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Regioselective synthesis of 1,2,4,5-tetrasubstituted pyridines from Baylis–Hillman adducts via consecutive [3+2+1] annulation protocol

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Abstract

An efficient synthetic method of poly-substituted pyridines was developed. Various poly-substituted pyridines were prepared from the combination of Baylis–Hillman adducts (3 carbons), activated methylene compounds (2 carbons) and ammonium acetate (1 nitrogen) via [3+2+1] annulation protocol in good yields, regioselectively.

Keywords: Poly-substituted pyridines; Baylis–Hillman adducts; [3+2+1] Annulation; NH_4OAc

Poly-substituted pyridines are an important class of compounds due to their abundance in biologically important natural substances and their usefulness as synthetic intermediates in organic synthesis.[1–4] Thus, various synthetic approaches have been examined and a variety of efficient and practical methods have been developed.[1–4] However, new and efficient synthetic procedures are still required for the synthesis of poly-substituted pyridines in a regioselective manner.[3]

Recently, we reported the synthesis of poly-substituted pyridine derivatives regioselectively starting from the easily available Baylis–Hillman adducts by way of [3+1+2] annulation process (Scheme 1).[3a] The pyridine ring was constructed in a consecutive manner: (i) introduction of tosylamide (one nitrogen source) at the primary position of the Baylis–Hillman adduct (three carbon source), (ii) reaction with Michael acceptor (two carbon source) and the following aldol cyclization and aromatization processes.[3a] Meantime, we imagined the possibility for the construction of pyridine skeleton in a different annulation protocol, namely [3+2+1] annulation (Scheme 1). As shown in Scheme 1, the introduction of activated methylene compounds **2** at the primary position of Baylis–Hillman adduct **1** could provide the starting material **3** easily.[5] The reaction of **3** and a suitable ammonia source would provide the desired 1,2,4,5-tetrasubstituted pyridine compound **4** via the corresponding enamine intermediate.[2b,4]

Thus, we synthesized **3a** by the reaction of Baylis–Hillman acetate **1a** and methyl acetoacetate (**2a**) in 82% yield in the presence of K_2CO_3 in CH_3CN at room temperature.[5] With this compound **3a** in our hand, we examined the reaction conditions and found that the use of NH_4OAc in acetic acid produced desired pyridine **4a** in good yield in short time (73%, entry 1 in Table 1).[6–8] Encouraged by the results, we synthesized starting materials **3b–h** by the reactions of Baylis–Hillman acetates **1a–c** and various activated methylene compounds **2a–f** in 63–81% yields as shown in Table 1.[5] The syntheses of poly-substituted pyridines **4b–h** were carried out under the same conditions of entry 1 and we obtained the products in good to moderate yields (52–72%) except compound **4h** (entry 8, vide infra). The reaction mechanism could be explained as the sequential enamine formation,[2b,4,7] cyclization, dehydration and the following double bond isomerization processes as depicted in Scheme 1.

As shown in Scheme 2 (entry 8 in Table 1), the reaction of compound **3h** under the same reaction conditions

