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## THE ONE-POT SYNTHESIS OF PYRIDINE DERIVATIVES FROM THE CORRESPONDING 1,5-DICARBONYL COMPOUNDS

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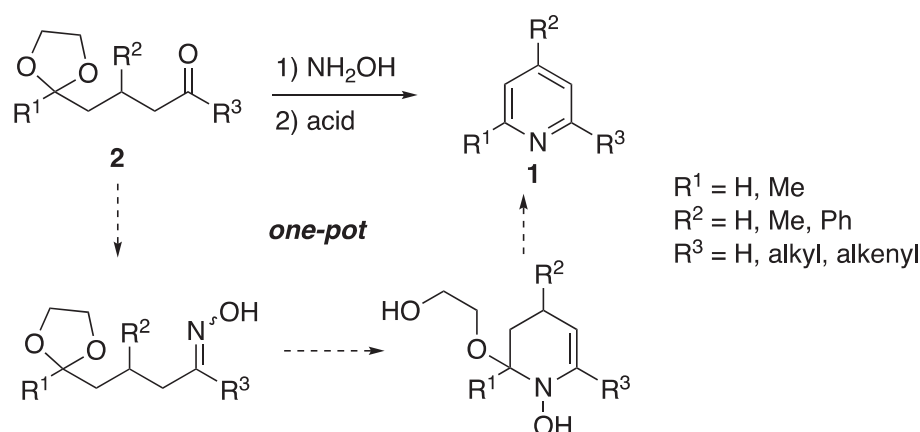
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**Abstract** – The optimization of the one-pot, acid-promoted synthesis of pyridine and alkyipyridine derivatives from simple alkyl-1,5-dicarbonyl derivatives and via the corresponding oxime intermediate is described. Of all the combinations of and solvents tested, the use of HCl in refluxing dioxane was found to result in the highest chemical yields. Twelve pyridines were prepared using this method.

### INTRODUCTION

The pyridine heterocyclic ring is found in numerous natural products, organic materials and pharmaceuticals,<sup>1-3</sup> and the development of pyridine synthesis has been ongoing for some time. A variety of metal<sup>4</sup> and metal-free<sup>5</sup> methods have been developed; however, a major limitation of the metal-free methods is that they are limited to the synthesis of substituted pyridines bearing bulky and rigid functionalities at the 2,6-positions<sup>5,6</sup> with less hindered, more flexible substrates tending to undergo aldol reaction instead.<sup>7</sup> Inspired by the chemistry of Kaiser,<sup>8</sup> Piccialli<sup>9</sup> and Knoevenagel,<sup>10</sup> we discovered that this problem could be obviated and the desired pyridine frameworks smoothly obtained from 1,5-dicarbonyl substrates, by converting them to the corresponding oximes first, and then converting these oximes to the desired pyridines.<sup>11</sup> The procedure was found to be compatible with a variety of substrates including unhindered 1,5-dicarbonyls, and its utility was exemplified in the total synthesis of the pyridyl natural product anibamine in overall yield of 12% - a yield roughly double that of the most recent total synthesis.<sup>11-13</sup> However, although this method has higher tolerance than previous metal-free methods in the point of practical applications, its optimization has yet to be reported. Herein, we disclose a study of the scope and limitations of the acid-promoted synthesis of pyridine and alkyipyridines **1** from simple alkyl-1,5-dicarbonyl derivatives **2** (Scheme 1).



