Mannich Bases as Enone Precursors for Water-Mediated Efficient Synthesis of 2,3,6-Trisubstituted Pyridines and 5,6,7,8-Tetrahydroquinolines

Essam Hamied Ahmed Hanashalshahaby and Canan Unaleroglu*

Hacettepe University, Chemistry Department, 06800 Beytepe, Ankara Turkey

ⓢ *Supporting Information*

ABSTRACT: A highly efficient, regioselective, and environmentally friendly method has been developed for water-mediated synthesis of 2,3,6-trisubstituted pyridines and 5,6,7,8-tetrahydroquinolines. The introduced method allows easy preparation of various polysubstituted pyridines and 5,6,7,8-tetrahydroquinolines via domino reaction of an enolizable ketone, ammonia and enones derived from different Mannich bases in mild reaction conditions. Montmorillonite K-10 promoted this one-pot three-component reaction and gave both new and known 2,3,6-trisubstituted pyridines and 5,6,7,8-tetrahydroquinolines in good yields. The reaction protocol provides a wide array of functionality in construction of polysubstituted pyridines and 5,6,7,8-tetrahydroquinolines from commercially available starting materials in easily applicable and environmentally friendly conditions.
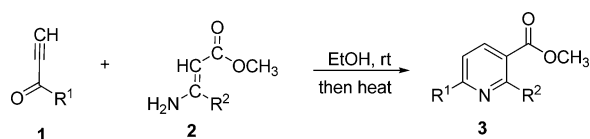
KEYWORDS: *2,3,6-trisubstituted pyridines, 5,6,7,8-tetrahydroquinolines, Mannich bases, pyridine synthesis in water*
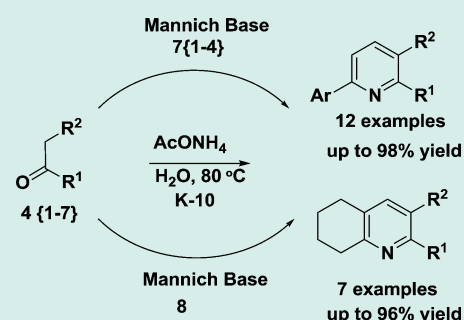
INTRODUCTION

Polysubstituted pyridines constitute a significant place in synthetic and medicinal chemistry. Dihydro-6H-quinolin-5-ones also have considerable attention because of their biological activities. These heterocycles are present in a large number of pharmaceutical agents[1] as a key unit or in supramolecular assemblies[2] as building blocks; therefore, there is currently a great interest in the synthesis of these scaffolds. Many synthetic approaches have been developed for the preparation of these scaffolds.[3] The Bohlmann−Rahtz method is the first report for the preparation of 2,3,6-trisubstituted pyridines **3** via addition of alkynone **1** and enamine **2** and subsequent cyclodehydration reactions in ethanol (Scheme 1).[4]

Scheme 1. Bohlmann−Rahtz 2,3,6-Trisubstituted Pyridine Synthesis

Bagley has made a remarkable improvement in the Bohlmann−Rahtz synthesis.[5] In this variant, three-component condensation of an enolizable ketone, alkynone, and ammonia under acidic condition afforded 2,3,6-trisubstituted pyridines with high yields. An important advantage of this domino reaction is the use of an enolizable ketone and ammonia instead of poorly available enamine substrate sited in Bohlmann−Rahtz pyridine synthesis.

Troschütz prepared 2-methylnicotinates by cyclocondensation of acetophenone-derived Mannich bases with methyl 3-aminocrotonate under reflux in ethanol.[6] Keuper and Nikolaus also used Mannich bases to prepare polycyclic pyridines from β-amino ketone hydrochlorides, cyclic ketones, and ammonium acetate in boiling acetonitrile. However, in many cases, yields were low, and the best results have been obtained in absolute ethanol.[7] The researchers generally applied this approach for construction of different-shaped oligopyridines.[8]

Multicomponent reactions (MCRs) are very efficient methods for the synthesis of important chemicals in a designated reaction conditions without a need of isolation and purification of intermediates. MCRs have become important protocols for the preparation of pyridines.[9] In this study, we researched the availability and the scope of multicomponent one-pot reactions of a Mannich base, an enolizable ketone, and NH$_4$OAc in water working in environmentally friendly reaction conditions.

