# A General Preparation of Pyridines and Pyridones via the **Annulation of Ketones and Esters**

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A general preparation of pyridines  $4\mathbf{a} - \mathbf{f}$  from stabilized ketones  $3\mathbf{a} - \mathbf{c}$  and any ketones  $3\mathbf{d} - \mathbf{f}$  is described. The annulation of stabilized esters **3g,h** gives access to the corresponding 2-pyridones **4g,h**. The annulation reactions proceed in fair to excellent yields (46–87%) with vinamidinium hexafluorophosphate salts 2a-d containing electron-withdrawing groups at the  $\beta$ -position. The mechanism of the reaction was investigated by NMR and proceeds through the formation of a dienaminone intermediate.

### Introduction

For the past century, classical methods for the formation of pyridines have been used extensively. Such methods include the Friedländer condensation of enaminoketones or  $\beta$ -ketoesters with 1,3-diketones,<sup>1</sup> the Hantzsch pyridine synthesis from  $\beta$ -dicarbonyl compounds in the presence of an aldehyde and ammonia,<sup>2</sup> and the related Knoevenagel cyclization of  $\beta$ -aminoacrylates with  $\alpha$ . $\beta$ -unsaturated carbonyl compounds.<sup>3</sup> Despite the numerous studies and applications that have appeared in the literature,<sup>4,5</sup> most methods are still severely limited in their use by the lack of generality, the harsh reaction conditions involved, the poor yields, or the formation of complex mixtures of side products. New methodologies alleviate some of these limitations.<sup>5</sup> They include the inverse electron-demand Diels-Alder cycloaddition of triazines with electron-rich alkenes,  $^{\rm 6}$  the cycloaddition of azadienes with Fisher carbenes,<sup>7</sup> and the sequential

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reaction of metalated phosphonates with nitriles and unsaturated carbonyl compounds.<sup>8</sup>

We have recently described how the COX-2 specific inhibitor Etoricoxib can be assembled by construction of the central pyridine ring with the introduction of the C-5 substituent in a single step from the readily accessible ketone 1, 2-chloro-N,N-dimethylamino trimethinium hexafluorophosphate salt 2a (CDT-phosphate) and ammonia (Scheme 1).9 As a result of these studies, CDTphosphate (2a) has become available in commercial quantities. The  $\beta$ -substituted vinamidinium hexafluorophosphate salts 2 are accessible in good yield by reacting the corresponding acetic acids or acetyl chlorides with phosphorus oxychloride in DMF at 70 °C followed by quenching in aqueous HPF<sub>6</sub>.<sup>10,11</sup> The convenient preparation and stability of hexafluorophosphate vinamidinium salts renders their use very attractive in synthesis.

We have recently applied this methodology to the preparation of substituted pyridine derivatives via the annulation of ketones with vinamidinium salts (Scheme 2).<sup>12</sup> The chloropyridine derivatives, which are accessible

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General Preparation of Pyridines and Pyridones



from CDT-phosphate, are of interest to us and can be further functionalized via efficient palladium-catalyzed carbon-carbon and carbon-nitrogen coupling reactions<sup>13</sup> as recently reported by Buchwald<sup>14</sup> and Fu.<sup>15</sup> Although this new reaction allows the direct formation of pyridines from ketones, it was limited to  $\alpha$ -aryl ketones or aldehydes and required the use of excess carboxylic acid (7-8)equiv) and ammonium hydroxide (10 equiv). The extension of the methodology to a broader range of carbonyl compounds is of strategic interest since it would be amenable to the generation of combinatorial libraries. Moreover, the simplicity of the reaction allows the largescale preparation of substituted pyridines in a very straightforward manner.

In this paper, we report the annulation of stabilized ketones and esters with vinamidinium salts under simplified reaction conditions to give the corresponding substituted pyridines and pyridones in fair to excellent yields.

#### **Results and Discussion**

Enolates of aldehydes, ketones, and esters are known to add to vinamidinium salts to produce dienaminones in moderate to good yields.<sup>16</sup> For initial studies, methyl acetoacetate (3a) was chosen as a representative ketone. The ketone was reacted with CDT-phosphate (2a) according to the Nair procedure<sup>16</sup> in the presence of sodium hydride and pyridine in THF, and the resulting intermediate was reacted in situ with an excess of ammonium hydroxide at reflux to give 27% assay yield of the desired 2-methyl-3-methoxycarbonyl-5-chloropyridine (4a). Preforming the enolate with *t*-BuOK followed by reaction in THF at 40-65 °C gave improved results, with the yield of 4a increasing to 60%, although substantial starting material remained unreacted. Upon further optimization, it was found that addition of an equimolar amount of DABCO to the mixture of preformed potassium enolate and CDT-phosphate in THF for 3 h at 45 °C gave complete conversion (Scheme 3).

