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NOTE

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Synthesis and DABCO-induced demethylation of 3-cyano-4-methoxy-2-pyridone derivatives

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Abstract

An efficient method for synthesis and demethylation of 3-cyano-4-methoxy-2-pyridone derivatives has been developed. DABCO-induced demethylation can lead to 3-cyano-4-hydroxy-2-pyridones in DMF at 90°C with high yield. The protocol is applicable for the synthesis of 3-cyano-4-hydroxy-2-pyridone derivatives. The method is simple, efficient, and practical.

1 | INTRODUCTION

4-Hydroxy-2-pyridone derivatives, regarded as an important class of nitrogen-containing heterocycles, have been attractive in both organic and pharmaceutical chemistry areas. 4-Hydroxy-2-pyridone skeleton is present in diverse natural products and drug candidates.[1] They exhibited valuable bioactivities such as antibacterial, antifungal, antiviral, and cytotoxic activities. Representative examples are Ilicicolin **H**, Pyridoxatin, Gimeracil, and so on.[1,2] 5-Chloro-2,4-dihydroxypyridine (Gimeracil, CDHP) is also a component of an oral resectable gastric cancer drugs S-1 containing tegafur, Gimeracil, and potassium oxonate (Figure 1).[3] Their derivatives are also used as versatile intermediates in organic synthesis.[4]

Generally, 4-hydroxy-2-pyridone derivatives was synthesized by heating ethyl *N*-(styrylcarbamoyl)acetates in diphenyl ether at 230°C to 240°C.[5] Debenzylation of 4-benzyloxy-2-pyridones by hydrogenation gave 4-hydroxy-2-pyridones.[6] In addition, 4-hydroxy-2-pyridone derivatives were also prepared from the raw materials malononitrile, trimethyl orthoacetate, and *N*,*N*-dimethylformamide dimethyl acetal by the reactions of condensation, cyclization, hydrolysis, and decarboxylation of 5-chloro-3-cyano-4-methoxy-2-pyridone in HBr solution.[7] However, the reported methods for the synthesis of 4-hydroxy-2-pyridones have many disadvantages such as low yield, high reaction temperature, tedious steps, and more by-products. Thus, an efficient synthetic methodology needs to be developed.

Traditionally, demethylation of phenyl methyl ether and related derivatives was carried out in stronger acid solution such as HBr or HI solution. Although a variety of cleavage methods are available such as using BF_3-Me_2S complex,[8] $AlCl_3$/NaI,[9] BBr_3,[10] Me_3SiI,[11] SmI_2,[12] Pd $(PPh_3)_4$/MeOH,[13] iodocyclohexane/DMF,[14] or reducing reagents such as L-selectride[15] are employed. They often resulted in undesired reactions and products and low yields. Several protocols were developed for demethylation in ionic liquids.[16] The procedures are expensive and need a long reaction time.

1,4-Diazabicyclo[2.2.2]octane (DABCO) is a tertiary amine base with weak basicity. During the past decade, DABCO has been served as an organic-hindered base to carry out various organic transformations such as Baylis–Hillman reaction and cycloaddition reactions.[17]

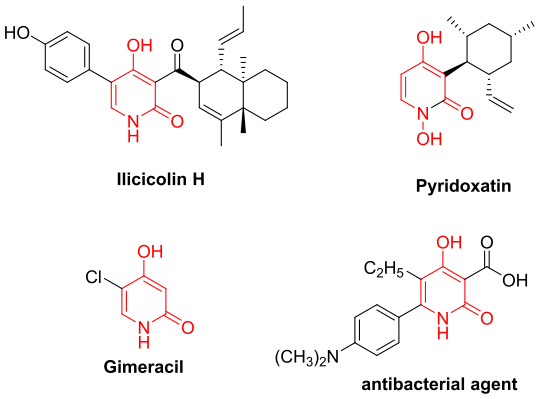


FIGURE 1 Selected examples of 4-hydroxy-2-pyridones [Color figure can be viewed at wileyonlinelibrary.com]

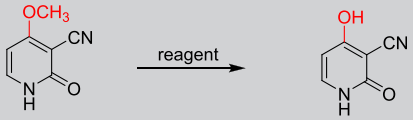
In our ongoing medicinal chemistry program,[1b, 1c, 5a, 7c] a key intermediate is needed for the synthesis of 4-hydroxy-2-pyridones, we herein disclose a simple and efficient method for demethylation of 3-cyano-4-methoxy-2-pyridones induced by DABCO.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

We have initiated our study with demethylation of 3-cyano-4-methoxy-2-pyridones in the presence of diverse organic bases such as DABCO, triethylamine, pyridine, and DBU (Table 1). The effectiveness of DABCO serving as the demethylation reagent under mild condition was demonstrated for the reaction of 3-cyano-4-methoxy-2-pyridones with DABCO. In the initial studies, we choose 3-cyano-4-methoxy-2-pyridone **1** as our model compound to carry out this reaction, because this material is commercial available. The product, 3-cyano-4-hydroxy-2-