RESULTS AND DISCUSSION

On the basis of our retrosynthetic strategy, we envisioned that domino reaction of enones **5**, ketones **4**, and ammonia would produce the desired 2,3,6-trisubstituted pyridines **6** (Scheme 2). According to the proposed retrosynthetic strategy, enones are easily prepared in situ from Mannich bases (Figure 1). To the best of our knowledge, this advantage of Mannich bases

Scheme 2. Retrosynthetic Strategy for the Synthesis of 2,3,6-Trisubstituted Pyridines
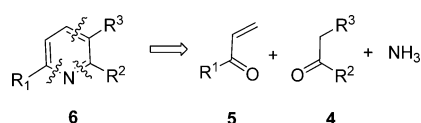
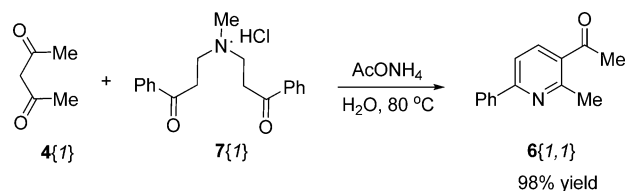does not seem to have been adequately assessed in the synthesis of 2,3,6-trisubstituted pyridines.

Figure 1. Three-component reaction of *N*-methyl-3-oxo-*N*-(3-oxo-3-phenylpropyl)-3-phenylpropan-1-aminium chloride 7{*1*}, pentane-2,4-dione 4{*1*}, and ammonia in water.

To test the validity of the multicomponent one-pot formation of polysubstituted pyridines, we chose *N*-methyl-3-oxo-*N*-(3-oxo-3-phenylpropyl)-3-phenylpropan-1-aminium chloride 7{*1*}, pentane-2,4-dione 4{*1*}, and ammonium acetate. *N*-Methyl-3-oxo-*N*-(3-oxo-3-phenylpropyl)-3-phenylpropan-1-aminium chloride 7{*1*} was prepared according to the reported procedure,[10] and these three components were heated in water

at 80 °C for 2 h (Figure 1). 1-(2-Methyl-6-phenylpyridin-3-yl)ethanone 6{*1,1*} formed as the only product in 98% yield. The structure of 6{*1,1*} was characterized by ^{1}H NMR, ^{13}C NMR, and MALDI-TOF-MS spectral data.

After obtaining compound 6{*1,1*} with excellent yield, we tested the reaction with *β*-keto esters 4{*2−4*} under the same reaction conditions. All *β*-keto esters furnished the target molecules regioselectively with moderate to high yields (Table 1, entries 1−4). After this stage, we chose 1-phenylbutane-1,3-dione 4{*5*} to examine the preparation of 2,3,6-trisubstituted pyridines from an unsymmetrical 1,3-diketone. With respect to a possible reaction pathway outlined in Scheme 3, unsymmetrical 1,3-diketone 4{*5*} allows the formation of two different enamines. Enamine **A** produced a new compound (2-methyl-6-phenylpyridin-3-yl)(phenyl)methanone 6a{*5,1*} as the major product in 56% yield, and enamine **B** produced 1-(2,6-diphenylpyridin-3-yl)ethanone 6b{*5,1*} as the minor product in 9% yield. These two compounds were separated by flash column chromatography and characterized by ^{1}H NMR, ^{13}C NMR, and HRMS spectral data. The structures of 6a{*5,1*} and 6b{*5,1*} were identified on the basis of ^{13}C NMR spectral signatures of the methyl carbon. The reported chemical shift values for methyl carbons of 1-(2-methyl-6-phenylpyridin-3-yl)ethanone,[3b] ethyl 2-methyl-6-phenylnicotinate,[3b,e] ethyl 6-(furan-2-yl)-2-methylnicotinate, and ethyl 6-(5-fluoro-2-methyl-2,3-dihydrobenzofuran-7-yl)-2-methylnicotinate[1d] are between 25.2 and 25.3 ppm, whereas the chemical shift value of methyl carbon on acetyl group of 1-(2-methyl-6-phenylpyridin-3-yl)ethanone[3b] is at 29.1 ppm. ^{13}C NMR spectra that we

Table 1. Synthesis of 2,3,6-Trisubstituted Pyridines 6{*1−6,1*} from the Three-Component Condensation Reaction of *N*-Methyl-3-oxo-*N*-(3-oxo-3-phenylpropyl)-3-phenylpropan-1-aminium Chloride 7{*1*}, Active Methylene Compounds 4{*1−6*} and Ammonia in Water[a]

