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A simple and general approach for the synthesis of highly functionalized 6-oxo-1,6-dihydropyridines

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ABSTRACT

A variety of 5-cyano-4-methylthio-6-oxo-1,6-dihydropyridine-3-carboxylates have been efficiently synthesized in a one-pot reaction from *N*-alkyl and *N*-aryl derivatives of 2-cyano-3,3-bis(methylthio)acrylamides and selected β-keto esters. The reaction proceeds via potassium hydrogen carbonate mediated conjugate addition of a β-keto ester to 2-cyano-3,3-bis(methylthio)acrylamide followed by loss of methyl mercaptan and subsequent intramolecular condensation of amide group with the acyl carbonyl group. The mechanism of the reaction has been established by isolation of the 2-acetyl-4-cyano-5-amino-3-(methylthio)-5-oxopent-3-enoate intermediate and its independent cyclization to the desired 6-oxo-1,6-dihydropyridine.

1. Introduction

6-Oxo-1,6-dihydropyridine (synonymous with 2-oxo-1,2-dihydropyridines and pyridine-2(1*H*)-ones) core structure frequently occurs in pharmaceuticals and biologically active compounds.[1] This highly important heterocyclic system is found in both natural products such as camptothecin, and its analogues,[2] huperzine A,[3] and pharmaceutical products or preclinical lead molecules such as milrinone,[4] perampanel,[5] pirfenidone,[6] piridicillin,[7] ciclopiroxolamine,[8] amrinone,[9] bimakalim,[10] and trametinib.[11] Therefore, development of new methods for pyridine-2(1*H*)-ones synthesis with broad scope and generality is of high importance. Many methods have been reported for the synthesis of this class of compounds.[12] One of the most generally used approaches is the reaction of an appropriate enamino ketone or aldehyde with 2-cyanoacetamide in the presence of a base to give pyridine-2(1*H*)-ones.[4,13] The condensation of 1,3-dicarbonyl compounds with 2-cyanoacetamides is also known to give pyridine-2(1*H*)-ones.[14] There are several reports on the preparation of pyridine-2(1*H*)-ones from ketene dithioacetals.[15] The reaction of α-acetyl-α-carbamoyl ketene dithioacetals with Vilsmeier reagent under domino reaction conditions is also reported for the synthesis of pyridine-2(1*H*)-ones.[16] The reaction of ketene dithioacetals derived from 2-cyanoacetamides with active methylene ketones and β-keto ester is also reported to give pyridine-2(1*H*)-ones.[17] However, this approach has limited scope for the synthesis of *N*-alkyl and *N*-aryl pyridine-2(1*H*)-ones. The *N*-alkyl pyridine-2(1*H*)-ones are generally prepared by N-alkylation of pyridine-2(1*H*)-ones, while the *N*-aryl derivatives are prepared by copper-catalyzed arylation of pyridine-2(1*H*)-ones.[18] A direct method for the preparation of 2-aminopyridine-2(1*H*)-one is reported by the reaction of the corresponding carbamoyl ketene dithioacetal with cyanothioacetamide.[19] A similar approach is also reported for 2-amino *N*-benzyl pyridine-2(1*H*)-ones starting from 3,3-bis(methylthio)-2-cyano-*N*-phenylacrylamide.[20] An approach for the synthesis of 6-oxo-1,6-dihydropyridine was discovered in the course of our experiments designed to prepare an intermediate required for one of our medicinal chemistry projects.

2. Results and discussion

We required ethyl [5-amino-4-(methylcarbamoyl)-1,2-oxazol-3-yl]acetate **4** as starting material for the synthesis of a lead molecule for one of our medicinal chemistry projects (Fig. 1). No such fully functionalized isoxazole has been reported in the literature as revealed by SciFinder and STN database searches. In 2011, we reported the first synthesis of this intermediate using an alternative novel approach.[21] We envisioned that the molecule could be prepared by the retrosynthetic approach given in Fig. 1. Thus, we planned a base-catalyzed Michael addition of ethyl acetoacetate to 2-cyano-*N*-methyl-3,3-bis(methylthio)acrylamide **1a**[22] with

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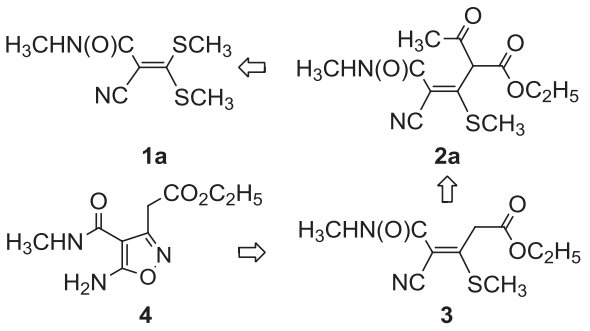


Fig. 1. Retrosynthetic approach for isoxazole **4**.

concomitant elimination of methyl mercaptan to prepare adduct **2a**. Acyl ester of the general formula **2a** was expected to give the deacylated intermediate **3** under appropriate basic reaction conditions. The regioselective addition of hydroxylamine to **2a** under basic reaction conditions was expected to give the desired functionalized isoxazole **4**.

With the retrosynthetic plan in place, we prepared the known ketene dithioacetal **1a** from 2-cyano-*N*-methylacetamide by using a modified approach.[23] The conjugate addition of ethyl acetoacetate **5a** to **1a** using excess (2.5 equiv) of anhydrous potassium carbonate (K_2CO_3) in dry dimethyl sulfoxide (DMSO) at room temperature for 4 h resulted in the formation of two major products along with a small amount of starting material **1a**. The less polar product, characterized as the required adduct **2a**, was isolated in 55% yield as a white solid by column chromatography. The more polar minor product (15%) isolated from the reaction mixture was characterized as pyridone **6a**. Both the products were fully characterized by analytical and spectroscopic data.

