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Use of the Curtius Rearrangement of Acryloyl Azides in the Synthesis of 3,5-Disubstituted Pyridines: Mechanistic Studies

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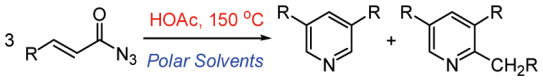

A series of disubstituted pyridine derivatives was synthesized from the corresponding acryloyl azides by acetic acid-promoted cycloaddition. This represents a novel and convenient synthetic approach to the symmetric 3,5-disubstituted pyridines. The nature of the substituent on the double bond and the utilized solvent were found to be crucial to the yield of pyridines. The reactivity of the acid-promoted cycloaddition increases with the presence of aryl groups, such as phenyl and pyridinyl. We also explored the comprehensive mechanism by the acid-promoted cycloaddition of ^{13}C-labeled cinnamoyl azide. The symmetric 3,5-disubstituted pyridines were synthesized from acryloyl azides by acetic acid-promoted trimolecular condensation.

Introduction

Many natural products and synthetic compounds containing the pyridine ring system display various pharmacological activities.[1] The methodologies for the synthesis of pyridine derivatives are an important research area in both medicinal and synthetic chemistry.[2] Among pyridine derivatives, Sch-21418, a 3,5-bis(4-hydroxyphenyl)pyridine, showed good inhibitory activity against inflammatory factors (e.g., interleukin-6),[3] and the bis-imidiazolyl pyridine **1** also demonstrated moderate anti-HIV-1 activity as well as toxicity against *Pneumonocystis carinii* in the immunosuppressed rat model.[4] In addition, dipyridinyl compound **2** was reported to represent a suitable substance with an inhibitory effect on the cortex of the adrenal gland.[5] Some of the 3,5-disubstituted pyridines displayed significant antimicrobial activity.[6] The extensive range of pharmacological properties that 3,5-substituted pyridines displayed had drawn the attention of chemists. Different methods have been utilized to access 3,5-disubstituted pyridines. These are Chichibabin-type condensation,[7] cross-Mannich reaction,[8] cycloadditions of azadienes with enamines,[9] and the palladium-catalyzed Suzuki–Miyaura coupling reaction from 3,5-dihalopyridines.[10] In this paper, we report an inexpensive and air/moisture-insensitive

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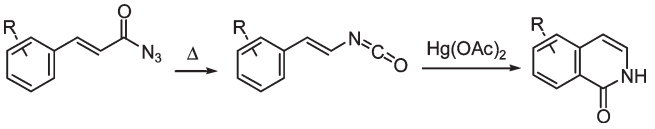
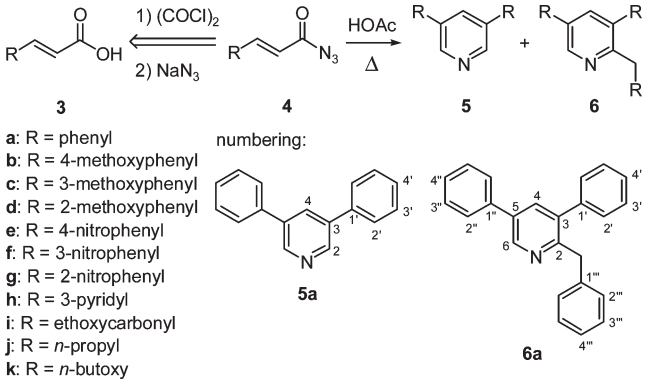
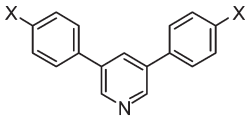
SCHEME 1. Synthesis of Isoquinolinones



SCHEME 2. Acid-Promoted Cycloaddition of Acryloyl Azides 4



synthetic approach to the symmetrical 3,5-disubstituted pyridines by thermal cycloaddition of acryloyl azides in acid solution. We also discuss the detailed mechanism, using ^{13}C-labeled cinnamoyl azide. This is the first time acid-promoted thermal cycloaddition of acryloyl azide has been studied.



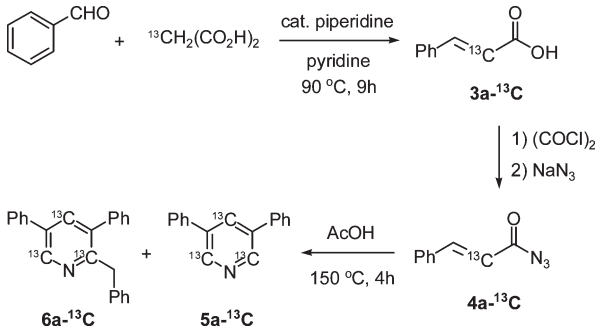
X = OH, **Sch-21418**
X = 4,5-dihydro-1*H*-imidazol-2-yl, **1**
X = β-(3-pyridyl)acryloyl, **2**

Results and Discussion

Previously, we reported that cinnamoyl azides in refluxing *o*-dichlorobenzene could undergo Curtius rearrangement to form the corresponding isocyanates and subsequent $Hg(OAc)_2$-catalyzed cyclization afforded isoquinolinones (Scheme 1).[11]

