JOC The Journal of Organic Chemistry

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# Synthesis of Pyridin-2(1*H*)-one Derivatives via Enamine Cyclization

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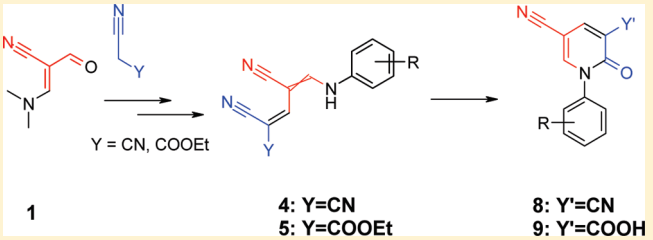
Supporting Information

**ABSTRACT:** The nucleophilic vinylic substitution reaction of the aliphatic enaminone 3-dimethylamino-2-formyl acrylonitrile **1** with the nucleophiles malononitrile and ethyl cyanoacetate produced the two unusual reaction adducts **3a** and **3b** in good to moderate yield under milder reaction conditions. Upon reaction with aromatic amines, these adducts yielded enamines **4** and **5**, which eventually cyclized in the presence of base to produce the novel pyridin-2(1*H*)-one derivatives **8** and **9**.




## INTRODUCTION

The chemistry of enamines and enaminones has numerous attractive features that have made them important building blocks in current organic trends.[1] They have gained considerable prominence due to their use in the treatment of epilepsy and because they possess a variety of other medicinal properties.[2] Over the decades, enaminones have been used for the synthesis of a wide variety of heterocyclic compounds.[3]

Likewise, the pharmacological importance of pyridin-2(1*H*)-one and its prevalent use as a synthetic intermediate in a number of heterocyclic compounds have emerged as important topics for researchers in recent years. These heterocyclic compounds are also known to possess antitumor activity and decrease the toxicity of cancer chemotherapy.[4]

Their evolution as valuable reagents with promising applications in heterocyclic chemistry,[4] along with the development of useful method for the synthesis of pyridin-2(1*H*)-ones via enamine cyclization, is the subject of this study.

## RESULTS AND DISCUSSION

**Preparation of Enaminone 1.** 3-Dimethylamino-2-formyl acrylonitrile **1** was first prepared by Trofimenko from 3-amino-2-cyanoacrolein and dimethyl amine, whereas Reichardt and Kermer demonstrated the synthesis of enaminone **1** via Vilsmeier–Haack formylation of acetonitrile. In 1993 we reported a new route toward the synthesis of **1** wherein cyanoacetaldehyde was treated with dimethylformamide-dimethylacetal to offer **1** in good to moderate yield (Figure 1).[5]

The synthetic utility of this enaminone has been reported by us[6] and other researchers[7] in the recent past. Though there have been a number of articles showcasing the reactivity of **1**, very little work has been reported about its behavior toward nucleophilic reagents.[8]

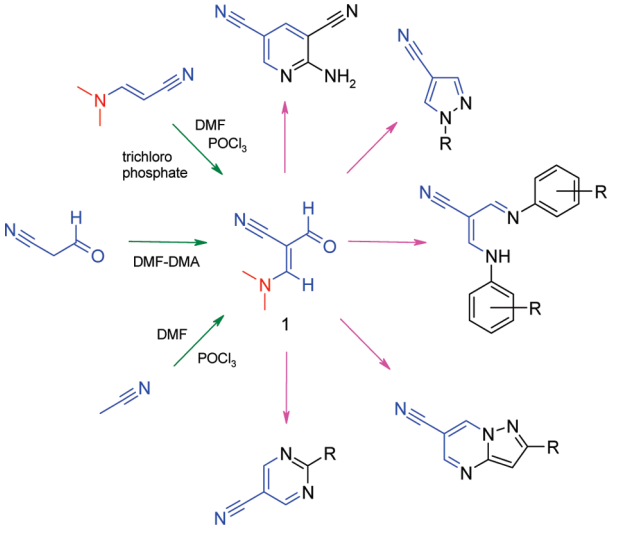



**Figure 1.** Synthesis and utility of enaminone **1**.

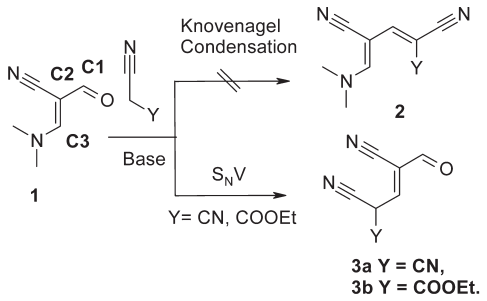
To address this point, in this paper we report the synthesis of stable reaction adducts (**3a** and **3b**) generated following unusual reactivity of enaminone **1** toward nucleophilic reagents. The nucleophilic reagents selected were malononitrile and ethyl cyanoacetate, and the reaction was carried out at ambient temperature in the presence of an inorganic base.

The structure of **1** is composed of an α,β-unsaturated enone moiety and an enamine subunit. Hence this molecule can behave both as an electrophile and as a nucleophile. This property of the molecule prompted us to carry out investigations concerning its reaction with nucleophilic reagents. Of the nucleophilic reagents

**Received:** January 27, 2011
**Published:** April 12, 2011

**Scheme 1. Regeoselectivity of Enaminone 1 with Nucleophiles**




Reagent and reaction condition : ACN, $K_2CO_3$, R.T.

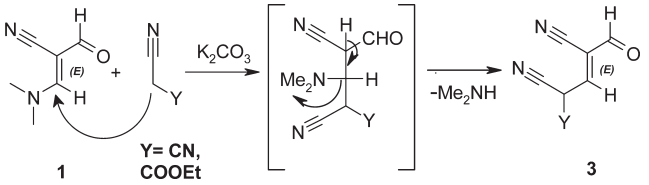
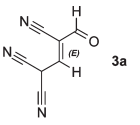
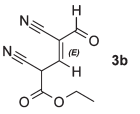



**Figure 2.** Mechanism of $S_NV$ reaction of enaminone **1**.

**Table 1. ($S_NV$) Reaction Adducts 3a and 3b**

| Entry | Nucleophilic reagent | Adduct | Yield (%)[c] |
|---|---|---|---|
| 1[a] | Malononitrile |  3a | 85 % |
| 2[b] | Ethyl cyanoacetate |  3b | 89 % |

[a,b] Reaction conditions: Nucleophilic reagents ([a]2.0 mmol; [b]2.5 mmol), $K_2CO_3$ ([a]2.5 mmol; [b]3.0 mmol). The reaction was carried out in acetonitrile (ACN, 5.0 mL) under a nitrogen atmosphere at ambient temperature. [c] Isolated yields were obtained.

available, compounds with active methylene groups that can act as nucleophiles were selected. We screened the reactions of **1** with alkyl acetoacetate esters, open and cyclic ketones containing active methylene sites and malononitrile, as reported in the literature.[9] However **1** failed to undergo any reactions under various reaction conditions.