**Scheme 1.** Acid-promoted synthesis of pyridines **1** from simple-1,5-dicarbonyl derivatives **2**

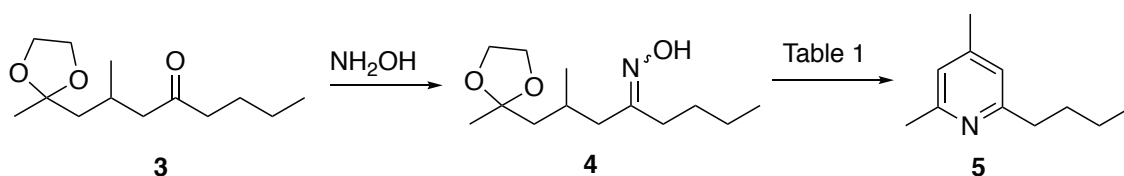
## RESULTS AND DISCUSSION

In our previous study, 2,4,6-trialkylpyridines were synthesized from alkyl-1,5-diketone derivatives by the refluxing them in AcOH.<sup>11</sup> Therefore, we first sought to optimize these reaction conditions with using oxime intermediate (**4**) derived from the 6-keto-2-ketal (**3**) as shown in Table 1. Refluxing **4** in AcOH for 1 h gave 2-butyl-4,6-dimethylpyridine (**5**) in 61% yield from **3** (entry 1). Treatment of oxime intermediate (**4**) with H<sub>2</sub>SO<sub>4</sub> in dioxane gave the desired **5** in 10% yield (entry 2). The use of PPTS and ZnCl<sub>2</sub> to accomplish this step resulted in very poor yields. (entries 3,4). Interestingly, refluxing **4** in toluene in the presence of silica gel for 12 h produced the pyridine **5** in moderate yield (entry 5). By using *p*-TsOH or H<sub>3</sub>PO<sub>4</sub> in place of silica gel, chemical yields of **5** were improved and compared favorably with the AcOH conditions (entries 6,7). Moreover, we found that 4N HCl/AcOEt or 4N HCl/1,4-dioxane than AcOH were better reagents. Pyridine formation of **4** with 50 equiv. of HCl in AcOEt or 1,4-dioxane at reflux for 1 h proceeded smoothly to give **5** in 72% yield (entries 8,9). The use of 50 equiv. of HCl in H<sub>2</sub>O failed to result in any desired product **5** (entry 10). On the other hand, produced oxime intermediate **4** from **3** was generally treated with usual workup, followed by pyridine formation with acidic condition to give **5**. Thereupon, we investigated the one-pot operation from the 6-keto-2-ketal (**3**) to 2-butyl-4,6-dimethylpyridine (**5**) toward work simplification. After the completion of oxime formation, the reaction mixture was concentrated *in vacuo*, diluted with 4N HCl/dioxane, and refluxed for 1 h. The one-pot method was found to result in a better chemical yield (76% yield) than previous one in entry 9. No deleterious side reactions were observed (entry 11) (Table 1).

Next, the pyridine cyclization reaction was optimized by testing various solvents and additives in Table 2. In all case, the yield of pyridine **5** was less than in 40% and accompanied by a roughly equivalent amount of the aldol adduct **6**. We assumed that the aldol condensation giving rise to **6** resulted from the presence of H<sub>2</sub>O in the reaction system, and thus added some dehydrating agents in Table 2. A variety of solvents were screened; in DMSO, pyridine **5** and aldol adduct **6** were obtained in yields of 46% and 20% yields,

respectively (entry 1). Use of MS 4A, silica gel, or MgSO<sub>4</sub> as dehydrating agents in 12N HCl aq./DMSO did not improve the chemical yields of **5** (entries 2-4). However, decreasing the number of equivalents of HCl did diminish the yield of **6** – it was obtained in a yield of only 3% when 5 equiv. of HCl (0.1 mL) were used - a tenth of the acidic amount (50 equiv.) we used initially in entry 1 (entry 5). Similarly, treatment of substrate **3** with 12N HCl aq. in dioxane gave pyridine **5** and aldol adduct **6** in 39% and 31% yields, respectively (entry 6). Finally, we discovered that undertaking the reaction in the presence of 4 equiv. of HCl in dioxane resulted in pyridine **5** in 84% yield without any aldol adducts (entry 7). This result was familiar with those of using 4N HCl/dioxane solution (entry 9, Table 1). We optimized the reaction condition of one-pot method with the treatment of NH<sub>2</sub>OH·HCl in MeOH and 4 equiv. of HCl in refluxed dioxane prepared from 4N HCl/dioxane to give alkylpyridines derived from 1,5-dicarbonyl compounds (Table 2).

