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Direct one-pot introduction of 2-methylpyridines to Baylis–Hillman adducts via base-mediated 3-aza-Cope rearrangement

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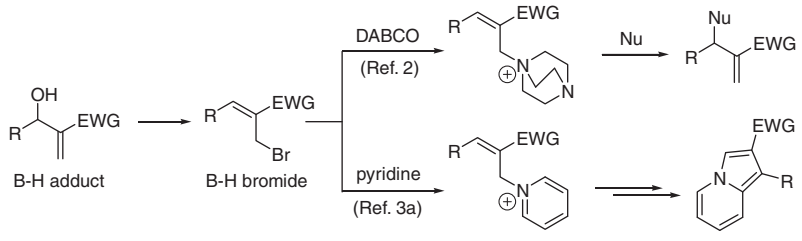
ABSTRACT

An efficient and regioselective introduction method of 2-methylpyridines to the secondary position of Baylis–Hillman adducts has been developed. A base treatment of 2-methylpyridinium salt of Baylis–Hillman bromide generated *N*-allylenamine intermediate which underwent a facile 3-aza-Cope rearrangement under mild conditions to produce the product.

Chemical transformations of Baylis–Hillman adducts have received much attention during the last two decades. Various cyclic and acyclic compounds have been prepared from Baylis–Hillman adducts by a variety of chemical transformations.[1] One of the useful transformations of Baylis–Hillman adducts starts from the formation of amine salts of Baylis–Hillman bromides.[2] As shown in Scheme 1, a DABCO salt of Baylis–Hillman bromide has been frequently used for the introduction of a nucleophile at the secondary position of a Baylis–Hillman adduct.[2] Some nitrogen atom-containing heterocycles, such as pyridine can form the corresponding salts with Baylis–Hillman bromide, and the salts were used as intermediates for the synthesis of more complex substances.[3] As an example, Basavaiah et al. reported a reaction between the Baylis–Hillman bromide and pyridine in the presence of K_2CO_3 to afford indolizine derivative via the consecutive salt formation and 1,5-cyclization of in situ generated nitrogen ylide.[3a] Subsequently a similar approach was applied to the bromide of Baylis–Hillman adducts of isatin by Shanmugam et al.[3b]

During our continuous studies on chemical transformations of Baylis–Hillman adducts, we were interested in the introduction of a 2-pyridylmethyl moiety into the Baylis–Hillman adduct.[4] The synthesis was carried out previously via a sequential introduction of allyl 2-pyridylacetate into Baylis–Hillman adduct, and a palladium-catalyzed decarboxylative protonation protocol, as shown in Scheme 2. However, both secondary and primary adducts, **3a** and **4a**, were produced as a 1:1 mixture.[4] In order to introduce a 2-pyridylmethyl moiety directly into the Baylis–Hillman adducts, we examined the reaction of Baylis–Hillman bromide **1a** and picoline (**2a**) instead of using allyl 2-pyridylacetate. At the outset of our experiments, the reaction of **1a** and **2a** was performed in the presence of $Pd(OAc)_2/PPh_3/Cs_2CO_3$ in CH_3CN (reflux, 2 h), based on the recent palladium-catalyzed C—H functionalization of picoline



Scheme 1.

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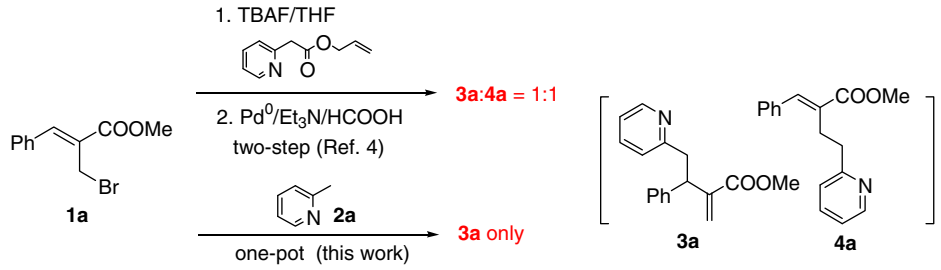
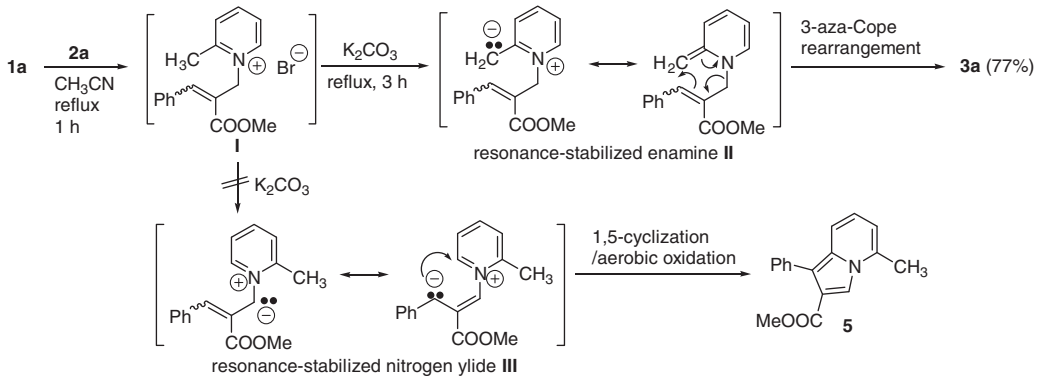