The disappearance of the starting material was monitored by <sup>1</sup>H NMR. Ammonium acetate was added to the resulting adduct, and ring closure to the pyridine occurred upon heating at reflux in THF for a few hours to give the desired pyridine 4a in 84% isolated yield (Table 1, entry 1). DABCO accelerated the addition reaction and led to complete consumption of the preformed potassium enolate. The reaction conducted with t-BuOK in the absence of DABCO did not go to completion and resulted in 68% assay yield of the desired pyridine (entry 2).



Although other bases such as triethylamine and pyridine could also be used, DABCO gave the best results. Preformation of the enolate with *t*-BuOK was essential for the reaction to proceed. The addition of DBU or stronger bases such as alkoxides or amides to the preformed enolate/CDT mixture led to extensive decomposition of CDT. The reaction did not proceed in toluene, dichloromethane, or DMSO. Although DMF is a suitable solvent, it was used only when a higher temperature of cyclization was required (vide infra) since under otherwise identical conditions the enolate reaction was slower and translated into lower conversions. The reaction is slow and incomplete when conducted in wet solvents.<sup>17</sup>

The ketoamide **3b** reacted in excellent yield under the reaction conditions (entry 3). 1,3-Diketones reacted more slowly, and the conversion was incomplete. In this case, the addition of DABCO did not accelerate or drive the reaction to completion. The annulation of 1,3-cyclohexadione proceeded in an unoptimized 46% assay yield to give the azatetralone **4c** in a *single step*. The azatetralone is an intermediate in the synthesis of an aldose reductase inhibitor, which was previously prepared in five steps from 3-bromo-5-chloro-2-pyridone.<sup>18</sup> Replacement of the CDT by the more electrophilic nitro-substituted iminium salt 2b allowed a complete consumption of the enolate in few minutes at room temperature and increased the yield of cyclization to 80% (Scheme 4). Nitropyridines are useful precursors to 3-aminopyridines. This result is significant since the  $\beta$ -phthalimidyl vinamidinium salt behaves poorly (vide infra) and alternative 2-amino vinamidinium salts did not react under standard conditions.19

Acyclic diketones such as dibenzoylmethane, trifluoromethylacetylacetone, and acetylacetone were unreactive and failed to give preparatively useful yields of the cyclized products. Enolates that are unstabilized reacted in lower yields. While the less stabilized enolate methoxymethyl phenyl ketone (Table 1, entry 6) proceeded in modest yield (36%), the condensation of acetophenone and 2-acetyl pyridine proceeded in only 14-15% to give the pyridines 4e-f (entries 7 and 8). This is a limitation of the current methodology, but studies are underway to extend the reactivity of unstabilized enolates with related vinamidinium analogues.<sup>20</sup>

Significantly, the reaction is not limited to ketones but can also be applied to esters. 3-Phenyl-5-chloropyri-

<sup>(13)</sup> The palladium-catalyzed Suzuki coupling of 4a with 4-methoxyphenyl boronic acid using (di-*tert*-butylphosphino)biphenyl as a ligand under reactions conditions reported in ref 14 gave the corresponding aryl pyridine in an unoptimized 60% yield. (14) Wolfe, J. P.; Singer, R. A.; Young, B. H., Buchwald, S. L. J.

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<sup>(17)</sup> Solvents that contain > 300  $\mu$ g H<sub>2</sub>O/mL as determined by Karl Fisher titration.

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<sup>(19)</sup> For the preparation of 2-amino vinamidinium salts, see: Arnold, Collect. Czech. Chem. Commun. 1973, 38, 1168.

<sup>(20)</sup> For the preparation and reactivity of vinamidinium analogues, see ref 11.

