d, Ar), 7.73 (2H, d, Ar), 10.3 (1H, br, NH); IR (KBr) υ 3345 (NH), 2213 cm^{-1} (CN); MS (EI)$^{+}$: *m/z* 449 M^{+}; Anal. Calcd for $C_{25}H_{19}N_7S$ (449.54): C, 66.80; H, 4.26; N, 21.81, Found: C, 66.69; H, 4.18; N, 21.6.

***6-Methyl-5-(1H-pyrazol-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine* (17)**

In flask a mixture of (*E*)-5-(3-(dimethylamino)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile **13** (2.61g, 10 mmol) and excess of hydrazine hydrate was left reflux for four hours, cool. The solid product was recovered by filtration and recrystallised from ethanol as yellowish crystals (1.6g, 75%), Mp. 260-262 ^{o}C; **^{1}H-NMR (DMSO)** δ = 2.49 (3H, s, CH_3), 6.47 (1H, d, CH pyrazole), 8.3 (1H, d, CH pyrazole), 7.8 (1H, s, CH py.), 5.54 (2H, s, NH_2), 11.75 (1H, s, NH), 12.91 (1H, s, NH); **IR** (KBr) υ at 3405, 3329, 3136 cm^{-1} (NH_2, NH); MS (EI)$^{+}$: *m/z* 214 M^{+}; Anal. Calcd for $C_{10}H_{10}N_6$ (214.23): C, 56.07; H, 4.71; N, 39.23, Found: C, 55.85; H, 4.56; N, 39.16.

***5-(5-cyano-1,6-dihydro-6-thioxopyridin-2-yl)-6-methyl-2-(methylthio)pyridine-3-carbonitrile* (18)**

In dry flask a mixture of (*E*)-5-(3-(dimethylamino)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile **13** (2.61g, 10 mmol) and cyanothioacetamide (1g, 10 mmol) in acetic acid and ammonium acetate was left under reflux for four hours. Cool and poured the mixture into ice cold water.

The product was recovered by filtration and recrystallised from ethanol as brown crystals (2.3g, 77.1%), Mp. 170-172 ^{o}C; ^{1}H-NMR (DMSO) δ = 2.63 (3H, s, CH_3), 2.65 (3H, s, SCH_3), 7.7 (1H, d, CH py.), 8 (1H, d, CH py.), 8.14 (1H, s, CH py.), 12.25 (1H, br, NH); IR (KBr) υ = 3428 (NH), 2221 cm^{-1}

(CN); MS (EI)$^+$: *m/z* 298 M^+; Anal. Calcd for $C_{14}H_{10}N_4S_2$ (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 (E)-5-(3-(dimethylamino)acryloyl)-2-ethoxy-6-methylnicotinonitrile 12 (2.59g, 10 mmol) or (E)-5-(3-(dimethylamino)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile 13 (2.61g, 10 mmol) and malononitrile dimmer (1.32g, 10 mmol) in acetic acid and ammonium acetate was heated under reflux for four hours, cool. The solid product was recovered by filtration and recrystallised from ethanol

***5-(5-Cyano-6-(dicyanomethylene)-1,6-dihydropyridin-2-yl)-2-ethoxy-6-methylpyridine-3-carbonitrile* (19a):** Obtained using (*E*)-5-(3-(dimethylamino)acryloyl)-2-ethoxy-6-methylnicotinonitrile **12.** Mp. 200-202 ^oC as brown crystals (2.4g, 73.1%); ^{1}H-NMR (DMSO) δ = 1.39 (3H, t, CH_3), 4.50 (2H, q, CH_2), 2.62 (3H, s, CH_3), 7.58 (1H, d, CH py.), 8.48 (1H, d, CH py.), 8.7 (1H, s, CH py. ring), 11.3 (1H, br, NH); IR (KBr) υ 3330 (NH), 2218 cm^{-1} (CN); MS (EI)$^+$: *m/z* 328 M^+; Anal. Calcd for $C_{18}H_{12}N_6O$ (328.34): C, 65.85; H, 3.68; N, 25.60, Found: C, 65.71; H, 3.52; N, 25.43.