Scheme 2.



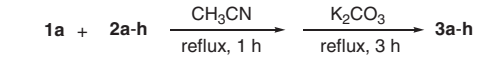
Scheme 3.

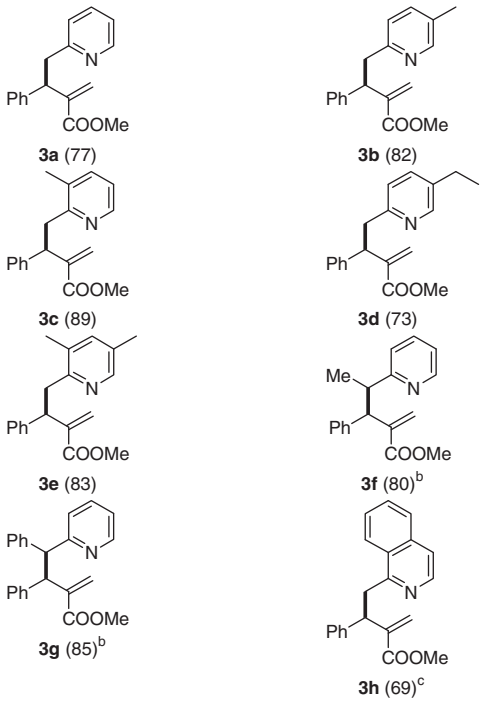
derivatives.[5] A secondary adduct **3a** was formed as a major product (62%) along with a trace amount of **4a** (<5%). Very interestingly, the reaction of **1a** and **2a** (Cs_2CO_3, CH_3CN, reflux, 3 h) showed the same results (64% of **3a** and 4% of **4a**) without a palladium catalyst. Thus, we examined regioselective introduction of 2-pyridylmethyl moiety at the secondary position of a Baylis–Hillman adduct to obtain **3a** (Scheme 2).

A few trials revealed that formation of *N*-cinnamylpicolinium salt **I** was crucial for the clean reaction and high yield of **3a** before the treatment with a base, as shown in Scheme 3. As noted above **4a** was formed together, albeit in low yield, when we ran the reaction of **1a** and **2a** in the presence of a base from the starting point of the reaction. In addition, the use of K_2CO_3 was sufficient as a base. Under the optimized conditions, formation of the primary adduct **4a** was not observed in any trace amount and the yield of **3a** increased to 77%.[6] Based on the above results, the reaction mechanism for the formation of **3a** could be proposed, as also shown in Scheme 3. Refluxing a mixture of **1a** and **2a** (**1a**:**2a** = 1:2) in CH_3CN for 1 h generated *N*-cinnamylpicolinium salt **I**. Treatment of **I** with a base afforded a resonance-stabilized enamine intermediate **II**. Subsequent 3-aza-Cope rearrangement[7,8] of this enamine afforded the product **3a**. In the reaction, we did not observe the formation of indolizine derivative **5** that could be produced via the nitrogen ylide intermediate **III**.[3a]

Encouraged by the results, we carried out the reactions of **1a**, as a representative example, with various pyridine derivatives, 2,5-lutidine (**2b**), 2,3-lutidine (**2c**), 5-ethyl-2-picoline (**2d**), 2,3,5-trimethylpyridine (**2e**), 2-ethylpyridine (**2f**), 2-benzylpyridine (**2g**) and 1-methylisoquinoline (**2h**). The results are summarized in Table 1. The corresponding pyridinium salts were formed quantitatively by refluxing the mixture of **1a** and **2a**–**h** in CH_3CN for 1–4 h. After the formation of salt, addition of K_2CO_3 and maintaining the reaction mixture under refluxing conditions for 3 h furnished the desired products **3b**–**h** in good yields (69–89%).