TABLE 1 Optimization of the demethylation reaction conditions



1 **2**

Entry	Reagent	Solvent	T, °C	Reaction Time, h	Yield, %[a]
1	DABCO	DMF	90	6	95
2[b]	DABCO	DMF	90	6	80
3[c]	DABCO	DMF	90	6	72
4[d]	DABCO	DMF	90	12	43
5	Triethylamine	DMF	90	24	0
6	Diisopropylethylamine	DMF	90	24	0
7	Pyridine	DMF	90	24	0
8	K_2CO_3	DMF	90	24	0
9	DBU	DMF	90	24	58
10	DABCO	*n*-butanol	Reflux	24	0
11	DABCO	THF	Reflux	24	0
12	DABCO	Dioxane	Reflux	24	0
13	DABCO	CH_3CN	Reflux	24	0
14	DABCO	Toluene	Reflux	24	0
15	DABCO	DMSO	100	24	0
16	HBr	CH_3COOH/H_2O	Reflux	12	0
17	$BF_3.Et_2O$	$ClCH_2CH_2Cl$	Reflux	24	0
18	BBr_3	$ClCH_2CH_2Cl$	Reflux	24	35

Note. All reactions were conducted on a 5-mmol scale in 10 mL of DMF using 1.0 equiv of reagent at indicated reaction temperature.

[a]Yields are based on isolated products.

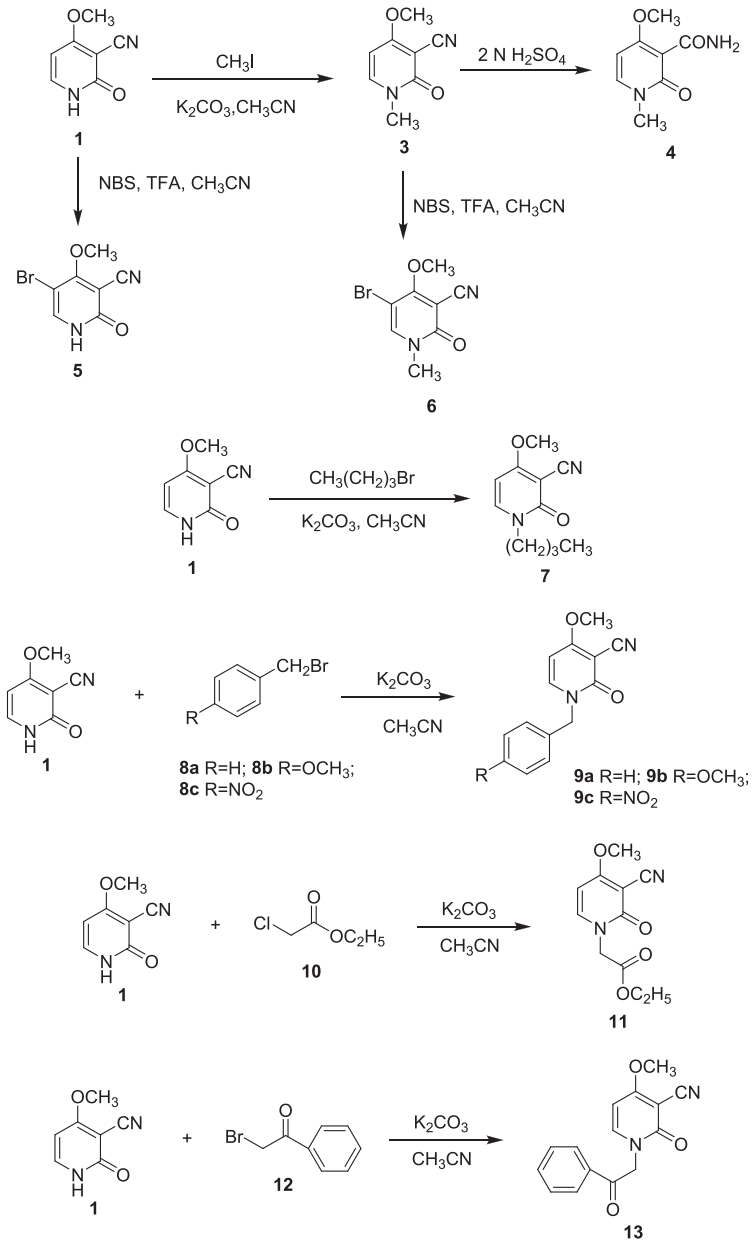
[b]0.6 equiv of DABCO was used.

[c]0.5 equiv of DABCO was used.

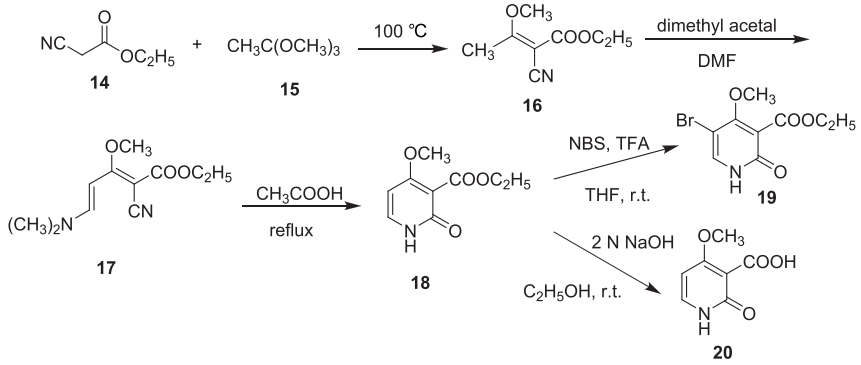
[d]0.3 equiv of DABCO was used.

pyridone **2**, is solid and easy to isolate. The result is shown in Table 1. DABCO-induced demethylation of 3-cyano-4-methoxy-2-pyridone was accomplished by heating the reagent in DMF at 90°C to 100°C for 6 hours (Table 1, entry 1). In the presence of 1.0 equiv of DABCO, the process provided the 3-cyano-4-hydroxy-2-pyridone in 95% yield with 6 hours. Subsequently, the influence of the loading DABCO on the reaction was investigated under identical reaction condition. Decreasing the amount of DABCO led to a decline in reaction yield (Table 1, entries 2-4). The result suggested DABCO can induce this reaction, not served as a catalyst.