Intriguingly, refluxing a solution of (*E*)-cinnamoyl azide **4a** in acetic acid for 4 h gave rise to two pyridine derivatives. The products were identified as 3,5-diphenylpyridine **5a** and 2-benzyl-3,5-diphenylpyridine **6a**. These were obtained in a yield of 36% and 8%, respectively, by comparing their physical data with those from the literature.[12] No isoquinolinone was obtained (Scheme 2). The complete assignments of the ^1H and ^{13}C NMR signals of these two pyridines (**5a** and **6a**) were easily obtained from the 2D-NMR spectra, using techniques such as COSY, HMQC, HMBC, and NOESY. In the case of **5a**, protons of the phenyl groups were assigned by the COSY correlations. The remaining two mutually coupled aromatic signals at δ 8.05 (1H, t, J = 2.2 Hz) and 8.83 (2H, d, J = 2.2 Hz) were assigned to H-4 and the two protons at H-2 and H-6, respectively. They showed a HMBC correlation with the quaternary carbons C-1′ (δ 137.8) of phenyl rings and NOE correlation with the ortho protons H-2′ (δ 7.65) of the phenyl rings, suggesting that **5a** was 3,5-diphenylpyridine. However, for **6a**, the ^1H NMR signals between δ 7.05 and 7.61 came from three phenyl moieties. Two doublets at δ 7.75 and 8.83 (J = 2.0 Hz) meta-coupled with each other and were assigned to H-4 and H-6, respectively. The aliphatic region of the ^1H NMR spectrum of **6a** presented a two-proton singlet at δ 4.19 attributed to benzylic protons. From the HMQC correlations, the assignments of hydrogen−carbon bonds were easily achieved. Further, the key HMBC correlations of CH_2 with C-2‴ (δ 128.8) and C-3 (δ 137.3); H-4 with C-1′ (δ 139.6) and C-1″ (δ 137.5); and H-6 with C-1″ and the NOE correlations of CH_2 with H-2′ and H-2‴; H-4 with H-2′ and H-2″; and H-6 with H-2″ confirmed compound **6a** had the structure of 2-benzyl-3,5-diphenylpyridine. Based on the presence of three phenyl rings in **6a**, our preliminary assumption was that the reaction involved a trimolecular condensation mechanism.

SCHEME 3. Insight into the Fate of a ^{13}C-Labeled Cinnamoyl Azide, 4a-^{13}C



To unequivocally establish that the cycloaddition was a trimolecular condensation reaction, a labeled [2-^{13}C]-cinnamoyl azide, **4a-^{13}C**, was synthesized using Knoevenagel condensation between benzaldehyde and [2-^{13}C]malonic acid to form (*E*)-[2-^{13}C]cinnamic acid, **3a-^{13}C**.[13] Chlorination and azide formation,[11] followed by subsequent treatment of a solution of the azide **4a-^{13}C** in HOAc at reflux, produced two labeled pyridines, **5a-^{13}C** and **6a-^{13}C** (Scheme 3). The distribution of ^{13}C in the resulting products was examined. Symmetric **5a-^{13}C** presented ^1H NMR signals similar to those of **5a** except the signals H-2 [δ 8.82 (2H, dddd, J = 165.4, 10.2, 5.5, 2.2 Hz)] and H-4 [δ 8.05 (1H, dtt, J = 159.3, 5.6, 2.2 Hz)] showed ^4J $^1H-^1H$ coupling (2.2 Hz) as well as ^1J and ^3J coupling between ^1H and labeled ^{13}C. In addition, the ^{13}C NMR spectrum displayed two intense peaks for the labeled C-2, C-6 (δ 147.0) and C-4 (δ 132.9). Thus, **5a-^{13}C** had the structure 3,5-diphenyl-[2,4,6-$^{13}C_3$]pyridine. Similarly, compound **6a-^{13}C** also showed two complicated ^1H signals for H-4 [δ 7.74 (1H, dtd, J = 159.7, 6.1, 2.4 Hz)] and H-6 [δ 8.83 (1H, dddd, J = 177.6, 11.2, 5.5, 2.4 Hz)] and three intense ^{13}C peaks for C-2 (δ 156.6), C-4 (δ 136.1), and C-6 (δ 146.7), indicating the structure 2-benzyl-3,5-diphenyl-[2,4,6-$^{13}C_3$]-pyridine. Therefore, from the pattern of incorporation of three ^{13}C units into each product, we drew the conclusion that

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TABLE 1. Formation of Pyridines 5a and 6a from Cinnamoyl Azide 4a

entry	solvent	HOAc (equiv)	temp (°C)	time (h)	product (%) 5a	6a
1	CH_3CO_2H		reflux	4	36	8
2	*o*-dicholrobenzene	10	150	4		5
3	*o*-dicholrobenzene	1.2	150	4		1
4	toluene	10	150[a]	4	15	6
5	toluene	1.2	150[a]	4	8	2
6	DMF	10	150	4	50	2
7	DMF	5	150	4	26	13
8	DMF	1.2	150	4	21	
9	DMSO	10	150	4	62	12
10	DMSO	5	150	4	45	8
11	DMSO	1.2	150	4	40	6
12	DMSO	10	100	4	28	21
13	DMSO	10	150	24	61	4
14	DMSO[b]	10	150	4	25	31

[a]Sealed tube was used. [b]0.5 mL of H_2O was added.

