Thioacetamide as an Ammonium Source for Multicomponent Synthesis of Pyridines from Aldehydes and Electron-Deficient Enamines or Alkynes

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Abstract: A generally applicable multicomponent method has been established for the synthesis of pyridines. In the reactions, thioacetamide is used as a cheap and efficient ammonium source in a multicomponent reaction with aldehydes and electron-deficient enamines or alkynes to give 3,4,5-trisubstituted pyridines in moderate to good yields and with a high product diversity.

Key words: multicomponent reactions, ring closure, pyridines, aldehydes, enamines, alkynes

The pyridine ring is a fundamental fragment of numerous organic molecules. This moiety is widely present as a central structure in many natural products, pharmaceuticals, pesticides, and functional materials.[1] As the most widely available heterocyclic compounds, pyridines have a rich and versatile synthetic utility. For example, pyridines are frequently used as alkali catalysts or additives in many organic reactions, and they are also important ligands in coordination chemistry.[2] More notably, as easily available starting materials, pyridines have been used as central building blocks in syntheses of numerous nitrogen-containing organic molecules.[3] As a result, the synthesis of pyridines has received a great deal of attention during recent decades.

The Hantzsch reaction, which involves the condensation and stepwise oxidation of aldehydes, 1,3-dicarbonyl methylene compounds, and ammonia, was one of the earliest methods used for the synthesis of pyridines.[4] Subsequently, a variety of other methods were devised to increase the synthetic efficiency and diversity of pyridine products. Typical examples of these methods include transition-metal-catalyzed [2+2+2] cycloaddition reactions involving two alkynes and one nitrile;[5] condensation reactions of enaminones, 1,3-dicarbonyl compounds, and ammonium ions;[6] and the Kröhnke two-step procedure using *N*-phenylacylpyridinium salts, enones, and ammonium ions.[7] In the wake of the rapid advance in new synthetic strategies, various novel protocols involving transformation patterns have also been developed to provide pyridine derivatives with an extended range of structural diversity.[8]

The main advantage of conventional methods, such as the Hantzsch and similar reactions,[9] is the ready availability of the starting materials. However, the requirement for an additional oxidation operation and the presence of 1,4-dihydropyridine byproducts have hindered the widespread application of these methods. In this context, the design of simpler routes that combine the advantages of readily available starting materials, one-pot operation, and high selectivity to give target pyridines is highly desirable. In continuation of our longstanding interest in exploring enaminone-based multicomponent reactions (MCRs) for synthesis of structurally diverse heterocycles,[10] we discovered an unexpected multicomponent protocol in which thioacetamide (ethanethioamide) acts as an ammonium source to permit direct one-step synthesis of pyridines from enaminones and aldehydes in the presence of cerium(IV) ammonium nitrate (CAN).[11] To the best of our knowledge, this is the first example of the use of thioacetamide as a source of ammonium for multicomponent pyridine synthesis.

Initially, we surmised that a three-component reaction of enaminone **1a**, 4-chlorobenzaldehyde (**2a**), and thioacetamide (**3a**) might give the 1,3-thiazine **4a** by making use of both the nucleophilic nitrogen and sulfur sites in thioacetamide (**3a**). Unexpectedly, however, when we performed the reaction in dimethyl sulfoxide in the presence of CAN at 90 °C, we did not obtain the expected product; instead, pyridine **5a** was the only isolable product (Scheme 1). This unprecedented result inspired us to investigate this reaction in more detail, not only for its potential use in the synthesis of pyridines, but also because of the significance of discovering alternative nitrogen sources with novel functions for the construction of nitrogen-containing molecules.[12]

Guided by our primary result (Table 1, entry 1), we performed a control experiment to confirm that thioacetamide (**3a**) was indeed the source of ammonium. In the absence of thioacetamide (**3a**) (entry 2), no target product **5a** was obtained, clearly suggesting that **3a** was the source of ammonium for the formation of **5a**. Subsequently, we