The next step in the retrosynthetic scheme is deacetylation of **2a** to the desired β,γ-unsaturated ester **3** using a suitable known procedure. Thus, **2a** was treated with catalytic amounts of sodium ethanolate in ethanol at room temperature for 6 h, but the expected deacetylated product was not detected in the reaction mixture.[24] A more polar product was isolated in small amounts, which was identical in all respects with the pyridone **6a** isolated from the previous experiment. The deacetylation was then attempted as reported using sodium acetate in a mixture of water and ethanol at room temperature.[25] A mixture of starting ester **2a** and pyridone **6a** was detected after 96 h at ambient temperature along with unidentifiable products. Heating the above reaction mixture at 80 °C for 6 h resulted in the conversion of **2a** to **6a**. The desired deacetylated product **3** was not detected in the mixture. Deacetylation was then attempted using excess propylamine in chloroform at ambient temperature for 12 h according to a published procedure, which also did not give the expected deacetylated ester **3**.[26] The reaction remained incomplete and both ester **2a** and pyridone **6a** were detected in the reaction mixture. Finally, deacetylation[27] was attempted using triethylamine in water at 60 °C, which resulted in the conversion of **2a** to pyridone **6a**. These results strongly suggest that the intermediate ethyl 2-acetyl-4-cyano-5-(methylamino)-3-(methylthio)-5-oxopent-3-enoate **2a** exists as its tautomer 5-oxopent-2-enoate **2a′** under the described conditions, which is not amenable to a deacetylation reaction (Fig. 2).

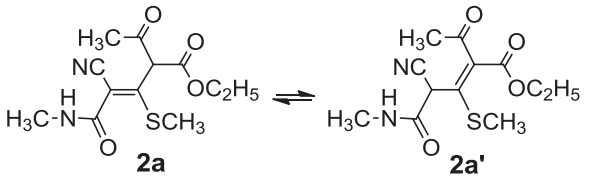
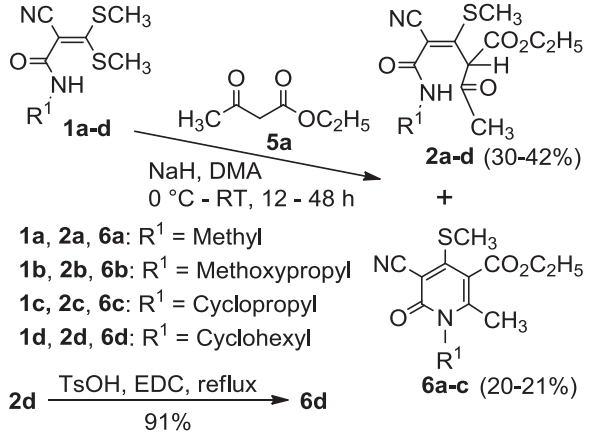


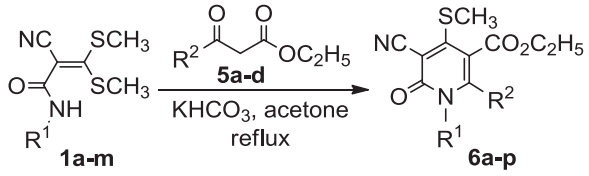
Fig. 2. Tautomeric forms **2a** and **2a′**.

Having failed in our efforts to prepare the intermediate **3** required for the synthesis of desired isoxazole **4** (Fig. 1), we reexamined this reaction with a view to develop a general approach for the synthesis of pyridone esters **6** with an optional substitution at its 2-position. In this paper, we describe an optimized simple, general and highly flexible single-step procedure for the syntheses of *N*-alkyl and *N*-aryl 6-oxo-1,6-dihydropyridine-3-carboxylates **6**.

We decided to study the base-assisted conjugate addition of **5a** to carbamoyl ketene dithioacetals **1a**–**d** in more detail before attempting optimization of a single-step procedure as shown overleaf in Scheme 2. To check the generality of the reaction and to confirm the intermediacy of ester **2** in the formation of pyridone **6**, we selected ketene dithioacetals **1a**–**d** bearing dissimilar substituents on the amide nitrogen. After a few trial experiments, sodium hydride (NaH) in *N*,*N*-dimethylacetamide (DMA) was selected for this optimization study (Scheme 1). Thus, the reaction of ketene dithioacetal **1a** with **5a** in the presence of NaH (1.2 equiv) in dry DMA at 0 °C followed by maintaining the mixture at ambient temperature for 12 h resulted in the formation of a mixture of ester **2a** (42%) and pyridone **6a** (21%) along with small amounts of **1a** (4%). The reaction of **5a** with the methoxypropyl derivative **1b** also showed a similar trend and ester **2b** (32%) and pyridone **6b** (20%) were isolated from the reaction mixture along with small amounts of starting material **1b** (5%). The structures of **2b** and **6b** were fully established by spectral and analytical data. Under identical conditions, the cyclopropyl derivative **1c** also yielded ester **2c** (34%) and pyridone **6c** (20%) along with unreacted starting material **1c** (7%). The cyclohexyl derivative **1d** yielded only the open chain ester **2d** (30%) and the pyridone **6d** was not formed in the reaction mixture even after 48 h at ambient temperature.



Scheme 1. Synthesis of esters **2a**–**d** and pyridones **6a**–**d**.



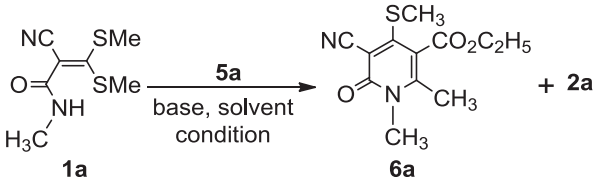
Scheme 2. $KHCO_3$ mediated synthesis of pyridones **6a**–**p**.

It is interesting to note that all the four reactions remained incomplete even after stirring for 12–48 h at room temperature. Heating the reactions at 80 °C resulted in a reddish brown mixture, probably due to decomposition of unreacted ketene dithioacetal **1**. The sterically more demanding cyclohexyl derivative stopped at the ester stage **2d** and subsequent cyclization to pyridone **6d** seemed unviable. In a separate experiment, the ester **2d** isolated was treated

with *p*-toluenesulfonic acid (TsOH) in boiling 1,2-dichloroethane (EDC) for 5 h. We were pleased to see that the desired 1-cyclohexylpyridone **6d** was formed quantitatively and was isolated in 91% yield. Having understood the reaction pathway in more detail, we explored the scope of this reaction for the exclusive synthesis of *N*-substituted 6-oxo-1,6-dihydropyridines **6** in a one-pot operation.