Next, our research plan was returned to other classic organic base, such as triethylamine, diisopropylethylamine, pyridine, K_2CO_3, and DBU. Unfortunately, triethylamine, diisopropylethylamine, pyridine, and K_2CO_3 do not promote this demethylation reaction (Table 1, entries 5-8). The starting material was recovered. In contrast, with use of 1.0 equiv of DBU, 3-cyano-4-hydroxy-2-pyridone was obtained with 58% yield (Table 1, entry 9); 35% starting material was recovered. It should be noted that the reaction does not carry out by using *n*-butanol, THF, dioxane, acetonitrile, toluene, and DMSO as solvent (Table 1, entries 10-15). The starting material was recovered. It should be noted the reaction did not provide the desired product at all in HBr solution because of the hydrolysis of cyano group. $BF_3.Et_2O$ is also not an efficient demethylation agent. When using BBr_3 as demethylation agent, only 35% product was obtained (Table 1, entries 16-18). The above results suggested that DABCO is a more effective inducer in this reaction.



SCHEME 1 The synthesis route of some commercial unavailable 4-methoxy-2-pyridones

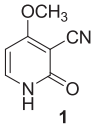
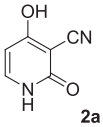
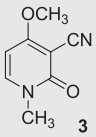
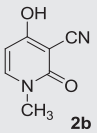
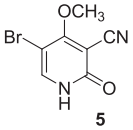
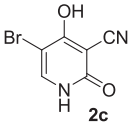
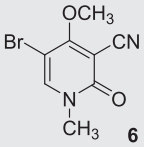
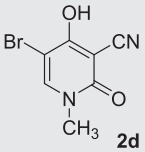


SCHEME 2 The synthesis route of 4-methoxy-2-pyridone-3-carboxylic acid derivatives

In order to further reveal the synthetic utility of this method, a series of 4-methoxy-2-pyridones including 3-cyano-4-methoxy-2-pyridones and related ethyl 4-methoxy-2-pyridone-3-carboxylates were applied to this protocol. The synthesized raw materials were shown in Scheme 1 because they are commercial unavailable. *N*-substituted 3-cyano-4-methoxy-2-pyridones were obtained by the treatment of 3-cyano-4-methoxy-2-pyridones with alkyl halide in CH_3CN at reflux with 90% yield. Their brominated derivatives **5** and **6** were synthesized by bromination of compounds **1** and **3** with NBS in acetonitrile around 80% yields. 4-Methoxy-2-pyridonecarboxamide **4** was prepared by hydrolysis of 3-cyano-4-methoxy-2-pyridone **3** in 2N sulfuric acid with 72% yield. The synthesis of ethyl 4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate was given in Scheme 2, according to our previous published paper.[7c] Ethyl 2-cyano-5-(dimethylamino)-3-methoxypenta-2,4-dienoate **17** was prepared by condensation of *N*,*N*-dimethylformamide dimethyl acetal with ethyl 2-cyano-3-methoxybut-2-enoate **16**, which was obtained by condensation of ethyl cyanoacetate **14** with trimethyl orthoacetate **15**. The cyclization of compound **17** in 80% acetic acid lead to provide ethyl 4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate **18** with 78% yield. Finally, the compound **18** was subjected to bromination to provide compound **19** and hydrolysis to give compound **20**.

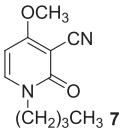
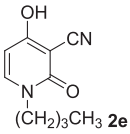
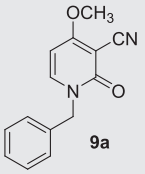
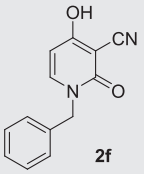
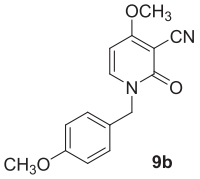
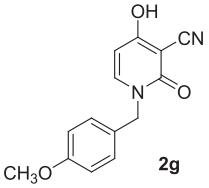
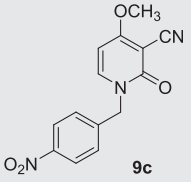
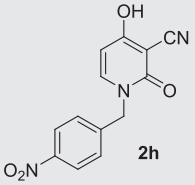
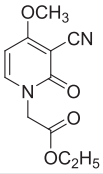
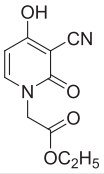
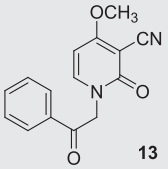
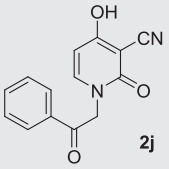
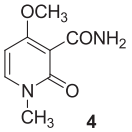
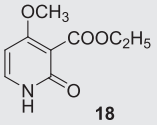
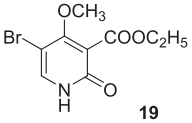
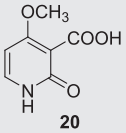
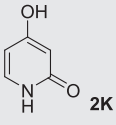
With those compounds in hand, the demethylation reaction was performed according to the above procedure. Their spectral data were given in experimental section. The reaction yields were satisfactory and ranged from 84% to 95%. In addition, the demethylation protocol showed a good chemical selectivity. The methoxy group attached to phenyl moiety was not removed in this