Table 1.	Annulation of Ketones and Esters with N,N-Dimethyl-2-chloro-trimethinium Hexafluorophosphate
	(CDT-phosphate) 2a <sup>a</sup>

Entry	Starting Material	Product	Assay Yield (%) <sup>b</sup>	Isolated Yield (%)
1 <sup>c</sup> 2	MeO 3a Me	MeO <sub>2</sub> C Me N 4a	87 68	84
3 <sup>c</sup>	Me <sub>2</sub> N 3b Me	Me2NOC CI Me N 4b	85	82
4 5	O J 3c		46 <sup>d</sup> 34	42 <sup>d</sup>
6 <sup>c</sup>	O Ph 3d	MeO Ph N 4d	36	19
7 <sup>c</sup>	Ph 3e	Ph N 4e	15	
8 <sup>c</sup>	Me N 3f		14	
9	O 3g	Ph O N H 4g	43	
10 <sup>e</sup>	MeO 3h	HO <sub>2</sub> C O N H 4h	78	68

<sup>*a*</sup> Unless otherwise noted, all reactions were conducted in THF using 1.05 equiv of 20 wt % *t*-BuOK/THF and 1.5 equiv of CDT-phosphate. <sup>*b*</sup> Assay determined by HPLC using an analytically pure sample of the final product as standard. <sup>*c*</sup> 1.0 equiv of DABCO was added to the CDT-enolate mixture. <sup>*d*</sup> 1.0 equiv of **3c** and 0.5 equiv of CDT-phosphate were used (yield based on CDT-phosphate). <sup>*e*</sup> The cyclization with ammonium acetate was performed at 120 °C in DMF.



done **4g** was formed cleanly from ethyl phenylacetate (entry 9). The cyclization on the ester required a solvent switch to DMF prior to the addition of ammonium acetate and heating at a temperature of 120 °C for 12 h. Dimethyl malonate reacted under similar reaction conditions to give 3-hydroxycarbonyl-5-chloro-2-pyridone **4h** in 78% yield after hydrolysis of the ester moiety (entry 10).

The scope of the reaction was examined by reacting methyl acetoacetonate with various substituted methinium salts (Table 2). As previously reported in the case of  $\alpha$ -aryl ketones,<sup>12</sup> the reaction was highly sensitive to the nature of the substituent at the  $\beta$ -position of the vinamidinium salts. Although excellent yields are obtained with CDT (entry 1), the replacement of chloride by a nitro group led to a very reactive electrophile that, in contrast with cyclohexanedione, reacted unselectively with methyl acetoacetonate to give a mixture of products.<sup>21</sup>

 Table 2. Annulation of Methyl Acetoacetate with

 Substituted N,N-Dimethylaminovinamidinium

 Hexafluorophosphate Salts<sup>a</sup>



The reaction did proceed in good yields in the case of aryl-substituted salts (entries 2–4). Previously, aryl-substituted vinamidinium salts were found to be unreactive when treated with the potassium enolate of ketosulfone **1** followed by quench in acetic acid and TFA.<sup>12</sup> The yields obtained are directly linked to the capacity of the  $\beta$ -substituent to stabilize a negative

<sup>(21)</sup> The major product identified was methyl 3-nitro-4-N,N-dimethylaminobenzoate and was isolated in 71% yield. A more detailed account of this work will be reported in due course.



charge; the more electron-withdrawing *p*-nitrophenyl substituent gave the highest yield at 67%. The unsubstituted phenyl group gave 61%, and the electron-donating *p*-methoxyphenyl substituent gave 46% yield (entries 2–4). The lower yield obtained using a phthalimidyl group is partly attributed to the weak electrophilicity of the substituent but also to partial decomposition via hydrolysis of the phthalimide moiety under the reaction conditions (entry 5). As expected, the methyl-substituted and unsubstituted methinium salts (R = H, Me) were unreactive.

## **Mechanistic Considerations**

Single-crystal X-ray structure determination revealed that vinamidinium salts adopt a symmetrical, planar "W" trans configuration.<sup>10–11,22</sup> Although the reaction of the enolate with the vinamidinium salt leads to the enamine intermediate **9**, two different transitions state models may be envisaged (Scheme 5). Reaction of the enolate via a 1,2-type addition on the imine function would go through the transition state **7**, decreasing the positive charge on the nitrogen atom. A 1,4-addition of the enolate (Michael-type) on the enaminone moiety leading to the transition state **8** can also be envisaged. This transition state would be stabilized by the presence of an electron-stabilizing substituent attached at the  $\beta$ -position (R<sub>3</sub>).

