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Simple methods to synthesize 2-pyridones: reactions of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes and cyanoacetamide

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Abstract

5-Aroyl-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitriles and 5-aroyl-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitriles are synthesized effectively by the reaction of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes and cyanoacetamide under two different conditions.

Keywords: Heterocycles; Thermal cyclization; Acrylaldehydes; Dithioacetals; 2-Pyridones

1. Introduction

The synthesis of a substituted 2-pyridone ring is an area of continuing interest due to the number of biologically active molecules containing this moiety.[1] Over the last decade, natural compounds with this structure have emerged as potent anti-microbial and anti-viral agents and efforts to develop an anti-HIV drug based on 2-pyridones are progressing worldwide.[2] Ketene dithioacetals have proved to be excellent precursors for the synthesis of alkylsulfanyl-substituted pyridones in high yields.[3] One of the most important methods for the synthesis of 2-pyridones involves cyclocondensation of ketene dithioacetals with compounds containing active methylene group like cyanoacetamide and scope of such reactions is well established.[4] Recently Mathews and Asokan have utilized 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes in the synthesis of new heterocyclic compounds.[5] In continuation of our extensive work on 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes we explored their synthetic utility in the synthesis of 2-pyridones using cyanoacetamide.

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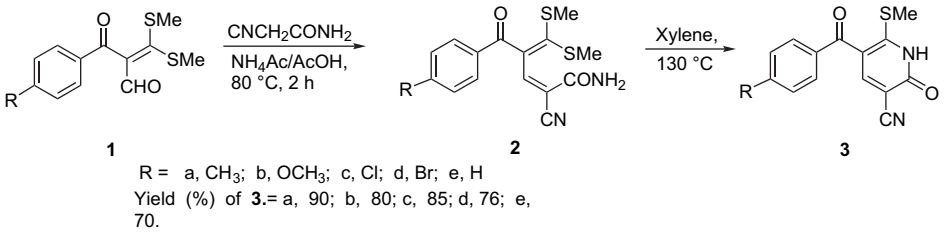
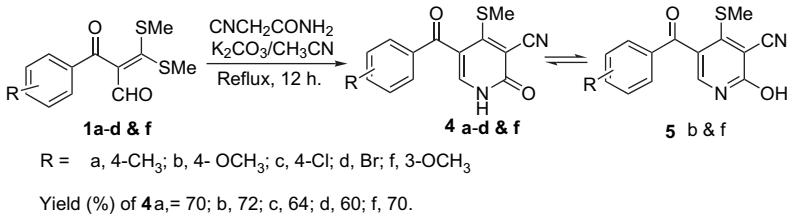
2. Results and discussion

Most of the earlier reported methods for the synthesis of 2-pyridones involving the condensation of 1,3-binucleophiles with cyanoacetamide need strong bases like sodium hydride, sodium hydroxide or alkoxides.[6] In many reactions we encountered the deformylation of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes with strong bases. Junjappa et al. used ammonium acetate/acetic acid medium to cyclize polarized dienes, obtained by the 1,2-addition of Reformatsky reagent to α-oxoketene dithioacetals, leading to the synthesis of substituted 2-pyridones.[7] So we used ammonium acetate/acetic acid medium to synthesize 2-pyridones from 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes using cyanoacetamide.

When we attempted the reaction of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes with cyanoacetamide in the presence of ammonium acetate/acetic acid at 80 °C, it afforded only the Knoevenagel condensation adduct, 4-aroyl-2-cyano-5,5-bis-(methylsulfanyl)-2,4-pentadienamides **2** in 80–90% yields and no 2-pyridone was formed. ^{1}H and ^{13}C NMR, EIMS, IR spectral data and CHN analysis supported the predicted structure. As the condensation product has the scope for cyclization to produce 2-pyridones by the elimination of an alkylsulfanyl



Scheme 1. Synthesis of 5-aroyl-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitriles **3** via 4-aroyl-2-cyano-5,5-bis(methylsulfanyl)-2,4-pentadienamide **2**.



Scheme 2. Synthesis of 5-aroyl-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitriles 4.

group, we tried the thermal cyclization of the condensation products **2** by heating in xylene at 130 °C (Scheme 1). As expected, the condensation products underwent thermal cyclization to produce 5-aroyl-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitriles **3** in 83–90% yield. The products were characterized by the ^{1}H and ^{13}C NMR, EIMS, IR spectral data and CHN analysis.