TABLE 2 Demethylation of 4-methoxy-2-pyridones induced by DABCO

Entry	Substrate	Product	Reaction Time, h	Yield, %[a]
1	 1	 2a	6	95
2	 3	 2b	6	92
3	 5	 2c	6	85
4	 6	 2d	6	87
5			6	93

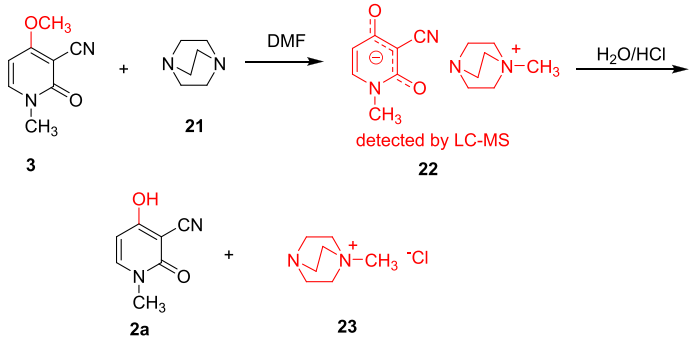
(Continues)

TABLE 2 (Continued)

Entry	Substrate	Product	Reaction Time, h	Yield, %[a]
	 7	 2e		
6	 9a	 2f	6	92
7	 9b	 2g	6	86
8	 9c	 2h	6	89
9	 11	 2i	6	90
10	 13	 2j	6	84
11	 4	No reaction	24	0
12	 18	No reaction	24	0
13	 19	No reaction	24	0
14	 20	 2K	24	5

Note. All reactions were conducted on a 5-mmol scale in 10 mL of DMF using 1.0 equiv of DABCO at 90°C.

[a]Yields are based on isolated products.



SCHEME 3 Proposed mechanism for demethylation of 3-cyano-4-methoxy-1-methyl-2-pyridone induced by DABCO. [Color figure can be viewed at wileyonlinelibrary.com]

reaction condition. (Table 2, entry 7). The reaction also can be happened when bromo, ester, ketone, and nitro groups attached to 3-cyano-4-methoxy-2-pyridone moiety (Table 2, entries 3, 4, 8, 9, 10). However, the methodology is unsuitable to compounds **4, 18** to **19** (Table 2, entries 11-13). Nothing happened for this running condition. When compounds **4** and **18** were treated with DABCO in 120°C to 130°C for 48 hours. The reaction does not still work smoothly. In addition, compound **20** was reacted with DABCO in DMF in 130°C to 140°C for 24 hours. 4-Hydroxy-2-pyridone was obtained in 5% yield. We suggested the hydrolysis and decarboxylation reaction of compound **20** happened in this reaction in high reaction temperature. We supposed a stronger electron-withdrawing cyano group in 4-hydroxy-2-pyridone ring may be necessary for the demethylation reaction.

2.2 | Reaction mechanism

According to the above experimental results, a plausible mechanism is proposed in Scheme 3 using compound **3** as an example. We hypothesized that DABCO readily coordinates to O atom of 4-methoxy-2-pyridones.[18] Rapid formation of **22** may be due to an enolate and carbonyl group tautomerization existed in compound **22**. A withdraw group in 3-position can make this compound stable. The production was released in the presence of hydrogen donor. The methyl group was transferred to DABCO to form compound **23** and generate compound **2a**. Compounds **22** and **23** were also detected through liquid chromatography–mass spectrometry (LC-MS) analysis (electrospray ionization [ESI] mass peak for compound **22** at 277 and mass peak for compound **23** at 127; see Supporting Information). We believe that DABCO functions as an inducer in the demethylation reaction.

3 | CONCLUSIONS

In summary, we have presented an efficient protocol for synthesis and demethylation of 3-cyano-4-methoxy-2-pyridones by employing DABCO as an inducer under mild reaction conditions. 3-Cyano-4-hydroxy-2-pyridones were obtained with high yields. This protocol provides a practical and environmentally friendly process for an important chemical transformation.

4 | EXPERIMENTAL

Melting points were determined with RY-1 apparatus and were uncorrected. Infrared (IR) spectra were recorded as KBr pellets on a Shimadzu model 470 spectrophotometer. ^{1}H NMR spectra were obtained using a Bruker AV 400-MHz spectrometer in DMSO-d_6 and $CDCl_3$ with tetramethylsilane as internal standard. Electron ionization (EI) mass spectra were determined on Waters Micromass GCT system and Shimadzu QP-2010 GC-MS system. ESI mass spectra were recorded on Shimadzu 2010A LC-MS instrument. All chemicals are commercial available and were used without further purification. Ethyl 4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate were synthesized according to our previous report.[7c] The data of mp and ^{1}H NMR for known products are in accord with that reported in literature.