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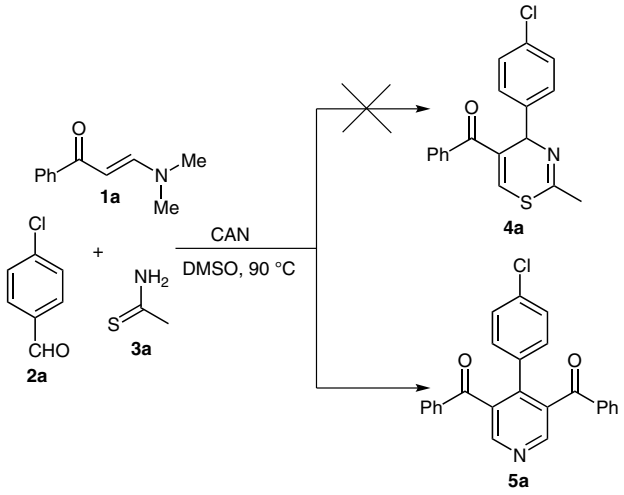


Scheme 1 Unexpected synthesis of pyridines

systematically screened various reaction parameters, including the catalyst, the solvent, and the temperature. Various Lewis and Brønsted acids and basic morpholine all displayed poor activities in catalyzing the reaction (entries 3–6). The uniquely catalytic efficiency of CAN in this reaction might be attributed to the polyfunctional behavior of CAN as a Lewis acid, a Brønsted acid, and an oxidant.[11] Having established that CAN is the optimal catalyst, we studied the effects of various amounts of CAN and found that a 50 mol% loading was optimal (entries 7 and 8). A subsequent study on the effects of the reaction temperature showed that a temperature at 110 °C gave a slightly better yield of pyridine **5a** (entry 9); further lowering of the temperature to 100 °C, however, led to a sharp decrease in the yield (entry 10). Finally, studies with *N*,*N*-dimethylformamide, benzyl alcohol, 1,4-dioxane, toluene, acetonitrile, or ethanol as the solvent confirmed that dimethyl sulfoxide is the best solvent for the reaction (entries 11–16). Additionally, replacement of CAN by cerium(III) chloride gave a 12% yield of **5a**, suggesting that CAN is a particularly effective cerium catalyst for the reaction (entry 17).

By using the optimized protocol, we examined the reactions of various aldehydes with enaminones or enaminonitriles. The reaction showed a broad scope in the synthesis of 3,4,5-trisubstituted pyridines and tolerated a variety of substrates bearing diverse functional groups, including alkyl, alkoxy, halo, cyano, and hetaryl groups (Table 1, entries 1–13). The electronic properties of the enamine **1** or aldehyde **2** displayed no obvious effects on the yield of the corresponding product. However, some aldehydes containing an electron-withdrawing group underwent the transformation more smoothly and gave the corresponding pyridines **5j**, **5m**, and **5n** in relatively higher yields (Table 2, entries 10, 13, and 14, respectively). Another noteworthy point was that enaminonitriles, as alternative building blocks, also reacted with aldehydes and thioacetamide, to give the corresponding 3,5-dicyanopyridines (**5i**–**n**) efficiently and in moderate to good yields (Table 2, entries 9–14).

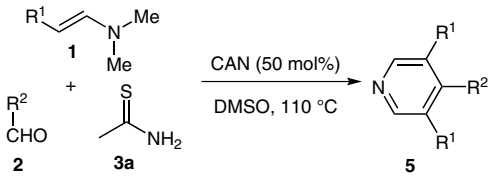
Table 1 Optimization of Reaction Conditions[a]

Entry	Catalyst	Solvent	T (°C)	Yield[b] (%)
1	CAN	DMSO	120	58
2	–	DMSO	120	–[c]
3	$FeCl_3$	DMSO	120	15
4	$AlCl_3$	DMSO	120	11
5	TsOH	DMSO	120	21
6	morpholine	DMSO	120	trace
7[d]	CAN	DMSO	120	55
8[e]	CAN	DMSO	120	24
9	CAN	DMSO	110	67
10	CAN	DMSO	100	27
11	CAN	DMF	110	21
12	CAN	BnOH	110	24
13	CAN	1,4-dioxane	reflux	45
14	CAN	toluene	110	37
15	CAN	MeCN	reflux	trace
16	CAN	EtOH	reflux	trace
17	$CeCl_3$	DMSO	110	12

[a] Reaction conditions: enamine **1a** (0.5 mmol), aldehyde **2a** (0.3 mmol), thioacetamide (**3a**; 0.3 mmol), catalyst (50 mol%), solvent (2 mL), 12 h, stirring (unless otherwise specified).
[b] Yield of isolated product based on enamine **1a**.
[c] No reaction.
[d] CAN (70 mol%).
[e] CAN (30 mol%).