Entry	Active Methylenes	R[1]	R[2]	Product	Yield[b] (%)
1	4{*1*}	CH_3	$COCH_3$	6{*1,1*}	98
2	4{*2*}	CH_3	$CO_2C_2H_5$	6{*2,1*}	79
3	4{*3*}	CH_3	$CO_2CH(CH_3)_2$	6{*3,1*}	50
4	4{*4*}	CH_3	$CO_2(CH_2)_2OCH_3$	6{*4,1*}	78
5	4{*5*}	CH_3 / C_6H_5	COC_6H_5 / $COCH_3$	6a{*5,1*} / 6b{*5,1*}	56 / 9
6	4{*6*}	C_2H_5	$PO(OC_2H_5)_2$	6{*6,1*}	18

[a]All reactions were performed with 4{*1−6*}/7{*1*}/NH_4OAc (1:1.5:4.4) molar ratios. [b]Isolated yields.

**Scheme 3. Plausible Formation Pathway of 6a{5,1} and 6b{5,1}**
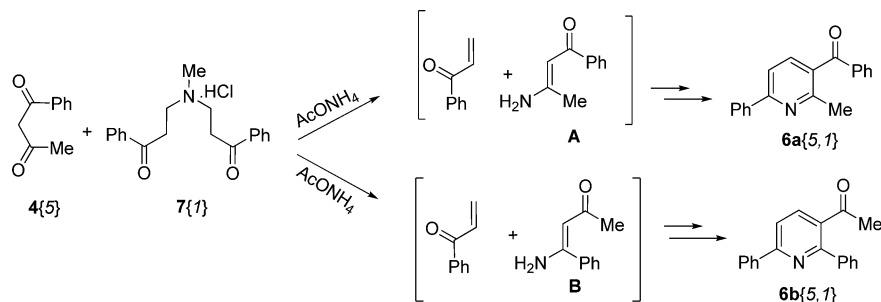
obtained displayed these methyl carbon signals at 23.9 ppm for the major product and at 30.4 ppm for the minor. According to these values, the major product was identified as (2-methyl-6-phenylpyridin-3-yl)(phenyl)methanone **6a**{*5,1*} and the minor product was identified as 1-(2,6-diphenylpyridin-3-yl)ethanone **6b**{*5,1*}. These successful results have led us to test diethyl (2-oxobutyl)phosphonate **4**{*6*} instead of 1,3-diketone to obtain phosphonate substituted pyridine. However, this reaction generated the desired product diethyl (2-ethyl-6-phenylpyridin-3-yl)phosphonate **6**{*6,1*} with the lowest yield (18%). All compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and HRMS analysis.

The above observations showed that this reaction protocol gave the target molecules in moderate high yields except **6**{*6,1*}. Accordingly, we next explored the Mannich base diversity on the three-component one-pot reaction of Mannich base, enolizable ketone, and NH$_4$OAc under the same reaction conditions. Pentane-2,4-dione **4**{*1*} and ethyl 3-oxobutanoate **4**{*2*} were chosen as representative active methylenes. Reaction of 3,3′-(methylazanediyl)bis(1-(thiophen-2-yl)propan-1-one) hydrochloride **7**{*2*}, 3,3′-(methylazanediyl)bis(1-(furan-2-yl)-propan-1-one) hydrochloride **7**{*3*}, and N-methyl-N-(2-morpholinoethyl)-1H-indole-2-carboxamide **7**{*4*} shown in Figure 2 with **4**{*1*} and **4**{*2*}, respectively, allowed the one-pot synthesis of corresponding pyridines **6**{*1−2,2−4*}. However, the target molecules were obtained with unsatisfactory yields (Table 2, entries 1−6).