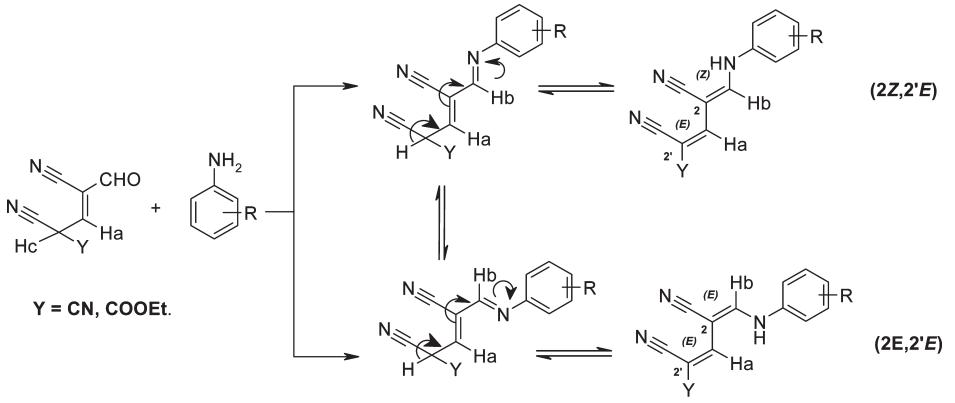
Though the results were discouraging, to our surprise **1** showed unusual reactivity with ethyl cyanoacetate and malononitrile in the presence of an inorganic base such as potassium carbonate. The reaction was found to be regioselective at the C3 carbon atom of **1** and followed the nucleophilic vinylic substitution pathway ($S_NV$) instead of a Knovenagel condensation reaction at the C1 carbonyl carbon atom (Scheme 1, Figure 2). It is noteworthy that both the above nucleophiles failed to react with **1** during our initial screenings with active methylene groups as reported in the literature.[9,10]

The structure of enaminone **1** has two electron-deficient sites, one being the carbonyl carbon atom and the other being the unsaturated carbon atom to which the dimethyl amine part is attached, C1 and C3, respectively. Hence there is competition between the C1 and C3 atoms in reacting with nucleophilic organic substrates. Over the decades, researchers have found that the C1 carbon atom of the aliphatic enaminones preferentially reacts with nucleophilic reagents under multiple sets of conditions.[9,10] Nonetheless, there have been a few reports demonstrating the participation of the C3 carbon atom rather than the C1 carbon atom.[11] Unfortunately most of the cited studies indicate the unstable nature of the reaction products obtained, which either reacted instantaneously with other organic substrates or underwent self-rearrangement, allowing no control over the final reaction product.

In contrast to the above observations, we successfully isolated the $S_NV$ reaction adducts **3a** and **3b** with efficient product yields of 80−90% (Table 1).

The configurations of **3a** and **3b** around the trisubstituted double bond were determined by 2D ROESY experiments and were found to be retaining the configuration of **1**, i.e. (*E*)-configuration,

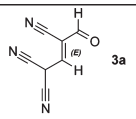
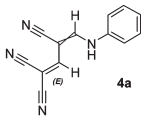
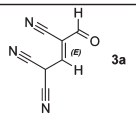
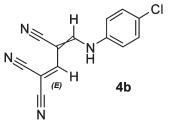
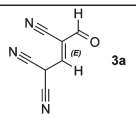
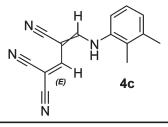
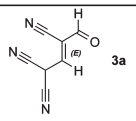
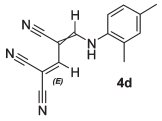
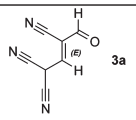
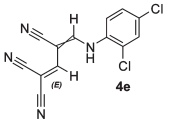
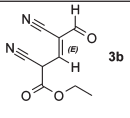
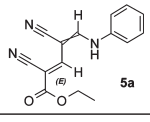
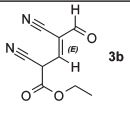
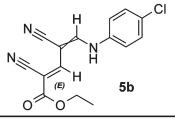
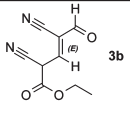
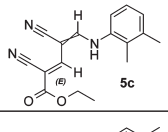
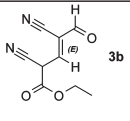
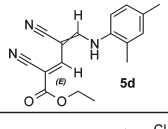
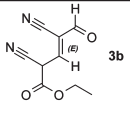
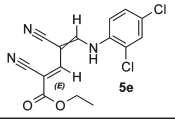
**Scheme 2. Enamine Synthesis from Synthones 3a and 3b**




Reagents and reaction condition : AcOH, R.T.


dx.doi.org/10.1021/jo200197g |*J. Org. Chem.* 2011, 76, 3829–3836

**Table 2. Preparation of Enamines 4 and 5**[a]

| Adduct | Aryl amine | Enamine | Yield (%)[b] |
|---|---|---|---|
|  3a |  |  4a | 81 % |
|  3a |  |  4b | 92 % |
|  3a |  |  4c | 65 % |
|  3a |  |  4d | 58 % |
|  3a |  |  4e | 94 % |
|  3b |  |  5a | 86 % |
|  3b |  |  5b | 88 % |
|  3b |  |  5c | 71 % |
|  3b |  |  5d | 82 % |
|  3b |  |  5e | 93 % |

[a] Reaction conditions: aryl amines (2 mmol). The reaction was carried out in glacial acetic acid (ACOH, 5.0 mL) under a nitrogen atmosphere at ambient temperature. [b] Isolated yields were obtained.

which has been determined by NMR using steady state differential NOE.[6]

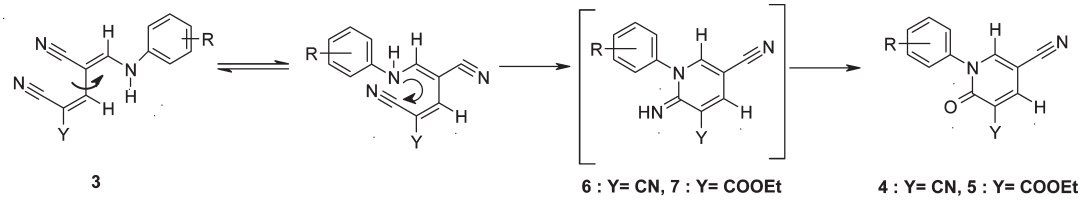
One of the important factors toward formation of **3** was the use of a weak base to which the products remained unreactive. In addition, the reaction proceeded at room temperature, permitting the use of milder reaction conditions. Both of the nucleophilic reagents were reacted with **1** in the presence of potassium carbonate at ambient temperature. The solvent of choice for the reaction was acetonitrile, and we selected inorganic bases over organic bases as in the presence of the latter the $S_NV$ reaction did not occur.