One-pot reaction of acrylaldehydes **1** and cyanoacetamide in the presence of ammonium acetate/acetic acid at 120 °C showed that the cyclization took place under these conditions also but in this case the yield of the reaction was low.

As a continuation to this we treated 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes **1** with cyanoacetamide in the presence of K_2CO_3 in acetonitrile and the reaction yielded new pyridones, 5-aroyl-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitriles via a thermodynamically controlled reaction (Scheme 2).

When acrylaldehyde **1a** was treated with 1 equiv of cyanoacetamide in the presence of potassium carbonate in acetonitrile under reflux for 12 h, the reaction afforded pale yellow solid having mp 200–202 °C in good yields and it was characterized on the basis of spectral data as 5-(4-methylbenzoyl)-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **4a** (the nature and melting points of **3a** and **4a** are also different). The reaction was also extended to other substituted acrylaldehydes as well in order to get corresponding 5-aroyl-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitriles in good yields. It was observed that a mixture of tautomers **4** and **5** was obtained when the aryl part contains a methoxy substituent.

The formation of 5-aroyl-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **4** is explained by a mechanism reported by Junjappa et al.[8] As the reaction is conducted in the presence of mild base like K_2CO_3 in acetonitrile at reflux temperature for 12 h, it facilitates thermodynamically controlled conjugate addition of carbanion formed from the cyanoacetamide to the ketene dithioacetal moiety. It is then possible for the addition of amino group to the aldehyde, followed by hydrolysis to produce the pyridones. Similar Michael addition reaction products are reported by Hu et al. in the synthesis of 2-pyridones using acetamidocyanoacetate and α,β-unsaturated ketones.[9]

2.1. Fluorescent study of 4-benzoyl-2-cyano-5,5-bis(methylsulfanyl)-2,4-pentadienamide

Recently number of ketene dithioacetal derivatives are emerging as chemoluminescent labelling compounds especially with peroxidase enzymes.[10] Narasaka et al. made attempts to synthesize ketene dithioacetal derivatives having fluorescent character.[11] The extensive conjugation of the 4-benzoyl-2-cyano-5,5-bis(methylsulfanyl)-2,4-pentadienamide **2** having a bright yellow colour spurred us to study the fluorescent nature of these derivatives. For that their UV–vis absorption and fluorescence spectra were recorded. We noticed that in $CHCl_3$

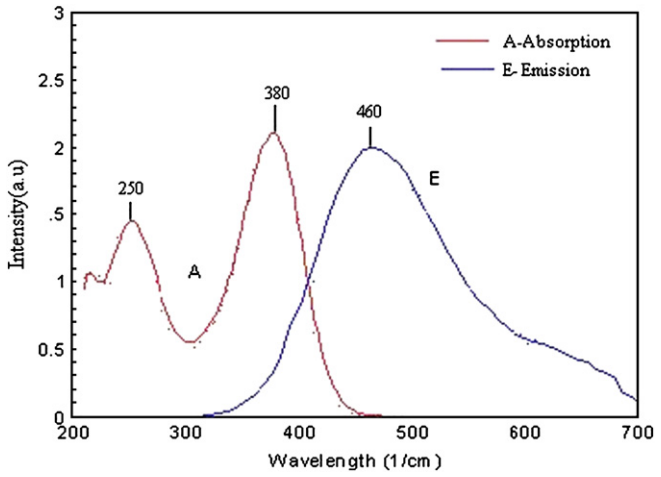


Figure 1. The UV spectrum and fluorescent spectrum (excited at 380 nm) of the 4-benzoyl-2-cyano-5,5-bis(methylsulfanyl)-2,4-pentadienamide **2d**.

4-benzoyl-2-cyano-5,5-bis(methylsulfanyl)-2,4-pentadienamide showed two absorption maxima at 380 and 250 nm. Thus we excited at 380 nm to study its fluorescent behaviour (Fig. 1). The emission maxima were found to be at 460 nm when the excitation was carried out at 380 nm. It clearly indicated that when pentadienamide derivative was excited, it could emit radiation in the visible region, thus showing the fluorescent nature of the 4-benzoyl-2-cyano-5,5-bis(methylsulfanyl)-2,4-pentadienamide fluorescent study on other pentadienamide derivatives also gave the emission maxima in the higher wavelength region, confirming the above observation. Further detailed studies on the quantum yield of the fluorescence and variation in emission maxima with respect to different solvents have to be done in future.