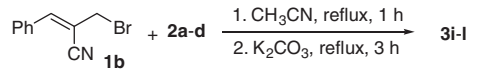
Table 1
One-pot synthesis of pyridylmethyl derivatives[a]

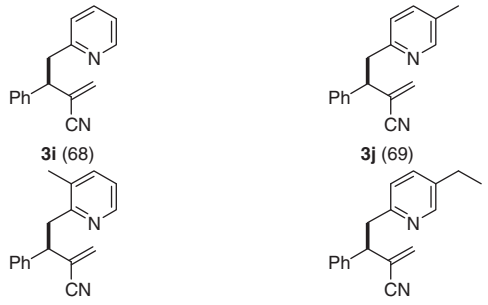




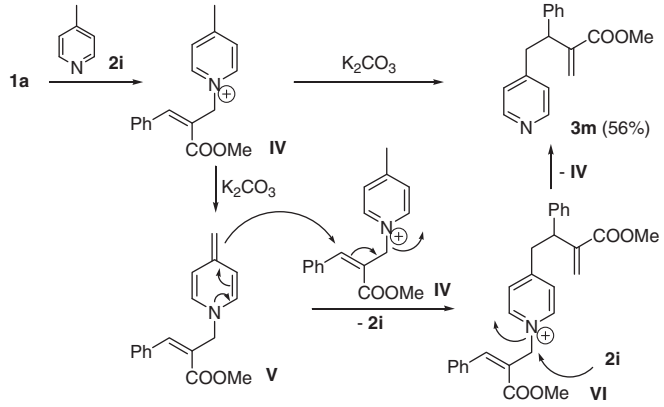
[a] Conditions: (i) **1a** (1.0 equiv), **2a**–**h** (2.0 equiv), CH_3CN, reflux, 1 h; (ii) K_2CO_3 (2.0 equiv), reflux, 3 h.
[b] Single isomer (*syn*/*anti* was not determined) was formed.
[c] Salt formation (step i) required 4 h.

Table 2
One-pot synthesis of pyridylmethyl derivatives[a]





[a] Conditions: (i) **1b** (1.0 equiv), **2a–d** (2.0 equiv), CH_3CN, reflux, 1 h; (ii) K_2CO_3 (2.0 equiv), reflux, 3 h.



Scheme 4.

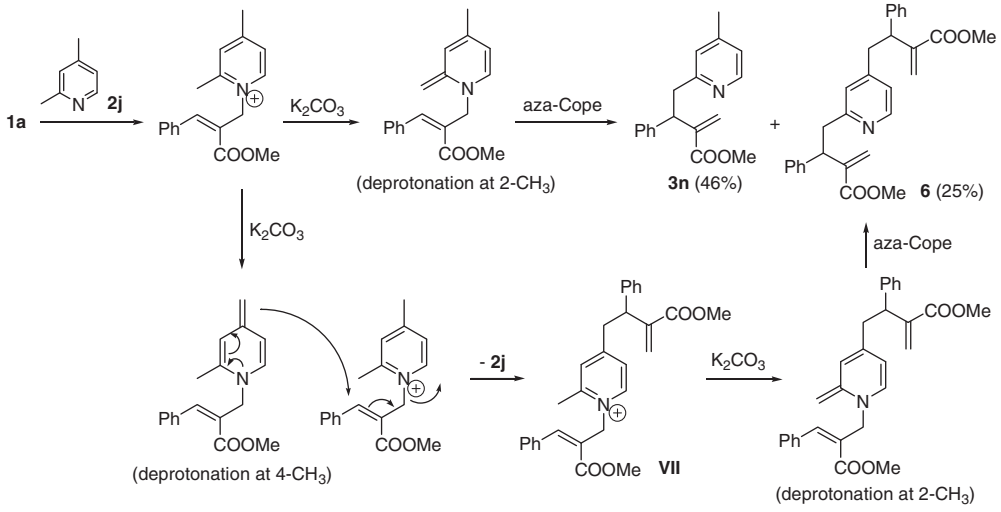
It is interesting to note that **3f** and **3g** were obtained as single isomers although we did not confirm their *syn/anti* stereochemistry. Isoquinoline derivative **3h** was obtained in a moderate yield (69%) although somewhat longer reaction time (4 h) was required for the salt formation with **2h**, presumably due to its lower nucleophilicity than the other 2-methylpyridine derivatives **2a–g**. However, the reactions of **1a** with 2-methylquinoline, 8-methylquinoline and 2,6-lutidine failed due to their sluggish salt formations. The reaction of a Baylis–Hillman bromide **1b**, bearing a nitrile moiety, showed the same reactivity with that of **1a**. As summarized in Table 2, we performed the reactions with four pyridine derivatives **2a–d** and obtained **3i–l** in good yields (68–78%).