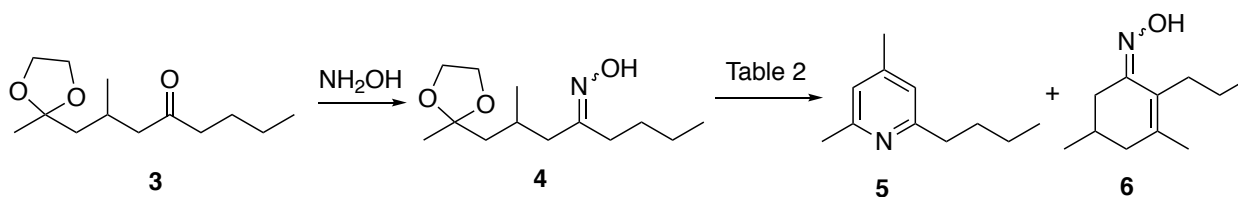
**Table 1.** Screening of acidic reagent for alkylpyridine formation via oxime intermediate



entry	Reagent (equiv.)	solvent	Temp (°C)	Time (h)	yield (%) <sup>a,b</sup>
1	AcOH (100)	-	reflux	1	61
2	H <sub>2</sub> SO <sub>4</sub> (50)	dioxane	reflux	1	10
3	PPTS (50)	dioxane	reflux	1	13
4	ZnCl <sub>2</sub> (10)	<i>n</i> -PrOH	reflux	1	29
5	silica gel	toluene	reflux	12	43
6	<i>p</i> -TsOH (50)	dioxane	reflux	1	50
7	H <sub>3</sub> PO <sub>4</sub> (50)	dioxane	reflux	1	67
8	4N HCl (50)	AcOEt	reflux	1	72 <sup>c</sup>
9	4N HCl (50)	dioxane	reflux	1	72 <sup>c</sup>
10	4N HCl (50)	H <sub>2</sub> O	90	1	0
11	4N HCl (50)	dioxane	reflux	1	76 <sup>d</sup>

<sup>a</sup> Isolation yield, <sup>b</sup> Overall yield for two steps, <sup>c</sup> Dehydrated 4N HCl/dioxane or 4N HCl/AcOEt were used,

<sup>d</sup> One-pot operation.

**Table 2.** Optimization of alkyipyridine formation with one-pot protocol<sup>a</sup>


entry	HCl (equiv.)	Additive/solvent	<b>5</b> (%)	<b>6</b> (%)
1	50	DMSO	46	20
2	50	MS 4A, DMSO	43	9
3	50	silica gel, DMSO	49	19
4	50	MgSO <sub>4</sub> , DMSO	48	13
5	5	DMSO	56	3
6 <sup>b</sup>	50	dioxane	39	31
7 <sup>b</sup>	4	dioxane	84	0

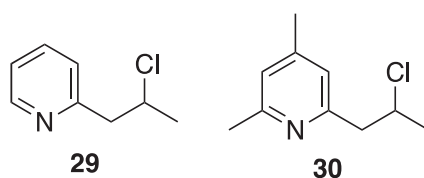
<sup>a</sup> Oximes from **3** (0.2 mmol), 12N HCl, solvent and additive were used and heated at 110 °C for 1 h. <sup>b</sup> 12N HCl was used.

A variety of 1,5-dicarbonyl compounds were submitted to these optimized conditions to obtain the corresponding alkyipyridines in Table 3. The reaction was found to generally high yielding and broad in scope, compatible with ketone (**3**, **7-9**), rigid substrates (**10**, **11**), oxo-acetals (**12-15**) and substrates with terminal alkene (**16**, **17**). All substrates (**3**, **7-17**) were prepared starting from heptane-1,5-diol derivatives, 3-oxo-phenylpropanoic acid derivatives, or pentane-2,4-diol derivatives and assigned by reasonable spectral data (see Supporting Information). 6-Keto-2-ketal (**3**) used in Tables 1 and 2 with optimized condition was transformed 2-butyl-4,6-dimethylpyridine (**5**) in 89% yield (entry 1). Substrates (**7**, **8** and **9**) to be similar with **3** also gave the same results with entry 1 to afford trialkyl pyridines (**18**, **19** and **20**) in good yields, respectively (entries 2-4). As expected, the reaction of rigid substrates **10** and **11** with phenyl groups at 1-position were carried out to give 1-phenylpyridines **21** and **22** in high yields (95% for **21** and 100% for **22**) (entries 5, 6). These results showed that optimized condition using HCl for pyridine formation of entries 1-6 exceeded its AcOH condition by our previous report<sup>11</sup> in chemical yields. Oxo-acetals (**12-15**) gave the corresponding pyridines (**23-26**) (entries 7-10). The moderate yield (48%) of pyridine (**24**) was attributed to produce loss during work-up due to its low boiling point (entry 8). The substrates with terminal alkene (**16**, **17**) gave pyridines (**27**, **28**) in 19% and 13% yields, respectively. In these cases, 2'-chloropyridines (**29**, **30**) were afforded in moderate yields (62% and 70%) as major products (entries 11, 12, Figure 1). It can be transformed 2'-chloropyridine (**29**) to *E*-alkenylpyridine (**27**) in 82% yield by the treatment of DBU in THF under reflux condition.