3. Conclusions

In this paper we described the formation of two different 2-pyridones, 5-aroyl-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **3** and 5-aroyl-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **4** by the reaction of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes and cyanoacetamide under different reaction conditions. The formation of 5-aroyl-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **4** is explained by a conjugate addition reaction of the cyanoacetamide in the presence of potassium carbonate followed by cyclization while that of 5-aroyl-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **3** is by the Knoevenagel condensation reaction of the aldehyde followed by cyclization reaction. The analogues of these compounds are important as drugs used in the clinical treatment of patients with severe heart failure.[12] Fluorescent study revealed the possibility of utilizing the 4-benzoyl-2-cyano-5,5-bis(methylsulfanyl)-2,4-pentadienamide derivatives **2** as a fluorescent material.

4. Experimental section

4.1. General

Melting points were determined on Buchi 530 melting point apparatus and were uncorrected. The IR spectra were on KBr pellets on Schimadzu IR-470 spectrometer and the frequencies are reported in cm^{-1}. The ^1H NMR spectra were recorded on a Brucker WM (300 MHz) spectrometer using TMS as internal standard and $CDCl_3$, $(CH_3)_2C{=}O$-d_6 or DMSO-d_6 as solvent. The ^{13}C NMR spectra were recorded on a Brucker WM 300 (75.47 MHz) spectrometer using $CDCl_3$ or acetone-d_6 as solvent. The CHN analyses were done on an Elementar VarioEL III Serial Number 11042022 instrument. The FAB mass spectra were recorded on a JOEL SX 102/DA-6000 Mass Spectrometer/Data System using Argon as the FAB gas. EIMS were recorded on a MICROMASS QUATTRO 11 triple quadrupole mass spectrometer.

All commercially available reagents were purified before use. The aroylketene dithioacetals and 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes were prepared by the known procedure.[13]

4.2. General procedure for the synthesis of 4-aroyl-2-cyano-5,5-bis(methylsulfanyl)-2,4-pentadienamide (2)

The appropriate 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde (2 mmol) was added to a solution of cyanoacetamide (0.168 g, 2 mmol) in ammonium acetate (0.77 g, 10 mmol) and acetic acid (5 mL). The solution mixture was heated at 80 °C for 2 h. The mixture was cooled and poured into ice-cold water and the solid obtained was filtered, washed and recrystallized from methanol.

4.2.1. 2-Cyano-4-(4-methylbenzoyl)-5,5-bis(methylsulfanyl)-2,4-pentadienamide **2a**

Yellow solid; yield 80% (0.53 g); mp 202–204 °C; IR (KBr, ν_{max})=3382, 3186, 2206, 1658, 1604, 1562, 1477 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.27 (s, 3H, Me), 2.42 (s, 3H, SCH_3), 6.31 (s, 2H, $CONH_2$), 7.29 (d, J=9 Hz, 2H, ArH), 7.78 (d, J=9 Hz, 2H, ArH), 8.64 (s, 1H, vinylic); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6, 1:1) δ=18.2 (SMe), 21.6 (Me), 103.1 (=*C*–$CONH_2$), 115.2 (CN), 129.2 (ArH), 129.5 (ArH), 134.2 [=*C*(SMe)$_2$], 137.1 [*C*=C(SMe)$_2$], 144.8 (ArH), 145.4 (ArH), 161.1 (vinylic), 162.3 ($CONH_2$), 192.8 (CO); FABMS *m/z* (%)=333 (100). Anal. Calcd for $C_{16}H_{16}N_2O_2S_2$ (332.44): C, 57.81; N, 8.43; H, 4.85. Found: C, 57.88; N, 8.46; H, 4.82.