TABLE 2. Thermal Cycloaddition of Acryloyl Azide 4 to Give Pyridine Derivatives 5 and 6[a]

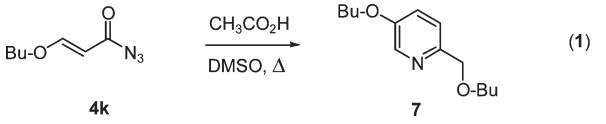
entry	4, R =	product (%)	
1	**4a**, phenyl	**5a** (62)	**6a** (12)
2	**4b**, 4-methoxyphenyl	**5b** (47)	**6b** (6)
3	**4c**, 3-methoxyphenyl	**5c** (58)	**6c** (7)
4	**4d**, 2-methoxyphenyl	**5d** (51)	**6d** (10)
5	**4e**, 4-nitrophenyl	**5e** (48)	
6	**4f**, 3-nitrophenyl	**5f** (66)	
7	**4g**, 2-nitrophenyl	**5g** (58)	
8	**4h**, pyridin-3-yl	**5h** (70)	
9	**4i**, ethoxycarbonyl	**5i** (33)	
10	**4j**, propyl	**5j** (2)	**6j** (21)
11	**4k**, butoxy		**7** (10)[b]

[a]Reaction conditions: acryloyl azides **4** and 10 equiv of HOAc in DMSO at 150 °C for 4 h. [b]2-Butoxymethyl-5-butoxypyridine **7** was obtained, as in eq1

formation of pyridines **5a** and **6a** involved a trimolecular condensation of cinnamoyl azide.

The effects of the reaction conditions on the reaction of **4a** are summarized in Table 1. First, a mixture of the azide **4a** and 1.2 equiv of HOAc in *o*-dichlorobenzene or toluene was heated at 150 °C, and only a few pyridine derivatives were obtained. Even when 10 equiv of HOAc was added, the yield of cycloaddition was not enhanced (entries 2−5). When polar solvents such as DMF and DMSO were used, the pyridine derivatives **5a** and **6a** were obtained in higher yields (entries 6−11). Therefore, the efficiency of cycloaddition depends on the solvent polarity and the amount of acetic acid added. Second, the pyridine derivatives remained intact even after an extended period of 24 h at high temperature (entry 13). In addition, the cycloaddition could proceed under milder temperature conditions (100 °C, entry 12), but was less efficient. Third, when wet DMSO was used as the solvent, the yield of 3,5-diphenylpyridine **5a** decreased and the yield of trisubstituted pyridine **6a** increased (compare entry 14 with entry 9). On the basis of the results above, all of the acid-promoted cycloadditions reported in Table 2 were conducted under the optimum conditions described in entry 9: a solution of the acryloyl azide and 10 equiv of HOAc in DMSO was heated at 150 °C under nitrogen for 4 h.

A series of acryloyl azides **4a**−**k** was obtained from the reactions of acrylic acids **3a**−**k** with oxalyl chloride followed by the addition of sodium azide.[11] The azide product yields were high. The results of one-pot reactions of a DMSO solution containing an acryloyl azide and 10 equiv of HOAc at 150 °C (or 100 °C for entry 12) for 4 h forming the corresponding pyridine derivatives **5** and **6** are shown in Table 2. The acryloyl azides **4b**−**d** with the methoxyphenyl group, an electron-donating substituent on the aromatic ring, produced the disubstituted pyridines **5b**−**d** in moderate yields and trisubstituted pyridines **6b**−**d** in minimum yields, as shown in entries 2−4. In cases of the acryloyl azides **4e**−**g** bearing an electron-deficient aromatic ring, such as the nitrophenyl group, the disubstituted pyridines **5e**−**g** were obtained in good to moderate yields and the production of **6** was inhibited (entries 5−7). The pyridinyl azide **4h** gave the best yield of **5h** (entry 8). However, when 3-(ethoxycarbonyl)-acryloyl azide **4i** and 2-hexenoyl azide **4j** were utilized, instead of the arylacryloyl azides, the cycloadditions were retarded based on the yields of disubstituted pyridines **5i** (33%) and **5j** (2%) as well as the trisubstituted pyridine **6j** (21%), respectively (entries 9 and 10). To our surprise, when the acryloyl azide **4k**, possessing the strong electron-donating group −OBu, directly attached to the terminal double bond, was subjected to the acidic conditions, it was almost impossible to isolate the anticipated pyridines **5k** and **6k**. Only 2-butoxymethyl-5-butoxypyridine **7** was obtained in 10% yield along several complicated irresolvable products (entry 11 and eq 1). Clearly, the reactivity of the acid-promoted cycloadditions of acryloyl azides was increased by the presence of the aryl groups on the double bond.



4k 7 (1)

Mechanistic Study

By carefully examining the crude products obtained from the cycloaddition using cinnamoyl azide **4a** as the starting material, acetamide (68%), and a trace amount of toluene, 4-benzyl-5-phenyl-3,4-dihydro-1*H*-pyrimidin-2-one **8a** and 3,5-diphenylpyridin-2-one **9a** could be isolated along with **5a** (62%) and **6a** (12%). The structures of both **8a** and **9a** were proven by COSY, HMQC, HMBC, and NOESY experiments. Similarly, if 3-nitrocinnamoyl azide **4f** was used, diarylpyridine **5f** (66%), acetamide (60%), and 3-nitrotoluene (5%) were isolated. On the basis of the above results, a complete mechanistic route for the formation of pyridines **5**, **6**, and **7**, pyrimidinone **8**, and pyridinone **9** through an acid-promoted cycloaddition of azides **4** as depicted in Scheme 4 is proposed.