To increase the yields of products, we tested the effect of different catalysts on the reaction of 3,3′-(methylazanediyl)bis-(1-(thiophen-2-yl)propan-1-one) hydrochloride **7**{*2*} with ethyl 3-oxobutanoate **4**{*2*}, and ammonium. Ce(OTf)$_3$, Cu-(OTf)$_2$, and CAN showed no catalytic effect on the reaction (Supporting Information Table S1, entries 2, 5, and 6). KSF significantly increased the yield of ethyl 2-methyl-6-(thiophen-2-yl)nicotinate **6**{*2,2*} from 42% to 74% (Supporting Information Table S1, entry 3). Further increases up to 82% yield were obtained with K-10 catalyst (Supporting Information Table S1, entry 4). When the reaction was performed only in glacial acetic acid, the target product was obtained with 81% yield (Supporting Information Table S1, entry 6). After these results were obtained, the previously worked reactions, except the one that yielded 98%, were run with the environmentally friendly montmorillonite K-10 catalyst in water and the results were summarized in Table 3. Reactions of Mannich base **7**{*1*} with **4**{*2*} or **4**{*3*} and ammonia in the presence of K-10 gave the products with increased yields, 89% and 66%, respectively (Table 3, entries 2 and 3). For the reaction of **7**{*1*} with **4**{*4*}, **4**{*5*}, or **4**{*6*} and ammonia, the K-10 catalyst does not seem to have a clear effect on the reaction yields (Table 3, entries 4−6). A remarkable effect of K-10 was observed in the yields of **6**{*1−*

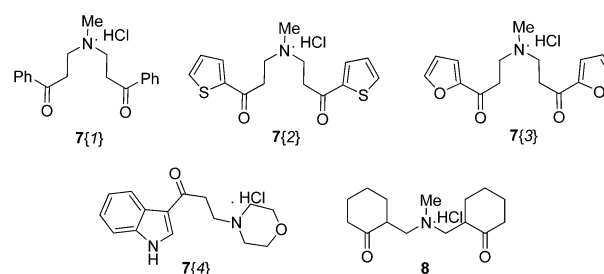a)   Active methylenes
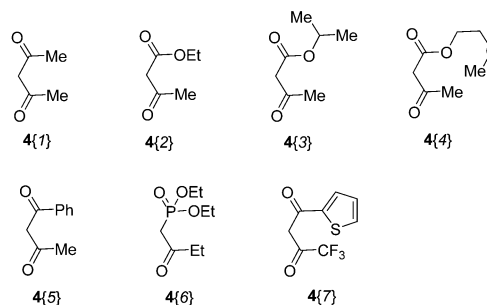
b)   Mannich bases

Figure 2. Diversity of reagents.

2,2−4} (Table 3, entries 7−12). Synthesis of ethyl 2-methyl-6-(thiophen-2-yl)nicotinate **6**{*2,2*} with 84% yield has been previously reported by the reaction of (E)-3-(dimethylamino)-1-(thiophen-2-yl)prop-2-en-1-one with **4**{*2*} and ammonium acetate in the presence of CeCl$_3$·H$_2$O−NaI in 2-propanol,[1d] whereas the introduced reaction protocol with metal-free conditions provided **6**{*2,2*} with a comparable yield (82%) in the presence of K-10 in water. New indolyl substituted pyridines **6**{*1,4*} and **6**{*2,4*} were also synthesized in 77% and 54% yields, respectively (Table 3, entries 11 and 12).

A plausible mechanism for this three-component hetero-annulation reaction taking into account the experimental results and literature reports[3d,6] is outlined in Scheme 4. First, the Mannich base **7** produces the enone compound **5** in situ, and the reaction of ammonia with ketone **4** produces enamine **I**. In the next step, the Michael addition reaction gives intermediate **II**, subsequent intramolecular cyclization forms intermediate **III**, and the following aromatization affords 2,3,6-trisubstituted pyridine **6**.

To expand the applicability of the current method, 2,2′-((methylazanediyl)bis(methylene))dicyclohexanone hydro-chloride **8** shown in Figure 2 was used as a Mannich base to derive 5,6,7,8-tetrahydroquinoline. K-10 catalyzed three-component reactions were performed with **8**, the corresponding

Table 2. Examining the Scope of the Mannich Bases in the Synthesis of 2,3,6-Trisubstituted Pyridines

6{1,2}, 6{2,2} Ar= 2-Thiophenyl
6{1,3}, 6{2,3} Ar= 2-Furanyl
6{1,4}, 6{2,4} Ar= 3-Indolyl

Entry	Active Methylenes	Mannich Bases	R^1	R^2	Product	Yield[a] (%)
1	4{1}	7{2}	CH_3	CH_3	6{1,2}	57
2	4{2}	7{2}	CH_3	OC_2H_5	6{2,2}	42
3	4{1}	7{3}	CH_3	CH_3	6{1,3}	58
4	4{2}	7{3}	CH_3	OC_2H_5	6{2,3}	43
5	4{1}	7{4}	CH_3	CH_3	6{1,4}	32
6	4{2}	7{4}	CH_3	OC_2H_5	6{2,4}	25

[a]Isolated yields.