4.1 | General procedure for preparation of compounds 3, 7, 9a-9c, 11, and 13

A mixture of 3-cyano-4-methoxy-2-pyridone (20 mmol), CH_3I (20 mmol) in acetonitrile (20 mL) was stirred and refluxed for 10 hours. After the completion of the reaction, the mixture was cooled to room temperature, and water (30 mL) was added. After extraction with EtOAc (15 mL × 2), the organic phase was washed with water (10 mL × 2) and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from ethanol to give yellow solid **3**. Compounds **7**, **9a-9c**, **11**, and **13** were synthesized from compound **1** following the procedure given above. Their spectral data are as follows.

4.1.1 | 4-Methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3)

White solid, yield: 78%, mp 198°C to 200°C. IR ν_{max} = 2219 (CN), 1653 (C=O), 1604-1457 (—CH=CH—), 1358 (CH_3), 1256 (C—O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.42 (s, 3H, NCH_3), 3.97 (s, 3H, OCH_3), 6.42 (d, J = 8.0 Hz, 1H, Ar-H), 8.11 (d, J = 8.0 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 37.15, 58.07, 86.18, 94.14, 115.10, 146.54, 161.30, 173.06.[19]

4.1.2 | 4-Methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonamide (4)

A mixture of 3-cyano-4-methoxy-1-methyl-2-pyridone **3** (20 mmol) in 2N H_2SO_4 (15 mL) was stirred and heated at 80°C to 90°C for 6 hours. After the completion of the reaction, the mixture was cooled to room temperature. The solid were filtrated and washed with water to give white solid, with 72% yield, mp 150°C to 152°C. IR ν_{max} = 3405 (NH_2), 2359 (CN), 1662 (C=O), 1553-1481-(—CH=CH—), 1409 (CH_3), 1259 (C—O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.38 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 6.28 (d, J = 8.0 Hz, 1H, Ar-H), 7.10 (s, 1H, NH_2), 7.58 (s, 1H, NH_2), 7.77 (s, J = 8.0 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 36.93, 56.68, 94.75, 111.06, 141.16, 161.04, 165.01, 166.19.[20]

4.1.3 | 5-Bromo-4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (5)

A mixture of 3-cyano-4-methoxy-2-pyridone (20 mmol), NBS (20 mmol), and trifluoroacetic acid (4 mmol) in acetonitrile (25 mL) was stirred and refluxed for 8 hours. After the completion of the reaction, the solvent was carefully removed in vacuo, and water (30 mL) was added. After extraction with EtOAc (15 mL × 2), the organic phase was washed with water (10 mL × 2) and dried over $NaSO_4$. The solvent was removed and the residue was recrystallized from ethanol to give white solids **5**. Compounds **6** and **19** were synthesized following the procedure given above. Their spectral data are as follows.

White solid, yield: 74%, mp 212°C to 214°C. IR ν_{max} = 3439 (NH), 2221 (CN), 1642 (C=O), 1597-1470 (—CH=CH—), 1346 (CH_3), 1229 (C—O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 4.32 (s, 3H, OCH_3), 8.04 (s, 1H, Ar-H), 12.42 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 61.28, 88.83, 92.87, 115.30, 141.55, 162.12, 169.18.[21]

4.1.4 | 5-Bromo-4-methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (6)

White solid, yield: 81%, mp 242°C to 244°C. IR ν_{max} = 2215 (CN), 1637 (C=O), 1596-1452 (—CH=CH—), 1406 (CH_3), 1093 (C—O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.41 (s, 3H, NCH_3), 4.31 (s, 3H, OCH_3), 8.43 (s, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 37.22, 61.33, 88.20, 92.20, 115.28, 145.36, 161.32, 168.45.[21]

4.1.5 | 1-*N*-Butyl-4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (7)

White solid, yield: 87%, mp 81°C to 83°C. IR ν_{max} = 2273 (CN), 1640 (C=O), 1601-1536 (—CH=CH—), 1492 (CH_2), 1384 (CH_3), 1259 (C—O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 0.89 (t, J = 8.0 Hz, 3H, CH_3), 1.23-1.29 (m, 2H, CH_2), 1.57-1.63 (m, 2H, CH_2), 3.89 (t, J = 7.2 Hz, 2H, CH_2), 3.99 (s, 3H, CH_3), 6.45 (d, J = 7.7 Hz, 1H, Ar-H), 8.13 (d, J = 7.7 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 13.99, 19.56, 31.11, 48.80, 58.08, 86.46, 94.41, 115.12, 145.90, 160.88, 172.97. MS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{14}N_2O_2Na$: 229.0947; found: 229.0948.

4.1.6 | 1-(4-Benzyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (9a)

White solid, yield: 86%, mp 200°C to 203°C. IR ν_{max} = 3102-2921 (=C—H aromatic), 2222 (CN), 1664 (C=O), 1598-1493(C=C aromatic, —CH=CH—), 1424 (CH_2), 1347 (CH_3), 1276 (C—O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.99 (s, 3H, OCH_3), 5.11 (s, 2H, CH_2), 6.50 (d, J = 8.0 Hz, 1H, Ar-H), 7.28-7.37 (m, 5H, Ar-H), 8.26 (d, J = 8.0 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 51.72, 58.20, 86.72, 95.05, 114.97, 128.15, 128.22, 129.10, 137.05, 145.90, 160.91, 173.25. MS (EI): m/z $[M^+]$ calcd for $C_{14}H_{12}N_2O_4$: 240.0899; found: 240.0893.

