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## FACILE SYNTHESIS OF PYRIDO[1,2-*a*]BENZIMIDAZOLE DERIVATIVES VIA NOVEL TANDEM REACTION INVOLVING HORNEMAN-EMMONS REACTION

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**Abstract** – Pyrido[1,2-*a*]benzimidazole derivatives were conveniently synthesized by a novel tandem reaction under mild conditions. The reaction mechanism was also proposed.

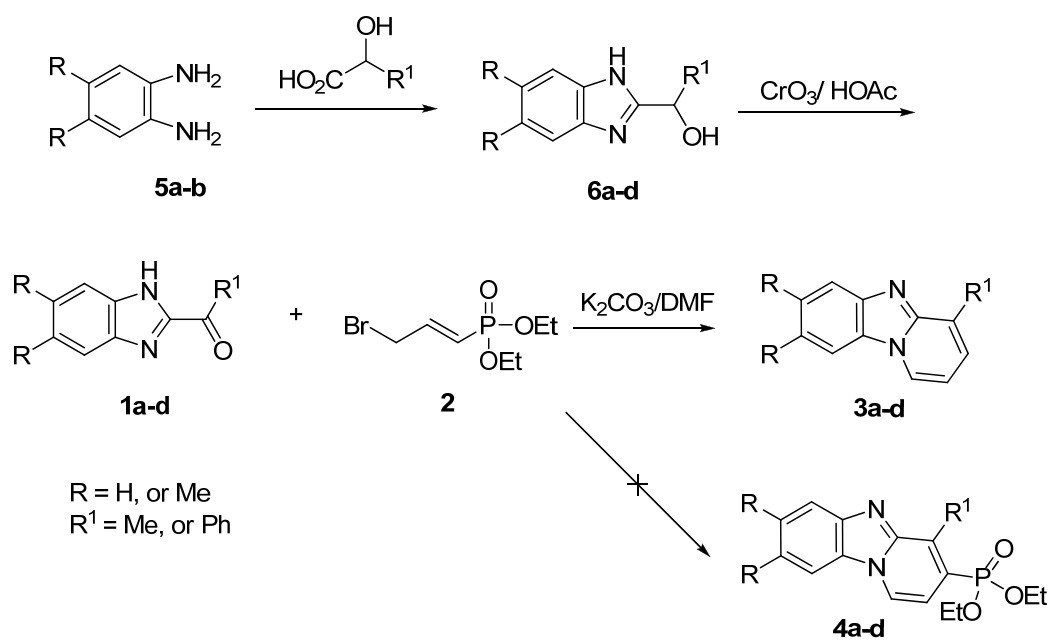
Imidazo[1,2-*a*]pyridines and related structures such as imidazo[1,2-*a*]pyrimidines, imidazo[1,2-*a*]quinoxaline or imidazo[1,2-*a*]isoquinoline have been extensively reported because of their pronounced biological activities.<sup>1-3</sup> In contrast, the related pyrido[1,2-*a*]benzimidazole derivatives have not been noticed until two decades ago when several reports in the literature described their pharmaceutical applications.<sup>4-7</sup> Furthermore, some of them also exhibit interesting photophysical and fluorescent properties.<sup>8-11</sup> However, as a class of compounds their pharmaceutical and spectroscopic properties have remained largely unexplored perhaps as a consequence of the lack of general synthetic methods to this class of heterocycles from easily accessible precursors.

