Synthesis of some new pyrazole, 1,3-thiazole and 1,3,4-thiadiazole derivatives incorporating 4-pyridyl moiety

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Síntesis de nuevos derivados de pirazol, 1,3-tiazol y 1,3,4-tiadiazol incorporando el fragmento 4-pyridilo

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RESUMEN

Se sintetizó el 2-ciano-*N*-(piridin-4-il) acetamida (**2**) y seguidamente fue tratado con cloruros de hidrazonoilo (**3**) para obtener los correspondientes aminopirazoles (**5**). Calentando la mezcla de (**2**) con benziliden-malononitrilos y con benziliden-cianoacetatos de etilo se obtuvieron las correspondientes bipiridinas (**10**) y (**16**), respectivemente. Mediante tratamiento de (**2**) con fenilisotiocianato en DMF/KOH seguido por la adición de los cloruros de hidrazonoilo (**5**), (**10**) apropiados, y de cloroacetato de etilo, se obtuvieron los correspondientes 1,2,4-tiadiazoles (**22**) y **(27**) y 1,3-tiazol (**24**), respectivamente.

Palabras clave: cianoacetamidas, piridinas, pirazoles, 1,3,4-tiadiazol, 1,3-thiazoles.

SUMMARY

2-Cyano-*N*-(pyridin-4-yl)acetamide (**2**) was prepared and then treated with hydrazonoyl chlorides **3** to afford the corresponding aminopyrazoles **5**. Heating a mixture of **2** with benzylidenemalononitriles and with ethyl benzylidenecyanoacetates afforded the corresponding bipyridines **10** and **16**, respectively. Treatment of **2** with phenylisothiocyanate in DMF/KOH followed by addition of the appropriate hydrazonoyl chlorides **5, 10** and ethyl chloroacetate gave the corresponding 1,2,4-thiadiazoles **22** and **27** and 1,3-thiazole **24**, respectively.

Keywords: cyanoacetamides, pyridines, pyrazoles, 1,3,4-thiadiazole, 1,3-thiazoles.

RESUM

Es va sintetitzar el 2-ciano-*N*-(piridin-4-il) acetamida (**2**) i seguidament va ser tractat amb clorurs d'hidrazonoil (**3**) per obtenir els corresponents aminopirazols (**5**). Escalfant la barreja de (**2**) amb benziliden-malononitrils i amb benziliden-cianoacetats d'etil es van obtenir les corresponents bipiridines (**10**) i (**16**), respectivement. Mitjançant tractament de (**2**) amb fenilisotiocianat en DMF/KOH seguit per l'addició dels clorurs d'hidrazonoilo (**5**), (**10**) apropiats, i de cloracetat d'etil, es van obtenir els corresponents 1,2,4-tiadiazols (**22**) i (**27**) i 1,3-tiazol (**24**), respectivament.

Paraules clau: cianoacetamides, piridines, pirazols, 1,3,4-tiadiazol, 1,3-thiazols.

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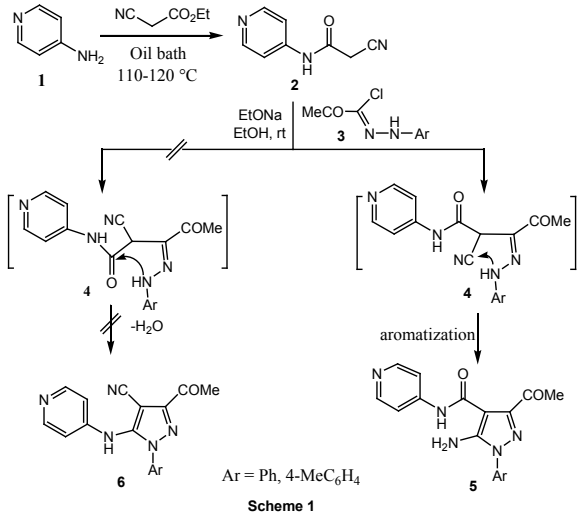
1. INTRODUCTION