The general applicability of the electron-deficient enamine-based pyridine synthesis inspired us to further expand the synthetic application of the catalytic method by employing electron-deficient alkynes directly as alternative building blocks. Our previous experience suggested that electron-deficient alkynes might be efficiently activated by a secondary amine through rapid formation of electron-deficient enamine intermediate.[13] Piperazine was therefore used to promote the reaction. To our delight, the conditions smoothly gave the pyridines **7**, as expected (Table 3). Electron-deficient alkynes **6** reacted with a variety of aldehydes **2** and thioacetamide (**3a**) to give the corresponding pyridines containing 3,5-dicarboxylate fragments (Table 3, entries 1–13). The yields of the products were determined mainly by the electronic properties of the aldehyde component. Aryl aldehydes containing electron-withdrawing groups generally gave higher yields than those containing electron-donating groups (entries 1–5, 8–11). The alkyne-based synthesis of pyridines, in combination with the enaminone/enaminonitrile-based synthe-

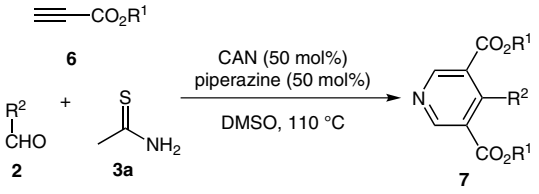
Table 2 Electron-Deficient Enamine-Based Multicomponent Synthesis of Pyridines[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	PhCO	4-ClC_6H_4	**5a**	67
2	PhCO	2-ClC_6H_4	**5b**	57
3	PhCO	2-furyl	**5c**	65
4	4-TolCO	2-BrC_6H_4	**5d**	63
5	4-TolCO	3-$MeOC_6H_4$	**5e**	57
6	4-BrC_6H_4CO	4-ClC_6H_4	**5f**	53
7	3-$MeOC_6H_4CO$	4-ClC_6H_4	**5g**	67
8	4-$F_3CC_6H_4CO$	4-ClC_6H_4	**5h**	56
9	CN	3-$MeOC_6H_4$	**5i**	63
10	CN	4-ClC_6H_4	**5j**	71
11	CN	4-Tol	**5k**	69
12	CN	4-$MeOC_6H_4$	**5l**	67
13	CN	2-ClC_6H_4	**5m**	88
14	CN	4-BrC_6H_4	**5n**	73

[a] Reaction conditions: enamine **1** (0.5 mmol), aldehyde **2** (0.3 mmol), thioacetamide (**3a**; 0.3 mmol), CAN (50 mol%), DMSO (2 mL), 110 °C, 12 h, stirring.
[b] Yield of isolated products based on enamine **1**.

Table 3 Electron-Deficient Alkyne-Based Synthesis of Pyridines[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	Me	4-ClC_6H_4	**7a**	57
2	Me	4-Tol	**7b**	48
3	Me	4-BrC_6H_4	**7c**	55
4	Me	3-$MeOC_6H_4$	**7d**	51
5	Me	4-$O_2NC_6H_4$	**7e**	58
6	Me	2,4-$Cl_2C_6H_3$	**7f**	51
7	Me	2-ClC_6H_4	**7g**	46
8	Et	4-ClC_6H_4	**7h**	66
9	Et	4-Tol	**7i**	52
10	Et	4-BrC_6H_4	**7j**	53
11	Et	4-$O_2NC_6H_4$	**7k**	65
12	Et	3-$O_2NC_6H_4$	**7l**	61
13	Et	Ph	**7m**	52