Sundberg and Ellis reported those compounds could be obtained by condensation of 1,2-benzenediamines and 2-halopyridine.<sup>12</sup> Recently, a number of synthetic procedures for the synthesis of the compounds were reported. For example, one-step synthesis of the compounds by a multicomponent reaction was developed.<sup>13</sup> They can also be prepared from 2-acylmethyl-1*H*-benzimidazoles.<sup>14</sup> Previously, a novel tandem reaction<sup>15</sup> found by our group has been successfully applied to the synthesis of indolizines,

pyrazolo[1,5-*a*]pyridine, imidazo[1,2-*a*]pyridines, pyrido[1,2-*a*]benzimidazole and [1,2,4]triazolo[1,5-*a*]pyridine.<sup>16-22</sup> We recently reported several nitrogen bridgehead heterocycles with phosphonates via the tandem reaction.<sup>23</sup> In continuation of our work on pyrido[1,2-*a*]benzimidazole heterocycles with phosphonates, we wish to expand this strategy as a convenient synthetic method for the synthesis of 4-substituted pyrido[1,2-*a*]benzimidazole phosphonates. However, when the material changed to benzimidazole ketone, we got the Horner-Emmons products not phosphonates. Herein, we reported the novel reaction and the proposed mechanism.

Benzimidazole ketones **1a-d** and diethyl (3-bromoprop-1-enyl)phosphonate **2** were prepared according to a literature method (Scheme 1).<sup>20,23</sup> The unexpected pyrido[1,2-*a*]benzimidazole **3a-d** were obtained by the reactions of ketones **1a-d** and diethyl (3-bromoprop-1-enyl)phosphonate **2** in the presence of K<sub>2</sub>CO<sub>3</sub> in dry DMF at room temperature for 6-10 h. The experimental results are collected in Table 1.

The structures of products **3a-d** were characterized by spectroscopic methods (<sup>1</sup>H and <sup>13</sup>C NMR, IR, and HRMS). The structure of **3b** was further confirmed by X-ray crystallographic analysis as shown in Figure 1.



Scheme 1

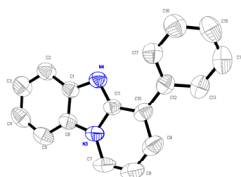
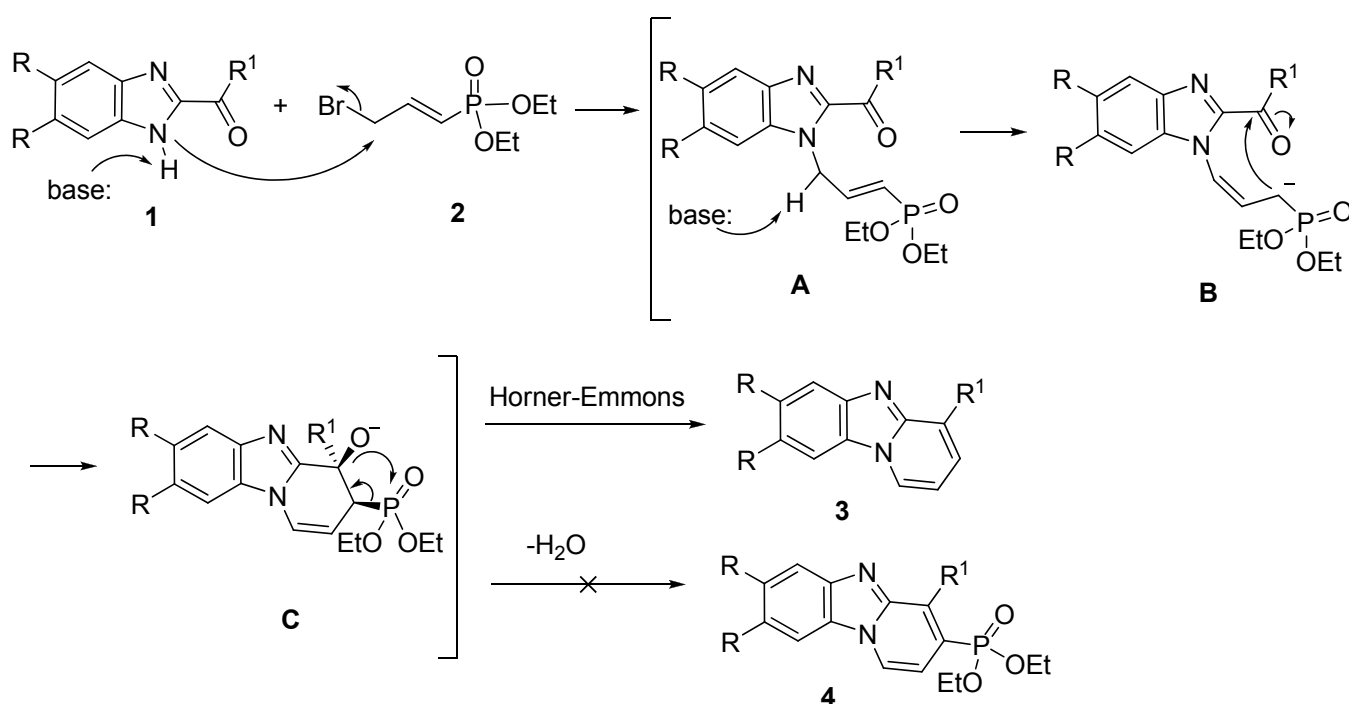