The results reported in Table 2 show that the electronaccepting character of the  $\beta$ -substituent has a dramatic effect on the rate and the yield of the reaction. Moreover, no reaction occurs unless an electron-stabilizing group is present at the  $\beta$ -position. Taken together, these observations suggest that the vinamidinium salt behaves as a Michael-type acceptor and that the transition state involves the formation of a partial negative charge at the  $\beta$ -carbon of the vinamidinium salt. Studies on unsymmetrically 1,3-disubstituted vinamidinium salts are currently underway to further study this mechanistic hypothesis.

Typically, the adduct **9** is not detected by NMR analysis of the crude reaction mixture and it undergoes elimination of dimethylamine to form the corresponding dienamine (Scheme 6). In some instances where the proton  $\alpha$  to the carbonyl is less acidic, the elimination is noticeably slower and can be accelerated by addition of a base such as DABCO. In the case of ketone **1**, the intermediate **7**, which required the use of an acid quench to drive the elimination, was isolated and characterized by NMR and HRMS.

The intermediates **10**, **11**, and **12** were isolated by concentration of the crude reaction mixture followed by purification on silica gel (1% Et<sub>3</sub>N, in EtOAc/hexanes) in 35%, 86%, and 98% yields, respectively (Scheme 6). The yield of formation of dienaminones **10** and **11** is within experimental error of the assay yields reported for the formation of pyridines **4c** and **4a** from the corresponding starting ketones. The cyclization of the two dienaminones **10** and **11**, when heated at reflux in THF in the presence of NH<sub>4</sub>OAc, proceeded in almost quan-

<sup>(22)</sup> CDT-phosphate **2a** was shown to have an all "W" conformation with bond lengths and bond angles within the expected range. The phenyl and 4-fluorophenyl vinamidinium salts also have identical conformations (see ref 10–11). See also: Koziol, A.; Palenik, G. J.; Marson, C. M.; Katritzky, A. R. *Acta Crystallogr.* **1990**, *C46*, 1282.



**Figure 1.** <sup>1</sup>H NMR data of **11** recorded at 27 °C in  $d^7$ -DMF in the presence of 1 equiv of NH<sub>4</sub>OAc. The content of the tube was heated at 45–65 °C for a period of 15–30 min between each accumulation.

titative yields, whereas in the presence of  $NH_4OH$  the reaction proceeded very slowly to give ca. 25% conversion after 2 days at 65 °C. Although high yields are obtained for the cyclization of dienamines onto a keto group, the cyclization on an ester or carboxylate is slower and proceeds in lower yields. The cyclization of the diester **12** does not proceed in THF at reflux, and a higher temperature of reaction in DMF is required.

The cyclization of intermediate **11** in the presence of ammonium acetate was followed by NMR (300 MHz <sup>1</sup>H and <sup>13</sup>C) in  $d^{7}$ -DMF (Figure 1). The reaction mixture was heated at 45-65 °C for a period of 15-30 min between each accumulation. The <sup>1</sup>H NMR spectra in Figure 1 show the appearance of an intermediate which was assigned to 13 (peaks B), along with the formation of dimethylamine (peak at 2.42 ppm). The concentration of the species 13 remains more or less constant during the whole transformation as the cyclization proceeds starting at a temperature of 45 °C. Coherent with our proposed mechanism, the concentration of dimethylamine, as measured by integration at any point during the reaction, equals the sum of the concentrations of 13 and the final pyridine 4a. No evidence of attack of ammonia on the ketone moiety to form an imine intermediate was detected by <sup>1</sup>H or <sup>13</sup>C NMR.

In conclusion, ketones and esters react with vinamidinium salts to give the corresponding pyridine and pyridone rings with high regioselectivity in fair to excellent yields. The reaction is dependent upon the nature of the substituent at the  $\beta$ -position of the vinamidinium species. This methodology represents a novel method to access the pyridine/pyridone systems and should find widespread application in heterocyclic chemistry. Further work is in progress to expand the scope of the reaction and explore the reactivity of structurally modified methinium reagents.

## **Experimental Section**

Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. High-resolution mass spectra were obtained from M-Scan, Inc., West Chester, PA. Water content was determined by Karl Fischer titration on a Metrohm 737 KF coulometer.