compounds 4{1−7} and ammonia in water (Table 4, entries 1−7). The reaction of 8 with 4{1} and ammonia yielded 2,3-dimethyl-5,6,7,8-tetrahydroquinoline 9{1} with excellent yield even in the absence of a catalyst (Table 4, entry 1). β-keto esters 4{2−4} gave the corresponding quinolines 9{2−4} with low to moderate yields (44%−70%). 9a{5} and 9b{5} were obtained from the reaction of Mannich base 8 with 4{5} and ammonia. These two compounds 9a{5} and 9b{5} were separated by flash column chromatography and identified on the basis of ^{13}C NMR spectral signatures of methyl carbon on acetyl group. The reported chemical shift values of methyl carbons of C(3)-acetyl functionalized pyridines were between 29.0 and 29.3 ppm.[3b] ^{13}C NMR spectrum of 9b{5} showed a peak at 30.3 ppm besides the methylene peaks of pyridine-fused cyclohexane. This peak was absent in the ^{13}C NMR spectrum of 9a{5}, while a another peak at 22.9 ppm arose assigning the methyl carbon attached to pyridine. According to the chemical shift values of methyl carbon in the ^{13}C NMR spectra of 9a{5} and 9b{5}, the major product was identified as (2-methyl-5,6,7,8-tetrahydroquinolin-3-yl)(phenyl)methanone 9a{5} and the minor as 1-(2-phenyl-5,6,7,8-tetrahydroquinolin-3-yl)-ethanone 9b{5}. Herein, the introduced procedure provided the target molecules in higher yields from easily available compounds under more favorable conditions. Three-component reaction of 4{6} or 4{7} with 8 and ammonia formed new compounds diethyl (2-ethyl-5,6,7,8-tetrahydroquinolin-3-yl)-phosphonate 9{6} and 2,2,2-trifluoro-1-(2-(thiophen-2-yl)-5,6,7,8-tetrahydroquinolin-3-yl)ethanone 9{7}, respectively. However, 9{6} (15%) and 9{7} (40%) were obtained in the lowest yields (Table 4, entries 6 and 7).

In conclusion, we have successfully developed a facile water-mediated three-component one-pot reaction of Mannich base, enolizable ketone and NH_4OAc in the presence of environmentally friendly heterogeneous catalyst K-10. Easily prepared Mannich bases as enone precursors can be alternative starting materials for pyridine synthesis. This simple and practical reaction protocol provides the synthesis of 2,3,6-trisubstituted pyridines and 5,6,7,8-tetrahydroquinolines from easily available compounds in good yields. The diversity of Mannich bases and enolizable ketones makes these compounds good candidates for construction of pyridine and pyridine base skeletons to be used in combinatorial processes such as drug discovery.

■ EXPERIMENTAL PROCEDURES

General Information. All reagents were commercial and purchased from Acros Organics, Sigma-Aldrich, and Merck. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data were recorded on a Bruker DPX-400-ultra shield FT-NMR spectrometer in $CDCl_3$ with chemical shifts given in ppm relative to TMS as internal standard. Melting points were determined with Gallenkamp electrothermal digital melting point apparatus and are uncorrected. HRMS spectra were recorded on an Agilent (1200/6210) TOF LC/MS spectrometer. Reactions were monitored by TLC using precoated silica gel alumina plates (Kieselgel 60, F254, E. Merck), visualization UV lamp. Flash column chromatography was performed by using silica gel (0.05−0.63 nm 230−400 mesh ASTM, Merck).

General Procedure for the Synthesis of 2,3,6-Trisubstituted Pyridines. A mixture of diketo-base hydrochloride 7{1} (0.22 g, 0.66 mmol), active methylene 4{1} (0.045 mL, 0.44 mmol), and ammonium acetate (0.2 g, 2.6 mmol) in 3 mL of water was heated at 80 °C for 2 h. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, and 20 mL of water was added. The product

Table 3. K-10 Catalyzed Three-Component Reaction of Mannich Bases 7{1−4}, Active Methylene Compounds 4{1−6}, and Ammonia in Water[a]

Reaction scheme:

$$4\{1\text{-}6\} + \text{Mannich Base } 7\{1\text{-}4\} \xrightarrow[\text{H}_2\text{O, 80 °C}]{\text{AcONH}_4,\ \text{K-10}} 6\{1\text{-}6,\ 1\text{-}4\}$$