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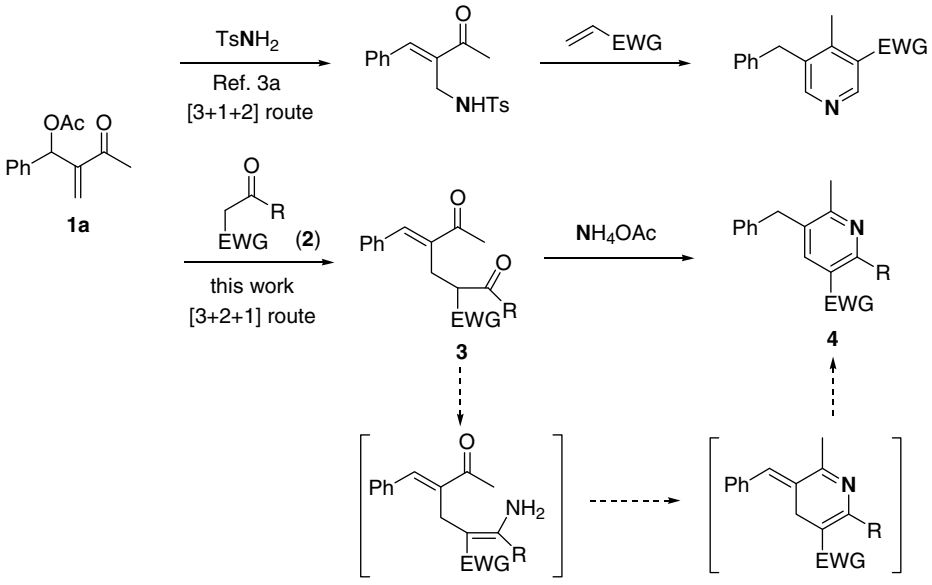
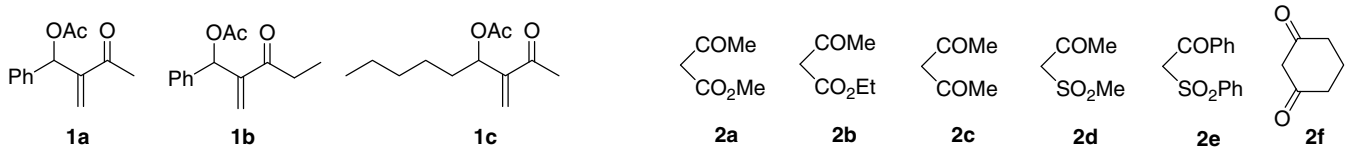
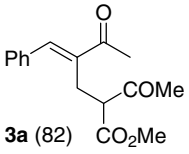
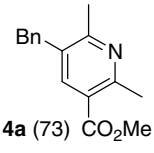
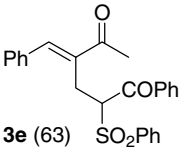
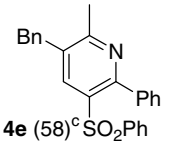
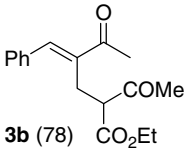
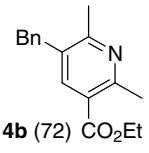
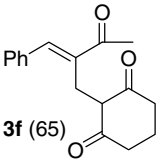
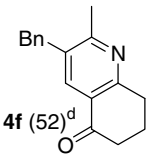
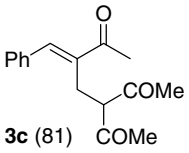
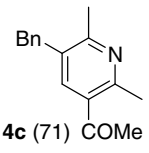
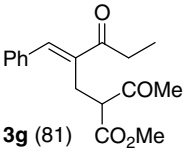
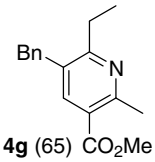
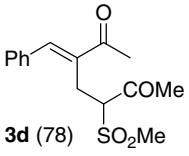
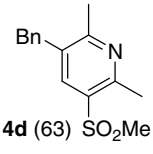
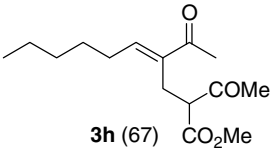
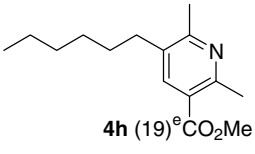


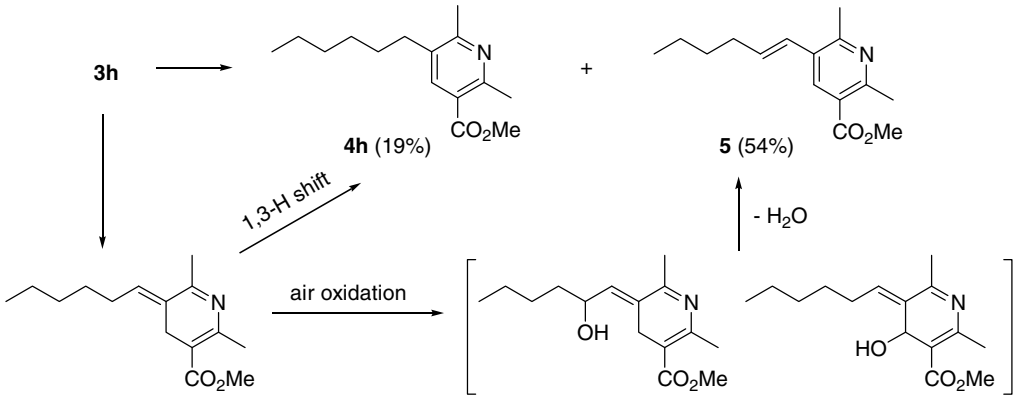
Scheme 1.