Our initial objectives were: (i) to drive the conjugate addition step to completion (ii) in situ conversion of the ester **2** to pyridone **6** and (iii) to minimize polymerization of ketene dithioacetal **1**. We used **1a** derived from 2-cyano-*N*-methylacetamide and ethyl acetoacetate **5a** as the model substrate for the optimization of reaction conditions (Table 1). Thus, reaction of **1a** with **5a** using anhydrous K_2CO_3 in dry DMSO at 100 °C for 3 h (Table 1, entry 1) resulted in a reddish brown oil and the pyridone **6a** was isolated in poor 10% yield after work-up and chromatographic purification. The reaction was repeated in dry DMSO at 80 °C with similar results (entry 2). In general, ketene dithioacetal **1a** was labile in the presence of strong inorganic bases at elevated temperature (above 80 °C). This was confirmed by heating ketene dithioacetal **1a** alone with K_2CO_3 in DMSO at 100 °C for 30 min, which resulted in significant polymerization as indicated by the reddish brown colour of the reaction mixture. A reaction mediated by stoichiometric amounts of sodium ethoxide in ethanol at room temperature for 4 h gave a mixture of **2a** (17%) and **6a** (15%) along with starting material **1a** (5%). A reaction

Table 1
Optimization of reaction conditions



Entry	Base, solvent	Conditions	Yield[a] (%) **1a**/**2a**/**6a**
1	K_2CO_3, DMSO	100 °C, 3 h	0:0:10
2	K_2CO_3, DMSO	80 °C, 3 h	0:0:12
3	NaOEt, EtOH	rt, 4 h	5:17:15
4	NaOEt, EtOH	rt, 24 h	0:0:18
5	NaH, DMF	0°C to rt, 48 h	0:0:20
6	K_2CO_3, acetone	rt, 24 h	0:0:13
7	Et_3N, EtOH	rt, 24 h	30:0:26
8	DBU, THF	rt, 24 h	92:0:0
9	DIEA, THF	rt, 24 h	90:0:0
10	$KHCO_3$, DMF	60 °C, 6 h	0:0:50
11	$KHCO_3$, acetone	Reflux, 5 h	0:0:75
12	$NaHCO_3$, acetone	Reflux, 9 h	0:0:68

[a] Yield of isolated products.

under the same conditions for 24 h resulted in pyridone **6a** (18%) as the only isolated product (entry 4). A reaction mediated by NaH in dry DMF at room temperature for prolonged time (48 h) resulted in pyridone **6a** (20%) as the only isolable product (entry 5). A reaction using anhydrous K_2CO_3 in dry acetone for 24 h at room temperature resulted in pyridone **6a** in poor 13% yield (entry 6). As in the previous cases, intermediate **2a** was present in the reaction mixture (monitored by TLC) up to 9 h. Similar yields were obtained when the above reaction was carried out under reflux conditions for 2 h.

With some insight into the issues related to the reaction, we screened a few selected organic bases for this transformation (Table 1, entries 7–9). Triethylamine as a base in ethanol at room temperature for 48 h resulted in the formation of pyridone **6a** in 26% yield along with starting material **1a** (30%). A reaction mediated by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and diisopropylethylamine (DIEA) failed to give pyridone **6a**. Heating the above reactions also failed to give the desired pyridone **6a**.

With limited success in optimizing the reaction conditions, we decided to try selected mild inorganic bases. To our delight, potassium hydrogen carbonate ($KHCO_3$) in dry DMF at 60 °C for 6 h resulted in complete consumption of starting material **1a** and the pyridone **6a** was isolated in 50% yield (Table 1, entry 10). The reaction in refluxing acetone was found to be very efficient and the yield of the product increased to 75%. Polymerization of ketene dithioacetal **1a** was not observed under this condition. Sodium hydrogen carbonate ($NaHCO_3$) in refluxing acetone also worked well, but with an increase in reaction time and slightly reduced yield (entry 12). The reaction showed strong dependence on temperature. The $KHCO_3$ mediated reaction carried out in acetone at room temperature for 12 h resulted in poor (<5%) conversion. A reaction carried out at 50 °C (bath temperature) for 5 h also resulted in low (<20%) conversion. The reaction rate was considerably accelerated in boiling acetone probably due to the favourable entropy of the reaction by the irreversible removal of methyl mercaptan from the reaction medium.

Having optimized conditions for the exclusive synthesis of 6-oxo-1,6-dihydropyridine **6a** in excellent isolated yield (75%), we turned our attention towards the synthesis of a variety of pyridones using the optimized conditions shown in Scheme 2. The results of successful application of this methodology for the synthesis of electronically and sterically diverse set of pyridones are shown in Table 2. The methoxypropyl derivative **1b** and cyclopropyl derivative **1c** on reaction with β-keto ester **5a** under the optimized conditions gave **6b** and **6c**, respectively, in 70 and

Table 2
Synthesis of 6-oxo-1,6-dihydropyridines **6a**–**p**

Entry	Dithioacetal	R^1	Ester	R^2	Pyridone	Yield[a] (%)
1	**1a**	CH_3	**5a**	CH_3	**6a**	75
2	**1b**	$CH_3O(CH_2)_3$–	**5a**	CH_3	**6b**	70
3	**1c**	Cyclopropyl	**5a**	CH_3	**6c**	71
4	**1d**	Cyclohexyl	**5a**	CH_3	**6d**	15 (70)[b]
5	**1e**	CH_2CH_3	**5a**	CH_3	**6e**	73
6	**1f**	CH_2CF_3	**5a**	CH_3	**6f**	56
7	**1g**	C_6H_5	**5a**	CH_3	**6g**	76
8	**1a**	CH_3	**5b**	C_6H_5	**6h**	73
9	**1g**	C_6H_5	**5b**	C_6H_5	**6i**	72
10	**1g**	C_6H_5	**5c**	CH_2CH_3	**6j**	73
11	**1h**	4-FC_6H_4	**5a**	CH_3	**6k**	76
12	**1i**	4-ClC_6H_4	**5a**	CH_3	**6l**	79
13	**1j**	4-$CH_3OC_6H_4$	**5a**	CH_3	**6m**	78
14	**1k**	3-$CF_3C_6H_4$	**5d**	$CH_2CH_2CH_3$	**6n**	74
15	**1l**	4-$(CH_3)_2CHC_6H_4$	**5a**	CH_3	**6o**	78
16	**1m**	4-Methylthiazol-2-yl	**5a**	CH_3	**6p**	56

[a] Yield of isolated pyridones.
[b] Parenthetic yield refers to the yield after TsOH treatment of mixture of **2d** and **6d**.