4.1.7 | 1-(4-Methoxybenzyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (9b)

White solid, yield: 85%, mp 206°C to 208°C. IR ν_{max} = 2923(=C—H aromatic), 2212 (CN), 1743 (C=O), 1629-1516 (C=C aromatic, —CH=CH—), 1463 (CH_2), 1383 (CH_3) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.73 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 5.03 (s, 2H, CH_2), 6.47 (d, J = 8.0 Hz, 1H, A r-H), 6.90 (d, J = 8.0 Hz, 2H, Ar-H), 7.27 (d, J = 8.0 Hz, 2H, Ar-H), 8.23 (d, J = 8.0 Hz,

1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 51.18, 55.58, 58.16, 86.64, 94.93, 114.48, 115.00, 128.97, 129.96, 145.67, 159.39, 160.89, 173.12. MS (EI): *m/z* [M^+] calcd for $C_{15}H_{14}N_2O_3$: 270.1004; found: 270.1001.

4.1.8 | 4-Methoxy-1-(4-nitrobenzyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (9c)

White solid, yield: 81%, mp 150°C to 152°C. IR ν_{max} = 3102-2921 (=C—H aromatic), 2222 (CN), 1664 (C=O), 1598-1493 (C=C aromatic, —CH=CH—, NO), 1424 (CH_2), 1347 (CH_3) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.02 (s, 3H, OCH_3), 5.25 (s, 2H, CH_2), 6.58 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.52 (d, *J* = 8.0 Hz, 2H, Ar-H), 8.22 (d, *J* = 8.0 Hz, 2H, Ar-H), 8.31 (d, *J* = 8.0 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 51.54, 58.33, 86.82, 95.43, 114.83, 124.22, 129.15, 144.62, 146.04, 147.42, 160.89, 173.52. MS (EI): *m/z* [M^+], calcd for $C_{14}H_{11}N_3O_4$: 285.0750; found: 285.0747.

4.1.9 | Ethyl 2-(3-cyano-4-methoxy-2-oxopyridin-1(2*H*)-yl)acetate (11)

White solid, yield: 83%, mp 154°C to 156°C. IR ν_{max} = 2210 (CN), 1753 (C=O), 1652 (C=O), 1610-1494 (—CH=CH—), 1473 (CH_2), 1374 (CH_3) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.21 (t, *J* = 8.0 Hz, 3H, CH_3), 4.0 (s, 3H, CH_2), 4.15 (q, *J* = 8.0 Hz, 2H, CH_3), 4.73 (s, 2H, CH_2), 6.55 (d, *J* = 8.0 Hz, 1H, Ar-H) ,8.09 (d, *J* = 8.0 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 13.97, 49.79, 57.84, 61.23, 85.75, 94.43, 114.21, 145.90, 160.34, 167.56, 173.20. MS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{12}N_2O_4$: 237.0870; found: 237.0865.

4.1.10 | 4-Methoxy-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydropyridine-3-carbonitrile (13)

White solid, yield: 75%, mp 228°C to 230°C. IR ν_{max} = 1695 (C=O), 1645 (C=O), 1603-1487 (C=C aromatic, —CH=CH—), 1450 (CH_2), 1360 (CH_3) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.0 (s, 3H, CH_3), 5.57 (s, 2H, CH_2), 6.59 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.62 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.77-7.72 (m, 1H, Ar-H), 8.10-8.06 (m, 3H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 55.18, 58.28, 86.34, 94.78, 114.87, 128.48, 129.48, 134.66, 134.73, 146.72, 160.89, 173.58, 192.92. MS (ESI): *m/z* [M + H] $^+$ calcd for $C_{16}H_{12}N_2O_3$: 269.0921; found: 269.0923.

4.1.11 | Ethyl 2-cyano-3-methoxybut-2-enoate (16)

Ethyl cyanoacetate (0.10 mol, 11 mL) and trimethyl orthoacetate (0.12 mol, 15 mL) were stirred at 110°C. After 4 hours, the mixture was heated to 135°C, and excess reagents were removed. Upon cooling, the mixture solidified. This mixture was recrystallized from water: methanol (2:1), yielding compound as a colorless powder 11.2 g, yield 66%, mp 132°C to 135°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 8.0 Hz, 3H, CH_3), 2.63 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.25 (q, *J* = 8.0 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.16, 15.03, 56.66, 61.19, 85.95, 115.03, 163.82, 184.25.[7c, 22]

4.1.12 | Ethyl 2-cyano-5-(dimethylamino)-3-methoxypenta-2,4-dienoate (17)

Ethyl 2-cyano-3-methoxybut-2-enoate **16** (11.2 g, 66 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (14.1 mL, 0.11 mol) were dissolved in methanol (5 mL) and heated to 130°C for 60 minutes. Excess solvents and reagents were carefully removed in vacuo. The dark red residue was purified by column chromatography (*n*-hexane:ethyl acetate = 8:1, v/v) to afford target compound **17** as a red powder 9.01 g, yield 61%, mp 150°C to 152°C. It was used in the next step without purification.