Table 1
Synthesis of poly-substituted pyridines

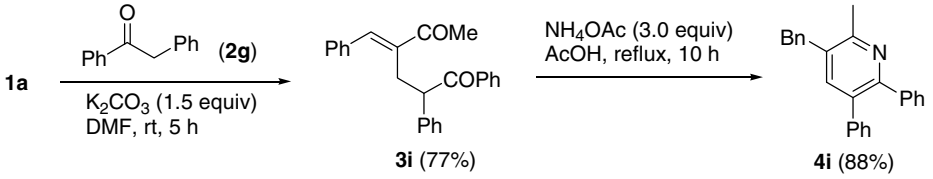


Entry	Substrates	Product **3**[a] (%)	Product **4**[b] (%)	Entry	Substrates	Product **3**[a] (%)	Product **4**[b] (%)
1	**1a** + **2a**	 **3a** (82)	 **4a** (73)	5	**1a** + **2e**	 **3e** (63)	 **4e** (58)[c]
2	**1a** + **2b**	 **3b** (78)	 **4b** (72)	6	**1a** + **2f**	 **3f** (65)	 **4f** (52)[d]
3	**1a** + **2c**	 **3c** (81)	 **4c** (71)	7	**1b** + **2a**	 **3g** (81)	 **4g** (65)
4	**1a** + **2d**	 **3d** (78)	 **4d** (63)	8	**1c** + **2a**	 **3h** (67)	 **4h** (19)[e]

[a] Conditions: compound **1** (1.0 equiv), compound **2** (1.0 equiv), K_2CO_3 (1.1 equiv), CH_3CN, rt, 3–5 h.
[b] Conditions: compound **3** (1.0 equiv), NH_4OAc (3.0 equiv), AcOH, reflux, 1–2 h.
[c] Reaction time is 15 h.
[d] Reaction time is 5 h.
[e] Hexenyl substituted compound **5** was obtained in 54% isolated yield (see Scheme 2).



Scheme 2.



Scheme 3.

produced expected compound **4h** in low yield (19%). Instead, we obtained hexenyl compound **5**, which might be produced via air oxidation[9] followed by acid-catalyzed dehydration, as the major product (54%). As a next step, we examined the synthesis of 1,2-diarylpyridine compound **4i**. Synthesis of starting material **3i** was inefficient in CH_3CN; however, we prepared **3i** in good yield (77%) when we used DMF as solvent. With this compound **3i**, we synthesized 1,2-diarylpyridine **4i** in high yield (88%) for 10 h. It is interesting to note that relatively longer reaction time was required for the synthesis of **4e** (entry 5), **4f** (entry 6), and **4i** (Scheme 3). The lower reactivity in these cases might be due to the larger steric crowdedness during the cyclization between enamine and carbonyl moieties.

In summary, we disclosed an efficient synthetic method of poly-substituted pyridines starting from the Baylis–Hillman adducts via [3+2+1] annulation protocol in good yields, regioselectively.[10]

References and notes

1. For the transition metal-catalyzed synthesis of poly-substituted pyridines, see: (a) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030–5031; (b) Heller, B.; Sundermann, B.; Fischer, C.; You, J.; Chen, W.; Drexler, H. J.; Knochel, P.; Bonrath, W.; Gutnov, A. *J. Org. Chem.* **2003**, *68*, 9221–9225; (c) Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7774–7780; (d) Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H. J.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, *67*, 4414–4422; (e) Young, D. D.; Deiters, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 5187–5190.
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4. For some examples for the synthesis of pyridine derivatives using ammonium acetate as the nitrogen source, see: (a) Ladouceur, G. H.; Cook, J. H.; Doherty, E. M.; Schoen, W. R.; MacDougall, M. L.; Livingston, J. N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 461–464; (b) Rodriguez, H.; Suarez, M.; Perez, R.; Petit, A.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 3709–3712; (c) Bowman, M. D.; Jacobson, M. M.; Pujanauski, B. G.; Blackwell, H. E. *Tetrahedron* **2006**, *62*, 4715–4727.
5. For the synthesis of starting materials and their synthetic applications, see: (a) Lee, M. J.; Park, D. Y.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 1833–1837; (b) Kim, J. N.; Kim, J. M.; Lee, K. Y. *Synlett* **2003**, 821–824; (c) Im, Y. J.; Lee, C. G.; Kim, H. R.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 2987–2990; (d) Kim, J. N.; Im, Y. J.; Kim, J. M. *Tetrahedron Lett.* **2002**, *43*, 6597–6600; (e) Im, Y. J.; Lee, K. Y.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2002**, *43*, 4675–4678.
6. The use of propionic acid or butyric acid can reduce the reaction time and the use of montmorillonite K10 as an additive did not improve the yield. The use of ammonium chloride or ammonium hydroxide did not afford the product in reasonable yield and the use of different solvents was less effective.
7. For the synthesis of pyridine and quinoline derivatives from Baylis–Hillman adducts using similar strategy including the reaction of anilines and enaminoketones, see: (a) Gowrisankar, S.; Na, J. E.; Lee, M. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 319–322; (b) Lee, C. G.; Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 7409–7413; (c) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493–1499; (d) Kim, S. C.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1001–1004.
8. *Typical procedure for the synthesis of compounds* **3a** *and* **4a**: To a solution of Baylis–Hillman acetate **1a** (436 mg, 2.0 mmol) and methyl