The role of solvent did not play a significant part in determining the reaction kinetics, although best results were obtained when polar aprotic solvents were used. Conversely, the substrates used as the base were found to alter the reaction equilibrium. When we screened the above reaction using organic bases such as triethyl amine, *N*-ethyl diisopropylamine, piperidine, pyridine, etc. at varying temperatures, no conversion was observed either in protic or aprotic solvents. Reactions in the presence of metal alkoxide bases degraded the enaminone **1** leading to the formation of multiple unknown products.

The use of inorganic bases such as metal carbonates in a polar aprotic solvent gave us best results when carried out at ambient


dx.doi.org/10.1021/jo200197g |*J. Org. Chem.* 2011, 76, 3829–3836

**Scheme 3. Proposed Synthetic Pathway towards Synthesis of Pyridin-2(1*H*)-one Derivatives**




temperature. Additionally, the use of ammonia in combination with metal carbonates accelerated the reaction rate. The reason could be the replacement of the dimethylamine group with an $NH_2$ group prior to nucleophilic attack and $NH_2$ being a fast leaving group as compared to the dimethylamine group, resulting in a faster reaction rate.

Though the findings signify participation of active methylene sites bearing an adjacent cyano group, cyanoacetic acid and cyanoacetamide failed to react under the given reaction conditions and further invention on them is in progress.

With the above discovery we obtained two novel stable synthones, $S_NV$ reaction adducts **3a** and **3b**, that we could utilize in the synthesis of higher derivatives of heterocyclic compounds. Amid the number of heterocycles, we focused on pyridin-2(1*H*)-one due to its frequent use in pharmacology[4] and because there is an urge of simple and efficient synthetic protocol for the synthesis of functionalized *N*-substituted pyridin-2(1*H*)-one compounds.[12]

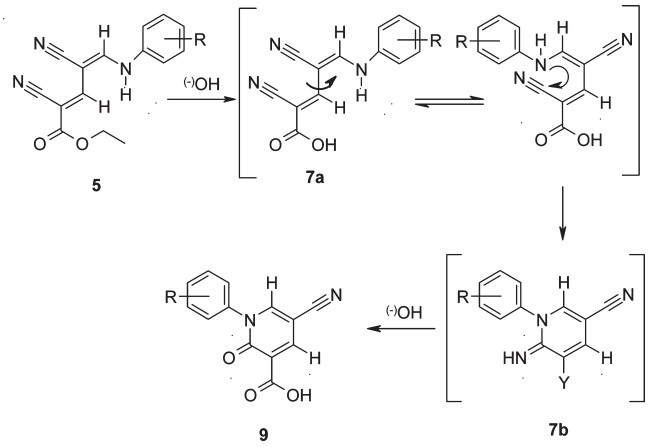
Our initial approach toward the synthesis of pyridin-2(1*H*)-one compounds was to develop a reliable synthetic method to introduce aromatic amines into synthones **3a** and **3b**. The protic solvent acetic acid provided the required protic condition for the reaction to occur and permitted product precipitation. Initially, the substituted anilines formed imines with the carbonyl moiety of **3a** and **3b** under protic conditions at ambient temperature, which upon further rearrangement yielded substituted aromatic enamines **4** and **5** (Scheme 2, Table 2).

The stereochemistry of **5** was determined by NMR using 2D ROESY experiments. The presence of crosspeaks between Ha, NH, and ArH hydrogens along with Ha and Hb hydrogens indicated existence of equilibrium between (*E*)- and (*Z*)-isomers at trisubstituted double bond (2), whereas the presence of crosspeaks between Ha and ester hydrogens for enamine **5** indicated (*E*)-configuration at trisubstituted double bond (2′).

Our next goal was to achieve the nucleophilic addition of the enamine NH group to the cyano group of **4** and **5** (Scheme 3). The paucity of reports in the literature suggests that enamines have little tendency to undergo this type of transformation.[13] Consistent with this, we also experienced difficulty in carrying out analogous nucleophilic attacks. All the initial reactions with organic bases and metal carbonates failed to produce any significant results. In contrast, we found that the presence of metal hydroxide played a vital role in promoting the reaction. The enamines **4a**−**e** and **5a**−**e** were cyclized in the presence of sodium hydroxide at ambient temperature in polar protic solvents such as methanol. The molecular identification of enamines **4** resulting from malononitrile-substituted synthone **3a** was consistent with our initial hypothesis (Scheme 3).

The enamines **5** obtained from the cyanoacetate-substituted synthone **3b** first underwent ester hydrolysis to produce acid **7a** and then underwent the nucleophilic addition reaction to produce 1,3,5-substituted pyridin-2(1*H*)-one derivatives **9** (Scheme 4, Table 3). In both cases, isolation of intermediates **6**, **7a**, and **7b** were unsuccessful as they rapidly hydrolyzed to give **8** and **9**, respectively, due to presence of alkali base within the reaction mass. Presumably the addition of water after reaction completion further eased the hydrolysis.

**Scheme 4. Synthesis of Pyridin-2(1*H*)-one Derivatives 9a−e[a]**




[a] Note: Actual path followed by enamines **5** toward formation of pyridin-2(1*H*)-one derivatives **9**.

## CONCLUSIONS

Moderate to excellent yields were obtained for most of the derivatives reported in this paper, and an operationally simple, inexpensive, and efficient method to prepare 1,3,5-substituted pyridin-2(1*H*)-one derivatives **8a**−**e** and **9a**−**e** starting from enaminone **1** has been developed.