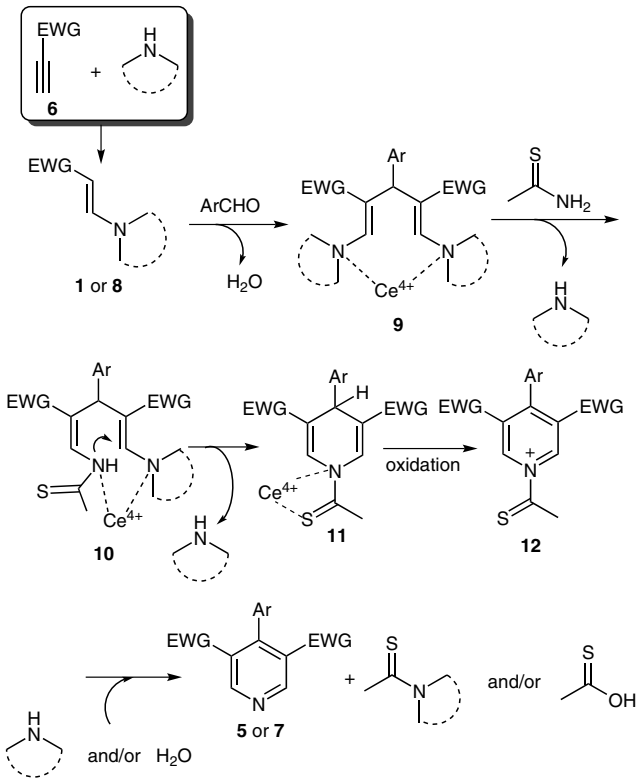
[a] Reaction conditions: alkynoate **6** (0.5 mmol), aldehyde **2** (0.3 mmol), thioacetamide (**3a**; 0.3 mmol), CAN (50 mol%), piperazine (50 mol%), DMSO (2 mL), 110 °C, 12 h, stirring.
[b] Yield of isolated product based on alkynoate **6**.

sis of pyridines **5**, demonstrated the genuinely broad range of applicability of our thioacetamide-initiated multicomponent method for pyridine synthesis. However, when an aliphatic aldehyde such as propanal was used as the aldehyde component, no product **7** containing a 4-alkyl substituent was obtained.

On the basis of the results from the synthesis of pyridines with thioacetamide, we propose the plausible reaction mechanism shown in Scheme 2. The reaction proceeds by a domino transformation consisting of enamine-based homocondensation, thioacetamide-initiated transamination, and cerium-promoted elimination–aromatization. First, the electron-deficient enamine **1** or **8**, as either a starting material or an intermediate formed in situ,[13] reacts with the aldehyde to give complex **9**. The cerium ion promotes transamination of **9** with thioacetamide to give the intermediate **10**. Intramolecular transamination of **10** gives the N-protected 1,4-dihydropyridine **11**. In the presence of CAN as an oxidant, **11** undergoes oxidative aromatization to form the thioacetylpyridinium salt **12**. Finally, the thioacetyl cation in **12** is removed by rapid incorporation of a secondary amine and/or water, present in the reaction system, to give the pyridine **5** or **7**.

In conclusion, by employing conventional aldehydes and electron-deficient enamines or alkynes as the main building blocks, we have, for the first time, achieved a direct one-step synthesis of pyridines by using thioacetamide as an ammonium source and CAN as a catalyst. Compared with known two-step methods that use other ammonium sources such as ammonium acetate, our protocol has the advantages of a simpler one-step operation and a much broader tolerance to various substrates. Our reaction therefore provides a new route for the synthesis of structurally diverse pyridines.

All chemicals were purchased from J & K or Energy Chemical Co., Ltd. and used directly. Enaminones **1** were synthesized following a literature procedure.[14] Melting points were determined on an X-4A apparatus and are uncorrected. IR spectra were recorded on a Nicolet 6700 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts (δ) are reported relative to TMS as an internal standard. Mass spectra were recorded on a Bruker micrOTOF-QII QTOF mass spectrometer operated in the ESI mode.



Scheme 2 Proposed reaction mechanism

3,4,5-Trisubstituted Pyridines 5; General Procedure

A 10 mL flask equipped with a stirrer bar was charged with enamine **1** (0.5 mmol), aldehyde **2** (0.3 mmol), thioacetamide (**3a**; 0.3 mmol), CAN (0.125 mmol), and DMSO (2 mL). The mixture was then stirred at 110 °C for 12 h. When the reaction was complete (TLC), H_2O (5 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The organic phases were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was subjected to preparative TLC (EtOAc–PE, 1:4).

[4-(4-Chlorophenyl)pyridine-3,5-diyl]bis(phenylmethanone) (5a)

White solid; yield: 66 mg (67%); mp 131–133 °C.