4.1.13 | Ethyl 4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate (18)

Ethyl 2-cyano-5-(dimethylamino)-3-methoxypenta-2,4-dienoate **17** (5.0 g, 22.3 mmol) was refluxed for 1 hour in 80% aqueous HOAc (15 mL). The solution was concentrated to about one-third of the original volume. Saturated $NaHCO_3$ solution (50 mL) was added and extracted with chloroform (30 mL × 2). After drying over Na_2SO_4 and filtration, the solvents were removed in vacuo. The product was recrystallized from ethyl acetate to provide compound **18** 2.7 g as colorless crystals with 62% yield, mp 152°C to 154°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 8.0 Hz, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.40 (q, *J* = 8.0 Hz, 2H, CH_2), 6.14 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.51 (d, *J* = 8.0 Hz, 1H, Ar-H), 13.54 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.16, 56.49, 61.40, 94.80, 108.71, 137.94, 163.65, 164.98, 167.00.[7b]

4.1.14 | Ethyl 5-bromo-4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate (19)

White solid, yield: 68%, mp 154°C to 156°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 8.0 Hz, 3H, CH_3), 3.88 (s, 3H, OCH_3), 4.26 (q, J = 8.0 Hz, 2H, CH_2), 7.81 (s, 1H, Ar-H), 12.05 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.31, 60.25, 61.89, 93.94, 112.48, 138.31, 161.08, 161.50, 165.08.[7b]

4.1.15 | 4-Methoxy-2-oxo-1,2-dihydropyridine-3-carboxylic acid (20)

To a solution of ethyl 4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate **18** (1.5 g, 7.6 mmol) in 50% ethanol, 2N NaOH solution (2 mL) was added and the reaction mixture was refluxed for 6 hours. Excess ethanol were carefully removed in vacuo. The reaction mixture was adjust pH to 4 to 5 with 2N HCl. The precipitate was collected and recrystallized from ethanol to yield specified product **15** 1.0 g with 78% yield. mp 216°C to 219°C. IR ν_{max} = 3189 (NH), 2198 (CN), 1645 (C═O), 1562-1485 (—CH═CH—), 1431 (CH_2), 1318 (CH_3) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.95 (s, 3H, OCH_3), 6.55 (d, J = 8.0 Hz, 1H, Ar-H), 7.84 (s, J = 8.0 Hz, 1H, Ar-H), 12.69 (s, 1H, NH), 15.02 (s, 1H, COOH). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 57.83, 97.76, 102.03, 140.68, 163.77, 166.42, 172.28. MS (ESI): m/z = 170 [M + H]$^+$.[22]

4.2 | Typical procedure for demethylation of 3-cyano-4-methoxy-2-pyridones induced by DABCO

A mixture of 4-hydroxy-2-pyridones (5 mmol), DABCO (5 mmol) in DMF (10 mL) was stirred at 90°C for 6 hours. The reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to room temperature, and water (30 mL) was added. The reaction mixture was adjust pH to 4 to 5 with 2N HCl solution. The precipitate was filtrated and recrystallized from ethanol to yield specified product.

4.2.1 | 4-Hydroxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (2a)

White solid, yield: 95%, mp 154°C to 156°C. IR ν_{max} = 3427 (OH), 2208 (CN), 1615 (C═O), 1569-1513 (—CH═CH—) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.59 (d, J = 8.0 Hz, 1H, Ar-H), 7.52 (d, J = 8.0 Hz, 1H, Ar-H), 11.71 (s, 1H, NH), 12.61 (s, 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 85.97, 98.35, 115.54, 140.97, 162.69, 173.46. high-resolution mass spectrometry (HRMS) (EI): m/z [M$^+$] calcd for $C_6H_4N_2O_2$: 136.0273; found: 136.0276.

4.2.2 | 4-Hydroxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (2b)

White solid, yield: 92%, mp 284°C to 286°C.IR ν_{max} = 3434 (OH), 2211(CN), 1633 (C═O), 1569-1507 (—CH═CH—), 1321 (CH_3) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.36 (s, 3H, NCH_3), 6.02 (d, J = 8.0 Hz, 1H, Ar-H), 7.82 (d, J = 8.0 Hz, 1H, Ar-H), 12.64 (s, 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 36.84, 85.55, 98.26, 115.61, 144.96, 161.96, 172.57. HRMS (EI): m/z [M$^+$] calcd for $C_4H_9N_2O_2$: 150.0434; found: 150.0432.

4.2.3 | 5-Bromo-4-hydroxxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (2c)

White solid, yield: 85%, mp 248°C to 250°C. IR ν_{max} = 3423 (OH), 2208 (CN), 1611 (C═O), 1569-1502 (—CH═CH—) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.32 (s, 1H, Ar-H), 8.64 (s, 1H, NH), 10.02 (s, 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 83.21, 102.85, 121.04, 135.25, 165.31, 174.24. HRMS (EI): calcd for $C_6H_3N_2O_2$ Br [M$^+$] 213.9378; found: 213.9380.