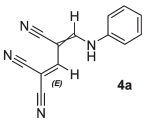
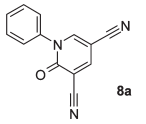
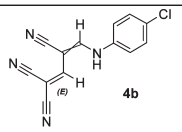
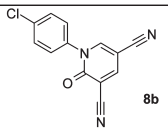
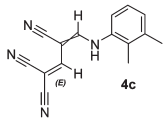
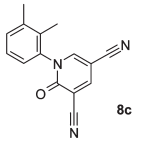
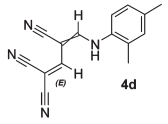
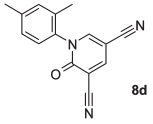
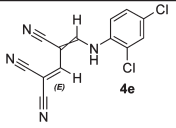
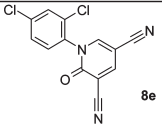
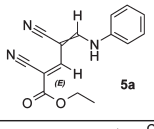
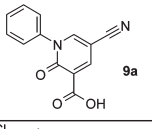
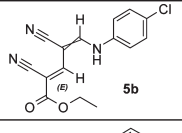
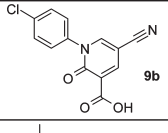
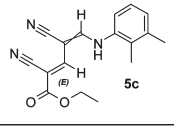
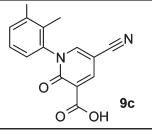
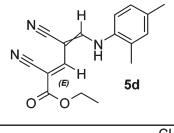
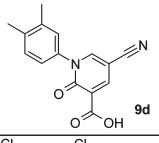
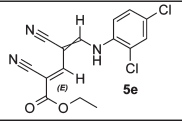
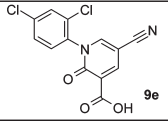
To the best of our knowledge, this is the first report of the synthesis of substituted pyridin-2(1*H*)-one derivatives using enamine as a preparatory material using the proposed synthetic pathway described above. It may be possible to develop relevant potent molecules by elaborating on this synthetic approach. Furthermore, the fact that the aliphatic enaminone underwent unusual $S_NV$ type reactions with nucleophiles as reported here has identified two stable novel synthones (**3a** and **3b**), which opens the possibility of synthesizing more diverse heterocycles.

## EXPERIMENTAL SECTION

**General.** Unless otherwise stated, materials were obtained from commercial suppliers and were used without further purification. Starting material 3-dimethylamino-2-formyl acrylonitrile was prepared as per our previously reported procedure.[5] All the reactions were carried out


dx.doi.org/10.1021/jo200197g |*J. Org. Chem.* 2011, 76, 3829–3836

**Table 3. Preparation of Pyridin-2(1*H*)-one Derivatives 8 and 9[a]**

| Entry | Enamine | Pyridin-2(1*H*)-one | Yield (%)[b] |
|---|---|---|---|
| 1. |  4a |  8a | 79 % |
| 2. |  4b |  8b | 83 % |
| 3. |  4c |  8c | 66 % |
| 4. |  4d |  8d | 73 % |
| 5. |  4e |  8e | 87 % |
| 6. |  5a |  9a | 84 % |
| 7. |  5b |  9b | 85 % |
| 8. |  5c |  9c | 69 % |
| 9. |  5d |  9d | 61 % |
| 10 |  5e |  9e | 80 % |

[a] Reaction conditions: The reaction was carried out in methanol (MeOH, 5.0 mL) in the presence of sodium hydroxide (NaOH, 2.5 mmol) at ambient temperature. [b] Isolated yields were obtained.

under nitrogen atmosphere in oven-dried flasks. Acetonitrile of analytical grade was used. Thin layer chromatography (TLC) was carried out using precoated 60 $F_{254}$ plates with a thickness of 0.25 mm, and mode of visualization was UV light (254 and 366 nm). Melting points were determined in an open mouth capillaries and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded at room temperature unless specified otherwise. Chemical shifts are reported in parts per million (ppm) as well in Hz relative to tetramethylsilane, and the abbreviations used to represent the multiplicity of the signal are s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), and m (multiplate). The solvent for NMR spectra was DMSO-$d_6$ unless otherwise stated. The 2D ROESY NMR experiments were carried out with 400 data points along the F1 dimension and 2 K data points along the F2 dimensions. An appropriate spinlock field was applied for a period of 300 ms. Infrared spectra were taken in potassium bromide pallets.

Mass spectrum was recorded with an ionization potential of 70 eV. Elemental analysis was within ±0.4 of the theoretical percentage. Preparative procedures for all the intermediates and final compounds are provided below. The obtained products were moisture- and oxygen-stable at ambient temperature.

**2,4-Dicyano-5-oxo-pent-3-enenitrile (3a).** In to an oven-dried flask were added 3-dimethylamino-2-formyl acrylonitrile **1** (0.124 g, 1.0 mmol), malononitrile (0.132 g, 2.0 mmol) and acetonitrile (5 mL) under the protection of $N_2$ at ambient temperature. Previously oven-dried potassium carbonate (0.345 g, 2.5 mmol) was added, and the reaction mass was then allowed to react for further 30 min. The reaction progress was monitored by thin layer chromatography using dichloromethane/methanol (9:1) as mobile phase. After completion of the reaction the mixture was filtered through a pad of Celite, and the filtrate was distilled until the solvent was completely removed so as to furnish the desired product as a yellow solid (0.123 g, 85%). The authentic sample for **3a** was prepared via short column chromatography using silica gel (60−100 mesh) and 2% methanol in dichloromethane as eluent. Mp: 212−215 °C. Mass: (*m*/*z*) 145, 130, 117, 103, 89, 77, 66, 44. FT-IR (KBR): 3556, 3436, 2215, 1627, 1538, 1347, 1256, 1162, 825, 772, 605 cm$^{-1}$. $^1$H NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 8.94 (s, 1H), 7.42 (d, $J$ = 6.8 Hz, 1H), 2.48 (d, $J$ = 7.0 Hz, 1H). $^{13}$C NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 186.5, 156.9, 119.5, 115.8, 115.7, 90.5, 34.4. Anal. Calcd for $C_7H_3N_3O$: C, 57.94; H, 2.08; N, 28.96. Found: C, 57.71; H, 1.842; N, 29.21.

**2,4-Dicyano-5-oxo-pent-3-enoic Acid Ethyl Ester (3b).** Into an oven-dried flask were added 3-dimethylamino-2-formyl acrylonitrile 1 (0.124 g, 1.0 mmol), ethylcyanoacetate (0.282 g, 2.5 mmol) and acetonitrile (10 mL) under the protection of $N_2$ at ambient temperature. Previously oven-dried potassium carbonate (0.414 g, 3 mmol) was added, and the reaction mass was then allowed to react for further 30 min. The reaction progress was monitored using thin layer chromatography using dichloromethane/methanol (9:1) as mobile phase. After completion of the reaction the mixture was filtered through a pad of Celite, and the filtrate was distilled until the solvent was completely removed so as to furnish the desired product as pale yellow solid (0.170 g, 89%). The authentic sample for **3b** was prepared via short column chromatography using silica gel (60−100 mesh) and 1.5% methanol in dichloromethane as eluent. Mp: 122−125 °C. Mass: (*m*/*z*) 192, 169, 153, 128, 113, 98, 86, 80, 68. FT-IR (KBr): 3571, 3453, 2988, 2215, 1671, 1648, 1541, 1409, 1369, 1305, 1194, 1020, 893, 787, 614 cm$^{-1}$. $^1$H NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 8.82 (s, 1H), 8.06 (s, 1H), 4.22 (q, $J$ = 7.4 Hz, 2H), 4.08 (s, 1H), 1.25 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 181.8, 163.5, 158.3, 152.6, 120.3, 120.1, 61.2, 30.0, 14.2. Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.42; H, 3.96; N, 14.25.