6{1-6, 1} Ar= Phenyl
6{1,2}, 6{2,2} Ar= 2-Thiophenyl
6{1,3}, 6{2,3} Ar= 2-Furanyl
6{1,4}, 6{2,4} Ar= 3-Indolyl

Entry	Active Methylenes	Mannich Bases	R^1	R^2	Product	Yield[b] (%)
1	4{1}	7{1}	CH_3	$COCH_3$	6{1,1}	98[c]
2	4{2}	7{1}	CH_3	$CO_2C_2H_5$	6{2,1}	89
3	4{3}	7{1}	CH_3	$CO_2CH(CH_3)_2$	6{3,1}	66
4	4{4}	7{1}	CH_3	$CO_2(CH_2)_2OCH_3$	6{4,1}	79
5	4{5}	7{1}	CH_3 / C_6H_5	COC_6H_5 / $COCH_3$	6a{5,1} / 6b{5,1}	57 / 9
6	4{6}	7{1}	C_2H_5	$PO(OC_2H_5)_2$	6{6,1}	22
7	4{1}	7{2}	CH_3	$COCH_3$	6{1,2}	74
8	4{2}	7{2}	CH_3	$CO_2C_2H_5$	6{2,2}	82
9	4{1}	7{3}	CH_3	$COCH_3$	6{1,3}	80
10	4{2}	7{3}	CH_3	$CO_2C_2H_5$	6{2,3}	60
11	4{1}	7{4}	CH_3	$COCH_3$	6{1,4}	77
12	4{2}	7{4}	CH_3	$CO_2C_2H_5$	6{2,4}	54

[a]All reactions were performed with 4{1−6}/7{1−4}/NH$_4$OAc (1:1.5:4.4) molar ratios in the presence of K-10. [b]Isolated yields. [c]K-10 free.

was extracted with EtOAc (2 × 5 mL) and dried (MgSO$_4$). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (Silica gel, EtOAc/hexane, 1:6). Experimental data of 6{1,1} are as follows: white solid; yield, 98%; mp, 91−92 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03−8.07 (m, 3H, ArH-PyrH), 7.64 (d, *J* = 8.0 Hz, 1H, PyrH), 7.44−7.50 (m, 3H, ArH), 2.83 (s, 3H, CH$_3$), 2.60 (s, 3H, COCH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.0, 158.7, 158.6, 138.4, 138.0, 130.7, 129.7, 128.9, 127.3, 117.3, 29.4, 25.4; HRMS (ESI) Calcd for C$_{14}$H$_{14}$NO [M + H]$^+$ 212.1075, found 212.1075.

General Procedure for the Synthesis of 2,3,6-Trisubstituted Pyridines in the Presence of K-10 Catalysis. To the mixture of diketo-base hydrochloride 7{1} (0.22 g, 0.66 mmol), active methylene 4{2} (0.045 mL, 0.44 mmol), and ammonium acetate (0.2 g, 2.6 mmol) in 3 mL of water was added K-10 (0.44 g) and heated at 80 °C for 2 h. After completion of the reaction (monitored by TLC), reaction mixture was cooled to room temperature and 20 mL of water was added. The product was extracted with EtOAc (2 × 5 mL) and dried (MgSO$_4$). Solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (Silica gel,

Scheme 4. Plausible Mechanism for the Synthesis of 2,3,6-Trisubstituted Pyridines
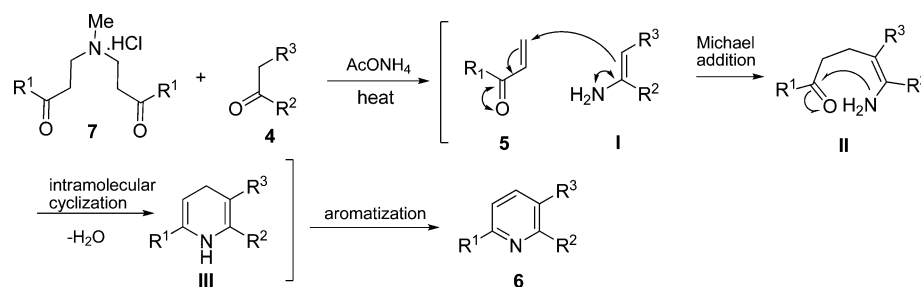
Table 4. Synthesis of 2,3-Disubstituted-5,6,7,8-tetrahydroquinoline[a]