Pyridine derivatives are among the most used frameworks for medicines, food flavorings, dyes and agrochemicals.[1] They were found to have antitumor,[2] anticonvulsant and anti-inflammatory,[3] and antiproliferative[4] activities. Pyrazole derivatives have important applications in the field of medicinal chemistry and pharmacueticals.[5-9] Cyanoacetamide derivatives have been found to be useful as herbicidals[10] and to be active against neoplastic disorder.[11] Furthermore, they have also been important for their antiinflammatory,[12] antibacterial,[13,14] antitumor,[15] neoplasm inhibitory,[16] tyrosine kinase inhibitory,[17] and analgesic properties,[18] and for the treatment of disorders related to vasculogenesis.[19] 1,3,4-Thiadiazoles were recently reported by us and others as highly anti-inflammatory,[20,21] anticonvulsant[20,22] and antiviral[23] agents. In continuation to our research work on 1,3,4-thiadiazole derivatives.[24-32] In the course of our investigations, we found that the *hitherto unreported* 2-cyano-*N*-(pyridin-4-yl)acetamide (**2**) is a highly versatile building block for the synthesis of a wide variety of several new pyridine-based heterocyclic derivatives.

2. RESULTS AND DISCUSSION

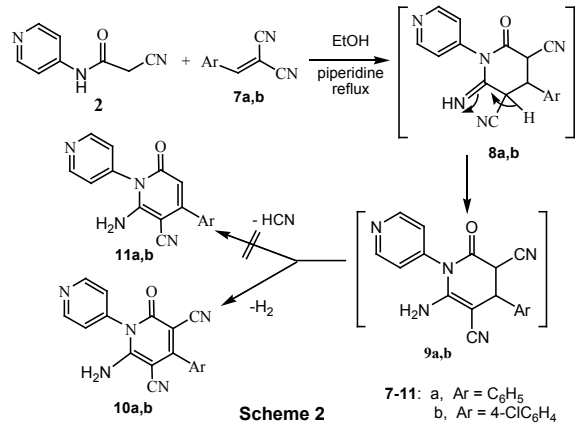
Heating a mixture of 4-aminopyridine (**1**) and ethyl cyanoacetate at 110-120 °C without solvent resulted in the formation of the novel 2-cyano-*N*-(pyridin-4-yl)acetamide (**2**) in a good yield (Scheme 1). The IR spectrum of the reaction product showed three absorption bands at 3348 (NH), 2193 (C≡N), 1637 (C=O) cm-1. Mass spectrum showed a peak at m/e 161 due to the molecular ion of the product **2**. The assignment is also based on the presence of four signals (CH2, two CH's and NH) in 1H NMR spectrum of the reaction product. Treatment of 2-cyano-*N*-(pyridin-4-yl) acetamide (**2**) with the hydrazonoyl chloride **3a** in ethanolic sodium ethoxide solution at room temperature furnished a single product for which the two possible structures **5** and **6** can be envisaged (Scheme 1).



Scheme 1

However, spectral data were in complete accordance with the aminopyrazole structure **5**. The IR spectrum of the reaction product was free of any nitrile function and showed absorption bands at 3443, 3331, 3042, 1670 and 1638 cm-1 due to amino, amide-NH and two carbonyl groups, respectively. Moreover, the mass spectrum of the isolated product revealed a molecular ion peak at m/z 321. The obtained data gave a firm support for the aminopyrazole derivative **5** and excluded the other possible cyanopyrazole derivative **6**. A plausible mechanism of the formation of compound **5** is outlined in Scheme 1.

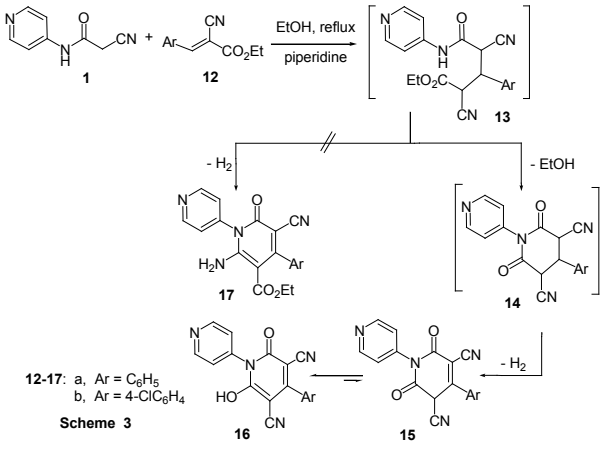
Next, when equimolar amounts of the cyanoacetamide derivative **2** and benzylidenemalononitrile **7a** were refluxed in the presence of a catalytic amount of piperidine,it afforded a single product proved to be a 1 : 1 cycloadduct. The structure of the isolated product was identified as 6-amino-1,2-dihydro-2-oxo-4-phenyl-1-(pyridin-4-yl)pyridine-3,5-dicarbonitrile **10a** (Scheme 3) on the basis of its spectral data. Structure **10a** is assumed to be formed via an initial Michael-type adduct **8a** followed by an intramolecular cyclization and subsequent oxidation to give the final product **10a** (Scheme 2).