Figure 1. Crystal structure of **3b**

Table 1 Synthesis of pyrido[1,2-*a*]benzimidazole derivatives

Entry	R	R <sup>1</sup>	Product	Isolated Yield (%)
1	H	Me	<b>3a</b>	72
2	H	Ph	<b>3b</b>	68
3	Me	Me	<b>3c</b>	71
4	Me	Ph	<b>3d</b>	66

On the basis of the structures of the products, we proposed the reaction mechanism as follows: Firstly, there would be an intermolecular S<sub>N</sub>2 reaction between **1** and phosphonate **2**, through which intermediate **A** was formed. Afterwards, in the presence of K<sub>2</sub>CO<sub>3</sub>, intermediate **A** was deprotonated to form a  $\gamma$ -carbanion of the phosphonate. In order to be more stable, it would transform to  $\alpha$ -carbanion of the phosphonate **B**. Then the final product **3** would be gained from **C** by intramolecular Horner-Emmons type reaction, but product **4** was not gained by the elimination of one water molecule; which may be due to the steric hindrance effect of Me or Ph group. The entire process is shown in Scheme 2.



Scheme 2. The mechanism of the tandem reaction

In summary, we described a novel tandem reaction to synthesize pyrido[1,2-*a*]benzimidazole derivatives under mild conditions in good yields. The reaction mechanism was also proposed. The compounds are particularly interesting molecules due to their fluorescent activity, which will be presented in due course.

## EXPERIMENTAL

All reagents and solvents were purchased from Sinopharm Chemical Reagent Co. Ltd and used without further purification unless otherwise noted. Starting materials were prepared according to literatures. Thin-layer chromatography (TLC) was conducted on silica gel 60 F254 plates (Merck KGaA).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer, using  $\text{CDCl}_3$  or  $\text{DMSO}-d_6$  as solvents and tetramethylsilane (TMS) as an internal standard. Melting points were determined on an XD-4 digital micro-melting point apparatus and are uncorrected. IR spectra were recorded with an IR spectrophotometer Avtar 370 FT-IR (Termo Nicolet). The High Resolution Mass Spectrometry (HRMS) spectra were recorded on a Q-TOF6510 spectrograph (Agilent).

### General procedure for the synthesis and analytical data of 3a-3d

Benzimidazole ketone **1** (6 mmol), diethyl (3-bromoprop-1-enyl)phosphonate **2** (12 mmol), potassium carbonate (1.8 g, 13.2 mmol) and DMF (40 mL) were added to a 100 mL round-bottomed flask. The reaction system was stirred for 6-10 h. Then the mixture was poured into water (200 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 50 mL). Organic layers were combined and dried over anhydrous  $\text{Na}_2\text{SO}_4$ , then filtered. By rotary evaporation, the mixture was concentrated. After that, these crude products were depurated by using column chromatography.