***5-(5-Cyano-6-(dicyanomethylene)-1,6-dihydropyridin-2-yl)-2-(methylthio)-6-methylpyridine-3-carbonitrile* (19b):** Obtained using (*E*)-5-(3-(dimethylamino)acryloyl)-6-methyl-2-(methylthio)nicotinonitrile **13.** Mp. = 190-192 ^oC as brown crystals (2.3g, 69.7%); ^{1}H-NMR (DMSO) δ = 2.58 (3H, s, CH_3), 2.64 (3H, s, SCH_3), 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) υ 3340 (NH), 2212 cm^{-1} (CN); MS (EI)$^+$: *m/z* 330 M^+; Anal. Calcd for $C_{17}H_{10}N_6S$ (330.37): C, 61.80; H, 3.05; N, 25.44, Found: C, 61.63; H, 2.89; N, 25.27.

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

A mixture of 5-acetyl-3-amino-6-methyl-N-(p-tolyl)thieno[2,3-b]pyridine-2-carboxamide 8b (3.39g, 10 mmol) in dry dioxane and DMFDMA (1.32ml, 10mmol) with stirring for 12 hrs. The product was recovered by filtration and recrystallised from acetic acid as gray crystals (2.6g, 74.5%), Mp. 200.202 oC; 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) υ at 1649, 1691 cm-1 (2C=O); MS (EI)+: m/z 349 M+; Anal. Calcd for C19H15N3O2S (349.41): C, 65.31; H, 4.33; N, 12.03, Found: C, 65.19; H, 4.26; N, 11.95.

General procedure for the preparation of compounds 21a,b

A mixture of N-substituted-5-acetyl-3-amino-6-methylthieno[2,3-b]pyridine-2-carboxamide 8b,c (10 mmol) in acetic acid and sodium nitrite (1.38g, 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][1,2,3]triazin-4(3H)-one (21a):

Obtained using 5-acetyl-3-amino-6-methyl-N-(p-tolyl)thieno[2,3-b]pyridine-2-carboxamide 8b (3.39g, 10 mmol). Mp. 170-172 oC as gray crystals (3g, 85.7%); 1HNMR (DMSO) δ = 2.4 (3H, s, CH3 Ar), 2.74 (3H, s, CH3 py.), 2.77 (3H, s, CH3CO), 7.4 (2H, d, Ar), 7.54 (2H, d, Ar), 9.17 (1H, s, CH py.); IR (KBr) υ 1687, 1700 cm-1 (2C=O); MS (EI)+: m/z 350 M+; Anal. Calcd for C18H14N4O2S (350.40): C, 61.70; H, 4.03; N, 15.99, Found: C, 61.56; H, 3.94; N, 15.78.

8-Acetyl-3-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-d][1,2,3]triazin-4(3H)-one (21b): Obtained using 5-acetyl-3-amino-N-(4-methoxyphenyl)-6-methylthieno[2,3-b]pyridine-2-carboxamide 8c (3.55g, 10 mmol). Mp. = 220-222 oC as gray crystals (2.9g, 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) υ 1687 cm-1 (C=O); Anal. Calcd for C18H14N4O3S (366.40): C, 59.01; H, 3.85; N, 15.29, Found: C, 58.96; 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 8-acetyl-7-methyl-3-(p-tolyl)pyrido[3',2':4,5]thieno[3,2-d][1,2,3]triazin-4(3H)-one 21a (3.5g, 10 mmol), malononitrile (0.66g, 10 mmol) and elemental sulfer (0.32g, 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 (3g, 69.7%), M.p 260-262 oC; IR (KBr) υ 3427 (NH2), 2208 (CN), 1683 cm-1 (C=O); MS (EI)+: m/z 430 M+; Anal. Calcd for C21H14N6OS2 (430.51): C, 58.59; H, 3.28; N, 19.52, Found: C, 58.43; H, 3.14; N, 19.36.

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 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 (3.5g, 10 mmol) and DMFDMA (1.32ml, 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 recrystallised from ethanol as brown crystals (2.9g, 71.6%), Mp. 210-212 oC; 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), 7.82 (1H, d, CH), 7.41 (2H, d, Ar), 7.54 (2H, d, Ar), 9.12 (1H, s, CH py.); IR (KBr) υ 16.44, 1693 cm-1 (C=O); MS (EI)+: m/z 405 M+; Anal. Calcd for C21H19N5O2S (405.48): C, 62.21; H, 4.72; N, 17.27, Found: C, 62.12; H, 4.59; N, 17.11.

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