Scheme 2

The other expected product **11a** via loss of hydrogen cyanide was not detected on the basis of the mass spectrum of the reaction product. Furthermore, when equimolar amounts of **2** and 4-chlorobenzylidenemalononitrile **7b** were refluxed under the same reaction condition above, it afforded the 1-(pyridin-4-yl)pyridine-3,5-dicarbonitrile derivative **10b** (Scheme 2) based on the spectral data of the isolated product.

When 2-cyano-*N*-(pyridin-4-yl)acetamide (**2**) was treated with ethyl benzylidenecyanoacetate **12a** in refluxing ethanol, in the presence of a catalytic amount of piperidine, it gave the corresponding 1,4'-bipyridine derivative **16** as outlined in Scheme 3.



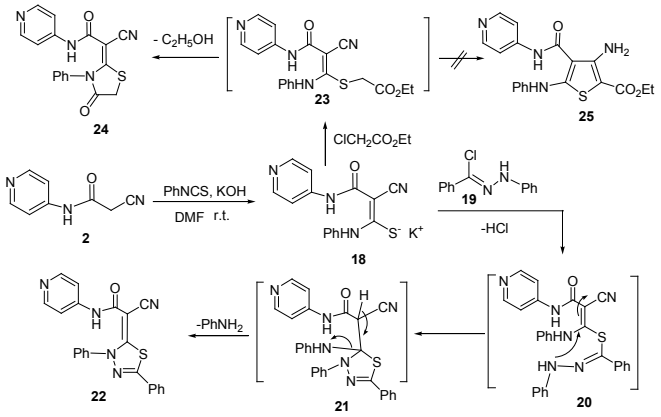
12-17: a, Ar = C_6H_5
b, Ar = 4-ClC_6H_4

Scheme 3

Compound **16** was formed initially via a Michael-type addition to give the intermediate **13a** followed by elimination of ethanol molecule to give the intermediate **14a** then of hydro-

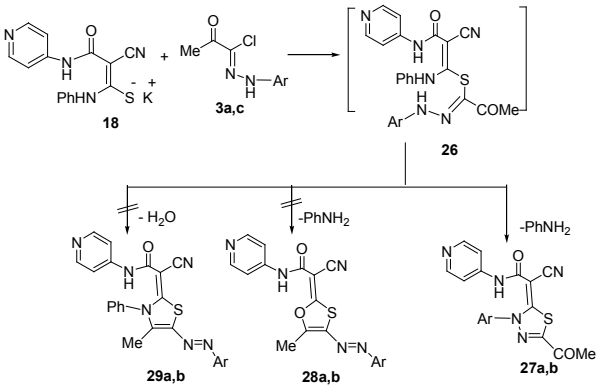
gen under the reaction condition to give the 1,4'-bipyridine derivative **16**. The absence of aliphatic-CH protons in the 1H NMR spectrum supports structure **16** which is the tautomer of **15**. The absence of absorption bands due to NH2 in the IR spectrum and the ester-protons in the 1H NMR spectrum of the reaction product ruled out structure **17**. Similarly, compound **2** reacted with ethyl 4-chlorobenzylidenecyanoacetate **12b** under the same reaction conditions to give the 4-(4-chlorophenyl)-1-(pyridin-4-yl)pyridine-3,5-dicarbonitrile **16b** (Scheme 3) on the basis of the elemental analyses and spectral data of the isolated product.