First, the reactant, **4**, underwent Curtius rearrangement to form the isocyanate **10**. Once **10** was formed, the electron-deficient isocyanate facilitated nucleophilic attack by HOAc to give adduct **11**,[14] resulting in a reversible dissociation−recombination process between **10** and **11**. The enamide **11** was supposed to equilibrate with unstable mixed anhydride **12** at high temperature.[15] The preferential product in the equilibrium was believed to be **11**.

Thus, the stepwise addition of isocyanate **10** to the C=C double bond of enamide **11** gave rise to the regiospecific

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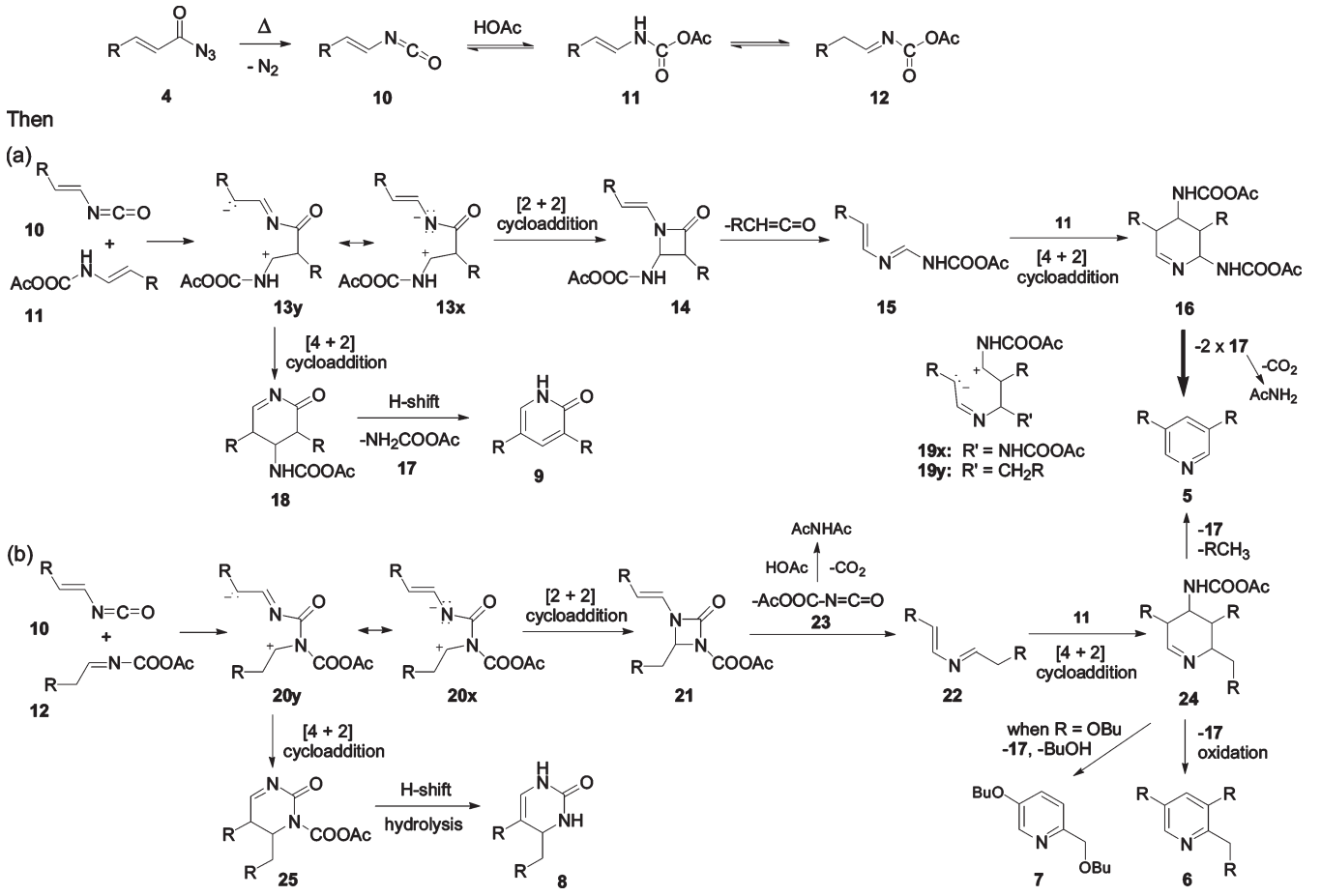
SCHEME 4. Mechanism of Acid-Promoted Cycloaddition of Acryloyl Azide