**4-Methylpyrido[1,2-*a*]benzimidazole(3a)** white solid; mp 158-159 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  2.71 (s, 3H), 7.79 (t,  $J = 6.8$  Hz, 1H), 7.22-7.26 (m, 1H), 7.36 (t,  $J = 7.7$  Hz, 1H), 7.53 (t,  $J = 7.7$  Hz, 1H), 7.86 (d,  $J = 8.4$  Hz, 1H), 8.00 (d,  $J = 8.4$  Hz, 1H), 8.33 (d,  $J = 6.6$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  17.6, 110.4, 110.5, 120.0, 121.0, 122.8, 125.5, 127.6, 127.8, 129.2, 144.2, 149.1; IR (KBr)  $\nu = 3055$ , 3019, 2957, 2918, 2852, 1633, 1605, 1492, 1465, 1356, 1338, 1266, 1220, 1164, 768, 750, 733  $\text{cm}^{-1}$ ; HRMS (ESI): 183.0922 ( $[\text{M}+\text{H}]^+$ ); Calcd for  $\text{C}_{12}\text{H}_{11}\text{N}_2$ : 183.0922.

**4-Phenylpyrido[1,2-*a*]benzimidazole(3b)** yellow solid; mp 138-140 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.97 (t,  $J = 6.9$  Hz, 1H), 7.37-7.47 (m, 2H), 7.52-7.57 (m, 4H), 7.93 (d,  $J = 8.1$  Hz, 1H), 8.01-8.07 (m, 3H), 8.47 (dd,  $J = 6.7$  Hz,  $J = 1.0$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  110.9, 111.0, 120.9, 121.6, 124.5, 126.1, 128.0, 128.9, 129.1, 129.4, 131.3, 137.0, 145.1, 148.1; IR (KBr)  $\nu = 3055$ , 2924, 2851, 1627, 1482, 1424, 1355, 1332, 1268, 1222, 1183, 893, 740, 694  $\text{cm}^{-1}$ ; HRMS (ESI): 245.1092 ( $[\text{M}+\text{H}]^+$ ); Calcd for  $\text{C}_{17}\text{H}_{13}\text{N}_2$ : 245.1079.

**4,7,8-Trimethylpyrido[1,2-*a*]benzimidazole(3c)** yellowish brown solid; mp 182-184 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  2.46 (s, 3H), 2.27 (s, 3H), 6.68 (s, 3H), 6.72 (t,  $J = 6.8$  Hz, 1H), 7.16 (m, 1H), 7.61 (s, 1H), 7.74 (s, 1H), 8.24 (d,  $J = 6.6$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  17.6, 20.62, 20.74, 110.1, 110.5, 119.8, 122.7, 126.9, 127.6, 127.7, 130.5, 134.9, 142.7, 148.6; IR (KBr)  $\nu = 3041$ , 2979, 2916, 1617, 1493, 1378, 1355, 1318, 1220, 1157, 1131, 999, 858, 769, 748  $\text{cm}^{-1}$ ; HRMS (ESI): 211.1238 ( $[\text{M}+\text{H}]^+$ ); Calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_2$ : 211.1235.

**7,8-Dimethyl-4-phenylpyrido[1,2-*a*]benzimidazole(3d)** pale yellow-green solid; mp 178-180 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 2.46 (s, 3H), 2.49 (s, 3H), 6.91 (t, *J* = 6.8 Hz, 1H), 7.40-7.46 (m, 1H), 7.48 (dd, *J* = 6.9 Hz, *J* = 0.9 Hz, 1H), 7.50-7.55 (m, 2H), 7.67 (s, 1H), 7.79 (s, 1H), 8.01-8.05 (m, 2H), 8.39 (dd, *J* = 1.0 Hz, *J* = 6.8 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 20.7, 20.8, 110.2, 110.4, 120.2, 123.9, 126.9, 127.4, 128.3, 128.6, 128.9, 130.6, 130.7, 135.0, 136.7; IR (KBr) ν = 3021, 2916, 1613, 1487, 1425, 1352, 1220, 1192, 1166, 837, 759, 697 cm<sup>-1</sup>; HRMS (ESI): 273.1379 ([M+H]<sup>+</sup>); Calcd for C<sub>19</sub>H<sub>17</sub>N<sub>2</sub>: 273.1392.