**General Experimental Procedure for the Annulation** of Ketones. To a suspension of the ketone (25 mmol) in dry THF (50 mL) at 0 °C was added dropwise a 20 wt % solution of t-BuOK in THF (16.4 mL, 26.3 mmol, 1.05 equiv). The slurry was stirred at room temperature for 45 min, and the vinamidinium hexafluorophosphate salt (11.5 g, 37.5 mmol, 1.5 equiv) was added in one portion. The resulting mixture was stirred at 45 °C for 3 h (in the presence of 1.0 equiv of DABCO when specified), and ammonium acetate (2 equiv) was added in one portion. The resulting dark solution was heated at reflux for 6 h and concentrated under reduced pressure. The residue was directly purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub> or CHCl<sub>3</sub>/MeOH was used as eluent). Alternatively, the residue after evaporation of the THF can be extracted with ethyl acetate and washed with water and saturated sodium chloride solution prior to the purification.

**2-Methyl-5-chloro Methylnicotinate (4a).** Mp 186–187 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.58 (d, J = 2 Hz, 1H), 8.18 (d, J = 2 Hz, 1H), 3.94 (s, 3H), 2.81 (3H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  165.6, 157.9, 150.5, 137.7, 129.1, 125.9, 52.4, 24.1. IR (cm<sup>-1</sup>): 3074, 3036, 3000, 2957, 2925, 2858, 1732. Anal. Calcd for C<sub>8</sub>H<sub>8</sub>ClNO<sub>2</sub>: C, 51.77; H,4.34; N, 7.55. Found: C, 51.98; H, 4.43; N, 7.44.

**2-Methyl-5-chloro Dimethylnicotinamide (4b).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.47 (d, J = 2 Hz, 1H), 7.48 (d, J = 2 Hz, 1H), 3.13 (s, 3H), 2.86 (s, 3H), 2.47 (s, 3H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  168.0, 152.5, 148.1, 133.4, 132.6, 129.2, 38.2, 34.7, 21.5. IR (cm<sup>-1</sup>): 3245, 3044, 3017, 2939, 1624, 1500, 1438, 1407, 1272, 1180, 1072, 914, 841. Anal. Calcd for C<sub>9</sub>H<sub>11</sub>ClN<sub>2</sub>O C, 54.42; H, 5.58; N, 14.10. Found: C, 54.85; H, 5.72; N, 13.72

**3-Chloro-7,8-dihydro-5(6***H***)-quinolone (4c).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.63 (d, *J* = 2 Hz, 1H), 8.23 (d, *J* = 2 Hz, 1H), 3.12–3.16 (m, 2H), 2.67–2.71 (m, 2H), 2.16–2.24 (m, 2H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>): δ 196.7, 161.3, 152.1, 134.1, 130.7,

128.6, 38.1, 31.8, 21.5. Anal. Calcd for  $C_9H_8$ ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.63; H, 4.63; N, 7.55.

**2-Phenyl-3-methoxy-5-chloropyridine (4d).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.30 (d, J = 2 Hz, 1H), 7.88–7.92 (m, 2H), 7.39–7.47 (m, 3H), 7.29 (d, J = 2 Hz, 1H), 3.86 (s, 3H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  153.7, 146.5, 139.9, 136.9, 130.7, 129.3, 128.7, 128.1, 118.8, 55.8. LC-MS [M + H]<sup>+</sup> 228.7.

**2-Phenyl-5-chloropyridine (4e).**<sup>23</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.66 (d, J = 2 Hz, 1H), 7.96–8.00 (m, 2H), 7.73 (dd, J = 8, 2 Hz, 1H), 7.68 (d, J = 8 Hz, 1H), 7.42–7.52 (m, 3H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  155.5, 148.3, 138.0, 136.6, 130.7, 129.4, 128.9, 126.8, 121.2.

**2-(Pyridin-2-yl)-5-chloropyridine (4f).**<sup>24</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.68 (dd, J = 5, 1 Hz, 1H), 8.62 (d, J = 2 Hz, 1H), 8.39 (d, J = 8 Hz, 1H), 8.38 (dt, J = 8, 1 Hz, 1H), 7.83 (dt, J = 8, 1 Hz, 1H), 7.79 (dd, J = 8, 2 Hz, 1H), 7.32 (ddd, J = 8,5,1 Hz). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  155.0, 154.1, 149.0, 147.9, 137.0, 136.5, 132.2, 123.8, 121.8, 121.0.