**General Procedure for Synthesis of Enamines (4a−e and 5a−e).** Flame-dried 50 mL double neck flask was charged with **3a** or **3b** (1 mmol) and aryl amines (2 mmol) under the protection of $N_2$ at ambient temperature. The reaction mass was then charged with glacial acetic acid (5 mL) to obtain a clear solution. The mass was then allowed to mix using magnetic stirrer for 3−12 h. The precipitated product was filtered and washed with small amount of glacial acetic acid. The obtained product was then dried in vacuum oven at 50−60 °C to afford compounds **4a**−**e** or **5a**−**e** as yellow solids. The authentic samples were prepared via short column chromatography using silica gel (60−100 mesh) and 1% methanol in dichloromethane as eluent.

**2,4-Dicyano-5-phenylamino-penta-2,4-dienenitrile (4a).** Yellow solid. Mp: 139−141 °C. Mass: (*m*/*z*) 219, 192, 165, 140, 115,


dx.doi.org/10.1021/jo200197g |*J. Org. Chem.* 2011, 76, 3829–3836

104, 89, 77. FT-IR (KBr): 3770, 3049, 2231, 1693, 1646, 1533, 1304, 1153, 915, 772, 693 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 8.76 (s, 1H), 8.51 (s, 1H), 8.13 (s, 1H), 7.36 (t, $J$ = 7.3 Hz, $J$ = 7.3 Hz, 2H), 7.21 (d, $J$ = 7.3 Hz, 2H), 7.15 (t, $J$ = 7.4 Hz, $J$ = 7.3 Hz, 1H). $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$, $D_2O$): $\delta$ 9.05 (s, 1H), 8.59 (s, 1H), 7.39−7.12 (m, 5H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 159.9, 154.7, 144.5, 130.1, 129.9, 129.2, 127.1, 127.1, 126.9, 116.0, 115.3, 104.0, 86.6. Anal. Calcd for $C_{13}H_8N_4$: C, 70.90; H, 3.66; N, 25.44. Found: C, 71.23; H, 3.542; N, 25.71.

**5-(4-Chloro-phenylamino)-2,4-dicyano-penta-2,4-dienenitrile (4b).** Yellow solid. Mp: 125−129 °C. Mass analysis (EI): ($m/z$, methanol) 254, 243, 226, 191, 172, 161, 136, 118, 109, 90, 75, 64, 44. FT-IR (KBr): 3095, 2215, 1566, 1408, 1281, 1168, 1090, 1012, 831, 650 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 10.71 (s, 1H), 8.36 (s, 1H), 7.87 (s, 1H), 7.69 (d, $J$ = 8.8 Hz, 2H), 7.13 (d, $J$ = 8.8 Hz, 2H). $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$, $D_2O$): $\delta$ 8.32 (s, 1H), 7.81 (s, 1H), 7.65 (d, $J$ = 8.8 Hz, 2H), 7.13 (d, $J$ = 8.8 Hz, 2H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 173.0, 155.4, 149.5, 134.7, 133.2, 131.3, 131.1, 129.2, 129.2, 122.6, 122.5, 118.2, 97.5. Anal. Calcd for $C_{13}H_7ClN_4$: C, 61.31; H, 2.77; N, 22.00. Found: C, 61.17; H, 2.558; N, 22.28.

**2,4-Dicyano-5-(2, 3-dimethyl-phenylamino)-penta-2,4-dienenitrile (4c).** Yellow solid. Mp: 208−212 °C. Mass analysis (EI): ($m/z$, methanol) 248, 234, 220, 206, 193, 179, 152, 130, 117, 103, 91, 77, 65, 44. FT-IR (KBr): 3272, 2228, 1692, 1535, 1469, 1389, 1291, 1249, 1208, 903, 810, 674, 566 $cm^{-1}$. $^1H$ NMR (500 MHz, TMS, DMSO-$d_6$): $\delta$ 9.68 (s, 1H),8.00 (s, 1H), 7.70 (s, 1H), 7.38 (d, $J$ = 7.4 Hz, 1H), 7.32 (t, $J$ = 7.4 Hz, $J$ = 7.8 Hz, 1H), 7.21 (d, $J$ = 7.8 Hz, 1H), 2.31 (s, 3H), 1.94 (s, 3H). $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$, $D_2O$): $\delta$ 8.27 (s, 1H), 7.99 (s, 1H), 7.37 (d, $J$ = 7.4 Hz, 1H), 7.31 (t, $J$ = 7.4 Hz, $J$ = 7.8 Hz, 1H), 7.16 (d, $J$ = 7.8 Hz, 1H), 2.30 (s, 3H), 1.93 (s, 3H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 172.0, 153.4, 149.6, 139.0, 138.1, 133.7, 131.4, 127.4, 125.5, 125.5, 120.1, 116.9, 86.5, 19.9, 13.6. Anal. Calcd for $C_{15}H_{12}N_4$: C, 72.56; H, 4.87; N, 22.57. Found: C, 72.91; H, 5.153; N, 22.72.

**2,4-Dicyano-5-(2,4-dimethyl-phenylamino)-penta-2,4-dienenitrile (4d).** Yellow solid. Mp: 223−227 °C. Mass analysis (EI): ($m/z$, methanol) 247, 234, 220, 206, 193, 179, 152, 130, 117, 103, 91. FT-IR (KBr): 3748, 3257, 2220, 1684, 1538, 1389, 1308, 1230, 1194, 916, 839, 772, 674, 559 $cm^{-1}$. $^1H$ NMR (500 MHz, TMS, DMSO-$d_6$): $\delta$ 9.57 (s, 1H), 8.02 (s, 1H), 7.72 (s, 1H), 7.28−7.21 (m, 3H), 2.34 (s, 3H), 2.00 (s, 3H). $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$, $D_2O$): $\delta$ 8.25 (s, 1H), 8.02 (s, 1H), 7.26−7.19 (m, 3H), 2.32 (s, 3H), 2.00 (s, 3H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 172.0, 153.4, 149.8, 139.9, 138.3, 134.6, 132.2, 128.6, 127.8, 127.7, 121.1, 116.8, 87.2, 20.7, 16.7. Anal. Calcd for $C_{15}H_{12}N_4$: C, 72.56; H, 4.87; N, 22.57. Found: C, 72.64; H, 5.138; N, 22.47.