**Table 3.** One-pot synthesis of alkylpyridines from simple alkyl 1,5-dicarbonyl compounds <sup>a</sup>

entry	substrate	product	yield (%)	entry	substrate	product	yield (%)
1			89	7			93
2			89	8			48
3			87	9			92
4			93	10			88
5			95	11			19 (62)
6			100	12			13 (70)

<sup>a</sup> Condition of one pot method: substrates (0.2 mmol) in MeOH (0.6 mL) were added to AcONa (0.3 mmol) and NH<sub>2</sub>OH·HCl (0.24 mmol) to afford the oxime intermediates, then replaced solvent to 1,4-dioxane (0.08 M), followed by adding 4N HCl/dioxane (0.2 mL) and refluxed for 1 h.

**Figure 1.** Chemical structure of 2'-chloropyridines **29** and **30**

In conclusion, we have developed novel, one-pot method for the formation of pyridines from simple alkyl-1,5-dicarbonyl derivatives by oximation followed by simple heating them in HCl/dioxane. Our reaction is generally broad in scope, high-yielding, and therefore expected to be useful for the synthesis of a variety of pyridine derivatives.

## EXPERIMENTAL

**General** All solvents were reagent grade. CH<sub>2</sub>Cl<sub>2</sub> was distilled from CaH<sub>2</sub> and THF from Na. All commercial reagents were of the highest purity available. <sup>1</sup>H (400, 500 or 600 MHz) and <sup>13</sup>C NMR (100, 125 or 150 MHz) spectra were recorded on JNM-ECX400, JNM-ECX500 or JNM-ECA600 spectrometers. Chemical shifts are expressed in ppm relative to CHCl<sub>3</sub> (7.26 ppm for <sup>1</sup>H and 77.16 ppm for <sup>13</sup>C). Analytical TLC was performed on Merck Silica gel 60F<sub>254</sub>. Crude products were purified by column chromatography on Silica Gel 60 N [Kanto, particle size, (spherical, neutral) 63–210 μm or 100–200 μm]. High-resolution mass spectra (HRMS) were obtained using a JEOL AccuTOF JMS-T100LC (ESIMS). GC-MS. IR spectra were recorded at FT/IR-460 plus (JASCO, Tokyo, Japan).

**General procedure** Substrates (0.2 mmol) in MeOH (0.6 mL) were added to AcONa (0.3 mmol) and NH<sub>2</sub>OH·HCl (0.24 mmol). After 1 h, the mixture was concentrated *in vacuo*. The residue was added to dioxane (2.5 mL) and 4N HCl/dioxane (0.2 mL) and refluxed for 1 h. After cooling to room temperature, the mixture was concentrated *in vacuo*. The residue was diluted with NaHCO<sub>3</sub> aq. and CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was separated, washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified with silica gel column chromatography to give the pyridine derivatives.

**4,6-Dimethyl-2-butylpyridine (5)** (29.1 mg, 89%) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.92 (t, *J* = 7.6 Hz, 3H), 1.37 (m, 2H), 1.65 (m, 2H), 2.25 (s, 3H), 2.46 (s, 3H), 2.69 (t, *J* = 8.0 Hz, 2H), 6.75 (s, 1H), 6.76 (s, 1H).<sup>11</sup>

**4,6-Dimethyl-2-propanylpyridine (18)** (26.6 mg, 89%) as a yellow oil. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 0.95 (t, *J* = 7.8 Hz, 3H), 1.70 (m, 2H), 2.26 (s, 3H), 2.47 (s, 3H), 2.67 (t, *J* = 7.8 Hz, 2H), 6.76 (s, 1H), 6.78 (s, 1H).<sup>11</sup>