3-Carboxy-5-chloro-2-pyridone (4h)<sup>25</sup> was prepared by adding dropwise a 20 wt % solution of t-BuOK in THF (26.3 mmol, 1.05 equiv) to a suspension of dimethyl malonate (25 mmol) in dry THF (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 45 min, and the vinamidinium hexafluorophosphate salt (37.5 mmol, 1.5 equiv) was added in one portion. The resulting mixture was stirred at 45 °C for 6 h. The volatiles were removed in vacuo. DMF was added (25 mL) followed by ammonium acetate (3 equiv). The resulting dark solution was heated at 120 °C for 20 h, cooled, and concentrated under reduced pressure. Water (100 mL) was added to the black residue, and the mixture was washed with dichloromethane (3  $\times$  100 mL). The pH of the water solution was adjusted to 7-8 by addition of aqueous NaOH, and the solution was further extracted with dichloromethane. The water layer was concentrated in vacuo until a thick dark oil was obtained. A brown solid was obtained by vigorous stirring of the oil in ethyl acetate for several hours at room temperature. The solid was filtered, and the cake was washed with ethyl acetate. The resulting beige solid can be recrystallized from ethyl acetate or IPAc. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  9.5– 6.5 (bs, 2H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>): δ 169.5, 166.8, 148.1, 138.4, 119.0, 115.4. HRMS: calcd for C<sub>6</sub>H<sub>4</sub>ClNO<sub>3</sub> 172.9880, found 172.9856.

**3-Nitro-7,8-dihydro-5(6***H***)-quinolone (5).** The general experimental procedure was followed with the following modification: the reaction mixture after the addition of the vinamidinium hexafluorophosphate salt was aged 45 min at 20 °C instead of 45 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  9.48 (d, J = 2 Hz, 1H), 9.02 (d, J = 2 Hz, 1H), 3.30 (t, J = 6 Hz, 2H), 2.79 (t, J = 6 Hz, 2H), 2.79 (quint., J = 6 Hz, 2H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  195.5, 169.0, 147.7, 143.4, 129.9, 127.9, 38.0, 32.7, 21.1. Anal. Calcd for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.40; H, 4.43; N, 14.35.

**2-Methyl-5-(4-nitrophenyl) methylnicotinate (6a).** Mp 180–182 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.89 (d, J = 2 Hz, 1H), 8.44 (d, J = 2 Hz, 1H), 8.34–8.38 (m., 2H), 7.76–7.80 (m, 2H), 3.99 (s, 3H), 2.92 (s, 3H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  166.6, 160.4, 150.0, 147.8, 143.2, 137.0, 131.9, 127.8, 125.6, 124.5, 52.6, 24.7. IR (cm<sup>-1</sup>): 3074, 3036, 3000, 2957, 2928, 1731, 1602, 1518, 1349, 1256, 1234, 1089, 856, 754. Anal. Calcd for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub> C, 61.76; H, 4.44; N, 10.29. Found: C, 60.73; H, 4.44; N, 9.76.

**2-Methyl-5-phenyl Methylnicotinate (6b).** Mp 85–85.5 °C.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.85 (d, J = 2 Hz, 1H), 8.40 (d, J = 2 Hz, 1H), 7.61–7.62 (m., 2H), 7.59–7.60 (m, 2H), 7.47–7.50 (m, 1H), 3.96 (s, 3H), 2.89 (s, 3H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  166.9, 158.4, 149.9, 136.7, 136.6, 134.0, 129.1, 128.2, 126.9, 125.1, 52.2, 24.4. IR (cm<sup>-1</sup>): 3058, 3031, 3003, 2975, 2948, 2843, 1728, 1455, 1437, 1319, 1247, 1230, 1085, 761, 698. Anal. Calcd for C<sub>14</sub>H<sub>13</sub>NO<sub>2</sub> C, 73.99; H, 5.77; N, 6.16. Found: C, 73.95; H, 5.97; N, 6.10.

**2-Methyl-5-(4-methoxyphenyl) Methylnicotinate (6c).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.81 (d, J = 2 Hz, 1H), 8.35 (d, J = 2 Hz, 1H), 7.50–7.54 (m., 2H), 6.98–7.01 (m, 2H), 3.94 (s, 3H), 3.85 (s, 3H), 2.85 (s, 3H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$ 167.1, 160.0, 157.8, 149.7, 136.1, 133.7, 129.2, 128.1, 125.2, 114.7, 55.4, 52.3, 24.4. IR (cm<sup>-1</sup>): 3058, 3048, 3010, 2961, 2928, 2838, 1730, 1612, 1518, 1454, 1249, 1088, 1031, 821, 783. Anal. Calcd for C<sub>15</sub>H<sub>15</sub>NO<sub>3</sub> C, 70.02; H, 5.88; N, 5.44. Found: C, 69.81; H, 5.78; N, 5.29.