4.2.4 | 5-Bromo-4-hydroxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (2d)

White solid, yield: 87%, mp 246°C to 248°C. IR ν_{max} = 3426 (OH), 2218 (CN), 1723 (C═O), 1534-1467 (—CH═CH—), 1356 (CH_3)cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.36 (s, 3H, NCH_3), 8.31 (s, 1H, Ar-H), 9.69 (s, 1H, OH); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 36.79, 86.86, 92.33, 115.73, 144.99, 161.37, 168.86. HRMS (EI): m/z [M$^+$] calcd for $C_6H_3N_2O_2$ Br: 227.9534; found: 227.9529.

4.2.5 | 1-*N*-Butyl-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (2e)

White solid, yield: 93%, mp 185°C to 187°C. IR ν_{max} = 3241 (OH), 2244 (CN), 1645 (C═O), 1594-1485 (—CH═CH—), 1441 (CH_2), 1392 (CH_3) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.89 (t, J = 8.0 Hz, 2H); 1.24 (p, J = 8.0 Hz, 1H), 1.56 (p, J = 8.0 Hz, 1H), 3.82(t, J = 7.2 Hz, 1H), 6.05(d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 12.66 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ =

14.01, 19.58, 31.18, 48.44, 85.76, 98.41, 115.60, 144.33, 161.52, 172.41. MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{12}N_2O_2$: 193.0972; found: 193.0975.

4.2.6 | 1-(4-Benzyl)-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (2f)

White solid, yield: 92%, mp 227°C to 229°C. IR ν_{max} = 3436 (OH), 3065 (=C—H aromtic), 2212 (CN), 1643 (C=O), 1595-1520 (—CH=CH—), 1452 (CH_2), 1356 (CH_3) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 5.05 (s, 2H, CH_2), 6.09 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.26-7.29 (m, 5H, Ar-H), 7.95 (d, *J* = 8.0 Hz, 1H, Ar-H), 12.78 (s, 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 51.40, 83.53, 99.06, 115.62, 128.10, 129.10, 129.14, 137.60, 144.48, 161.82, 172.97. HRMS (EI): *m/z* $[M^+]$ calcd for $C_{13}H_{10}N_2O_2$: 226.0744; found: 226.0742.

4.2.7 | 4-Hydroxy-1-(4-methoxybenzyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2g)

White solid, yield: 86%, mp 238°C to 240°C. IR ν_{max} = 3437 (OH), 2922-2843 (=C—H aromtic), 2210 (CN), 1629 (C=O), 1587-1508 (—CH=CH—), 1440 (CH_2), 1345 (CH_3) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.73 (s, 3H, OCH_3), 4.97 (s, 2H, CH_2), 6.07 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.90 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.24 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.93(d, *J* = 8.0 Hz, 1H, Ar-H), 12.74 (s, 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 50.79, 55.58, 85.89, 98.91, 114.47, 115.48, 129.24, 129.84, 144.14, 159.31, 161.55, 172.57. HRMS (EI): m/z $[M^+]$ calcd for $C_{14}H_{12}N_2O_3$: 256.0848; found: 256.0852.

4.2.8 | 4-Hydroxy-1-(4-nitrobenzyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2h)

White solid, yield: 89%, mp 252°C to 254°C. IR ν_{max} = 3429 (OH), 3075-2858 (=C—H aromtic), 2218 (CN), 1645 (C=O), 1519-1482 (—CH=CH—), 1388 (CH_2) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 5.20 (s, 2H, CH_2), 6.14 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.49 (d, *J* = 8.0 Hz, 2H, Ar-H), 8.01 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.23 (*d*, *J* = 8.0 Hz, 2H, Ar-H), 12.91 (s, 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 51.18, 86.04, 99.46, 115.37, 124.21, 129.02, 144.44, 145.01, 147.36, 161.59, 173.07. HRMS (EI): *m/z* $[M^+]$ calcd for $C_{13}H_9N_3O_4$: 271.0593; found: 271.0592.

4.2.9 | Ethyl 2-(3-cyano-4-hydroxy-2-oxopyridin-1(2*H*)-yl)acetate (2i)

White solid, yield: 90%, mp 210°C to 212°C. IR ν_{max} = 1726 (C=O), 1650(C=O), 1560-1476 (—CH=CH—), 1392 (CH_2), 1375 (CH_3) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 1.21 (t, *J* = 8.0 Hz, 3H, CH_3), 4.14 (q, *J* = 8.0 Hz, 2H, CH_2), 4.66 (s, 2H, CH_2), 6.12 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.82 (d, *J* = 8.0 Hz, 1H, Ar-H), 12.91 (s, 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 13.98, 49.54, 61.12, 85.00, 98.43, 114.73, 144.32, 161.02, 167.81, 172.73. MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{110}N_2O_4$: 223.0713; found: 223.0712.

4.2.10 | 4-Hydroxy-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydropyridine-3-carbonitrile (2j)

White solid, yield: 84%, mp 271°C to 273°C.IR ν_{max} = 1687 (C=O), 1658 (C=O), 1565-1472 (—CH=CH—), 1393 (CH_2), 1339 (CH_3) cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 5.49 (s, 2H, CH_2), 6.17 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.73 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.81 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.05 (d, *J* = 8.0 Hz, 2H, Ar-H), 12.89 (s, 1H, OH). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 54.95, 85.57, 98.80, 115.43, 128.48, 129.48, 134.63, 134.75, 145.19, 161.56, 173.12, 193.23. MS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{10}N_2O_3$: 255.0764; found: 255.0766.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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