acetoacetate (**2a**, 232 mg, 2.0 mmol) in CH_3CN (3 mL) was added K_2CO_3 (305 mg, 2.2 mmol) and stirred for 4 h at rt. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 10:1), we obtained **3a** as a colorless oil, 450 mg (82%). A stirred mixture of compound **3a** (274 mg, 1.0 mmol) and NH_4 OAc (231 mg, 3.0 mmol) in AcOH (6 mL) was heated to reflux for 1 h. After cooling to room temperature, the usual aqueous workup, and column chromatographic purification process (hexanes/EtOAc, 15:1) we obtained **4a** as a pale yellow oil, 187 mg (73%). Other compounds were synthesized analogously and the spectroscopic data of compounds **3a**, **4a**, **4c**, **4g**, and **5** are as follows.

Compound **3a**: 82%; colorless oil; IR (film) 2952, 1747, 1716, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.12 (s, 3H), 2.45 (s, 3H), 3.02–3.18 (m, 2H), 3.57 (s, 3H), 3.73 (dd, $J = 8.1$ and 6.6 Hz, 1H), 7.32–7.45 (m, 5H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.49, 25.95, 28.62, 52.23, 57.85, 128.67, 128.89, 129.01, 134.89, 138.66, 142.49, 169.81, 199.97, 202.27; ESIMS *m/z* 275 (M^++1).

Compound **4a**: 73%; pale yellow oil; IR (film) 2925, 2854, 1726, 1433, 1277 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.48 (s, 3H), 2.79 (s, 3H), 3.88 (s, 3H), 3.99 (s, 2H), 7.08–7.11 (m, 2H), 7.19–7.32 (m, 3H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.68, 24.27, 38.22, 52.02, 122.83, 126.44, 128.51, 128.63, 131.29, 138.77, 139.69, 157.26, 160.29, 167.15; ESIMS *m/z* 256 (M^++1). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.44; H, 6.78; N, 5.32.

Compound **4c**: 71%; pale yellow oil; IR (film) 3030, 2925, 1685, 1442, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.50 (s, 3H), 2.51 (s, 3H), 2.72 (s, 3H), 4.01 (s, 2H), 7.09–7.12 (m, 2H), 7.21–7.34 (m, 3H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.63, 24.30, 29.25, 38.23, 126.57, 128.56, 128.71, 130.50, 131.17, 138.30, 138.62, 155.56, 159.68, 200.18; ESIMS *m/z* 240 (M^++1). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.18; H, 7.31; N, 5.72.

Compound **4g**: 65%; pale yellow oil; IR (film) 3030, 2954, 1726, 1433, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, $J = 7.5$ Hz, 3H), 2.78 (q, $J = 7.5$ Hz, 2H), 2.80 (s, 3H), 3.87 (s, 3H), 4.02 (s, 2H), 7.08–7.11 (m, 2H), 7.18–7.31 (m, 3H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.21, 24.41, 28.53, 37.63, 52.00, 122.66, 126.41, 128.53, 128.60, 130.48, 139.39, 140.11, 157.43, 164.79, 167.25; ESIMS *m/z* 270 (M^++1). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.74; H, 6.99; N, 5.22.

Compound **5**: 54%; colorless oil; IR (film) 2954, 2927, 2856, 1730, 1433, 1279 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, $J = 7.2$ Hz, 3H), 1.26–1.53 (m, 4H), 2.26 (qd, $J = 7.2$ and 1.5 Hz, 2H), 2.56 (s, 3H), 2.77 (s, 3H), 3.91 (s, 3H), 6.16 (dt, $J = 15.6$ and 6.9 Hz, 1H), 6.48 (d, $J = 15.6$ Hz, 1H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.92, 22.25, 22.73, 24.37, 31.36, 33.01, 52.06, 122.97, 124.95, 129.74, 135.03, 135.25, 157.09, 157.86, 167.29; ESIMS *m/z* 248 (M^++1). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.95; H, 8.77; N, 5.52.

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10. In order to check the possibility for the synthesis of **4f** in a one-pot reaction, we examined the reaction of Baylis–Hillman acetate **1a** and 3-amino-2-cyclohexen-1-one in the presence of AcOH (cat) in EtOH. We observed the formation of the desired product **4f** in only trace amounts (4%), and instead we isolated the corresponding primary acetate of **1a** (31%).