Next, the synthesis of some pyridine-based 1,3,4-thiadiazole derivatives is attempted. Thus, treatment of 2-cyano-*N*-(pyridin-4-yl)acetamide (**2**) with phenyl isothiocyanate in dimethyl formamide, in the presence of potassium hydroxide, at room temperature gave the non-isolable intermediate potssium salt **18** as shown in Scheme 4. Addition of an equimolar amount of the hydrazonoyl chloride **19** furnished only one isolable product which was identified as the 2-cyano-*N*-(pyridin-4-yl)-2-[3,5-diphenyl-2(3*H*)-1,3,4-thiadiazolylidene]acetamide **22** as confirmed by the spectroscopic analyses (IR, ^{1}H NMR and MS spectra) of the isolated product. The formation of the thiadiazole derivative **22** indicates that the reaction proceeds *via* loss of potassium chloride and aniline from the intermediates **20** and **21,** respectively. Next, treatment of the intermediate **2,** formed *in situ* under the same reaction condition, with ethyl chloroacetate afforded a single product identified as 2-cyano-2-(4-oxo-3-phenylthiazolidin-2-ylidene)-*N*-(pyridin-4-yl)acetamide (**24**) as shown in Scheme 4. Its ^{1}H NMR spectrum revealed two singlets at d 4.07 and 11.30 due to thiazolidinone-CH_2 and NH protons in addition to aromatic multiplets signal at d 8.05-8.55. The obtained data excludes the other possible thiophene structure **25**.



Scheme 4

In a similar manner, reaction of the hydrazonoyl chloride **3a** with the potassium salt **18** under the same reaction condition gave the assigned structure 2-[5-acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-2-cyano-*N*-(pyridin-4-yl) acetamide **27a** (Scheme 5) and the other structures **28a**, **29a** were excluded based on the elemental and spectroscopic data of the reaction product. In addition, treatment of C–acetyl-*N*-(4-tolyl)hydrazonoyl chloride **3c** with the intermediate salt **18** gave similarily only one product for which structures **27b-29b** can be assigned as outlined in Scheme 5. However, spectral data of the reaction product were in complete accordance with structure **27b**. The IR spectrum of the reaction product revealed the presence of two carbonyl absorptions which excludes structures **28b** and 29b. Also, 1H NMR spectrum of 27b showed two singlets at d 2.28 and 2.44 due to 4-CH3 and COCH3 protons in addition to the aromatic multiplets at d 7.07–8.43 and a broad singlet at d 11.22 for NH proton. The presence of the two singlets due to two CH3-protons confirms the loss of aniline and not p-toluidine from the intermediate 26b. The mass spectrum revealed a molecular ion peak due to 27b.



Scheme 5

26--28 : a; Ar = C_6H_5
b; Ar = 4-$CH_3C_6H_4$

3. EXPERIMENTAL SECTION

All melting points were measured on a Gallenkamp electrothermal melting point apparatus. The infrared spectra were recorded for potassium bromide pellets on a Pye Unicam SP 3-300 and FT IR 8101 PC Schimadzu infrared spectrophotometers. The 1H NMR spectra were recorded in deuterated chloroform or dimethyl sulfoxide at 300 MHz on a Varian Mercury NMR spectrometers using tetramethylsilane as an internal reference. Mass spectra were recorded on a GCMS–QP 1000 EX Shimadzu mass spectrometer at 70 eV. Hydrazonoyl chlorides **2a,**[33] **2b,c**[34] and **19**[35] arylmethylenepropane dinitrile **7a,b**[36] and ethyl benzylidenecyanoacetate **12a,b**[36] were prepared following literature procedures.

3.1. Synthesis of 2-cyano-*N*-(pyridin-4-yl)acetamide (2)

In a 100 mL three-necked round–bottomed flask, fitted with air condenser and thermometer were placed ethyl cyanoacetate (2.26 g, 2.1 ml, 20 mmol). The flask was immersed in an oil bath heated to 110-120 °C then 4-aminopyridine (1.9 g, 20 mmol) was added portion-wise over a period of 30 min. and heating was continued for an additional 3 min. The reaction flask was removed from the oil bath, left to cool and triturated with methanol. The solid product was filtered off washed with ethanol several times and dried. Recrystallization from ethanol afforded yellowish-white crystals of **2** in 65% yield. Mp. 242-244 °C; IR υ (cm^{-1}): 3348 (NH), 2193 (C≡N), 1637 (C=O), 1520 (C=N); ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 2H, CH_2), 8.01 (d, 2H, *J* = 7.2 Hz), 8.53 (d, 2H, *J* = 7.2 Hz), 11.73 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) d 28.7, 108.7, 112.9, 149.7, 159.5, 178.9; MS *m/z* (%) 161 (M^+, 76.6), 121 (37.6), 94 (100), 78 (86.3). Anal. for $C_8H_7N_3O$ Calcd: C, 59.62; H, 4.38; N, 26.07. Found: C, 60.01; H, 4.17; N, 26.12%.