4.2.2. 2-Cyano-4-(4-methoxybenzoyl)-5,5-bis(methylsulfanyl)-2,4-pentadienamide **2b**

Yellow solid; yield 63% (0.43 g); mp 198–200 °C; IR (KBr, ν_{max})=3359, 3182, 2206, 1658, 1600, 1562, 1473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.48 (s, 3H, SMe), 3.88 (s, 3H, OCH_3), 6.43–6.56 (m, 2H, $CONH_2$), 6.97 (d, J=6 Hz, 2H, ArH), 7.85 (d, J=6 Hz, 2H, ArH), 8.64 (s, 1H, vinylic); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6, 1:1) δ=18.1 (SMe), 55.3 (OMe), 103.0 (=C–$CONH_2$), 114.0 (ArH), 115.1 (CN), 129.6 (ArH), 131.5 (ArH), 137.1 [=C(SMe)$_2$], 145.2 [C=C(SMe)$_2$], 160.7 (vinylic), 162.3 ($CONH_2$), 164.0 (ArH), 191.8 (CO); FABMS *m/z* (%)=349 (100). Anal. Calcd for $C_{16}H_{16}N_2O_3S_2$ (348.44): C, 55.15; N, 8.04; H, 4.63. Found: C, 55.28; N, 8.01; H, 4.62.

4.2.3. 4-(4-Chlorobenzoyl)-2-cyano-5,5-bis(methylsulfanyl)-2,4-pentadienamide **2c**

Yellow solid; yield 85% (0.59 g); mp 218–220 °C; IR (KBr, ν_{max})=3379, 3182, 2206, 1658, 1585, 1562, 1477 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.43 (s, 6H, SCH_3), 5.62 (s, 1H, NH_2), 6.01 (s, 1H, NH_2), 7.48 (d, J=9 Hz, 2H, ArH), 7.84 (d, J=9 Hz, 2H, ArH), 8.65 (s, 1H, vinylic); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6, 1:1) δ=17.9 (SMe), 105.4 (=*C*–$CONH_2$), 114.9 (CN), 129.1, 130.7 (ArH), 135.5 (ArH), 138.6 [=*C*(SMe)$_2$], 144.2 [*C*=C(SMe)$_2$], 158.5 (vinylic), 162.41 ($CONH_2$), 189.9 (CO); EIMS *m/z* (%)=353 (100). Anal. Calcd for $C_{15}H_{13}ClN_2O_2S_2$ (352.86): C, 51.06; N, 7.94; H, 3.71. Found: C, 51.26; N, 7.96; H, 3.72.

4.2.4. 2-Cyano-4-(4-bromobenzoyl)-5,5-bis(methylsulfanyl)-2,4-pentadienamide **2d**

Yellow solid; yield 86% (0.68 g); mp 224–226 °C; IR (KBr, ν_{max})=3363, 3182, 2206, 1658, 1562, 1477 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.42 (s, 3H, SCH_3), 5.60 (s, 1H, NH_2),

6.09 (s, 1H, NH_2), 7.65 (d, J=9 Hz, 2H, ArH), 7.76 (d, J=9 Hz, 2H, ArH), 8.65 (s, 1H, vinylic); ^{13}C NMR (75 MHz, DMSO-d_6) δ=17.8 (SMe), 106.9 (=C–$CONH_2$), 115.9 (CN), 128.4, 130.2 (ArH), 134.9 (ArH), 138.6 [=C(SMe)$_2$], 142.9 [C=C(SMe)$_2$], 161.2 (vinylic), 164.4 ($CONH_2$), 192.5 (CO); EIMS m/z (%)=399 (98), 397 (100). Anal. Calcd for $C_{15}H_{13}BrN_2O_2S_2$ (397.31): C, 45.34; N, 7.05; H, 3.30. Found: C, 45.44; N, 6.99; H, 3.32.

4.2.5. 4-Benzoyl-2-cyano-5,5-bis(methylsulfanyl)-2,4-pentadienamide **2e**

Yellow solid; yield 85% (0.5 g); mp 170–172 °C; IR (KBr, ν_{max})=3375, 3182, 2210, 1650, 1554, 1469 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.42 (s, 3H, SCH_3), 5.65 (s, 1H, NH_2), 6.12 (s, 1H, $CONH_2$), 7.60–7.49 (m, 3H, ArH), 7.89–8.02 (m, 2H, ArH), 8.69 (s, 1H, vinylic); ^{13}C NMR (75 MHz, DMSO-d_6) δ=16.8 (SMe), 105.9 (=C–$CONH_2$), 115.9 (CN), 129.4, 130.5 (ArH), 135.9 (ArH), 137.6 [=C(SMe)$_2$], 143.2 [C=C(SMe)$_2$], 160.8 (vinylic), 163.4 ($CONH_2$), 190.8 (CO); FABMS m/z (%)=319 (100). Anal. Calcd for $C_{15}H_{14}N_2O_2S_2$ (318.42): C, 56.58; N, 8.80; H, 4.43. Found: C, 56.63; N, 8.85; H, 4.42.