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## REFERENCES

1. M. Leopoldo, E. Lacivita, E. Passafiume, M. Contino, N. A. Colabufo, F. Berardi, and R. Perrone, *J. Med. Chem.*, 2007, **50**, 5043.
2. C. Enguehard-Gueiffier and A. Gueiffier, *Mini-Rev. Med. Chem.*, 2007, **7**, 888.
3. O. Barun, H. Ila, and H. Junjappa, *J. Org. Chem.*, 2000, **65**, 1583.
4. N. Fletcher, D. Abeln, and A. Zelewsky, *J. Org. Chem.*, 1997, **62**, 8577.
5. K. Panda, J. R. Suresh, H. Ila, and H. Junjappa, *J. Org. Chem.*, 2003, **68**, 3498.
6. A. B. Reitz, D. A. Gauthier, W. Ho, and B. E. Maryanoff, *Tetrahedron*, 2000, **56**, 8809.
7. E. Badawey and T. Kappe, *Eur. J. Med. Chem.*, 1995, **30**, 327.
8. R. B. Bangar and T. S. Varadarajan, *Spectrosc. Lett.*, 1993, **26**, 1953.
9. S. V. Dhamnaskar and D. W. Rangnekar, *Dyes Pigments*, 1988, **9**, 467.
10. R. W. Sabnis and D. W. Rangnekar, *J. Heterocycl. Chem.*, 1990, **27**, 417.
11. D. A. Lener, P. M. Horowitz, and E. W. Evieth, *J. Phys. Chem.*, 1977, **81**, 12.
12. R. J. Sundberg and J. E. Ellis, *J. Heterocycl. Chem.*, 1982, **19**, 585.
13. C. G. Yan, Q. F. Wang, X. K. Song, and J. Sun, *J. Org. Chem.*, 2009, **74**, 710.
14. I. B. Dzvinchuk, A. V. Turov, and M. O. Lozinskii, *Chem. Heterocycl. Compd.*, 2006, **42**, 929.
15. J. W. Wang, J. Jia, D. J. Hou, H. M. Li, and J. Yin, *Chin. J. Org. Chem.*, 2003, **23**, 173.
16. Y. Q. Ge, J. Jia, Y. Li, L. Yin, and J. W. Wang, *Heterocycles*, 2009, **78**, 197.
17. Y. Q. Ge, J. Jia, H. Yang, G. L. Zhao, F. X. Zhan, and J. W. Wang, *Heterocycles*, 2009, **78**, 725.
18. J. Jia, Y. Q. Ge, X. T. Tao, and J. W. Wang, *Heterocycles*, 2010, **81**, 185.
19. W. M. Zhao, Y. Q. Ge, W. R. Xu, G. L. Zhao, J. Jia, and J. W. Wang, *Heterocycles*, 2013, **87**, 869.

20. Y. Q. Ge, J. Jia, H. Yang, X. T. Tao, and J. W. Wang, *Dyes Pigments*, 2011, **88**, 344.
21. Y. Q. Ge, B. Q. Hao, G. Y. Duan, and J. W. Wang, *J. Lumin.*, 2011, **131**, 1070.
22. Y. Q. Ge, T. Wang, G. Y. Duan, L. H. Dong, X. Q. Cao, and J. W. Wang, *J. Fluoresc.*, 2012, **22**, 1531.
23. Y. F. Xie, Y. Q. Ge, L. Feng, H. Q. Xu, S. Meng, G. L. Zhao, W. R. Xu, J. Jia, and J. W. Wang, *Heterocycles*, 2013, **87**, 815.