[2+2] cycloadduct **14** through the zwitterionic intermediate **13** (path a).[16] The reaction proceeded in polar solvents, such as DMSO or DMF, further supporting the existence of the polar **13**. In addition, the [4+2] cycloadduct **18** was also formed with the same intermediate **13**.[16a] Hydrogen-shift as well as loss of acetyl carbamate **17** afforded pyridinone **9**. The isolation of **9a** supported the formation of the [4+2] adduct. The more stable **13x**, with a negative charge on the nitrogen, compared with **13y**, with a negative charge on carbon, led to [2+2] adduct **14**. Subsequently, cycloreversion of **14** formed 2-aza-1,3-butadiene derivative **15** and arylketene. The reaction of **15** and **11** through the polar intermediate **19x** generated a regiospecific [4+2] cycloadduct **16**, which was known to occur under acidic conditions.[9a,17] Finally, tetrahydropyridine **16**, with loss of 2 equiv of **17**, converted into pyridine **5**. The elimination of **17** was ascertained by the isolation of acetamide since it was known that the acetic acid adduct **17** of isocyanic acid (HN=C=O) easily loses CO_2 to form acetamide by heating.[13]

An alternative path to the formation of disubstituted pyridine **5** (path b) was proposed through cycloaddition of the isocyanate **10** to the C=N double bond of mixed anhydride **12**.[16a,18] Both regiospecific [2+2] adduct **21** and [4+2] adduct **25** were similarly generated through the polar intermediate **20**. Hydrogen-shift followed by hydrolysis upon basic workup converted **25** into pyrimidinone **8**. Cycloreversion of **21** formed another 2-aza-1,3-butadiene **22** and isocyanate derivative **23**. The elimination product **23** was transformed to diacetamide, which would further decompose to acetamide and ketene.[19] Subsequently, the [4+2] cycloaddition of **22** to the C=C double bond of acetic acid adducts **11** gave tetrahydropyridine **24**. The generation of regiospecific **24** also probably occurred through zwitterion **19y**. The presence of the intermediate **24** was supported by the fact that 2-butoxymethyl-5-butoxypyridine **7**, not 3,5-dibutoxypyridine **5k** or 2-butoxymethyl-3,5-dibutoxypyridine **6k**, was obtained from the acid-promoted reaction of 3-butoxyacryloyl azide **4k**. This might be the result of the good leaving ability of the butoxy group. Finally, tetrahydropyridine **24** transferred to pyridines **5** and **6** by loss of **17** followed by elimination of RCH_3[7a] or oxidation, respectively. The isolation of 3-nitrotoluene in the case of heating **4f** supported this alternative process to the formation of **5**. Owing to the yield of 3-nitrotoluene being 5%, not comparable with that of **5f** (66%), the former mechanistic path was proposed as the major route.

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Conclusion

In summary, a series of pyridine derivatives was synthesized from the corresponding acryloyl azides by the acetic acid-promoted cycloaddition. The reaction involved a trimolecular condensation mechanism. The yield of the pyridine product depends on the substituent on the double bond and the solvent used. The reactivity of the acid-promoted cycloaddition increases with the presence of aryl groups, such as phenyl and pyridinyl. Here, we report a novel and convenient synthetic approach to the symmetrical 3,5-disubstituted pyridines from acryloyl azides.

Experimental Section

General Procedure for the Acid-Promoted Cycloaddition of an Acryloyl Azide, 4. A mixture of acryloyl azide **4** (4 mmol) and HOAc (3.00 g, 40 mmol) in DMSO (4 mL) was heated under N_2 at 150 °C for 4 h. After cooling, the resulting solution was diluted with ethyl acetate (400 mL), washed with 4 N aqueous NaOH (16 mL) and water (8 × 25 mL), dried with anhydrous $MgSO_4$, and filtered. The filtrate was concentrated, and the residue was purified by column chromatography over Al_2O_3 eluting with hexane−EtOAc (5:1) to give pyridine derivatives **5a**−**j**, **6a**−**d**, **6j**, and **7**, as well as the pyrimidinone **8a** and pyridinone **9a** when **4a** was used. The full spectral data of these compounds are described as follows.

3,5-Diphenylpyridine (5a). Yield 62%; white solid, mp 137−138 °C (hexane−EtOAc) (lit.[20] mp 137−138 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, t, J = 7.5 Hz, 2 × H-4′), 7.51 (4H, t, J = 7.5 Hz, 4 × H-3′), 7.65 (4H, d, J = 7.5 Hz, 4 × H-2′), 8.05 (1H, t, J = 2.2 Hz, H-4), 8.83 (2H, d, J = 2.2 Hz, 2 × H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.3 (4 × C-2′), 128.2 (2 × C-4′), 129.1 (4 × C-3′), 132.9 (C-4), 136.7 (2 × C-3), 137.8 (2 × C-1′), 147.0 (2 × C-2); IR (KBr) 3021, 1598, 1584 cm^{-1}; EIMS m/z (rel int) 231 (100, M$^+$). Anal. Calcd for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.20; H, 5.67; N, 6.02.

3,5-Diphenyl-[2,4,6-$^{13}C_3$]pyridine (5a-^{13}C). Yield 51%; white solid, mp 139−140 °C (hexane−EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (6H, m), 7.65 (4H, m), 8.05 (1H, dtt, J = 159.3, 5.6, 2.2 Hz, H-4), 8.82 (2H, dddd, J = 165.4, 10.2, 5.5, 2.2 Hz, 2 × H-2); ^{13}C NMR (75 MHz, $CDCl_3$) two labeled signals δ 132.9 (C-4), 147.0 (2 × C-2); IR (KBr) 3035, 1599, 1578 cm^{-1}; EIMS m/z (rel int) 234 (100, M$^+$); HREIMS m/z calcd for $^{12}C_{14}{}^{13}C_3H_{13}N$ 234.1148, found 234.1145 [M]$^+$.