71% isolated yield (Table 2, entries 2 and 3). However, the reaction of the cyclohexyl derivative **1d** with **5a** was sluggish and resulted in an easily separable mixture of ester **2d** (53%) and pyridone **6d** (15%) after refluxing in acetone for 24 h. In another experiment, a crude mixture of ester **2d** and pyridone **6d** was treated with TsOH in refluxing EDC. The ester **2d** was quantitatively converted to the desired pyridone **6d** and was isolated in 70% yield (entry 4) after chromatographic purification. It is worthy to note that **6d** was not formed under the original reaction conditions (NaH, DMA, 24 h) described in Scheme 1. As expected, the *N*-ethyl derivative **1e** reacted smoothly with **5a** to give **6e** in 73% isolated yield as viscous oil. The hitherto unknown *N*-trifluoroethyl derivative **1f** also reacted with **5a** to give the 1-trifluoroethyl pyridone **6f** in moderate yield (56%). Based on the observation that low yields were obtained in the case of *N*-cyclohexyl derivative

1d (entry 4), we attempted a reaction of *N*-phenyl ketene dithioacetal **1g** with the ester **5a** to study the effect of *N*-phenyl group in the condensation step. We were surprised to find that **1g** reacted smoothly with **5a** and *N*-phenylpyridone **6g** was formed in 76% yield. Similarly, **1a** also smoothly condensed with the benzoyl ester **5b** to give the 2-phenylpyridone **6h** in 73% isolated yield. To maximize steric crowding during the final condensation step, we attempted reaction of **1g** with **5b**. It is gratifying to note that **1g** reacted with **5b** smoothly under identical conditions and the desired 1,6-diphenylpyridone **6i** was isolated in 72% yield, suggesting that the two phenyl groups adopted a coplanar conformation during the final condensation step. Various other 1,6-disubstituted pyridones **6j**–**o** were prepared in 73–79% yield (entries 10–15). The *N*-(4-methylthiazol)-2-yl derivative **1m** also reacted with ester **5a** to give **6p** in 56% isolated yield.

3. Conclusion

In summary, we have developed a versatile synthetic method for the preparation of a variety of poly-functional *N*-alkyl and *N*-aryl 6-oxo-1,6-dihydropyridines using appropriate 2-cyano-3,3-bis(methylthio)acrylamides and a β-keto ester in a single-step using potassium hydrogen carbonate as the base in boiling acetone. The method developed has potential applications for assembling a variety of structurally diverse functionalized pyridones from readily available starting materials. The use of inexpensive starting materials, mild reaction conditions, relatively short reaction time, a straightforward purification process and good yields of products are the main attractions of the method. The present method for the synthesis of dihydropyridones with two points of structural diversity and bearing three functional groups for additional structural modification represents superiority over existing methods and holds enormous potential in synthetic and medicinal chemistry.

4. Experimental

4.1. General information

Melting points were determined on a Polmon digital melting point apparatus model MP-96 and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz FT NMR spectrometer in either $CDCl_3$ or DMSO-d_6 as specified using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) (δ) relative to TMS. IR spectra were obtained on a Perkin–Elmer Spectrum One spectrophotometer. High-resolution mass spectra (HRMS) of compounds were measured on a Thermo Scientific LTQ Orbitrap Discovery MS system coupled with an LQT Tune Plus (version 2.5.5 SPI) software. Compounds were purified by flash silica gel (SRL, 100–200 mesh) chromatography using an appropriate solvent mixture as given in the procedure. Petroleum ether (PE) refers to the fraction boiling in the 40–60 °C range.

All β-keto esters used were from commercial sources and used as received. The *N*-substituted cyanoacetamides were prepared by known procedures by coupling appropriate amine with ethyl cyanoacetate or cyanoacetic acid.[28]

4.2. Synthesis of carbamoyl ketene dithioacetals (1a–m); general procedure[23]

The carbamoyl ketene dithioacetals were prepared by reported procedure by the reaction of 2-cyanoacetamides (100 mmol) with carbon disulfide (7.22 mL, 120 mmol) in the presence of excess potassium fluoride (116 g, 2000 mmol) in dry DMF (150 mL) followed by alkylation of the intermediate potassium dithiolate with methyl iodide (13.70 mL, 220 mmol) in a one-pot reaction.

The spectral and analytical data of known carbamoyl ketene dithioacetals **1a**,[22] **1b**,[29] **1d**,[30] **1e**,[31] **1g**,[15b] **1h**,[32] **1i**,[15b] **1j**[15b] were in agreement with those reported in the literature.

*4.2.1. 2-Cyano-N-cyclopropyl-3,3-bis(methylthio)acrylamide **1c**.* Yield 16.60 g (73%); white crystalline solid. Mp 118–119 °C; IR (KBr): 3012, 2203, 1645, 1526, 1422, 1296 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.61 (br s, 2H), 0.82–0.88 (m, 2H), 2.60 (s, 3H), 2.68 (s, 3H), 2.75–2.79 (m, 1H), 6.29 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 6.0 (2C), 18.9, 20.7, 23.2, 102.2, 117.4, 163.0, 176.0; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_9H_{12}N_2OS_2$: 229.0463; found: 229.0460.

*4.2.2. 2-Cyano-3,3-bis(methylthio)-N-(2,2,2-trifluoroethyl)acrylamide **1f**.* Yield: 22.10 g (82%); yellow crystalline solid. Mp 110–111 °C; IR (KBr): 3363, 2209, 1658, 1543, 1251, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 3H), 2.71 (s, 3H), 3.93–4.04 (m, 2H), 6.52 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 20.8, 41.0 (q, *J*=34.3 Hz, CH_2CF_3), 99.8, 117.1, 124.0 (q, *J*=277 Hz, CF_3), 161.8, 179.3; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_8H_9F_3N_2OS_2$: 271.0181; found: 271.0177.

*4.2.3. 2-Cyano-3,3-bis(methylthio)-N-[3-(trifluoromethyl)phenyl]acrylamide **1k**.* Yield: 25.30 g (76%); off-white solid. Mp 112–113 °C; IR (KBr): 3331, 2209, 1660, 1548, 1448, 1315, 1120, 881, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3H), 2.75 (s, 3H), 7.41 (d, *J*=7.8 Hz, 1H), 7.47 (d, *J*=7.8 Hz, 1H), 7.70 (d, *J*=7.2 Hz, 1H), 7.93 (s, 1H), 7.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 21.0, 101.1, 117.1, 117.2, 121.6, 123.4, 123.9 (q, *J*=271.4 Hz, CF_3), 129.7, 131.6 (q, *J*=32.0 Hz, CCF_3), 137.9, 160.0, 179.3; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{11}F_3N_2OS_2$: 333.0337; found: 333.0332.