IR (KBr): 3050, 3030, 1665, 750, 730 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.84 (s, 2 H), 7.61 (d, *J* = 7.6 Hz, 4 H), 7.50 (t, *J* = 7.2 Hz, 2 H), 7.34 (t, *J* = 7.6 Hz, 4 H), 7.00 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.4, 149.9, 145.6, 136.5, 135.3, 135.0, 133.9, 133.2, 130.5, 129.7, 128.6, 128.5.

ESI-MS: *m*/*z* = 398 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{17}ClNO_2$: 398.0948; found: 398.0950.

[4-(2-Chlorophenyl)pyridine-3,5-diyl]bis(phenylmethanone) (5b)

White solid; yield: 57 mg (57%); mp 182–183 °C.

IR (KBr): 3045, 3031, 1667, 745, 720 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.85 (s, 2 H), 7.63 (d, *J* = 7.2 Hz, 4 H), 7.44 (t, *J* = 7.2 Hz, 2 H), 7.30 (t, *J* = 7.6 Hz, 4 H), 7.08 (d, *J* = 7.6 Hz, 1 H), 7.01–6.94 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 150.9, 145.4, 136.4, 135.3, 133.8, 133.6, 131.9, 131.5, 130.0, 129.8, 129.3, 128.4, 126.6.

ESI-MS: *m*/*z* = 398 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{17}ClNO_2$: 398.0948; found: 398.0949.

[4-(2-Furyl)pyridine-3,5-diyl]bis(phenylmethanone) (5c)

Brown solid; yield: 57 mg (65%); mp 138–139 °C.

IR (KBr): 3035, 3021, 1670, 1392, 720 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.79 (s, 2 H), 7.71 (d, *J* = 7.6 Hz, 4 H), 7.52 (d, *J* = 7.2 Hz, 2 H), 7.37 (t, *J* = 7.6 Hz, 4 H), 7.05 (s, 1 H), 6.39 (d, *J* = 3.2 Hz, 1 H), 6.05 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6, 150.0, 146.3, 144.5, 136.2, 134.1, 133.8, 132.5, 129.5, 128.6, 115.2, 112.2.

ESI-MS: *m*/*z* = 354 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{16}NO_3$: 354.1130; found: 354.1125.

[4-(2-Bromophenyl)pyridine-3,5-diyl]bis[(4-tolyl)methanone] (5d)

Pale-yellow solid; yield: 74 mg (63%); mp 161–164 °C.

IR (KBr): 3035, 3021, 1661, 720, 550 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 8.80 (s, 2 H), 7.59 (d, *J* = 7.6 Hz, 4 H), 7.19 (d, *J* = 7.2 Hz, 1 H), 7.13–7.06 (m, 6 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 2.31 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.0, 150.7, 147.0, 144.7, 135.7, 135.4, 133.9, 132.4, 131.6, 130.3, 129.9, 129.1, 126.9, 122.1, 21.6.

ESI-MS: *m*/*z* = 470 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{21}BrNO_2$: 470.0756; found: 470.0744.

[4-(3-Methoxyphenyl)pyridine-3,5-diyl]bis[(4-tolyl)methanone] (5e)

White solid; yield: 60 mg (57%); mp 163–165 °C.

IR (KBr): 3038, 3027, 1661, 1185, 720 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.79 (s, 2 H), 7.54 (d, *J* = 7.6 Hz, 4 H), 7.11 (d, *J* = 8.0 Hz, 4 H), 6.92 (t, *J* = 8.0 Hz, 1 H), 6.66 (d, *J* = 7.6 Hz, 1 H), 6.62 (s, 1 H), 6.55 (d, *J* = 8.8 Hz, 1 H), 3.53 (s, 3 H), 2.34 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.3, 159.0, 149.3, 146.4, 144.8, 136.1, 135.6, 134.1, 130.0, 129.4, 129.1, 121.8, 115.2, 114.3, 55.1, 21.7.

ESI-MS: *m*/*z* = 422 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{24}NO_3$: 422.1756; found: 422.1768.

[4-(4-Chlorophenyl)pyridine-3,5-diyl]bis[(4-bromophenyl)methanone] (5f)

Orange solid; yield: 73 mg (53%); mp 188–191 °C.

IR (KBr): 3038, 3027, 1670, 723, 565 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.83 (s, 2 H), 7.50–7.45 (m, 8 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 6.98 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 150.0, 145.3, 135.5, 135.0, 134.8, 132.9, 132.0, 131.1, 130.4, 129.6, 128.9.