3,5-Bis(4-methoxyphenyl)pyridine (5b). Yield 47%; white solid, mp 233−235 °C (hexane−EtOAc) (lit.[21] mp 229 °C); ^{1}H NMR ($CDCl_3$) δ 3.87 (6H, s), 7.03 (4H, d, J = 8.7 Hz), 7.58 (4H, d, J = 8.7 Hz), 7.96 (1H, t, J = 2.0 Hz), 8.74 (2H, d, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 55.4, 114.6, 128.3, 130.3, 131.9, 136.2, 146.1, 159.8; IR (KBr) 3013, 1609, 1513 cm^{-1}; EIMS m/z (rel int) 291 (100, M$^+$). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.02; H, 5.80; N, 4.67.

3,5-Bis(3-methoxyphenyl)pyridine (5c). Yield 58%; white solid, mp 110−111 °C (hexane−EtOAc) (lit.,[10e] mp 111 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (6H, s), 6.96 (2H, dd, J = 8.0, 2.1 Hz), 7.15 (2H, br s), 7.21 (2H, d, J = 8.0 Hz), 7.40 (2H, t, J = 8.0 Hz), 8.02 (1H, br s), 8.81 (2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 112.9, 113.4, 119.6, 130.1, 132.8, 136.4, 139.1, 147.0, 160.1; IR (KBr) 3001, 1607, 1584 cm^{-1}; EIMS m/z (rel int) 291 (100, M$^+$). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 77.95; H, 5.97; N, 4.80.

3,5-Bis(2-methoxyphenyl)pyridine (5d). Yield 51%; white solid, mp 125−126 °C (hexane−EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (6H, s), 7.04 (4H, m), 7.36 (4H, m), 8.02 (1H, br s), 8.72 (2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 111.2, 121.0, 127.1, 129.4, 130.7, 133.3, 137.6, 148.4, 156.6; IR (KBr) 3003, 1601, 1582 cm^{-1}; EIMS m/z (rel int) 291 (100, M$^+$). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.30; H, 5.76; N, 4.65.

3,5-Bis(4-nitrophenyl)pyridine (5e). Yield 48%; white solid, mp 315−317 °C (EtOAc) (lit.[12b] mp 222−224 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.21 (4H, d, J = 8.4 Hz), 8.37 (4H, d, J = 8.4 Hz), 8.60 (1H, br s), 9.10 (2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.1, 128.6, 133.5, 133.7, 143.2, 147.4, 148.3; IR (KBr) 3030, 1672, 1601, 1512 cm^{-1}; EIMS m/z (rel int) 321 (100, M$^+$). Anal. Calcd for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.34; H, 3.45; N, 13.23.

3,5-Bis(3-nitrophenyl)pyridine (5f). Yield 66%; white solid, mp 257−259 °C (EtOAc−CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (2H, t, J = 8.0 Hz), 8.01 (2H, dt, J = 8.0, 1.9 Hz), 8.15 (1H, t, J = 2.2 Hz), 8.34 (2H, dt, J = 8.0, 1.9 Hz), 8.53 (2H, t, J = 1.9 Hz), 8.96 (2H, d, J = 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 122.2, 123.3, 130.4, 133.0, 132.2, 134.7, 138.9, 148.0, 148.9; IR (KBr) 3049, 1521, 1352 cm^{-1}; EIMS m/z (rel int) 321 (100, M$^+$). Anal. Calcd for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.40; H, 3.39; N, 12.92.

3,5-Bis(2-nitrophenyl)pyridine (5g). Yield 58%; white solid, mp 141−142 °C (hexane−EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (2H, d, J = 7.4 Hz), 7.59 (3H, m), 7.72 (2H, t, J = 7.4 Hz), 8.03 (2H, d, J = 8.2 Hz), 8.62 (2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.8, 129.4, 132.4, 132.5, 133.0, 133.3, 135.0, 148.0, 148.7; IR (KBr) 3032, 1530, 1348 cm^{-1}; EIMS m/z (rel int) 321 (100, M$^+$). Anal. Calcd for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.41; H, 3.27; N, 12.77.

3,5-Bis(pyridine-3-yl)pyridine (5h). Yield 70%; white solid, mp 157−158 °C (hexane−EtOAc) (lit.[22] mp 159−160 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (2H, dd, J = 8.0, 4.8 Hz), 7.96 (2H, m), 8.06 (1H, t, J = 2.0 Hz), 8.71 (2H, m), 8.91 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.9, 132.9, 133.1, 133.8, 134.6, 147.7, 148.3, 149.7; IR (KBr) 3026, 1568, 1481, 1447, 1400 cm^{-1}; EIMS m/z (rel int) 233 (100, M$^+$). Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.03; H, 4.65; N, 17.71.

3,5-Bis(ethoxycarbonyl)pyridine (5i). Yield 33%; white solid, mp 48−48.5 °C (hexane) (lit.[23] mp 48.5−50 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (6H, t, J = 7.1 Hz), 4.46 (4H, q, J = 7.1 Hz), 8.86 (1H, t, J = 1.9 Hz), 9.37 (2H, d, J = 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 61.8, 126.3, 137.9, 154.1, 164.5; IR (KBr) 2988, 1717, 1605 cm^{-1}; EIMS m/z (rel int) 223 (100, M$^+$); HREIMS m/z calcd for $C_{11}H_{13}NO_4$ 223.0845, found 223.0842 [M]$^+$.