*4.2.4. 2-Cyano-N-(4-isopropylphenyl)-3,3-bis(methylthio)acrylamide **1l**.* Yield: 22.70 g (74%); yellow crystalline solid. Mp 118–119 °C; IR (KBr): 3235, 2959, 2190, 1641, 1509, 1320, 842 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, *J*=6.9 Hz, 6H), 2.60 (s, 3H), 2.71 (s, 3H), 2.84–2.91 (m, 1H), 7.20 (d, *J*=8.4 Hz, 2H), 7.45 (d, *J*=8.4 Hz, 2H), 7.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 20.8, 24.1 (2C), 33.7, 102.3, 117.4, 120.4, 120.5, 127.1 (2C), 134.8, 145.9, 159.6, 177.1; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{18}N_2OS_2$: 307.0933; found: 307.0930.

*4.2.5. 2-Cyano-N-(4-methyl-1,3-thiazol-2-yl)-3,3-bis(methylthio)acrylamide **1m**.* Yield: 17.70 g (62%); yellow crystalline solid. Mp 154–155 °C; IR (KBr): 3260, 2192, 1647, 1541, 1420, 1268 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.64 (s, 3H), 2.77 (s, 3H), 6.55 (s, 1H) 7.94 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.0, 19.3, 21.0, 99.5, 108.7, 116.5, 146.7, 157.8, 159.8, 180.4; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{10}H_{11}N_3OS_3$: 286.0137; found: 286.0133.

4.3. NaH mediated synthesis of esters 2 and pyridones 6

Carbamoyl ketene dithioacetal **1a**–**d** (3.00 mmol) was added to a stirred and cooled (0 °C) suspension of 60% sodium hydride (3.30 mmol) and ethyl acetoacetate **5a** (3.60 mmol) in dry DMA (6 mL). The cooling bath was removed and the mixture was further stirred at ambient temperature for 12–48 h. The mixture was quenched with ice-cold water (50 mL) and acidified till pH 6.0 using 1 N HCl. The mixture was then extracted with EtOAc (2×100 mL). The combined organic layers were washed with water (2×50 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to afford the crude mixture. Purification and separation of the mixture by flash silica gel column chromatography using 20–30% EtOAc in petroleum ether (PE) yielded esters **2a**–**d** and pyridones **6a**–**c**.

*4.3.1. Ethyl 2-acetyl-4-cyano-5-(methylamino)-3-(methylthio)-5-oxopent-3-enoate **2a**.* Off-white crystalline solid (42%). Mp

107–109 °C; R_f 0.52 (EtOAc/PE, 1:1); IR (KBr): 3357, 2209, 1660, 1615, 1530, 1259, 1212, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H), 2.04 (s, 3H), 2.15 (s, 3H), 2.92 (d, J=4.8 Hz, 3H), 4.26–4.32 (q, J=7.2 Hz, 2H), 6.20 (br s, 1H), 13.12 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 16.3, 19.1, 26.4, 61.6, 99.7, 102.8, 116.6, 162.7, 169.2, 170.8, 175.2; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{12}H_{15}N_2O_4S$: 283.0747; found: 283.0754.

4.3.2. Ethyl 5-cyano-1,2-dimethyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-3-carboxylate ***6a***. Off-white solid (21%). Mp 83–84 °C; R_f 0.32 (EtOAc/PE, 1:1); IR (KBr): 2219, 1721, 1655, 1518, 1278, 1186 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, J=6.9 Hz, 3H), 2.41 (s, 3H), 2.74 (s, 3H), 3.56 (s, 3H), 4.37 (q, J=6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.6, 19.0, 32.1, 62.4, 102.4, 114.9, 116.9, 148.7, 157.5, 159.8, 165.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{14}N_2O_3S$: 267.0797; found: 267.0794.

4.3.3. Ethyl 2-acetyl-4-cyano-5-[(3-methoxypropyl)-amino]-3-(methylthio)-5-oxopent-3-enoate ***2b***. Brown oil (32%); R_f 0.40 (EtOAc/PE, 1:1); IR (neat): 3019, 2207, 1651, 1525, 1262, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, J=6.9 Hz, 3H), 1.84 (t, J=6.0 Hz, 2H), 2.04 (s, 3H), 2.14 (s, 3H), 3.37 (s, 3H), 3.45–3.55 (m, 4H), 4.29 (q, J=6.9 Hz, 2H), 7.11 (br s, 1H), 13.11 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 16.3, 19.1, 28.4, 39.0, 58.8, 61.6, 72.0, 99.8, 103.4, 116.5, 162.1, 169.3, 170.1, 175.2; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{15}H_{21}N_2O_5S$: 341.1165; found: 341.1172.

4.3.4. Ethyl 5-cyano-1-(3-methoxypropyl)-2-methyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-3-carboxylate ***6b***. Brown oil (20%); R_f 0.35 (EtOAc/PE, 1:1) IR (neat): 3019, 2224, 1724, 1654, 1648, 1511, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, J=6.9 Hz, 3H), 1.97 (q, J=6.6 Hz, 2H), 2.44 (s, 3H), 2.74 (s, 3H), 3.33 (s, 3H), 3.43 (t, J=6.5 Hz, 2H), 4.14 (t, J=6.9 Hz, 2H), 4.37 (q, J=6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 18.1, 18.4, 28.0, 43.4, 58.6, 62.4, 69.3, 102.7, 114.8, 117.0, 148.3, 157.3, 159.6, 165.6; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{20}N_2O_4S$: 325.1216; found: 325.1212.

4.3.5. Ethyl 2-acetyl-4-cyano-5-(cyclopropylamino)-3-(methylthio)-5-oxopent-3-enoate ***2c***. White crystalline solid (34%). Mp 115–117 °C; R_f 0.48 (EtOAc/PE, 1:1); IR (KBr): 3276, 3012, 2203, 1645, 1527, 1296 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.61 (br s, 2H), 0.83 (br s, 2H), 1.29 (t, J=6.8 Hz, 3H), 2.03 (s, 3H), 2.15 (s, 3H), 2.78 (br s, 1H), 4.29 (q, J=6.8 Hz, 2H), 6.28 (br s, 1H), 13.12 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 6.6, 10.6, 14.1, 16.4, 19.1, 23.0, 61.6, 99.7, 102.5, 116.6, 163.6, 169.2, 171.4, 175.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{17}N_2O_4S$: 309.0903; found: 309.0908.

