# Synthesis of Tetrahydropyridines from Morita–Baylis–Hillman Acetates of α,β-Unsaturated Aldehydes Via an Intramolecular 1,6-Conjugate Addition

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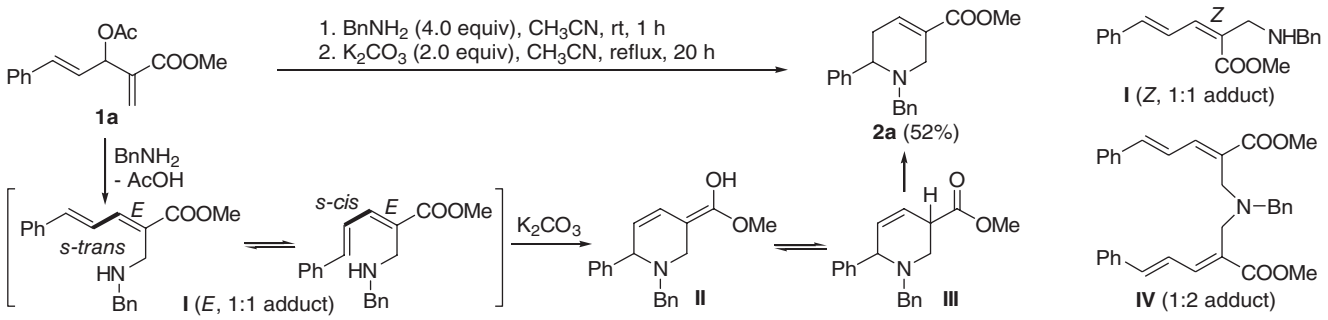
Tetrahydropyridine-3-carboxylic acid derivatives have shown many interesting biological activities.[1,2] The syntheses of tetrahydropyridine-3-carboxylic acids have been carried out by phosphine-catalyzed ring-forming reactions between allenoates and imines,[2a–d] ring-closing metathesis (RCM) reaction of homoallylic amine derivatives,[2e] chemical transformations of Morita–Baylis–Hillman (MBH) adducts,[2f–i] and intramolecular 1,6-conjugate addition of 2,4-dienylamines.[2j]

MBH adducts have been used for the synthesis of many interesting cyclic compounds.[3–5] Recently the MBH adducts of α,β-unsaturated aldehydes have been studied extensively by us[4] and other groups.[5] During our recent studies using the MBH adducts of cinnamaldehydes,[4] we reasoned out that introduction of a primary amine such as benzylamine at the primary position of MBH acetate **1a** could provide methyl tetrahydropyridine-3-carboxylate **2a**, as shown in Scheme 1. The $S_N2'$ reaction between **1a** and benzylamine would afford 1:1 adduct **I**,[6] and the following intramolecular 1,6-conjugate addition[2j,7] would provide 1,2,5,6-tetrahydropyridine-3-carboxylate **2a**.

At the outset of our experiment, the reaction of **1a** and benzylamine (4.0 equiv) was examined in $CH_3CN$.[6] The corresponding 1:1 adduct **I** (*E*-isomer) was formed as a major product at room temperature in short time (1 h); however, the separation of **I**-*E* in pure form was somewhat difficult due to the formation of many side products including unreactive 1:1 adduct **I**-*Z* and 1:2 adduct **IV**,[8] as also shown in Scheme 1. Thus, we decided to carry out the synthesis of **2a** without separation of **I**-*E*. The cyclization of crude **I** to **2a** did not proceed at room temperature even after a long time (20 h). After some trials, we found that **2a** could be formed in a reasonable yield (52%) under the influence of $K_2CO_3$ in refluxing $CH_3CN$ for 20 h. The cyclization was less effective in the absence of $K_2CO_3$ even under refluxing $CH_3CN$ condition.[9] The role of $K_2CO_3$ is unclear at this stage; however, similar observation for the requirement of base in conjugate addition reactions was reported.[10]

Encouraged by the successful synthesis of **2a**, the reactions with some representative MBH acetates of α,β-unsaturated aldehydes **1a–e** were examined, and the results are summarized in Table 1. The reactions of **1a** with *p*-methoxybenzylamine, 2-phenethylamine, 3-phenyl-1-propylamine, and *n*-octylamine afforded **2b–2e** in moderate yields (48–58%). The reaction of MBH acetate of crotonaldehyde **1b** and benzylamine provided **2f** in good yield (68%). The reaction of **1b** and 1-phenethylamine afforded **2g** in a similar yield (63%) as an inseparable diastereomeric mixture (3:1).

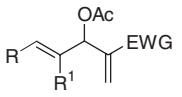
The reaction of 4-methyl derivative **1c** and benzylamine afforded double bond-isomerized product **2h** in good yield (79%) instead of generally expected product **2h′**. As shown in Scheme 2, a double bond isomerization of initially formed product **2h** did not occur presumably due to stabilizing hyperconjugation effect of the methyl group. Similar observation




**Scheme 1.** Synthesis of tetrahydropyridine **2a**.

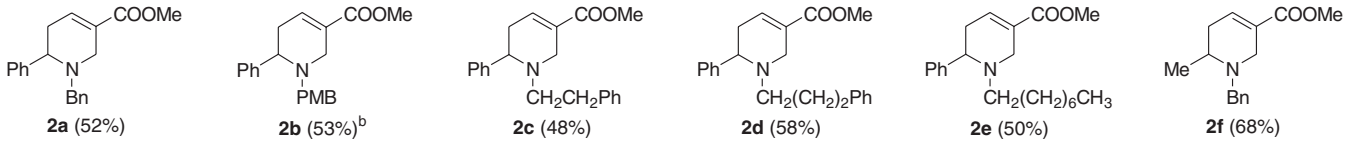
**Table 1.** Synthesis of tetrahydropyridines.[a]