**2,4-Dicyano-5-(2,4-dichloro-phenylamino)-penta-2,4-dienenitrile (4e).** Yellow solid. Mp: 134−139 °C. Mass analysis (EI): ($m/z$, methanol) 288, 271, 254, 226, 191, 172, 161, 145, 118, 109. FT-IR (KBr): 3738, 3071, 2214, 1678, 1575, 1396, 1327, 1247, 1102, 771 $cm^{-1}$. $^1H$ NMR (500 MHz, TMS, DMSO-$d_6$): $\delta$ 10.71 (s, 1H), 8.36 (s, 1H), 7.87 (s, 1H), 7.69 (d, $J$ = 9.1 Hz, 1H), 7.40 (dd, $J$ = 8.6 Hz, $J$ = 1.9 Hz 1H), 7.13 (d, $J$ = 1.9 Hz, 1H). $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$, $D_2O$): $\delta$ 8.34 (s, 1H), 7.84 (s, 1H), 7.67 (d, $J$ = 8.6 Hz, 1H), 7.37 (t, $J$ = 8.6 Hz, $J$ = 2.0 Hz, 1H), 7.14 (d, $J$ = 2.0 Hz, 1H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 172.7, 159.3, 155.3, 149.5, 148.9, 131.3, 131.0, 129.1, 128.9, 122.6, 122.5, 118.2, 91.5. Anal. Calcd for $C_{13}H_6Cl_2N_4$: C, 54.01; H, 2.09; N, 19.38. Found: C, 53.70; H, 1.916; N, 19.76.

**2,4-Dicyano-5-phenylamino-penta-2,4-dienoic Acid Ethyl Ester (5a).** Pale yellow solid. Mp: 148−150 °C. Mass analysis: ($m/z$) 266, 238, 220, 193, 165, 140, 114, 104, 77, 64, 51. FT-IR (KBr): 3211, 2983, 2221, 1704, 1578, 1649, 1341, 1241, 1199, 1098, 992, 758, 699 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 11.30 (s, 1H), 8.84 (s, 1H), 8.09 (s, 1H), 7.52 (d, $J$ = 8.3 Hz, 2H), 7.42 (t, $J$ = 8.3 Hz, $J$ = 7.3 Hz, 2H), 7.23 (t, $J$ = 7.3 Hz, $J$ = 7.3 Hz, 1H), 4.22 (q, $J$ = 7.3 Hz, 2H), 1.25 (t, $J$ = 7.3 Hz, 3H). $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$, $D_2O$): $\delta$ 8.72 (s, 1H), 8.08 (s, 1H), 7.47 (t, $J$ = 6.3 Hz, 4H), 7.30 (t, $J$ = 6.3 Hz, 1H), 4.26 (q, $J$ = 7.3 Hz, 2H), 1.29 (t, $J$ = 7.3 Hz, 3H); $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 164.5, 158.7, 153.5, 139.3 (× 2C), 126.9, 130.4 (× 2C), 119.3, 115.5, 114.1, 90.07, 81.6, 62.2, 14.7. Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.24; H, 4.72; N, 15.47.

**5-(4-Chloro-phenylamino)-2,4-dicyano-penta-2,4-dienoic Acid Ethyl Ester (5b).** Pale yellow solid. Mp: 137−142 °C. Mass analysis (EI): ($m/z$, methanol) 301, 272, 254, 227,220, 192, 174, 165, 147, 138, 111, 75. FT-IR (KBr): 3287, 3219, 2991, 2220, 1703, 1649, 1627, 1574, 1334, 1241, 1198, 1096, 989, 838 $cm^{-1}$. $^1H$ NMR (500 MHz, TMS, DMSO-$d_6$): $\delta$ 11.32 (s, 1H), 8.82 (s, 1H), 8.06 (s, 1H), 7.53 (d, $J$ = 8.8 Hz, 2H), 7.47 (d, $J$ = 8.9 Hz, 2H), 4.22 (q, $J$ = 7.4 Hz, Hz, 2H), 1.25 (t, $J$ = 7.4 Hz, 3H); $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 163.5, 158.3, 152.6, 138.1, 129.8, 129.4, 120.3, 114.4, 113.3, 89.9, 81.4, 61.2, 14.2. Anal. Calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93, Found: C, 59.87; H, 4.27; N, 13.64.

**2,4-Dicyano-5-(2, 3-dimethyl-phenylamino)-penta-2,4-dienoic Acid Ethyl Ester (5c).** Dark yellow solid. Mp: 123−125 °C. Mass analysis (EI): ($m/z$, methanol) 295, 280, 266, 252, 248, 234, 220, 206, 193, 179, 152, 130, 117, 103, 84, 77. FT-IR (KBr): 3204, 2978, 2225, 1710, 1634, 1574, 1338, 1206, 1019, 789, 755 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 10.90 (s, 1H), 8.46 (s, 1H), 8.01 (s, 1H), 7.155 (m, 3H), 4.19 (q, $J$ = 7.3 Hz, 2H), 2.25 (s, 3H), 2.16 (s, 3H), 1.23 (t, $J$ = 7.3 Hz, 3H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 163.7, 162.9, 152.9, 138.4, 137.8, 130.2, 128.8, 126.2, 121.3, 114.7, 113.6, 88.2, 80.2, 61.0, 19.8, 14.2, 13.9. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.82; H, 5.95; N, 14.41.

**2,4-Dicyano-5-(2,4-dimethyl-phenylamino)-penta-2,4-dienoic Acid Ethyl Ester (5d).** Dark brown solid. Mp: 111−113 °C. Mass analysis (EI): ($m/z$, methanol) 295, 280, 266, 252, 248, 234, 220, 206, 193, 179, 153, 130, 117, 103, 77. FT-IR (KBr): 3268, 3170, 2228, 1705, 1635, 1557, 1342, 1205, 1175, 1021, 759, 671 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 10.19 (s, 1H), 7.82 (s, 1H), 7.53 (s, 1H), 6.90 (s, 1H), 6.87 (d, $J$ = 7.8 Hz, 1H), 6.71 (d, $J$ = 7.8 Hz, 1H), 4.05 (q, $J$ = 7.4 Hz, 2H), 2.19 (s, 3H), 2.15 (s, 3H), 1.17 (t, $J$ = 7.4 Hz, 3H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$. 163.8, 163.5, 152.4, 138.0, 136.9, 130.3, 128.6, 126.1, 120.8, 114.4, 113.8, 96.4, 80.1, 61.6, 21.7, 13.8, 15.6. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.36; H, 5.97; N, 13.95.