4.3.6. Ethyl 5-cyano-1-cyclopropyl-2-methyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-3-carboxylate ***6c***. Off-white crystalline solid (20%). Mp 99–100 °C; R_f 0.30 (EtOAc/PE, 1:1); IR (KBr): 2981, 2219, 1711, 1668, 1500, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (br s, 2H), 1.33 (br s, 2H), 1.38 (t, J=6.9 Hz, 3H), 2.52 (s, 3H), 2.72 (s, 3H), 2.86 (br s, 1H), 4.37 (q, J=6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.5 (2C), 13.9, 18.4, 18.8, 29.0, 62.3, 103.2, 114.7, 116.8, 150.9, 157.8, 160.6, 165.3; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{16}N_2O_3S$: 293.0954; found: 293.0950.

4.3.7. Ethyl 2-acetyl-4-cyano-5-(cyclohexylamino)-3-(methylthio)-5-oxopent-3-enoate ***2d***. Off-white solid (30%). Mp 90–92 °C; R_f 0.60 (EtOAc/PE, 1:1); IR (KBr): 3345, 2924, 2853, 2207, 1655, 1638, 1530, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.16–1.28 (m, 2H), 1.30 (t, J=7.0 Hz, 3H), 1.32–1.43 (m, 2H), 1.55–1.62 (m, 2H), 1.70–1.76 (m, 2H), 1.93–1.99 (m, 2H), 2.05 (s, 3H), 2.14 (s, 3H), 3.83 (br s, 1H), 4.31 (q, J=7.0 Hz, 2H), 6.02 (br s, 1H), 13.12 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 16.3, 19.1, 24.7 (2C), 25.3, 32.8 (2C), 48.9, 61.6, 99.8, 103.1, 116.7, 161.2, 169.3, 170.7, 175.2; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{17}H_{23}N_2O_4S$: 351.1373; found: 351.1376.

4.4. TsOH mediated cyclization of 2d to ethyl 5-cyano-1-cyclohexyl-2-methyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-3-carboxylate 6d

A mixture of ester **2d** (200 mg, 0.60 mmol) and TsOH (170 mg, 0.90 mmol) in 1,2-dichloroethane (2 mL) was refluxed with stirring for 5 h. The mixture was cooled to ambient temperature and quenched carefully with saturated aqueous $NaHCO_3$ (2 mL). The layers were separated. The organic layer was washed with water (25 mL) and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was purified on a short length flash silica gel column (20% EtOAc/PE) to afford 173 mg (91%) of **6d** as a white solid. Mp 101–103 °C; R_f 0.55 (EtOAc/PE, 1:1); IR (KBr): 2941, 2925, 2217, 1717, 1670, 1509, 1269, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (br s, 4H), 1.39 (t, J=7.2 Hz, 3H), 1.62 (br s, 2H), 1.91 (br s, 2H), 2.39 (s, 3H), 2.72 (s, 3H), 2.73–2.81 (m, 2H), 3.98 (br s, 1H), 4.37 (q, J=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.3, 19.2, 24.7, 26.2 (2C), 27.8, 32.7, 62.1, 62.4, 104.7, 114.9, 117.4, 147.5, 156.7, 160.1, 165.9; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{22}N_2O_3S$: 335.1423; found: 335.1424.

4.5. $KHCO_3$ mediated synthesis of pyridines 6a–p

To a stirred solution of ketene dithioacetal **1a**–**m** (3.00 mmol) and β-keto ester **5a**–**d** (3.60 mmol) in dry acetone (5 mL) was added $KHCO_3$ (6.00 mmol) and the resultant heterogeneous mixture was stirred under reflux for 5–9 h. *CAUTION*: Toxic methyl mercaptan was liberated during this reaction. The reaction should be carried out in an efficient fume hood. Most of the acetone was evaporated under reduced pressure and the residue was taken up in water (50 mL) and acidified till pH 6 using 1 N HCl. The mixture was extracted with ethyl acetate (2×100 mL) and the combined extracts were washed with water (25 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product thus obtained was purified by flash silica gel column chromatography using 30–40% ethyl acetate in petroleum ether (PE) as eluent to yield pure products **6a**–**p**.

4.5.1. Pyridone ***6a***. Reaction of **1a** (500 mg, 2.47 mmol) with ethyl acetoacetate **5a** (0.37 mL, 2.96 mmol) for 5 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 494 mg (75%) of **6a** as a white solid. The analytical and spectral data for the product obtained by this method were identical to those obtained above by NaH/DMA method.

4.5.2. Pyridone ***6b***. Reaction of **1b** (500 mg, 1.92 mmol) with **5a** (0.29 mL, 2.30 mmol) for 6 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 436 mg (70%) of **6b** as a brown oil. The analytical and spectral data for the product obtained by this method were identical to those obtained above by NaH/DMA method.

4.5.3. Pyridone ***6c***. Reaction of **1c** (500 mg, 2.19 mmol) with **5a** (0.33 mL, 2.63 mmol) for 9 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 454 mg (71%) of **6c** as an off-white crystalline solid. The analytical and spectral data for the product obtained by this method were identical to those obtained above by NaH/DMA method.

4.5.4. Pyridone ***6d***. Reaction of **1d** (500 mg, 1.85 mmol) with **5a** (0.28 mL, 2.22 mmol) for 24 h, resulted in a mixture of **2d** and **6d** (78:22 by HPLC). Work-up of the reaction as described gave the mixture as syrup. The mixture on treatment with TsOH (527 mg,

2.77 mmol) in boiling EDC for 5 h resulted in complete consumption of **2d** (TLC). Work-up and purification of the reaction mixture as described earlier gave 433 mg (70%) of **6d** as a white solid, which was identical with the product prepared by TsOH assisted cyclization of pure ester **2d**.