3.2. 3-Acetyl-5-amino-1-aryl-*N*-(pyridin-4-yl)-1H-pyrazole-4-carboxamides 5.

2-Cyano-*N*-(pyridin-4-yl)acetamide (**2**) (0.322 g, 2 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (46 mg, 2 mmol) and absolute

ethanol (20 mL)] with stirring. After stirring the resulting solution for 15 min., the appropriate hydrazonoyl halide **3a,b** (2 mmol) was added portion-wise and the reaction mixture was stirred for further 12h at room temperature. The solid that formed was filtered off, washed with water and dried. Recrystallization from ethanol afforded the corresponding pyrazole derivatives **5a,b** in 55-61% yields.

3-Acetyl-5-amino-1-phenyl-*N*-(pyridin-4-yl)-1H-pyrazole-4-carboxamide (5a)

Yield (61%), mp. 173-175 ºC; IR (KBr) υ 3414, 3330, 3110 (NH_2, NH), 1670, 1621 (2 C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (s, 3H, $COCH_3$), 7.09-7.63 (m, 9H, ArH), 8.15 (s, 1H, D_2O-exchangeable, NH), 8.45 (s, 2H, D_2O-exchangeable, NH_2); MS *m/z* (%) 322 (M^++1, 7.8), 321 (M^+, 42.9), 278 (14.3), 228 (100), 160 (24.7), 135 (46.8), 119 (27.3), 104 (44.2), 95 (18.2), 77 (92.2), 51 (63.6). Anal. Calcd. for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79. Found: C, 63.29; H, 4.55; N, 21.90%.

3-Acetyl-5-amino-*N*-(pyridin-4-yl)-1-(p-tolyl)-1H-pyrazole-4-carboxamide (5b)

Yield (55%); mp. 164-166 ºC; IR (KBr) υ 3418, 3310, 3132 (NH_2, NH), 1674, 1655 (2C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 2.71 (s, 3H, $COCH_3$), 5.99 (s, 2H, NH_2), 6.96 (m, 1H), 7.34-7.49 (m, 5H), 8.27 (d, 1H, *J* = 8.4 Hz), 8.4 (d, 1H, *J* = 5.8 Hz), 12.45 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.7, 26.8, 95.8, 113.5, 119.1, 124.5, 130.1, 134.3, 138, 138.5, 145.9, 148.1, 152, 153.1, 162.3, 198.2; MS *m/z* (%) 335 (M^+, 28.6), 292 (100), 242 (88.9), 91 (21.6). Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.51; H, 5.15; N, 20.79%.

3.3. 6-Amino-4-aryl-1,2-dihydro-2-oxo-1-(pyridin-4-yl) pyridine-3,5-dicarbonitrile 10

To a solution of the appropriate arylmethylenepropanedinitrile **7a,b** (5 mmol) in ethanol (20 mL) was added 2-cyano-*N*-(pyridin-4-yl)acetamide (**2**) (0.81 g, 5 mmol), and few drops of piperidine and the reaction mixture was heated under reflux for 4h, then left to cool to room temperature. The solid product that formed was collected by filtration, washed with ethanol and then recrystallized from DMF/water to give the 1,4-bipyridine derivatives **10a,b.**

6-Amino-1,2-dihydro-2-oxo-4-phenyl-1-(pyridin-4-yl) pyridine-3,5-dicarbonitrile (10a): Yield (66%), mp. > 300 ºC (DMF); IR (KBr) υ 3356 and 3153 (NH_2), 2205 (C≡N), 1698 (C=O), 1636 (C=N), 1528 (C=C) cm^{-1}; ^1H NMR (DMSO) δ 7.51-7.60 (m, 7H, ArH), 8.05 (br. s, 2H, NH_2), 8.51 (d, 2H, *J* = 6 Hz, ArH); MS *m/z* (%) 314 (M^++1, 24.7), 313 (M^+, 78), 285 (27.7), 209 (8.0), 156 (10.4), 120 (8.9), 104 (12.8), 78 (62.2), 51 (100). Anal. Calcd for $C_{18}H_{11}N_5O$: C, 69.00; H, 3.54; N, 22.35. Found: C, 69.24; H, 3.45; N, 22.18%.