**2-Methyl-5-phthalymidyl Methylnicotinate (6d).** Mp 206–208 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.77 (s, 1H), 8.36 (s, 1H), 7.96–2.00 (m, 2H), 7.82–7.85 (m, 2H), 3.94 (s, 3H), 2.91 (3H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  166.5, 165.9, 159.3, 149.0, 135.7, 134.7, 131.4, 126.3, 125.2, 123.9, 52.4, 24.5. IR (cm<sup>-1</sup>): 3058, 3040, 3026, 2960, 2923, 2853, 1728, 1561, 1470, 1381, 1282, 1218, 1085, 877, 714. Anal. Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub> C, 64.86; H, 4.08; N, 9.46. Found: C, 63.44; H, 4.05; N, 9.06.

**Dienamine 10.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.93 (s, 1H), 5.64 (s, 1H), 2.51–2.54 (m, 2H), 2.43 (s, 6H), 2.36–2.40 (m, 2H), 1.96–2.03 (m, 2H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>):  $\delta$  193.9, 171.8, 119.8, 117.9, 109.9, 96.5, 38.2, 36.2, 27.4, 20.8. LC-MS: [M + H]<sup>+</sup> 228.7, [M + Na]<sup>+</sup> 250.7.

**Dienamine 11.** Approximately 2:1 mixture of isomers. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.17 (s, 0.5H), 6.83 (s, 1H), 6.73 (s, 0.5H), 5.64 (s, 1H), 3.78 (s, 1.5H), 3.69 (s, 3H), 3.18 (s, 3H), 2.47 (s, 6H), 2.34 (s, 3H), 2.18 (s, 1.5H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) 192.9, 170.0, 165.8, 149.0, 143.3, 125.6 (broad), 121.0, 112.9 (broad), 97.5, 51.8, 51.2, 43.2, 38.7, 26.4, 20.5. Anal. Calcd for C<sub>10</sub>H<sub>14</sub>ClNO<sub>3</sub> C, 51.84; H, 6.09; N, 6.05. Found: C, 51.97; H, 6.01; N, 5.93.

 $\begin{array}{l} \textbf{Dienamine 12.}\ ^{1}\text{H NMR (400 MHz, CDCl_3):}\ \delta\ 7.26\ (\text{s},\ 1\text{H}),\\ 6.66\ (\text{s},\ 1\text{H}),\ 3.82\ (\text{s},\ 3\text{H}),\ 3.75\ (\text{s},\ 3\text{H}),\ 3.19\ (\text{s},\ 6\text{H}).\ ^{13}\text{C NMR}\\ (100\ \text{MHz}\ \text{CDCl}_3):\ \delta\ 168.4,\ 166.1,\ 147.8,\ 143.7,\ 111.3,\ 97.3,\\ 52.0,\ 51.9,\ 43.1,\ 29.6.\ \text{Anal. Calcd for } C_{10}\text{H}_{14}\text{ClNO}_4\ \text{C},\ 48.49;\\ \text{H},\ 5.70;\ \text{N},\ 5.66.\ \text{Found:}\ \text{C},\ 48.52;\ \text{H},\ 5.73;\ \text{N},\ 5.51.\\ \textbf{Dienamine 13.}\ ^{1}\text{H NMR (300\ MHz,\ CDCl_3):}\ \delta\ 8.58\ (\text{s},\ 1\text{H}),\\ \end{array}$ 

**Dienamine 13.** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.58 (s, 1H), 7.84 (s, 1H), 8.36 (s, 1H), 7.46–7.52 (m, 2H), 7.11–7.20 (m, 2H), 3.95 (s, 3H), 2.80 (s, 3H). <sup>13</sup>C NMR (75 MHz CDCl<sub>3</sub>):  $\delta$  165.2, 149.4, 139.5, 135.4, 129.5, 128.7, 128.6, 125.3, 116.6, 116.4, 53.0, 14.7. LC-MS: [M<sup>+</sup>+1] 262.1.

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