*4.5.5. Ethyl 5-cyano-1-ethyl-2-methyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-3-carboxylate **6e**.* Reaction of **1e** (500 mg, 2.31 mmol) with **5a** (0.35 mL, 2.77 mmol) for 6 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 473 mg (73%) of **6e** as an amber oil. R_f 0.34 (EtOAc/PE, 1:1); IR (neat): 2983, 2935, 2222, 1725, 1651, 1276, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J=6.6 Hz, 3H), 1.39 (t, J=6.9 Hz, 3H), 2.43 (s, 3H), 2.74 (s, 3H), 4.12 (q, J=6.6 Hz, 2H), 4.37 (q, J=6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 13.9, 18.0, 18.4, 40.7, 62.3, 102.8, 114.8, 117.0, 147.8, 157.2, 159.3, 165.5; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{16}N_2O_3S$: 281.0954; found: 281.0950.

*4.5.6. Ethyl 5-cyano-2-methyl-4-(methylthio)-6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carboxylate **6f**.* Reaction of **1f** (500 mg, 1.85 mmol) with **5a** (0.28 mL, 2.22 mmol) for 8 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 346 mg (56%) of **6f** as an off-white solid. Mp 82–84 °C; R_f 0.57 (EtOAc/PE, 1:1); IR (KBr): 2992, 2222, 1731, 1656, 1510, 1283, 1185, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.2 Hz, 3H), 2.44 (s, 3H), 2.81 (s, 3H), 4.39 (q, J=7.2 Hz, 2H), 4.78 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 18.4 (2C), 44.3 (q, J=35.4 Hz, CH_2CF_3), 62.7, 102.2, 114.3, 117.5, 122.9 (q, J=279.4 Hz, CH_2CF_3), 147.2, 159.1, 159.9, 164.9; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{13}F_3N_2O_3S$: 335.0671; found: 335.0672.

*4.5.7. Ethyl 5-cyano-2-methyl-4-(methylthio)-6-oxo-1-phenyl-1,6-dihydropyridine-3-carboxylate **6g**.* Reaction of **1g** (500 mg, 1.89 mmol) with **5a** (0.29 mL, 2.27 mmol) for 5 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 472 mg (76%) of **6g** as an off-white crystalline solid. Mp 126–127 °C; R_f 0.50 (EtOAc/PE, 1:1); IR (KBr): 2222, 1720, 1658, 1288, 1184, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=6.9 Hz, 3H), 2.03 (s, 3H), 2.81 (s, 3H), 4.39 (q, J=6.9 Hz, 2H), 7.16 (d, J=6.9 Hz, 2H), 7.52–7.56 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 18.6, 19.9, 62.5, 103.6, 114.6, 116.5, 127.4 (2C), 129.8, 130.2 (2C), 136.7, 148.6, 159.1, 159.7, 165.3; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{16}N_2O_3S$: 329.0954; found: 329.0951.

*4.5.8. Ethyl 5-cyano-1-methyl-4-(methylthio)-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxylate **6h**.* Reaction of **1a** (300 mg, 1.48 mmol) with ethyl benzoylacetate **5b** (0.31 mL, 1.78 mmol) for 7 h followed by chromatographic purification (EtOAc/PE, 2:3) afforded 355 mg (73%) of **6h** as a white crystalline solid. Mp 127–128 °C; R_f 0.58 (EtOAc/PE, 1:1); IR (KBr): 2960, 2222, 1709, 1664, 1544, 1485, 1185 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J=7.2 Hz, 3H), 2.79 (s, 3H), 3.26 (s, 3H), 3.91 (q, J=7.2 Hz, 2H), 7.29 (d, J=6.9 Hz, 3H), 7.49–7.53 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.3, 18.3, 34.7, 61.9, 103.4, 114.8, 117.4, 128.0 (2C), 129.0 (2C), 130.5, 131.7, 150.5, 157.7, 159.7, 164.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{16}N_2O_3S$: 329.0954; found: 329.0950.

*4.5.9. Ethyl 5-cyano-4-(methylthio)-6-oxo-1,2-diphenyl-1,6-dihydropyridine-3-carboxylate **6i**.* Reaction of **1g** (500 mg, 1.89 mmol) with **5b** (0.39 mL, 2.27 mmol) for 7 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 532 mg (72%) of **6i** as a yellow crystalline solid. Mp 157–158 °C; R_f 0.70 (EtOAc/PE, 1:1); IR (KBr): 2999, 2220, 1714, 1666, 1552, 1484, 1226, 1138 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J=6.6 Hz, 3H), 2.87 (s, 3H), 3.93 (q, J=6.6 Hz, 2H), 6.98 (d, J=6.6 Hz, 2H), 7.06 (d, J=6.3 Hz, 2H), 7.16–7.24 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.3, 18.4, 62.0, 103.9, 114.6, 127.9 (2C), 128.5 (2C), 128.8 (2C), 128.9, 129.0 (2C), 129.6 (2C), 131.7, 136.5, 150.1, 159.2, 159.3, 164.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{18}N_2O_3S$: 391.1110; found: 391.1113.

*4.5.10. Ethyl 5-cyano-2-ethyl-4-(methylthio)-6-oxo-1-phenyl-1,6-dihydropyridine-3-carboxylate **6j**.* Reaction of **1g** (500 mg, 1.89 mmol) with ethyl propionylacetate **5c** (0.32 mL, 2.27 mmol) for 6 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 473 mg (73%) of **6j** as an off-white crystalline solid. Mp 97–99 °C; R_f 0.58 (EtOAc/PE, 1:1); IR (KBr): 2989, 2220, 1721, 1650, 1565, 1499, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (t, J=7.5 Hz, 3H), 1.40 (t, J=7.2 Hz, 3H), 2.40 (q, J=7.2 Hz, 2H), 2.81 (s, 3H), 4.39 (q, J=7.5 Hz, 2H), 7.19 (d, J=5.7 Hz, 2H), 7.52–7.56 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.3, 13.9, 18.5, 25.4, 62.4, 103.2, 114.5, 116.1, 127.8 (2C), 129.7 (2C), 129.8, 136.1, 153.5, 159.2, 159.9, 165.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{18}N_2O_3S$: 343.1110; found: 343.1111.