4.3. General procedure for the synthesis of 2-pyridones from 2-cyano-4-benzoyl-5,5-bis(methylsulfanyl)-2,4-pentadienamide (**3**)

Xylene (10 mL) was added to 2-cyano-4-(4-methylbenzoyl)-5,5-bis(methylsulfanyl)-2,4-pentadienamide (0.39 g, 1 mmol) and refluxed at 130 °C for 10 h. Hexane was added to the cooled solution. The pale yellow solid obtained was filtered and recrystallized from methanol.

4.3.1. 5-(4-Methylbenzoyl)-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **3a**

Pale solid; yield 90% (0.26 g); mp 210–212 °C; IR (KBr, ν_{max})=3182, 3056, 2231, 1677, 1645, 1534 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ=2.23 (s, 3H, CH_3), 2.37 (s, 3H, SCH_3), 7.27–7.35 (m, 4H, ArH), 8.4 (s, 1H, pyridone H-4), 13.07 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=11.9 (SCH_3), 22.4 (CH_3), 102.8, 115.3 (CN), 118.8, 126.7, 128.3, 129.8, 142.6, 147.4, 154.1, 160.1 (CO), 189.4 (CO); EIMS m/z (%)=284 (M$^+$, 5), 268 (16), 253 (18), 237 (100), 219 (2), 209 (9), 194 (10), 179 (13), 153 (16), 127 (8), 118 (20), 91 (34), 77 (8). Anal. Calcd for $C_{15}H_{12}N_2O_2S$ (284.33): C, 63.36; N, 9.85; H, 4.25. Found: C, 63.44; N, 9.89; H, 4.32.

4.3.2. 5-(4-Methoxybenzoyl)-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **3b**

Pale yellow solid; yield 80% (0.24 g); mp 194–196 °C; IR (KBr, ν_{max})=2965, 2365, 2225, 1656, 1610, 1310, 1263, 1186, 1025, 901 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.36 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 7.24 (d, J=9 Hz, 2H, ArH), 7.45 (d, J=9 Hz, 2H, ArH), 8.24 (s, 1H, pyridone H-4), 12.14 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=12.8 (SCH_3), 54.5 (OCH_3), 101.0, 113.5 (CN), 117.7, 124.8, 129.5, 130.8, 147.6, 153.5, 162.3, 162.8 (CO/COH), 188.7 (CO); EIMS m/z (%)=301 (M$^+$, 19), 284 (11), 269 (16), 253 (100), 238 (8), 210 (16), 182 (10), 170 (15), 127 (20), 119 (14), 91 (13), 77 (12). Anal. Calcd for $C_{15}H_{12}N_2O_3S$ (300.33): C, 59.99; N, 9.33; H, 4.03. Found: C, 59.79; N, 9.45; H, 4.06.

4.3.3. 5-(4-Chlorobenzoyl)-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **3c**

Colourless solid; yield 85% (0.25 g); mp 210–212 °C; IR (KBr, ν_{max})=3405, 3054, 2896, 2226, 1727, 1656, 1485, 1187, 1092, 904 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.73 (s, 3H, SCH_3), 7.40 (d, J=8 Hz, 2H, ArH), 7.46 (d, J=8 Hz, 2H, ArH), 8.32 (s, 1H, pyridone H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ=12.1 (SCH_3), 102.5, 114.7 (CN), 116.4, 127.8, 128.2, 130.1, 136.5, 146.6, 153.2, 159.8 (CO), 188.3 (CO); EIMS m/z (%)=304 (M$^+$, 9), 288 (18), 273 (24), 257 (100), 232 (13), 222 (33), 194 (19), 174 (29), 138 (43), 111 (29), 75 (35). Anal. Calcd for $C_{14}H_9ClN_2O_2S$ (304.75): C, 55.18; N, 9.19; H, 2.98. Found: C, 54.92; N, 9.34; H, 2.89.