ESI-MS: *m*/*z* = 554 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{15}Br_2ClNO_2$: 553.9153; found: 553.9150.

[4-(4-Chlorophenyl)pyridine-3,5-diyl]bis[(3-methoxyphenyl)methanone] (5g)

Orange solid; yield: 77 mg (67%); mp 118–121 °C.

IR (KBr): 3041, 3021, 1657, 1225, 724 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.82 (s, 2 H), 7.25 (t, *J* = 8.0 Hz, 4 H), 7.13 (d, *J* = 7.6 Hz, 2 H), 7.08–7.03 (m, 6 H), 3.79 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 159.7, 149.8, 145.7, 137.9, 135.3, 135.0, 133.3, 130.5, 129.6, 128.6, 123.1, 120.1, 113.4, 55.5.

ESI-MS: *m*/*z* = 458 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{21}ClNO_4$: 458.1159; found: 458.1161.

[4-(4-Chlorophenyl)pyridine-3,5-diyl]bis{[4-(trifluoromethyl)phenyl]methanone} (5h)
Pale-yellow solid; yield: 75 mg (56%); mp 125–129 °C.

IR (KBr): 3033, 3018, 1660, 1395, 724 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.90 (s, 2 H), 7.69 (d, *J* = 8.4 Hz, 4 H), 7.59 (d, *J* = 8.0 Hz, 4 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 150.4, 145.7, 139.0, 135.8, 135.2, 134.6, 132.7, 130.5, 129.9, 128.9, 125.6 (d, *J* = 3.6 Hz), 121.9.

ESI-MS: *m*/*z* = 534 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{15}ClF_6NO_2$: 534.0696; found: 534.0699.

4-(3-Methoxyphenyl)pyridine-3,5-dicarbonitrile (5i)
Pale-yellow solid; yield: 37 mg (63%); mp 173–174 °C.

IR (KBr): 3033, 3018, 2230, 1215, 731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.09 (s, 2 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.15 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 2 H), 7.09–7.08 (m, 1 H), 3.89 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 156.0, 155.3, 132.8, 130.8, 121.0, 117.5, 114.7, 114.1, 110.7, 55.2.

ESI-MS: *m*/*z* = 236 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}N_3O$: 236.0824; found: 236.0825.

4-(4-Chlorophenyl)pyridine-3,5-dicarbonitrile (5j)
Pale-yellow solid; yield: 42 mg (71%); mp 157–160 °C.

IR (KBr): 3039, 3022, 2238, 755, 726 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 2 H), 7.61 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 154.2, 138.4, 130.2, 129.9, 129.8, 114.5, 110.6.

ESI-MS: *m*/*z* = 240 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_7ClN_3$: 240.0328; found: 240.0332.

4-(4-Tolyl)pyridine-3,5-dicarbonitrile (5k)
Pale-yellow solid; yield: 38 mg (69%); mp 129–132 °C.

IR (KBr): 3029, 3018, 2870, 2218, 715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.07 (s, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 2.47 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 155.6, 142.4, 130.1, 128.8, 114.9, 110.6, 21.6.

ESI-MS: *m*/*z* = 220 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}N_3$: 220.0875; found: 220.0879.

4-(4-Methoxyphenyl)pyridine-3,5-dicarbonitrile (5l)
Pale-yellow solid; yield: 39 mg (67%); mp 168–170 °C.

IR (KBr): 3035, 3028, 2875, 1218, 735 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.05 (s, 2 H), 7.59 (d, *J* = 8.8 Hz, 2 H), 7.11 (d, *J* = 8.8 Hz, 2 H), 3.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 156.2, 155.1, 130.7, 123.7, 115.1, 114.9, 110.4, 55.6.

ESI-MS: *m*/*z* = 236 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}N_3O$: 236.0824; found: 236.0824.

4-(2-Chlorophenyl)pyridine-3,5-dicarbonitrile (5m)
Pale-yellow solid; yield: 53 mg (88%); mp 119–122 °C.

IR (KBr): 3029, 3014, 2243, 730, 716 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 2 H), 7.64 (d, *J* = 8.0 Hz, 1 H) 7.58 (t, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 7.2 Hz, 1 H), 7.36 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 153.7, 132.6, 132.3, 131.2, 130.7, 130.0, 127.8, 113.9, 112.0.