3,5-Dipropylpyridine (5j). Yield 2%; colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (6H, t, J = 7.4 Hz), 1.64 (4H, sextet, J = 7.4 Hz), 2.56 (4H, t, J = 7.4 Hz), 7.29 (1H, t, J = 1.9 Hz), 8.26 (2H, d, J = 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 24.3, 34.9, 135.9, 137.2, 147.4; IR (KBr) 2961, 1456 cm^{-1}; EIMS m/z (rel int) 163 (43, M$^+$); HREIMS m/z calcd for $C_{11}H_{17}N$ 163.1361, found 163.1365 [M]$^+$.

2-Benzyl-3,5-diphenylpyridine (6a). Yield 12%; white solid, mp 72−73 °C (hexane−EtOAc) (lit.[24] mp 74−75 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (2H, s, CH_2), 7.05 (2H, d, J = 7.4 Hz, 2 × H-2‴), 7.14 (1H, t, J = 7.4 Hz, H-4‴), 7.20 (2H, t, J = 7.4 Hz, 2 × H-3‴), 7.28 (2H, d, J = 7.4 Hz, 2 × H-2′), 7.40 (4H, m, 2 × H-3′ and H-4′, H-4″), 7.46 (2H, t, J = 7.4 Hz, 2 × H-3″), 7.61 (2H, d, J = 7.4 Hz, 2 × H-2″), 7.75 (1H, d, J = 2.0 Hz, H-4), 8.83 (1H, d, J = 2.0 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.3 (CH_2), 126.0 (C-4‴), 127.0 (2 × C-2″), 127.7 (C-4′), 128.0

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(C-4″), 128.2 (2 × C-3‴), 128.4 (2 × C-3′), 128.8 (2 × C-2‴), 129.1 (2 × C-3″), 129.2 (2 × C-2′), 134.2 (C-5), 136.1 (C-4), 137.3 (C-3), 137.5 (C-1″), 139.6 (C-1′), 140.0 (C-1‴), 146.7 (C-6), 156.6 (C-2); IR (KBr) 3028, 1601 cm^{-1}; FABMS *m*/*z* (rel int) 322 (100, $[MH]^+$); HRFABMS *m*/*z* calcd for $C_{24}H_{20}N$ 322.1592, found 322.1602 $[MH]^+$.

2-Benzyl-3,5-diphenyl-[2,4,6-$^{13}C_3$]pyridine (6a-^{13}C). Yield 4%; white solid, mp 72−73 °C (hexane−EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (2H, d, J = 6.5 Hz, CH_2), 7.05 (2H, d, J = 7.0 Hz), 7.14 (1H, t, J = 7.0 Hz), 7.20 (2H, t, J = 7.0 Hz), 7.27 (2H, dd, J = 7.5, 2.0 Hz), 7.40 (4H, m), 7.46 (2H, t, J = 7.5 Hz), 7.61 (2H, dd, J = 7.5, 2.0 Hz), 7.74 (1H, dtd, J = 159.7, 6.1, 2.4 Hz, H-4), 8.83 (1H, dddd, J = 177.6, 11.2, 5.5, 2.4 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) three labeled signals δ 136.1 (C-4), 146.7 (C-6), 156.6 (C-2); IR (KBr) 3028, 1601 cm^{-1}; EIMS *m*/*z* (rel int) 324 (35, M^+); HREIMS *m*/*z* calcd for $^{12}C_{21}{}^{13}C_3H_{19}N$ 324.1618, found 324.1610 $[M]^+$.

2-(4-Methoxybenzyl)-3,5-Bis(4-methoxyphenyl)pyridine (6b). Yield 6%; syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 4.11 (2H, s), 6.76 (2H, d, J = 8.6 Hz), 6.97 (6H, m), 7.20 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.6 Hz), 7.67 (1H, d, J = 2.3 Hz), 8.76 (1H, d, J = 2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3, 55.2, 55.3 (2 × C), 113,7, 113.8, 114.5, 128.1, 129.7, 130.0, 130.4, 132.1, 132.3, 133.7, 135.8, 136.8, 146.1, 156.5, 157.8, 159.1, 159.6; IR (KBr) 2933, 1611, 1512 cm^{-1}; EIMS *m*/*z* (rel int) 411 (72, M^+); HREIMS *m*/*z* calcd for $C_{27}H_{25}NO_3$ 411.1834, found 411.1829 $[M]^+$.

2-(3-Methoxybenzyl)-3,5-bis(3-methoxyphenyl)pyridine (6c). Yield 7%; syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (3H, s), 3.73 (3H, s), 3.85 (3H, s), 4.17 (2H, s), 6.67 (3H, m), 6.78 (1H, t, J = 1.9 Hz), 6.91 (3H, m), 7.15 (3H, m), 7.36 (2H, m), 7.74 (1H, d, J = 2.3 Hz), 8.83 (1H, d, J = 2.3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 41.3, 55.0, 55.1, 55.3, 111.5, 112.6, 113.4, 113.5, 114.4, 114.6, 119.4, 121.2, 121.5, 129.1, 129.4, 130.1, 134.1, 136.0, 137.2, 138.9, 140.8, 141.6, 146.7, 156.5, 159.4, 159.5, 160.1; IR (KBr) 2938, 1602, 1584 cm^{-1}; FABMS *m*/*z* (rel int) 412 (100, $[MH]^+$); HRFABMS *m*/*z* calcd for $C_{27}H_{26}NO_3$ 412.1913, found 412.1920 $[MH]^+$.