**2-Decanyl-4,6-dimethylpyridine (19)** (21.4 mg, 87% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.24 (brs, 14H), 1.66 (m, 2H), 2.25 (s, 3H), 2.47 (s, 3H), 2.68 (t, *J* = 8.0 Hz, 2H), 6.76 (s, 1H), 6.77 (s, 1H).<sup>11</sup>

**4,6-Dimethyl-2-(3-pivaloyloxypropyl)pyridine (20)** (46.5 mg, 93%) as a yellow oil. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 1.19 (s, 9H), 2.06 (m, 2H), 2.26 (s, 3H), 2.47 (s, 3H), 2.77 (t, *J* = 7.8 Hz, 2H), 4.08 (t, *J* = 6.6 Hz, 2H), 6.76 (s, 1H), 6.80 (s, 1H).<sup>11</sup>

**2-Phenyl-4,6-dimethylpyridine (21)** (34.8 mg, 95%) as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.37 (s, 3H), 2.59 (s, 3H), 6.94 (s, 1H), 7.34 (s, 1H), 7.39 (tt, *J* = 7.3, 1.5 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.97 (dt, *J* = 6.5, 2.0 Hz, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 21.2, 24.7, 118.9, 122.7, 127.2, 128.67, 128.73, 140.1, 147.9, 157.1, 158.2. IR (film) ν<sub>max</sub> cm<sup>-1</sup>: 3060, 3029, 2955, 2925, 2854, 2359, 2338, 1741, 1607, 1456, 1230, 1029. HRMS (ESI) *m/z*: calcd. for C<sub>13</sub>H<sub>14</sub>N [M+H]<sup>+</sup> 184.1126, found 184.1100.

**2-*p*-Methylphenyl-4,6-dimethylpyridine (22)** (39.4 mg, 100%) as a pink oil.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  2.35 (s, 3H), 2.40 (s, 3H), 2.57 (s, 3H), 6.91 (s, 1H), 7.25 (d,  $J = 7.8$  Hz, 2H), 7.31 (s, 1H), 7.86 (d,  $J = 8.4$  Hz, 2H).<sup>11</sup>

**4-Phenylpyridine (23)** (28.9 mg, 93%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta = 7.42$ -7.51 (m, 5H), 7.63-7.65 (m, 2H), 8.65 (s, 2H).<sup>14</sup>

**Pyridine (24)** (7.6 mg, 48%) as a yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  7.24 (m, 1H), 7.63 (tt,  $J = 7.8$  Hz, 1.8 Hz, 2H), 8.57-8.60 (m, 2H).<sup>15</sup>

**2-Butylpyridine (25)** (24.9 mg, 92%) as a yellow solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  0.92 (t,  $J = 6.6$  Hz, 3H), 1.34-1.40 (m, 2H), 1.67-1.72 (m, 2H), 2.77 (t,  $J = 7.8$  Hz, 2H), 7.07 (dd,  $J = 8.4$ , 4.4 Hz, 1H), 7.12 (d,  $J = 8.4$  Hz, 1H), 7.56 (td,  $J = 8.4$ , 1.2 Hz, 1H), 8.50 (d,  $J = 4.4$  Hz, 1H).<sup>16</sup>

**2-(2-Methylpropyl)pyridine (26)** (23.8 mg, 88%) as a yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.88 (d,  $J = 6.8$  Hz, 6H), 1.94 (m, 1H), 2.61 (t,  $J = 7.2$  Hz, 2H), 7.06 (m, 2H), 7.54 (td,  $J = 7.6$ , 2.0 Hz, 1H), 8.49 (d,  $J = 4.8$  Hz, 1H).<sup>17</sup>

**2-[(1*E*)-Propenyl]pyridine (27)** (3.1 mg, 13%) as a yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.92 (dd,  $J = 6.8$ , 1.2 Hz, 3H), 6.49 (dq,  $J = 15.8$ , 1.2 Hz, 1H), 6.73 (dq,  $J = 15.8$ , 6.8 Hz, 1H), 7.07 (dd,  $J = 8.0$ , 4.0 Hz, 1H), 7.22 (d,  $J = 8.0$  Hz, 1H), 7.58 (td,  $J = 8.0$ , 1.6 Hz, 1H), 8.51 (d,  $J = 4.0$  Hz, 1H).<sup>18</sup>