ESI-MS: *m*/*z* = 240 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_7ClN_3$: 240.0328; found: 240.0323.

4-(4-Bromophenyl)pyridine-3,5-dicarbonitrile (5n)
Pale-yellow solid; yield: 52 mg (73%); mp 153–156 °C.

IR (KBr): 3031, 3023, 2233, 720, 570 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 2 H), 7.77 (d, *J* = 7.6 Hz, 2 H), 7.47 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 154.3, 132.9, 130.4, 130.3, 126.8, 114.5, 110.5.

ESI-MS: *m*/*z* = 284 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_7BrN_3$: 283.9823; found: 283.9818.

4-Substituted Pyridine-3,5-dicarboxylates 7; General Procedure
A 10 mL flask equipped with a stirrer bar was charged with alkynoate **6** (0.5 mmol), aldehyde **2** (0.3 mmol), thioacetamide (**3**; 0.3 mmol), CAN (0.125 mmol), piperazine (0.125 mmol), and DMSO (2 mL). The mixture was stirred at 110 °C for 12 h until the reaction was complete (TLC). Workup was identical to that for the 3,4,5-trisubstituted pyridines **5**.

Dimethyl 4-(4-Chlorophenyl)pyridine-3,5-dicarboxylate (7a)
Orange solid; yield: 43 mg (57%); mp 107–109 °C.

IR (KBr): 3061, 1730, 880, 810, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.12 (s, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 3.70 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 152.8, 148.8, 134.9, 134.6, 129.0, 128.1, 127.6, 52.5.

ESI-MS: *m*/*z* = 306 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}ClNO_4$: 306.0533; found: 306.0528.

Dimethyl 4-(4-Tolyl)pyridine-3,5-dicarboxylate (7b)
Orange solid; yield: 34 mg (48%); mp 121–122 °C.

IR (KBr): 3051, 2915, 1719, 860, 735 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (s, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 7.6 Hz, 2 H), 3.66 (s, 6 H), 2.40 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 152.1, 150.0, 138.3, 133.3, 128.7, 128.2, 127.5, 52.5, 21.4.

ESI-MS: *m*/*z* = 286 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{16}NO_4$: 286.1079; found: 286.1080.

Dimethyl 4-(4-Bromophenyl)pyridine-3,5-dicarboxylate (7c)
Orange solid; yield: 48 mg (55%); mp 113–115 °C.

IR (KBr): 3066, 1719, 855, 745, 588 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 2 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 3.68 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 152.6, 149.1, 135.3, 131.1, 129.3, 127.6, 122.8, 52.5.

ESI-MS: *m*/*z* = 350 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}BrNO_4$: 350.0028; found: 350.0026.

Dimethyl 4-(3-Methoxyphenyl)pyridine-3,5-dicarboxylate (7d)
Orange solid; yield: 38 mg (51%); mp 105–107 °C.

IR (KBr): 3055, 1728, 1090, 810, 715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.07 (s, 2 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 7.6 Hz, 1 H), 6.78 (d, *J* = 7.6 Hz, 1 H), 6.74 (s, 1 H), 3.81 (s, 3 H), 3.66 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 159.2, 152.2, 149.5, 137.7, 129.1, 127.9, 120.1, 113.9, 113.5, 55.2, 52.3.

ESI-MS: *m*/*z* = 302 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{16}NO_5$: 302.1028; found: 302.1023.

Dimethyl 4-(4-Nitrophenyl)pyridine-3,5-dicarboxylate (7e)
Orange solid; yield: 46 mg (58%); mp 192–194 °C.

IR (KBr): 3070, 1730, 1535, 840, 720 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 2 H), 8.29 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 3.70 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 153.5, 148.7, 147.5, 143.7, 128.7, 126.7, 123.0, 52.7.

ESI-MS: *m*/*z* = 317 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2O_6$: 317.0774; found: 317.0771.

Dimethyl 4-(2,4-Dichlorophenyl)pyridine-3,5-dicarboxylate (7f)
Orange solid; yield: 43 mg (51%); mp 103–106 °C.

IR (KBr): 3071, 1725, 890, 790, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 2 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.03 (d, *J* = 8.4 Hz, 1 H), 3.73 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 153.9, 147.4, 134.8, 134.5, 132.9, 129.5, 128.9, 128.7, 126.8, 52.8.