The reaction of **1a** and 4-picoline (**2i**) produced the same type product **3m** in 56% yield, as shown in Scheme 4. However, the reaction mechanism for the formation of **3m** is thought to be somewhat different from that of **3a–l**. Deprotonation of *N*-cinnamylpicolinium salt **IV** at the 4-methyl group produced dienamine intermediate **V**. Nucleophilic substitution reaction of **IV** with dienamine **V** generated **VI**, and the following nucleophilic displacement of **VI** with **2i** afforded the product **3m** along with **IV**.

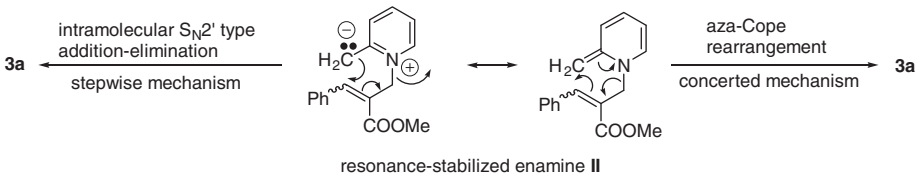
Similarly, the reaction of **1a** and 2,4-lutidine (**2j**) produced two products, **3n** and **6**, as shown in Scheme 5. Compound **3n** was formed via salt formation, deprotonation at the 2-methyl group, and subsequent aza-Cope rearrangement as in the cases of **3a–l**. The formation of compound **6** (as a 1:1 diastereomeric mixture) could be explained via salt formation, deprotonation at the 4-methyl group, nucleophilic substitution reaction as in Scheme 4 to form **VII**, deprotonation at the 2-methyl group, and the final aza-Cope rearrangement.

The reactions of picoline (**2a**) failed completely under the same conditions when we use cinnamyl bromide or allyl bromide instead of Baylis–Hillman bromide. The results implied that the cyclization of **II** leading to **3a** might be a stepwise Michael-type addition and elimination of a pyridyl moiety (an intramolecular S_N2' type reaction) of the former canonical structure instead of aza-Cope rearrangement of the latter canonical structure,[8] as shown in Scheme 6. However, further studies must be needed for a detail reaction mechanism.

In summary, a base treatment of various 2-methylpyridinium salts of Baylis–Hillman bromides generated *N*-allylenamine intermediates. The intermediates underwent a facile 3-aza-Cope rearrangement under mild conditions to produce 2-pyridylmethyl-substituted Baylis–Hillman adducts, regioselectively.



Scheme 5.



Scheme 6.