Entry	Active Methylenes	R[1]	R[2]	Product	Yield[b] (%)
1	4{1}	CH_3	$COCH_3$	9{1}	96[c]
2	4{2}	CH_3	$CO_2C_2H_5$	9{2}	70
3	4{3}	CH_3	$CO_2CH(CH_3)_2$	9{3}	44
4	4{4}	CH_3	$CO_2(CH_2)_2OCH_3$	9{4}	65
5	4{5}	CH_3 / C_6H_5	COC_6H_5 / $COCH_3$	9a{5} / 9b{5}	51 / 8
6	4{6}	C_2H_5	$PO(OC_2H_5)_2$	9{6}	15
7	4{7}	CF_3	COC_4H_3S	9{7}	40

[a]All reactions were performed with 4{1−7}/8/NH₄OAc (1:1.5:4.4) molar ratios in the presence of K-10. [b]Isolated yields. [c]K-10 free.

EtOAc/hexane, 1:6). Experimental data of 6{2,1} is as follows: pale yellow solid; yield, 89%; mp, 54−56 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.2 Hz, 1H, PyrH), 8.06 (d, J = 8.0 Hz, 2H, ArH), 7.62 (d, J = 8.2 Hz, 1H, PyrH), 7.42−7.51 (m, 3H, ArH), 4.40 (q, J = 7.1 Hz, 2H, CH_2CH_3), 2.91 (s, 3H, CH_3), 1.42 (t, J = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 160.0, 159.1, 139.3, 138.5, 129.7, 128.8, 127.3, 123.7, 117.4, 61.1, 25.3, 14.3; HRMS (ESI) Calcd for $C_{15}H_{16}NO_2$ [M + H]$^+$ 242.1181, found 242.1183.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Further details on the experimental procedures and results. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00046.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: canan@hacettepe.edu.tr. Phone:+90-3122977962. Fax: +90-3122992163.

Notes
The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Son, K.-J.; Zhao, L.-X.; Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeong, T. C.; Jeong, B.-S.; Lee, C.-S.; Lee, E.-S. Synthesis

of 2,6-diaryl-substituted pyridines and their antitumor activities. *Eur. J. Med. Chem.* **2008**, *43*, 675−682. (b) Kantevari, S.; Santhosh, R. P.; Sridhar, B.; Yogeeswari, P.; Sriram, D. Synthesis and antitubercular evaluation of novel substituted aryl and thiophenyl tethered dihydro-6H-quinolin-5-ones. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1214−1217. (c) Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeong, B.-S.; Jeong, T. C.; Lee, C.-S.; Lee, E.-S. 2,4,6-Trisubstituted pyridines: Synthesis, topoisomerase I and II inhibitory activity, cytotoxicity, and structure−activity relationship. *Bioorg. Med. Chem.* **2007**, *15*, 4351−4359. (d) Kantevari, S.; Patpi, S. R.; Addla, D.; Putapatri, S. R.; Sridhar, B.; Yogeeswari, P.; Sriram, D. Facile diversity-oriented synthesis and antitubercular evaluation of novel aryl and heteroaryl tethered pyridines and dihydro-6H-quinolin-5-ones derived via variants of the Bohlmann−Rahtz reaction. *ACS Comb. Sci.* **2011**, *13*, 427−435.

(2) (a) Lawrence, D. S.; Jiang, T.; Levet, M. Self-assembling supramolecular complexes. *Chem. Rev.* **1995**, *95*, 2229−2260. (b) Bunker, B. C.; Huber, D. L.; Kushmerick, J. G.; Dunbar, T.; Kelly, M.; Matzke, C.; Cao, J.; Jeppesen, J. O.; Perkins, J.; Flood, A. H.; Stoddart, J. F. Switching surface chemistry with supramolecular machines. *Langmuir* **2007**, *23*, 31−34. (c) Campbell, K.; McDonald, R.; Tykwinski, R. R. Functionalized macrocyclic ligands for use in supramolecular chemistry. *J. Org. Chem.* **2002**, *67*, 1133−1140. (d) Ott, C.; Kranenburg, J. M.; Carlos, G.-S.; Hoeppener, S.; Wouters, D.; Schubert, U. S. Supramolecular assembly via noncovalent metal coordination chemistry: Synthesis, characterization, and elastic properties. *Macromolecules* **2009**, *42*, 2177−2183.