ESI-MS: *m*/*z* = 340 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{12}Cl_2NO_4$: 340.0143; found: 340.0142.

Dimethyl 4-(2-Chlorophenyl)pyridine-3,5-dicarboxylate (7g)
Orange oil; yield: 35 mg (46%).

IR (KBr): 3065, 1720, 870, 820, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (s, 2 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.40–7.32 (m, 2 H), 7.10 (d, *J* = 7.2 Hz, 1 H), 3.70 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 153.5, 148.4, 135.9, 132.0, 129.6, 128.9, 128.6, 127.1, 126.3, 52.6.

ESI-MS: *m*/*z* = 306 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}ClNO_4$: 306.0533; found: 306.0528.

Diethyl 4-(4-Chlorophenyl)pyridine-3,5-dicarboxylate (7h)
Pale-yellow solid; yield: 55 mg (66%); mp 72–75 °C.

IR (KBr): 3055, 1725, 890, 815, 735 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 4.11 (q, *J* = 7.2 Hz, 4 H), 1.05 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 152.6, 148.4, 135.3, 134.4, 129.2, 128.0, 127.9, 61.8, 13.7.

ESI-MS: *m*/*z* = 334 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}ClNO_4$: 334.0846; found: 334.0841.

Diethyl 4-(4-Tolylpyridine-3,5-dicarboxylate) (7i)
Orange oil; yield: 41 mg (52%).

IR (KBr): 3061, 2911, 1729, 875, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.97 (s, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 4.01 (q, *J* = 7.2 Hz, 4 H), 2.32 (s, 3 H), 0.94 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 151.9, 149.6, 138.1, 133.6, 130.0, 128.5, 127.7, 61.6, 21.3, 13.6.

ESI-MS: *m*/*z* = 314 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{20}NO_4$: 314.1392; found: 314.1389.

Diethyl 4-(4-Bromophenyl)pyridine-3,5-dicarboxylate (7j)
Orange solid; yield: 50 mg (53%); mp 66–68 °C.

IR (KBr): 3055, 1730, 865, 735, 535 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.12 (s, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 4.11 (q, *J* = 7.2 Hz, 4 H), 1.06 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 152.6, 148.6, 135.8, 131.0, 129.5, 127.9, 122.5, 61.8, 13.7.

ESI-MS: *m*/*z* = 378 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}BrNO_4$: 378.0341; found: 378.0338.

Diethyl 4-(4-Nitrophenyl)pyridine-3,5-dicarboxylate (7k)
Orange solid; yield: 60 mg (65%); mp 81–85 °C.

IR (KBr): 3065, 1721, 1525, 845, 730 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17 (s, 2 H), 8.21 (d, *J* = 8.8 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 4.05 (q, *J* = 7.2 Hz, 4 H), 1.01 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 153.4, 148.1, 147.6, 144.0, 128.9, 126.9, 122.9, 62.0, 13.8.

ESI-MS: *m*/*z* = 345 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_6$: 345.1087; found: 345.1089.

Diethyl 4-(3-Nitrophenyl)pyridine-3,5-dicarboxylate (7l)
Orange solid; yield: 52 mg (61%); mp 80–81 °C.

IR (KBr): 3070, 1725, 1515, 850, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 2 H), 8.19 (d, *J* = 8.0 Hz, 1 H), 8.00 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 5.6 Hz, 1 H), 4.02 (q, *J* = 7.2 Hz, 4 H), 0.96 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 153.4, 147.6, 138.6, 133.9, 128.7, 128.6, 127.2, 123.0, 122.9, 61.9, 13.7.

ESI-MS: *m*/*z* = 345 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_6$: 345.1087; found: 345.1089.

Diethyl 4-Phenylpyridine-3,5-dicarboxylate (7m)
Orange oil; yield: 39 mg (52%).

IR (KBr): 3055, 1715, 855 825, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.08 (s, 2 H), 7.41–7.38 (m, 3 H), 7.21–7.19 (m, 2 H), 4.07 (q, *J* = 7.2 Hz, 4 H), 0.97 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 152.5, 152.2, 152.1, 136.8, 128.3, 127.9, 127.7, 61.6, 13.5.

ESI-MS: *m*/*z* = 300 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{18}NO_4$: 300.1236; found: 300.1230.

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