6-Amino-4-(4-chlorophenyl)-1,2-dihydro-2-oxo-1-(pyridin-4-yl)pyridine-3,5-dicarbonitrile (10b): Yield (74%), mp. > 300 ºC (DMF); IR (KBr) υ 3343 and 3166 (NH_2), 2220 (C≡N), 1679 (C=O), 1625 (C=N), 1520 (C=C) cm^{-1}; ^1H NMR (DMSO) δ 7.49 (d, 2H, *J* = 6 Hz, ArH), 7.56 (d, 2H, *J* = 8.4 Hz, ArH), 7.68 (d, 2H, *J* = 8.4 Hz, ArH), 8.10 (br. s, 2H, NH_2), 8.82 (d, 2H, *J* = 6 Hz, ArH); ^{13}C NMR (DMSO) δ 75.6, 88.1, 115.3, 115.8, 123.8, 128.8, 129.8, 133.4, 135.2, 141.8, 151.9, 156.5, 158.8, 160.4; MS *m/z* (%) 349 (M^++2, 24.5), 348 (M^++1, 16.4), 347 (M^+, 51.0), 319 (23.0), 284 (6.6), 243 (8.8), 180 (12.4), 156 (5.8), 120 (10.1), 105 (6.6), 78 (69.4), 51 (100). Anal. Calcd for $C_{18}H_{10}ClN_5O$: C, 62.17; H, 2.90; N, 20.14. Found: C, 62.04; H, 2.85; N, 20.21%.

3.4. Reaction of the cyanoacetamide 2 with ethyl benzylidenecyanoacetates 12a,b.

To a solution of the appropriate ethyl benzylidenecyanoacetate **12a,b** (5 mmol) in ethanol (20 mL) was added 2-cyano-*N*-(pyridin-4-yl)acetamide (**2**) (0.81 g, 5 mmol), and few drops of piperidine and the reaction mixture was heated under reflux for 4h, then left to cool to room temperature. The solid product that formed was collected by filtration, washed with ethanol and then recrystallized from DMF/water to give brownish-white solid of the corresponding 1,4-bipyridine derivatives **16a,b.**

6-Hydroxy-2-oxo-4-phenyl-1-(pyridin-4-yl)pyridine-3,5-dicarbonitrile (16a):

Yield (82%), mp. 258-260 oC; IR (KBr) υ 3419 (OH), 2212 (C≡N), 1626 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 7.44-7.87 (m, ArH); ^{13}C NMR (DMSO-d_6) δ 95.6, 119.8, 128.6, 128.8, 128.9, 129.1, 130.3, 130.8, 133.6, 136.5, 146.3, 148.8, 168; MS *m/z* (%) 314 (M^+, 11.5), 247 (40.4), 173 (11.5), 160 (59.6), 149 (30.8), 121 (44.2), 118 (46.2), 104 (38.5), 94 (100), 78 (73.1), 67 (63.5). Anal. Calcd for $C_{18}H_{10}N_4O_2$ (314.3): C, 68.79; H, 3.21; N, 17.83. Found: C, 69.02; H, 3.39; N, 17.61%.

4-(4-Chlorophenyl)-6-hydroxy-2-oxo-1-(pyridin-4-yl) pyridine-3,5-dicarbonitrile (16b):

Yield (60%), mp. > 300 ºC; IR (KBr): υ 3425 (OH), 2204 (C≡N), 1650 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 4.31 (br. s, 1H, OH), 7.31-7.68 (m, 6H, ArH), 8.06 (d, 2H, *J* = 6.9 Hz); MS: *m/z* (%) 348 (M^+, 30.8), 284 (15.4), 236 (48.7), 188 (17.9), 164 (17.9), 156 (15.4), 94 (59.0), 51 (100). Anal. Calcd for $C_{18}H_9ClN_4O_2$ (348.75): C, 61.99; H, 2.60; N, 16.07. Found: C, 62.07; H, 2.49; N, 16.11%.