**2,4-Dicyano-5-(2,4-dichloro-phenylamino)-penta-2,4-dienoic Acid Ethyl Ester (5e).** Bright yellow solid. Mp: 123−125 °C. Mass analysis (EI): ($m/z$, methanol) 336, 334, 300, 288, 272, 254, 226, 191, 172, 145, 109, 75. FT-IR (KBr): 3334, 2983, 2225, 1705, 1624, 1577, 1329, 1231, 1200, 1099, 873, 764, 649 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 10.73 (s, 1H), 8.58 (s, 1H), 7.97 (s, 1H), 7.75 (d, $J$ = 9.8 Hz, 1H), 7.57−7.51 (m, 2H), 4.21 (q, $J$ = 7.3 Hz, 2H), 1.24 (t, $J$ = 7.3 Hz, 3H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 161.4, 155.9, 141.6, 140.1, 130.9, 129.1, 128.4, 127.8, 121.7, 120.1 (× 2C), 104.5, 91.7, 64.7, 13.9. Anal. Calcd for $C_{15}H_{11}Cl_2N_3O_2$: C, 53.59; H, 3.30; N, 12.50. Found: C, 53.45; H, 3.22; N, 12.62.

**General Procedure Preparation of Pyridin-2(1*H*)-ones (8a−e and 9a−e).** To a flame-dried 50 mL double neck flask **4a−e** or **5a−e** (1 mmol) charged with methanol (10 mL) was added sodium hydroxide pellets (2.5 mmol) in one portion under the protection of $N_2$ at ambient temperature. The reaction mass was then allowed to react for 10−12 h so as to obtain a clear solution, and the reaction progress was monitored by thin layer chromatography using dichloromethane/methanol (9:1) as mobile phase. After completion of reaction the react


dx.doi.org/10.1021/jo200197g |*J. Org. Chem.* 2011, 76, 3829–3836

mass was concentrated under vacuum until the solvent was completely removed. The obtained residue was then charged with water (10 mL) and cooled to 5 °C. Dilute HCl was added to make the pH of the obtained mixture acidic (pH 3−4), and the product was extracted from aqueous phase using dichloromethane. Distillation of dichloromethane under vacuum furnished the desired product. The authentic samples were prepared via short column chromatography using silica gel (60−100 mesh) and 1% methanol in dichloromethane as eluent to give **8** or **9** as final products.

**2-Oxo-1-phenyl-1,2-dihydro-pyridine-3,5-dicarbonitrile (8a).** White solid. Mp: 204−207 °C. Mass analysis (EI): (*m*/*z*, methanol) 221, 206, 193, 180, 154, 140, 128, 118, 106, 91, 77. FT-IR (KBr): 3052, 2215, 1692, 1650, 1596, 1266, 1153, 769, 692 $cm^{-1}$. $^1H$ NMR (500 MHz, TMS, DMSO-$d_6$): $\delta$ 8.13 (s, 1H), 7.53 (s, 1H), 7.27 (d, $J$ = 7.3 Hz, 2H), 7.04 (t, $J$ = 7.9 Hz, $J$ = 7.3 Hz, 2H), 6.82 (t, $J$ = 7.3 Hz, $J$ = 7.3 Hz, 1H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 161.2, 159.0, 153.1, 149.1, 129.1 (× 2C), 123.9, 121.5 (× 2C), 120.8 (× 2C), 100.5, 86.5. Anal. Calcd for $C_{13}H_7N_3O$: C,70.58; H, 3.19; N, 19.00. Found: C, 70.74; H, 2.947; N, 18.67.

**1-(4-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (8b).** Off white Solid. Mp: 240−245 °C. Mass analysis (EI): (*m*/*z*, methanol) 255, 227, 192, 165, 140, 111, 75. FT-IR (KBr): 3348, 2209, 1613, 1566, 1488, 1384, 1200, 1090, 821 $cm^{-1}$. $^1H$ NMR (500 MHz, TMS, DMSO-$d_6$): $\delta$ 8.58 (s, 1H), 8.08 (s, 1H), 7.93 (d, $J$ = 8.6 Hz, 2H), 7.48 (d, $J$ = 8.6 Hz, 2H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 159.7, 155.1, 148.3, 138.2, 129.3, 129.3, 128.7, 126.6, 122.9, 122.8, 122.0, 105.0, 79.8. Anal. Calcd for $C_{13}H_6ClN_3O$: C, 61.07; H, 2.37; N, 16.44. Found: C, 60.78; H, 2.183; N, 16.12.

**1-(2, 3-Dimethyl-phenyl)-2-oxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (8c).** Buff colored solid. Mp: 245−248 °C. Mass analysis (EI): (*m*/*z*, methanol)249, 221, 210, 196, 183, 168, 151, 132, 120, 103. FT-IR(KBr): 3265, 2226, 1691,1596, 1533, 1302, 1237, 1187, 815, 766 $cm^{-1}$. $^1H$ NMR (500 MHz, TMS, DMSO-$d_6$): $\delta$ 9.46 (s, 1H), 8.37 (s, 1H), 8.05 (d, $J$ = 7.8 Hz, 1H), 7.06 (t, $J$ = 7.8 Hz, $J$ = 7.3 Hz, 1H), 6.94 (d, $J$ = 7.3 Hz, 1H), 2.26 (s, 3H), 2.16 (s, 3H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 161.4, 158.4, 156.5, 146.9, 137.0, 136.7, 127.7, 125.7, 125.4, 121.2 (× 2C), 106.2, 100.8, 20.4, 13.6. Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.56; H, 4.829; N, 16.55.

**1-(2,4-Dimethyl-phenyl)-2-oxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (8d).** Buff colored solid. Mp: 250−255 °C. Mass analysis (EI): (*m*/*z*, methanol) 249, 221, 210, 196, 178, 151, 132, 120, 105. FT-IR (KBr): 3391, 3293, 2221, 1633, 1581, 1392, 1224, 1155, 926, 799, 751 $cm^{-1}$. $^1H$ NMR (500 MHz, TMS, DMSO-$d_6$): $\delta$ 9.44 (s, 1H), 8.36 (s, 1H), 8.28 (d, $J$ = 8.3 Hz, 1H), 7.03 (s, 1H), 6.98 (d, $J$ = 8.3 Hz, 1H), 2.24(s, 3H), 2.23 (s, 3H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 161.4, 156.1, 146.9, 134.8, 132.4, 130.8, 128.0, 126.8, 122.2, 119.9 (× 2C), 100.7, 82.0, 20.4, 17.9. Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.47; H, 4.751; N, 16.63.