*4.5.11. Ethyl 5-cyano-1-(4-fluorophenyl)-2-methyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-3-carboxylate **6k**.* Reaction of **1h** (500 mg, 1.77 mmol) with **5a** (0.27 mL, 2.12 mmol) for 6 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 466 mg (76%) of **6k** as a white crystalline solid. R_f 0.63 (EtOAc/PE, 1:1); Mp 163–164 °C; IR (KBr): 2984, 2223, 1725, 1656, 1572, 1502, 1288, 1234, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.2 Hz, 3H), 2.03 (s, 3H), 2.81 (s, 3H), 4.39 (q, J=7.2 Hz, 2H), 7.10–7.20 (m, 2H), 7.21–7.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.5, 19.8, 62.5, 103.1, 114.4, 116.6, 117.3 (d, J=22.8 Hz, 2C), 129.4 (d, J=9.0 Hz, 2C), 132.5 (d, J=3.4 Hz), 148.4, 159.4, 159.7, 162.8 (d, J=249.5 Hz, *C*F), 165.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{15}FN_2O_3S$: 347.0860; found: 347.0856.

*4.5.12. Ethyl 1-(4-chlorophenyl)-5-cyano-2-methyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-3-carboxylate **6l**.* Reaction of **1i** (300 mg, 1.00 mmol) with **5a** (0.15 mL, 1.20 mmol) for 6 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 287 mg (79%) of **6l** as a white crystalline solid. Mp 197–198 °C; R_f 0.69 (EtOAc/PE, 1:1); IR (KBr): 2983, 2223, 1723, 1651, 1573, 1504, 1489, 1230, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.2 Hz, 3H), 2.03 (s, 3H), 2.81 (s, 3H), 4.39 (q, J=7.2 Hz, 2H), 7.11 (d, J=8.4 Hz, 2H), 7.53 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.6, 19.9, 62.6, 103.1, 114.4, 116.6, 128.9 (2C), 130.5 (2C), 135.0, 135.9, 148.1, 159.6 (2C), 165.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{15}ClN_2O_3S$: 363.0564; found: 363.0560.

*4.5.13. Ethyl 5-cyano-1-(4-methoxyphenyl)-2-methyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-3-carboxylate **6m**.* Reaction of **1j** (300 mg, 1.02 mmol) with **5a** (0.15 mL, 1.22 mmol) for 6 h followed by chromatographic purification (EtOAc/PE, 2:3) afforded 285 mg (78%) of **6m** as an off-white crystalline solid. Mp 131–132 °C; R_f 0.47 (EtOAc/PE, 1:1); IR (KBr): 2975, 2223, 1714, 1666, 1509, 1252, 1169, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, J=7.2 Hz, 3H), 2.05 (s, 3H), 2.80 (s, 3H), 3.85 (s, 3H), 4.38 (q, J=7.2 Hz, 2H), 7.01 (d, J=7.5 Hz, 2H), 7.07 (d, J=7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.5, 19.9, 55.5, 62.4, 103.2, 114.6, 115.3 (2C), 116.4, 128.4 (2C), 129.0, 149.1, 158.8, 159.9, 160.2, 165.3; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{18}N_2O_4S$: 359.1060; found: 359.1055.

*4.5.14. Ethyl 5-cyano-4-(methylthio)-6-oxo-2-propyl-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxylate **6n**.* Reaction of **1k** (300 mg, 0.90 mmol) with ethyl butyrylacetate **5d** (0.17 mL, 1.08 mmol) for 5 h followed by chromatographic purification (EtOAc/PE, 3:7) afforded 284 mg (74%) of **6n** as a white crystalline solid. Mp 158–159 °C; R_f 0.77 (EtOAc/PE, 1:1); IR (KBr): 2983, 2964, 2221, 1719, 1666, 1568, 1181, 1068, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.69 (t, J=7.2 Hz, 3H), 1.40 (t, J=7.2 Hz, 3H), 1.40–1.45 (m, 2H), 2.25–2.31

(m, 2H), 2.82 (s, 3H), 4.39 (q, J=7.2 Hz, 2H), 7.42 (d, J=8.4 Hz, 1H), 7.49 (s, 1H), 7.71 (t, J=7.5 Hz, 1H), 7.80 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (2C), 18.5, 22.5, 33.8, 62.5, 103.1, 114.3, 116.5, 123.2 (q, J=271.4 Hz, CF_3), 125.2, 126.7, 130.5, 131.6, 132.4 (q, J=33.1 Hz, C–CF_3), 136.7, 151.6, 159.6, 160.0, 164.9; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{19}F_3N_2O_3S$: 425.1141; found: 425.1143.

4.5.15. Ethyl 5-cyano-2-methyl-4-(methylthio)-6-oxo-1-[4-(pro-pan-2-yl)phenyl]-1,6-dihydropyridine-3-carboxylate ***6o***. Reaction of **1l** (500 mg, 1.63 mmol) with **5a** (0.25 mL, 1.96 mmol) for 5 h followed by chromatographic purification (EtOAc/PE, 2:3) afforded 471 mg (78%) of **6o** as an off-white crystalline solid. Mp 197–198 °C; R_f 0.72 (EtOAc/PE, 1:1); IR (KBr): 2963, 2221, 1716, 1667, 1503, 1228 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, J=6.6 Hz, 6H), 1.39 (t, J=7.2 Hz, 3H), 2.04 (s, 3H), 2.80 (s, 3H), 2.98 (septet, J=6.6 Hz, 1H), 4.38 (q, J=7.2 Hz, 2H), 7.06 (d, J=8.4 Hz, 2H), 7.38 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.6, 19.9, 23.7 (2C), 33.8, 62.4, 103.2, 114.6, 116.4, 127.0 (2C), 128.1 (2C), 134.1, 148.9, 150.6, 158.8, 159.8, 165.3; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{22}N_2O_3S$: 371.1423; found: 371.1419.

4.5.16. Ethyl 5-cyano-2-methyl-4-(methylthio)-1-(4-methyl-1,3-thiazol-2-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate ***6p***. Reaction of **1m** (500 mg, 1.75 mmol) with **5a** (0.27 mL, 2.10 mmol) for 4 h followed by chromatographic purification (EtOAc/PE, 1:4) afforded 343 mg (56%) of **6p** as an off-white crystalline solid. Mp 118–120 °C; R_f 0.55 (EtOAc/PE, 1:1); IR (KBr): 2995, 2222, 1723, 1670, 1566, 1485, 1291 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J=7.5 Hz, 3H), 2.15 (s, 3H), 2.48 (s, 3H), 2.82 (s, 3H), 4.38 (q, J=7.5 Hz, 3H), 7.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 17.1, 18.6, 18.8, 62.5, 102.6, 114.0, 116.8, 117.6, 148.2, 151.5, 154.4, 159.3, 160.9, 164.6; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{15}N_3O_3S_2$: 350.0627; found: 350.0623.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.04.082.

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