Acknowledgments

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6. Typical experimental procedure for the synthesis of compound **3a**: A mixture of Baylis–Hillman bromide **1a** (255 mg, 1.0 mmol)[1–4] and picoline (**2a**, 186 mg, 2.0 mmol) in CH_3CN (2.0 mL) was heated to reflux for 60 min. To the reaction mixture, K_2CO_3 (276 mg, 2.0 mmol) was added and maintain refluxing temperature for 3 h. After the usual aqueous extractive workup and column chromatographic process (hexanes/ether/CH_2Cl_2, 1:1:3) compound **3a** was obtained as colorless oil, 206 mg (77%). Other compounds were synthesized similarly and the selected spectroscopic data of **3a**, **3d**, **3g**, **3i**, **3m**, and **3n** are as follows.
Compound **3a**: 77%; colorless oil; IR (film) 1720, 1438, 1249, 1143 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.23 (dd, J = 13.8 and 8.4 Hz, 1H), 3.39 (dd, J = 13.8 and 7.2 Hz, 1H), 3.63 (s, 3H), 4.51 (dd, J = 8.4 and 7.2 Hz, 1H), 5.76 (s, 1H), 6.31 (s, 1H), 6.92 (d, J = 7.5 Hz, 1H), 7.05 (dd, J = 7.5 and 4.8 Hz, 1H), 7.11–7.25 (m, 5H), 7.46 (t, J = 7.5 Hz, 1H), 8.50 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.07, 46.41, 51.79, 121.15, 123.46, 124.82, 126.44, 128.02, 128.23, 135.98, 141.89, 142.85, 149.20, 159.53, 167.13; ESI-MS m/z 268 (M^++H). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.63; H, 6.77; N, 5.03.
Compound **3d**: 73%; colorless oil; IR (film) 1720, 1487, 1445, 1271, 1253, 1139 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, J = 7.5 Hz, 3H), 2.56 (q, J = 7.5 Hz, 2H), 3.20 (dd, J = 13.8 and 8.4 Hz, 1H), 3.36 (dd, J = 13.8 and 7.8 Hz, 1H), 3.61 (s, 3H), 4.50 (dd, J = 8.4 and 7.8 Hz, 1H), 5.76 (s, 1H), 6.30 (s, 1H), 6.85 (d, J = 7.8 Hz, 1H), 7.10–7.25 (m, 5H), 7.29 (d, J = 7.8 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.14, 25.52, 42.53, 46.29, 51.67, 122.88, 124.73, 126.30, 127.94, 128.11, 135.29, 136.41, 141.98, 142.76, 148.72, 156.62, 167.05; ESI-MS m/z 296 (M^++H). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.27; N, 4.74. Found: C, 77.32; H, 7.44; N, 4.82.
Compound **3g**: 85%; white solid, mp 166–168 °C; IR (KBr) 1714, 1435, 1263, 1143 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.61 (s, 3H), 4.72 (d, J = 12.3 Hz, 1H), 5.07 (d, J = 12.3 Hz, 1H), 5.73 (s, 1H), 6.16 (s, 1H), 6.95–7.20 (m, 11H), 7.29 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 8.53 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.35, 51.83, 57.65, 121.25, 123.00, 125.30, 126.18 (2C), 127.86, 128.01, 128.47, 128.78, 136.38, 140.60, 141.44, 142.12, 149.32, 162.08, 167.17; ESI-MS m/z 344 (M^++H). Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.28; H, 6.41; N, 3.97.
Compound **3i**: 68%; colorless oil; IR (film) 2221, 1590, 1438, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.30 (dd, J = 13.8 and 7.2 Hz, 1H), 3.43 (dd, J = 13.8 and 8.7 Hz, 1H), 4.23 (dd, J = 8.7 and 7.2 Hz, 1H), 5.72 (s, 1H), 5.77 (s, 1H), 7.05-7.10 (m, 2H), 7.20–7.34 (m, 5H), 7.51 (t, J = 7.5 Hz, 1H), 8.53 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.46, 49.72, 117.73, 121.46, 123.81, 126.03, 127.33, 127.39, 128.64, 130.61, 136.22, 139.53, 149.32, 157.81; ESI-MS m/z 235 (M^++H). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.89; H, 6.25; N, 11.87.
Compound **3m**: 56%; colorless oil; IR (film) 1718, 1600, 1250, 1139 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.04 (dd, J = 13.8 and 9.3 Hz, 1H), 3.21 (dd, J = 13.8 and 6.6 Hz, 1H), 3.67 (s, 3H), 4.21 (dd, J = 9.3 and 6.6 Hz, 1H), 5.69 (s, 1H), 6.33 (s, 1H), 6.96 (d, J = 5.1 Hz, 2H), 7.12–7.27 (m, 5H), 8.40 (d, J = 5.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.98, 47.04, 51.91, 124.32, 124.91, 126.80, 128.04, 128.36, 140.76, 142.57, 148.72, 149.45, 166.92; ESI-MS m/z 268 (M^++H). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.57; H, 6.34; N, 5.17.
Compound **3n**: 46%; colorless oil; IR (film) 1721, 1605, 1443, 1271, 1142 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.21 (s, 3H), 3.17 (dd, J = 13.8 and 8.4 Hz, 1H), 3.34 (dd, J = 13.8 and 7.8 Hz, 1H), 3.62 (s, 3H), 4.51 (dd, J = 8.4 and 7.8 Hz, 1H), 5.76 (s, 1H), 6.31 (s, 1H), 6.76 (s, 1H), 6.86 (d, J = 5.1 Hz, 1H), 7.11–7.27 (m, 5H), 8.34 (d, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.77, 42.83, 46.23, 51.66, 122.10, 124.25, 124.75, 126.30, 127.91, 128.10, 141.95, 142.70, 146.89, 148.78, 159.12, 167.05; ESI-MS m/z 282 (M^++H). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.59; H, 6.97; N, 5.06.
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