4.3.4. 5-(4-Bromobenzoyl)-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **3d**

Pale yellow solid; yield 76% (0.26 g); mp 218–220 °C; IR (KBr, ν_{max})=3055, 2233, 1658, 1631, 1593 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ=2.64 (s, 3H, SMe), 7.38 (d, J=9 Hz, 2H, ArH), 7.56 (d, J=9 Hz, 2H, ArH), 8.31 (s, 1H, pyridone); ^{13}C NMR (75 MHz, $CDCl_3$) δ=12.1 (SCH_3), 102.5, 114.7 (CN), 116.4, 127.8, 128.2, 130.1, 136.5, 146.6, 153.2, 159.8 (CO), 188.3 (CO); FABMS m/z (%)=351 (80), 349 (80). Anal. Calcd for $C_{14}H_9BrN_2O_2S$ (349.20): C, 48.15; N, 8.02; H, 2.60. Found: C, 48.54; N, 8.19; H, 2.34.

4.3.5. 5-Benzoyl-6-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **3e**

Colourless solid; yield 70% (0.2 g); mp 220–222 °C; IR (KBr, ν_{max})=3178, 2364, 2227, 1680, 1643, 1546, 1191, 896, 777, 702, 522 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.46 (s, 3H, SCH_3), 7.25–7.58–7.75 (m, 5H, ArH), 8.45 (s, 1H, pyridone H-4), 13.15 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=12.8 (SCH_3), 102.6, 115.0 (CN), 127.9, 128.2, 130.7, 131.3, 148.6, 150.3, 154.3, 166.7 (CO), 188.6 (CO); EIMS m/z (%)=270 (M$^+$, 6), 229 (15), 223 (100), 198 (8), 180 (22), 140 (38), 104 (52), 95 (51), 83 (76). Anal. Calcd for $C_{14}H_{10}N_2O_2S$ (270.31): C, 62.21; N, 10.36; H, 3.73. Found: C, 62.28; N, 10.25; H, 3.78.

4.4. General procedure for the synthesis of 5-aroyl-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile (**4**)

The appropriate 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde **1** (2 mmol) was dissolved in acetonitrile (10 mL) at room temperature. To the above solution cyanoacetamide (0.168 g, 2 mmol) followed by K_2CO_3 (0.55 g, 4 mmol) were added and the reaction mixture was refluxed at 80 °C for 12 h. The mixture was then cooled, poured in to ice-cold water and acidified with 20% acetic acid. The resulting material was extracted with ethyl acetate (3×25 mL), dried over anhydrous sodium sulfate and purified by column chromatography on silica gel (60×120)

using hexane/ethylacetate (1:1) as the eluent and then recrystallized from methanol.

*4.4.1. 5-(4-Methylbenzoyl)-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **4a***

Pale yellow solid; yield 70% (0.39 g); mp 200–202 °C; IR (KBr, ν_{max})=3430, 3160, 2226, 1650, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.42 (s, 3H, Me), 3.06 (s, 3H, SCH_3), 6.76 (br, NH/OH), 7.16 (m, 2H, ArH), 7.73–7.76 (m, 2H, ArH), 8.57 (s, 1H, pyridone); ^{13}C NMR (75 MHz, $CDCl_3$) δ=16.2 (SMe), 19.6 (Me), 103.4 (5C pyridone), 113.0 (CN), 127.2, 127.6, 132.5, 134.9 (ArH and 3C pyridone), 142.4 (6C pyridone), 157.5 (4C pyridone), 160.6 (2C, CO), 190.7 (CO); FABMS *m/z* (%)=285 (80). Anal. Calcd for $C_{15}H_{12}N_2O_2S$ (284.33): C, 63.36; N, 9.85; H, 4.25. Found: C, 63.44; N, 9.95; H, 4.32.