2-(2-Methoxybenzyl)-3,5-bis(2-methoxyphenyl)pyridine (6d). Yield 10%; syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (3H, s), 3.65 (3H, s), 3.77 (3H, s), 4.07 (2H, s), 6.70 (1H, d, J = 8.2 Hz), 6.80 (1H, t, J = 7.7 Hz), 7.00 (7H, m), 7.33 (3H, m), 7.71 (1H, d, J = 2.2 Hz), 8.76 (1H, d, J = 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.0, 55.1 (2 × C), 55.4, 109.9, 110.5, 111.1, 120.1, 120.2, 120.9, 126.8, 126.9, 128.7 (2 × C), 128.9, 129.1, 130.2, 130.6, 131.1 (2 × C), 133.3, 138.8, 148.5, 156.6 (2 × C),157.0, 157.3; IR (KBr) 2936, 1601, 1584 cm^{-1}; EIMS *m*/*z* (rel int) 411 (25, M^+); HREIMS *m*/*z* calcd for $C_{27}H_{25}NO_3$ 411.1834, found 411.1838 $[M]^+$.

2-Butyl-3,5-dipropylpyridine (6j). Yield 21%; colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (9H, m), 1.42 (2H, sextet, J = 7.4 Hz), 1.63 (6H, m), 2.52 (2H, t, J = 7.8 Hz), 2.56 (2H, t, J = 7.5 Hz), 2.75 (2H, t, J = 7.8 Hz), 7.21 (1H, s), 8.20 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 14.0 (2 × C), 23.0, 23.9, 24.3, 32.0, 34.2, 34.3, 34.6, 134.5, 134.7, 136.8, 146.6, 157.6; IR (KBr) 2959, 1460 cm^{-1}; EIMS *m*/*z* (rel int) 219 (8, M^+); HREIMS *m*/*z* calcd for $C_{15}H_{25}N$ 219.1987, found 219.1981 $[M]^+$.

2-Butoxymethyl-5-butoxypyridine (7). Yield 10%; colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.4 Hz), 0.98 (3H, t, J = 7.4 Hz), 1.46 (4H, m), 1.63 (2H, m), 1.78 (2H, m), 3.53 (2H, t, J = 6.6 Hz), 4.00 (2H, t, J = 6.5 Hz), 4.56 (2H, s), 7.19 (1H, dd, J = 8.6, 2.8 Hz), 7.34 (1H, d, J = 8.6 Hz), 8.23 (1H, d, J = 2.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 13.9, 19.1, 19.3, 31.1, 31.8, 68.1, 70.6, 73.4, 121.7, 122.0, 136.9, 150.5, 154.3; IR (KBr) 2961, 1248, 1119 cm^{-1}; FABMS *m*/*z* (rel int) 238 (100, $[MH]^+$); HRFABMS *m*/*z* calcd for $C_{14}H_{24}NO_2$ 238.1807, found 238.1808 $[MH]^+$.

4-Benzyl-5-phenyl-3,4-dihydro-1*H*-pyrimidin-2-one (8a). White solid; mp 215−217 °C (hexane−acetone) (lit.[24] mp 212−214 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (1H, dd, J = 13.5, 9.0 Hz,), 2.94 (1H, dd, J = 13.5, 2.7 Hz), 4.69 (1H, m), 5.26 (1H, br s), 6.44 (1H, d, J = 5.1 Hz), 7.29 (10H, m), 7.47 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.2, 55.3, 113.7, 121.7, 124.7, 126.8, 128.7, 129.0, 129.6, 135.9, 136.7, 154.1; IR (KBr) 3225, 1713, 1669 cm^{-1}; EIMS *m*/*z* (rel int) 264 (20, M^+). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.12; H, 6.12; N, 10.53.

3,5-Diphenylpyridin-2-one (9a). White solid; mp 206−207 °C (hexane−EtOAc) (lit.[25] mp 202 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (1H, t, J = 7.5 Hz), 7.33 (1H, t, J = 7.3 Hz), 7.40 (4H, m), 7.64 (2H, d, J = 7.5 Hz), 7.70 (1H, d, J = 2.6 Hz), 7.81 (2H, d, J = 7.3 Hz), 7.95 (1H, d, J = 2.6 Hz), 12.02 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 118.5, 125.7, 126.9, 127.6, 128.0, 128.6, 129.1, 130.2, 131.9, 136.4, 136.8, 137.8, 160.8; IR (KBr) 3421, 1633, 1567, 1514 cm^{-1}; EIMS *m*/*z* (rel int) 247 (100, M^+); HREIMS *m*/*z* calcd for $C_{17}H_{13}NO$ 247.0997, found 247.1004 $[M]^+$.

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Supporting Information Available: The synthetic procedures, spectroscopic data of **3a-^{13}C** and acryloyl azides **4**, and copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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