(3) (a) Henry, G. D. De novo synthesis of substituted pyridines. *Tetrahedron* **2004**, *60*, 6043−6061. and references cited therein. (b) Kantevari, S.; Chary, M. V.; Vuppalapati, S. V. N. A highly efficient regioselective one-pot synthesis of 2,3,6-trisubstituted pyridines and 2,7,7-trisubstituted tetrahydroquinolin-5-ones using $K_5CoW_{12}O_{40}$·$3H_2O$ as a heterogeneous recyclable catalyst. *Tetrahedron* **2007**, *63*, 13024−13031. (c) Satoh, Y.; Obora, Y. Low-valent niobium-catalyzed intermolecular [2 + 2 + 2] cycloaddition of *tert*-butylacetylene and arylnitriles to form 2,3,6-trisubstituted pyridine derivatives. *J. Org. Chem.* **2013**, *78*, 7771−7776. (d) Aulakh, V. S.; Ciufolini, M. A. An improved synthesis of pyridine-thiazole cores of thiopeptide antibiotics. *J. Org. Chem.* **2009**, *74*, 5750−5753. (e) Bagley, M. C.; Fusillo, V.; Jenkins, R. L.; Lubinu, M. C.; Mason, C. Continuous flow processing from microreactors to mesoscale: The Bohlmann−Rahtz cyclodehydration reaction. *Org. Biomol. Chem.* **2010**, *8*, 2245−2251.

(4) Bohlmann, F.; Rahtz, D. Über eine neue pyridinsynthese. *Chem. Ber.* **1957**, *90*, 2265−2272.

(5) (a) Bagley, M. C.; Dale, J. W.; Bower, J. A new modification of the Bohlmann−Rahtz pyridine synthesis. *Synlett* **2001**, *7*, 1149−1151. (b) Bagley, M. C.; Dale, J. W.; Bower, J. A new one-pot three-component condensation reaction for the synthesis of 2,3,4,6-tetrasubstituted pyridines. *Chem. Commun.* **2002**, 1682−1683.

(6) Graf, E.; Troschütz, R. Synthesis of 6-phenyl substituted 2-formylnicotinates. *Synthesis* **1999**, *7*, 1216−1222.

(7) Keuper, R.; Risch, N. Facile synthesis of polycyclic pyridines, bipyridines, and oligopyridines. *Liebigs Ann.* **1996**, 717−723.

(8) (a) Sielemann, D.; Keuper, R.; Risch, N. Efficient preparation of substituted 5,6,7,8-tetrahyroquinolines and octahydroacridine derivatives. *J. Prakt. Chem.* **1999**, *341*, 487−491. (b) Sielemann, D.; Keuper, R.; Risch, N. Synthesis of novel functionalized bi- and oligopyridines. *Eur. J. Org. Chem.* **2000**, 543−548. (c) Keuper, R.; Risch, N.; Flörke, U.; Haupt, H.-J. A versatile domino synthesis affording novel S- and U-shaped terpyridines — Synthesis, properties and crystal structure. *Liebigs Ann.* **1996**, 705−715. (d) Keuper, R.; Risch, N. Synthesis and characterization of novel pyridines and 3,3′-bridge bipyridines using 1,*x*-cyclohexanediones. *Eur. J. Org. Chem.* **1998**, 2609−2615.

(9) (a) Tu, X.-J.; Fan, W.; Hao, W.-J.; Jiang, B.; Tu, S.-J. Three-component bicyclization providing an expedient access to pyrano-[2′,3′:5,6]pyrano[2,3-*b*]pyridines and its derivatives. *ACS Comb. Sci.* **2014**, *16*, 647−651. (b) Wu, X.-J.; Jiang, R.; Xu, X.-P.; Su, X.-M.; Lu, W.-H.; Ji, S.-J. Practical multi-component synthesis of di- or tri-aryl (heteraryl) substituted 2-(pyridin-2-yl)imidazoles from simple building blocks. *J. Comb. Chem.* **2010**, *12*, 829−835. (c) Tu, S.-J.; Zhang, X.-H.; Han, Z.-G.; Cao, X.-D.; Wu, S.-S.; Yan, S.; Hao, W.-J.; Zhang, G.; Ma, N. Synthesis of isoxazolo[5,4-*b*]pyridines by microwave-assisted multi-component reactions in water. *J. Comb. Chem.* **2009**, *11*, 428−432.

(10) Plat, J. T.; Wenner, W. The reaction of acetophenone with formaldehyde and methylamine hydrochloride. *J. Org. Chem.* **1949**, *14*, 447−452.