**1-(2,4-Dichloro-phenyl)-2-oxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (8e).** Brown solid. Mp: 266 −269 °C. Mass analysis (EI): (*m*/*z*, methanol) 288, 263, 248, 234, 224, 210, 196, 178, 160, 145, 126, 99, 90. FT-IR (KBr): 3454, 3362, 2199, 1619, 1596, 1471, 1247, 1104, 785, 666, 589 $cm^{-1}$. $^1H$ NMR (500 MHz, TMS, DMSO-$d_6$): $\delta$ 7.81 (s, 1H), 7.40 (s, 1H), 7.32 (d, $J$ = 2.2 Hz, 1H), 7.20 (t, $J$ = 2.2 Hz, $J$ = 8.8 Hz, 1H), 6.96 (d, $J$ = 8.8 Hz, 1H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 159.3, 155.3, 149.9, 147.9, 137.1, 134.4, 131.3, 131.0, 129.1, 122.6, 122.5, 100.0, 79.7. Anal. Calcd for $C_{13}H_5Cl_2N_3O$: C, 53.82; H, 1.74; N, 14.48. Found: C, 53.55; H, 1.48; N, 14.47.

**5-Cyano-2-oxo-1-phenyl-1,2-dihydro-pyridine-3-carboxylic Acid (9a).** White solid. Mp: 208−212 °C. Mass analysis (EI): (*m*/*z*, methanol) 240/239, 223, 210, 195, 166, 142, 119, 104, 77. FT-IR (KBr): 3312, 3164, 2229, 1682, 1632, 1589, 1273, 1186, 1006, 942, 755, 694 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 12.92 (s, 1H), 9.54 (s, 1H), 8.43 (s, 1H), 7.81 (d, $J$ = 7.9 Hz, 2H), 7.59 (t, $J$ = 8.0 Hz, 8.0 Hz, 2H), 7.40 (t, $J$ = 7.9 Hz, 8.0 Hz, 1H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 168.6, 159.3, 152.9, 149.4, 143.4, 133.1, 130.4, 130.0, 129.4, 128.9, 128.8, 120.7, 87.9. Anal. Calcd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66. Found: C, 65.18; H, 3.127; N, 11.98.

**1-(4-Chloro-phenyl)-5-cyano-2-oxo-1,2-dihydro-pyridine-3-carboxylic Acids (9b).** Pale brown solid. Mp: 189−193 °C. Mass analysis (EI): (*m*/*z*, methanol) 274, 257, 229, 216, 177, 149, 127, 99, 84, 49. FT-IR (KBr): 3327, 3187, 2227, 1638, 1606, 1490, 1288, 1189, 946, 852 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 12.83 (s, 1H), 9.54 (s, 1H), 8.44 (s, 1H), 7.63 (d, $J$ = 7.3 Hz, 2H), 7.44 (d, $J$ = 7.3 Hz, 2H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 170.0, 158.1, 146.2, 141.1, 132.9, 131.5, 128.7 (X2C), 124.0, 122.3 (X2C), 100.9, 81.0. Anal. Calcd for $C_{13}H_8ClN_2O_3$: C, 56.85; H, 2.57; N, 10.20. Found: C, 56.53; H, 2.44; N, 9.91.

**5-Cyano-1-(2, 3-dimethyl-phenyl)-2-oxo-1,2-dihydro-pyridine-3-carboxylic Acid (9c).** Pale buff colored Solid. Mp: 180−183 °C. Mass analysis (EI): (*m*/*z*, methanol) 268, 252, 238, 224, 210, 196, 179, 168, 152, 133, 120, 103, 91, 77, 65, 44. FT-IR (KBr): 3340, 2947, 2227, 1692, 1614, 1582, 1396, 1287, 1192, 1092, 797 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 13.11 (s, 1H), 9.66 (s, 1H), 8.45 (s, 1H), 7.93 (d, $J$ = 8 Hz, 1H), 7.06 (t, $J$ = 7.3 Hz, 8.0 Hz, 1H), 6.93 (d, $J$ = 7.3 Hz, 1H), 2.18 (s, 3H), 2.16 (s, 3H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 168.4, 160.0, 150.0, 143.9, 137.6, 137.6, 128.3, 126.5, 125.9, 122.7, 119.9, 107.4, 79.9, 20.9, 12.9. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.42; H, 4.762; N, 10.26.

**5-Cyano-1-(2,4-dimethyl-phenyl)-2-oxo-1,2-dihydro-pyridine-3-carboxylic Acid (9d).** Buff colored solid. Mp: 169−174 °C. Mass analysis (EI): (*m*/*z*, methanol) 268, 252, 238, 224, 210, 196, 179, 168, 152, 133, 120, 103, 91, 77, 44. FT-IR (KBr): 3434, 2920, 2851, 2225, 1681, 1620, 1592, 1275, 1188, 941, 877, 800 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 12.83 (s, 1H), 9.54 (s, 1H), 8.39 (s, 1H), 7.74 (d, $J$ = 7.9 Hz, 1H), 7.03 (s, 1H), 6.98 (d, $J$ = 7.9 Hz, 1H), 2.23 (s, 6H) $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 168.3, 156.2, 149.3, 143.5, 134.9, 134.3, 133.1, 130.9, 128.1, 126.3, 123.1, 116.9, 79.8, 20.2, 18.0. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.55; H, 4.517; N, 10.29.

**5-Cyano-1-(2,4-dichloro-phenyl)-2-oxo-1,2-dihydro-pyridine-3-carboxylic Acid (9e).** Yellow solid. Mp: 185−189 °C. Mass analysis (EI): (*m*/*z*, methanol) 309 (m+2), 300, 290, 252, 244, 226, 210, 191, 172, 160, 145, 109. FT-IR (KBr): 3330, 3168, 2228, 1688, 1646, 1579, 1509, 1388, 1232, 1101, 865, 810 $cm^{-1}$. $^1H$ NMR (499.85 MHz, TMS, DMSO-$d_6$): $\delta$ 12.93 (s, 1H), 9.54 (s, 1H), 8.44 (s, 1H), 7.86 (d, $J$ = 7.9 Hz, 1H), 7.52 (s, 1H), 7.39 (d, $J$ = 7.9 Hz, 1H). $^{13}C$ NMR (125.70 MHz, DMSO-$d_6$): $\delta$ 165.1, 159.1, 146.9, 172.4, 136.3, 135.1, 134.4, 132.0, 126.3, 123.9, 123.7, 117.0, 81.9. Anal. Calcd for $C_{13}H_6Cl_2N_2O_3$: C, 50.51; H, 1.96; N, 9.06. Found: C, 50.28; H, 1.739; N, 9.19.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures and full spectroscopic data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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## ■ ACKNOWLEDGMENT

The authors gratefully acknowledge financial support for this project from UGC, New Delhi, India. We thank Mamta Joshi (National Facility for High Field NMR, T.I.F.R. Mumbai) for 2D ROESY NMR assistance. We also acknowledge support and facilities provided by Bhavans and K.T.H.M. Colleges M.S. India.

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