3.5. Synthesis of 1,3,4-thiadiazole derivatives 22 and 27.

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 mL) was added 2-cyano-*N*-(pyridin-4-yl)acetamide (**2**) (0.322 g, 2 mmol). After stirring for 30 min, phenylisothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6h, then the appropriate hydrazonoyl chlorides **3** or 19a,b (2 mmol) were added portionwise over a period of 30 min. After the addition was complete, the reaction mixture was stirred for additional 12h, during which reactants dissolved and a yellowish–red colored product precipitated. The solid product was filtered off, washed with water and dried. Recrystallization from the suitable solvent afforded the corresponding products 1,3,4-thiadiazole derivatives **22** and **27a,b** respectively.

2-Cyano-2-[3,5-diphenyl)-2(3H)-1,3,4-*thiazolylidene]-N*-(pyridin-4-yl)acetamide (22).

Yellowish-white powder; yield (81%); m.p. > 300 ºC (DMF/H_2O), IR υ 3412 (NH), 2185 (C≡N), 1633 (C=O), 1594 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.19–8.40 (m, 14H, ArH), 9.97 (br.s, 1H, NH); MS *m/z* (%) 397 (M^+, 43.8), 304 (100), 173 (14.9), 169 (34.7), 146 (37.2), 109 (19), 77 (49.6). Anal. for $C_{22}H_{15}N_5OS$ Calcd: C, 66.48; H, 3.80; N, 17.62; S, 8.07. Fund: C, 66.38; H, 3.97; N, 18.02; S, 17.46%.

2-(5-Acetyl-3-p-tolyl-1,3,4-thiadiazol-2(3H)-ylidene)-2-cyano-*N*-(pyridin-4-yl)acetamide (27a).

Yield (67%); Mp: 206-206 ºC (DMF/H_2O), IR υ 3416 (NH), 2192 (C≡N), 1644 (C=O), 1532 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.28 (s, 3H, p-CH_3), 2.44 (s, 3H, $COCH_3$), 7.20–8.43 (m, 8H, ArH), 11.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 20.38, 25.0, 80.0, 114.8, 115.3, 122.8, 128.1, 129.9, 132.9, 139.4, 140.4, 144.5, 155.4, 165.1, 194.3; MS *m/z* (%) 377 (M^+, 10.2), 291 (3.2), 261 (73.1), 208 (32.3), 165 (7.0), 132 (27.4), 106 (100), 77 (57.0). Anal. for $C_{19}H_{15}N_5O_2S$ Calcd: C, 60.46; H, 4.01; N, 18.56; S, 8.50. Found: C, 60.31; H, 3.88; N, 18.42; S, 8.69%.

2-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-2-cyano-*N*-(pyridin-4-yl)acetamide (27b).
Yield (70%); Mp. 165-168 °C (DMF/H_2O), IR υ 3416 (NH), 2190 (C≡N), 1649 (C=O), 1611 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.45 (s, 3H, $COCH_3$), 7.08–7.68 (m, 9H, ArH), 11.18 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 25.2, 80, 115.4, 121.2, 122.1, 124.1, 128.6, 129.1, 129.3, 129.7, 136.2, 141.6, 144.7, 152.6, 196.0; MS m/z (%) 363 (M^+, 4.5), 247 (51.7), 205 (14.7), 194 (21.8), 118 (100), 92 (75.2), 77 (66.8). Anal. for $C_{18}H_{13}N_5O_2S$ Calcd: C, 59.49; H, 3.61; N, 19.27; S, 8.82. Found: C, 59.31; H, 3.68; N, 19.14; S, 8.67%.

3.6. Synthesis of Synthesis of 1,3-thiazolidine derivative 24.
The above procedure was repeated using ethyl chloroacetate (2 mmol) instead of the hydrazonoyl chlorides **3** and **19a,b**. The reaction mixture was then heated at reflux for 6h, during which reactants were dissolved and a yellowish–red colored product was precipitated. The solid product was filtered off, washed with water and dried. Recrystallization from the DMF/water afforded 2-cyano-2-(4-oxo-3-phenylthiazolidin-2-ylidene)-*N*-(pyridin-4-yl) acetamide (**24**) in 81% yield; Mp 268-270 oC, IR u 3179 (NH), 1719 (C=O), 1622 (C=N) cm-1; 1H NMR (DMSO-d6) d 4.07 (s, 2H, CH2), 7.84–8.55 (m, 9H, ArH), 11.30 (s, 1H, NH). Anal. for C17H12N4O2S (336.38).Calcd: C, 60.70; H, 3.60; N, 16.66; S, 9.53. Found: C, 60.51; H, 3.45; N, 16.39; S, 9.42%.

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