***E*-4,6-Dimethyl-2-(penten-1-yl)pyridine (28)** (5.6 mg, 19%) as a yellow oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.91 (dd,  $J = 7.0$ , 2.0 Hz, 3H), 2.27 (s, 3H), 2.48 (s, 3H), 6.45 (dq,  $J = 19.5$ , 2.0 Hz, 1H), 6.67 (dq,  $J = 19.5$ , 8.5 Hz, 1H), 6.79 (s, 1H), 6.88 (s, 1H), 6.90 (s, 1H).<sup>11</sup>

**2-(2-Chloropropyl)pyridine (29)** (19.3 mg, 62%)  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.57 (d, 3H,  $J = 5.0$  Hz), 3.07 (t, 2H,  $J = 5.0$  Hz), 4.50 (m, 1H), 7.06 (dd, 1H,  $J = 6.0$ , 4.0 Hz), 7.21 (d, 1H,  $J = 6.0$  Hz), 7.57 (t, 1H,  $J = 6.0$ , 1.0 Hz), 8.50 (dd, 1H,  $J = 4.0$ , 1.0 Hz).

**2-(2-Chloropropyl)-4,6-dimethylpyridine (30)** (25.7 mg, 70%)  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.53 (d, 3H,  $J = 7.0$  Hz), 2.28 (s, 3H), 2.47 (s, 3H), 3.07 (t, 2H,  $J = 7.0$  Hz), 4.47 (m, 1H), 6.81 (s, 1H), 6.83 (s, 1H).

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## REFERENCES

1. C. Allais, J. M. Grassot, J. Rodriguez, and T. Constantieux, *Chem. Rev.*, 2014, **114**, 10829.
2. H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, and K. Itoh, *Organometallics*, 1989, **8**, 846.
3. (a) R. Sakai, T. Higa, C. W. Jefford, and G. Bernardinelli, *J. Am. Chem. Soc.*, 1986, **108**, 6404; (b) V.