*4.4.2. 5-(4-Methoxybenzoyl)-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **4b***

Pale yellow solid; yield 72% (0.43 g); mp 184–186 °C; IR (KBr, ν_{max})=3433, 3190, 2221, 1639, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=2.50 (s, 3H, SCH_3), 4.52 (s, 3H, OMe), 7.36–7.29 (m, 2H, ArH), 7.62–7.53 (m, 3H, ArH and proton of **4b**), 9.34 (s, 1H, **5b**), 13.15 (br, NH/OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.2 (SMe), 55.6 (OMe), 90.5 (3C pyridone), 112.0, 117.0 (CN), 122.3, 129.2, 130.6, 132.5 (ArH and 5C pyridone), 138.4 (6C pyridone), 168.5 (4C pyridone), 170.6 (2C, CO), 189.7 (CO); FABMS *m/z* (%)=301 (90). Anal. Calcd for $C_{15}H_{12}N_2O_3S$ (300.33): C, 59.99; N, 9.33; H, 4.03. Found: C, 59.34; N, 9.23; H, 4.12.

*4.4.3. 5-(4-Chloro)-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **4c***

Pale yellow solid; yield 64% (0.39 g); mp 198–200 °C; IR (KBr, ν_{max})=3430, 3160, 2226, 1650, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.89 (s, 3H, SCH_3), 7.48 (d, J=8.4 Hz, 2H, ArH), 7.60 (d, J=8.9 Hz, 2H, ArH), 9.59 (s, 1H, pyridone); ^{13}C NMR (75 MHz, $CDCl_3$) δ=17.6 (SMe), 100.2 (5C pyridone), 111.7 (CN), 127.0, 130.0, 135.0 (ArH and 3C pyridone), 156.3 (6C pyridone), 157.9 (4C pyridone), 162.0 (2C, CO), 184.0 (CO); EIMS *m/z* (%)=304 (M^+, 9), 257 (100), 232 (15), 222 (23), 194 (19), 174 (29), 138 (43), 111 (29), 75 (35). Anal. Calcd for $C_{14}H_9ClN_2O_2S$ (304.75): C, 55.18; N, 9.19; H, 2.98. Found: C, 55.34; N, 9.35; H, 2.89.

*4.4.4. 5-(4-Bromobenzoyl)-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **4d***

Pale yellow solid; yield 60% (0.42 g); mp 210–212 °C; IR (KBr, ν_{max})=3430, 3160, 2224, 1637, 1604 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=2.78 (s, 3H, SCH_3), 7.57–7.62 (m, 4H, ArH), 7.68 (br, 1H, NH/OH), 9.40 (s, 1H, pyridone); ^{13}C NMR (75 MHz, $CDCl_3$) δ=16.5 (SMe), 101.4 (5C pyridone), 112.5 (CN), 126.0, 129.2, 134.2 (ArH and 3C pyridone), 156.6 (6C pyridone), 158.2 (4C pyridone), 163.6 (2C, CO), 186.2 (CO); EIMS *m/z* (%)=351 (85), 349 (82), 304 (90), 232 (20), 222 (25), 194 (15), 174 (22), 138 (45), 111 (28), 75 (30). Anal. Calcd for $C_{14}H_9BrN_2O_2S$ (349.20): C, 48.15; N, 8.02; H, 2.60. Found: C, 48.44; N, 8.19; H, 2.52.

*4.4.5. 5-(3-Methoxybenzoyl)-4-(methylsulfanyl)-2-oxo-1,2-dihydro-3-pyridinecarbonitrile **4f***

Pale yellow solid; yield 70% (0.42 g); mp 170–172 °C; IR (KBr, ν_{max})=3420, 3160, 2220, 1660, 1605 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=2.74 (s, 3H, SCH_3), 3.86 (s, 3H, OMe), 7.12–7.05 (m, 2H, C-5H, ArH and 1H, **4a**), 7.54 (d, J= 9 Hz, 1H, ArH), 7.77 (s, 1H, C-2H, ArH), 7.84 (d, J=9 Hz, 1H, ArH), 9.33 (s, 1H, **5a**), 12.87 (br, NH/OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=12.8 (SMe), 53.6 (OMe), 93.5 (3C pyridone), 115.0, 116.0 (CN), 119.2, 122.6, 129.2, 130.6, 132.5, 137.2 (ArH and 5C pyridone), 139.4 (6C pyridone), 167.9 (4C pyridone), 173.6 (2C, CO), 189.4 (CO); FABMS *m/z* (%)=301 (85). Anal. Calcd for $C_{15}H_{12}N_2O_3S$ (300.33): C, 59.99; N, 9.33; H, 4.03. Found: C, 60.14; N, 9.35; H, 4.32.

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