- A. F. F. M. Santos, L. O. Regasini, C. R. Nogueira, G. D. Passerini, I. Martinez, V. S. Bolzani, M. A. S. Graminha, R. M. B. Cicarelli, and M. Furlan, *J. Nat. Prod.*, 2012, **75**, 991; (c) A. Evidente and A. Kornienko, *Phytochem. Rev.*, 2009, **8**, 449; (d) J. E. Leet, D. R. Schroeder, S. J. Hofstead, J. Golik, K. L. Colson, S. Huang, S. E. Klohr, T. W. Doyle, and J. A. Matson, *J. Am. Chem. Soc.*, 1992, **114**, 7946; (e) B.-S. Yun, T. Hidaka, K. Furihata, and H. Seto, *J. Antibiot.*, 1994, **47**, 510.
4. (a) M.-N. Zhao, L. Yu, N.-F. Mo, Z.-H. Ren, Y.-Y. Wang, and Z.-H. Guan, *Org. Chem. Front.*, 2017, **4**, 597; (b) W.-W. Tan, Y.-J. Ong, and N. Yoshikai, *Angew. Chem. Int. Ed.*, 2017, **56**, 8240; (c) F. Xu, C. Wang, H. Wang, X. Li, and B. Wan, *Green Chem.*, 2015, **17**, 799; (d) R. M. Martin, R. G. Bergman, and J. A. Ellman, *J. Org. Chem.*, 2012, **77**, 2501; (e) H. Huang, X. Ji, W. Wu, L. Huang, and H. Jiang, *J. Org. Chem.*, 2013, **78**, 3774; (f) Z. Li, X. Huang, F. Chen, C. Zhang, X. Wang, and N. Jiao, *Org. Lett.*, 2015, **17**, 584.
5. (a) D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223; (b) A. E. Chichibabin, *J. Russ. Phys. Chem. Soc.*, 1906, **37**, 1229; (c) F. Bohlmann and D. Rahtz, *Chem. Ber.*, 1957, **90**, 2265.
6. (a) H. Huang, J. Cai, L. Tang, Z. Wang, F. Li, and G.-J. Deng, *J. Org. Chem.*, 2016, **81**, 1499; (b) J. A. Hilf, M. S. Holzwarth, and S. D. Rychnovsky, *J. Org. Chem.*, 2016, **81**, 10376; (c) L.-G. Xie, S. Shaaban, X. Chen, and N. Maulide, *Angew. Chem. Int. Ed.*, 2016, **55**, 12864; (d) J. Shen, D. Cai, C. Kuai, Y. Liu, M. Wei, G. Cheng, and X. Cui, *J. Org. Chem.*, 2015, **80**, 6584; (e) J.-C. Xiang, M. Wang, Y. Cheng, and A.-X. Wu, *Org. Lett.*, 2016, **18**, 24; (f) Z. Song, X. Huang, W. Yi, and W. Zhang, *Org. Lett.*, 2016, **18**, 5640; (g) Q. Wang, C. Wan, Y. Gu, J. Zhang, L. Gao, and Z. Wang, *Green Chem.*, 2011, **13**, 578.
7. (a) V. G. Kharchenko, L. I. Markova, O. V. Fedotova, and N. V. Pchelintseva, *Chem. Heterocycl. Compd.*, 2003, **39**, 1121; (b) G. D. Henry, *Tetrahedron*, 2004, **60**, 6043; (c) M. D. Hill, *Chem. Eur. J.*, 2010, **16**, 12052; (d) T. J. Donohoe, J. A. Basutto, J. F. Bower, and A. Rathi, *Org. Lett.*, 2011, **13**, 1036; (e) T. J. Donohoe, J. F. Bower, D. B. Baker, J. A. Basutto, L. K. M. Chan, and P. Gallagher, *Chem. Commun.*, 2011, **47**, 1061; (f) G. Jones, in: *Comprehensive Heterocyclic Chemistry*, ed. by A. R. Katritzky and C. W. Rees, Pergamon: Oxford, 1984, Vol. 2.
8. S. Kaiser, S. P. Smidt, and A. Pfaltz, *Angew. Chem. Int. Ed.*, 2006, **45**, 5194.
9. V. Piccialli, S. D. Errico, N. Borbone, G. Oliviero, R. Centore, and S. Zaccaria, *Eur. J. Org. Chem.*, 2013, 1781.
10. (a) E. Knoevenagel, *Justus Liebigs Ann. Chem.*, 1894, **281**, 25; (b) F. Brody and P. R. Rudy, in: *Heterocyclic Compounds. Pyridine and Derivatives*, part I, ed. by E. Klingsberg, Interscience Publishers, New York, 1960, pp. 99-589; (c) N. S. Boodman, J. O. Hawthorne, P. X. Masciantonio, and A. W. Simon, in: *Pyridine and Its Derivatives: Supplement, Part One* ed. by R. A. Abramovitch, Wiley, New York, 1974, pp. 183-308.



11. T. Miyakoshi and H. Konno, *Org. Biomol. Chem.*, 2019, **17**, 2896.
12. H. Jayasuriya, B. K. Herath, J. G. Ondeyka, J. D. Polishook, G. F. Bills, A. W. Domdrowski, M. S. Springer, S. Siciliano, L. Malkowitz, M. Sanchez, Z. Guan, S. Tiwari, D. W. Stevenson, R. P. Borris, and S. B. Singh, *J. Nat. Prod.*, 2004, **67**, 1036.
13. G. Li, K. Watson, R. B. Buckheit, and Y. Zhang, *Org. Lett.*, 2007, **9**, 2043.
14. L. Ackermann, H. K. Potukuchi, A. Althammer, R. Born, and P. Mayer, *Org. Lett.*, 2010, **12**, 1004.
15. A. V. Afonin, I. A. Ushakov, S. Yu. Kuznetsova, O. V. Petrova, E. Yu. Schmidt, and A. I. Mikhaleva, *Magn. Reson. Chem.*, 2002, **40**, 114.
16. G. Chelucci, S. Gladiali, and M. Marchetti, *J. Heterocycl. Chem.*, 1988, **25**, 1761.
17. X. Chen, X.-S. Hao, C. E. Goodhue, and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 12634.
18. W. Jerome, G. Boris, H. Nambu, and E. M. Carreira, *J. Am. Chem. Soc.*, 2006, **128**, 11693.