**1a-e**

**1a**: R = Ph, $R^1$ = H, EWG = COOMe
**1b**: R = Me, $R^1$ = H, EWG = COOMe
**1c**: R = Ph, $R^1$ = Me, EWG = COOMe
**1d**: R = Ph, $R^1$ = H, EWG = COOEt
**1e**: R = Ph, $R^1$ = H, EWG = COMe

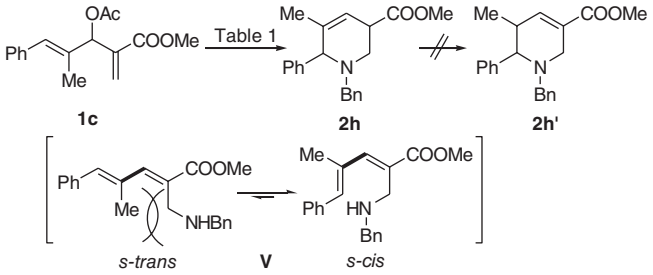
amines: benzylamine
*p*-methoxybenzylamine
2-phenethylamine
3-phenyl-1-propylamine
*n*-octylamine
1-phenethylamine
aniline



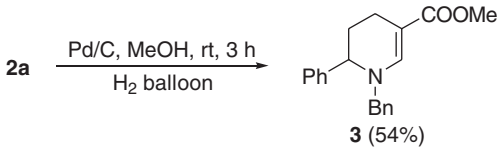

**2a** (52%) **2b** (53%)[b] **2c** (48%) **2d** (58%) **2e** (50%) **2f** (68%)

**2g** (63%)[c] **2h** (79%)[d] **2i** (65%)[b,e] **2j** (51%) **2k** (31%) **2l** (0%)

[a] Conditions: (i) MBH acetate (0.5 mmol), amine (2.0 mmol), $CH_3CN$, room temperature, 1 h; (ii) $K_2CO_3$ (1.0 mmol), reflux, 20 h.
[b] PMB, *p*-methoxybenzyl.
[c] Inseparable diastereomeric mixture (3:1).
[d] Each stereoisomer was separated in pure forms (47%/32%).
[e] Each stereoisomer was separated in pure forms (34%/31%).




**Scheme 2.** Selective formation of **2h**.




**Scheme 3.** Double bond isomerization of **2a**.

was also reported by Ramage and co-workers.[2j] In addition, the yield of **2h** was higher than other entries presumably due to favorable *s-cis* conformation of the 1:1 adduct **V**, as shown in Scheme 2. It is interesting to note that the synthesis of **2h** could also be carried out even at room temperature without the assistance of $K_2CO_3$ in a similar yield (76%) after 20 h. Each stereoisomer (*cis/trans*) was separated in pure forms (47%/32%); however, the stereochemistry was not confirmed.[11] The reaction of **1c** and *p*-methoxybenzylamine afforded **2i** in good yield (65%).

The reaction of ethyl ester **1d** and benzylamine gave **2j** in moderate yield (51%). However, the reaction of acetyl derivative **1e** and benzylamine afforded **2k** in low yield (31%) due to unwanted formation of the corresponding 1:2 adduct in a larger amount. The 1:2 adduct was formed in appreciable quantity during the synthesis of 1:1 adduct, even though benzylamine was used in large excess (4.0 equiv).[12] The reaction of **1a** and aniline failed to produce **2l**. Although the corresponding 1:1 adduct was formed, a subsequent intramolecular 1,6-conjugate addition to **2l** was ineffective under the reaction conditions.

The synthesis of *N*-unsubstituted derivative with ammonia source, such as $NH_4OH$ or $NH_4OAc$, was unsuccessful due to the formation of 1:2 and 1:3 adducts.[8c,13] Thus, we examined *N*-debenzylation of **2a** under the typical hydrogenolysis conditions, as shown in Scheme 3. Interestingly, a double bond isomerization to 1,4,5,6-tetrahydropyridine derivative **3** was observed unexpectedly.[14,15]

In summary, various tetrahydropyridine-3-carboxylates were synthesized from MBH acetates of α,β-unsaturated aldehydes via $S_N2'$ type introduction of primary alkylamines and the following intramolecular 1,6-conjugate addition reaction.

## Experimental

**Typical Procedure for the Synthesis of** 2a**.** To a stirred solution of benzylamine (214 mg, 2.0 mmol) in $CH_3CN$ (1.0 mL) was added a solution of **1a** (130 mg, 0.5 mmol, 0.5 mL of $CH_3CN$), and the reaction mixture was stirred for 1 h. $K_2CO_3$ (138 mg, 1.0 mmol) was added, and the reaction mixture was heated to reflux for 20 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 20:1), **2a** was obtained as a pale

yellow solid, 80 mg (52%). Other compounds were synthesized similarly, and the selected spectroscopic data of **2a**, **2b**, **2h** (major), **2h** (minor), and **3** are as follows.

**Methyl 1-benzyl-6-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2a):** 52%; pale yellow solid, mp 88–90 °C; IR (KBr) 1715, 1436, 1258 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.56–2.64 (m, 2H), 3.00–3.12 (m, 1H), 3.11 (d, *J* = 13.5 Hz, 1H), 3.47–3.57 (m, 1H), 3.62 (t, *J* = 6.6 Hz, 1H), 3.71 (s, 3H), 3.77 (d, *J* = 13.5 Hz, 1H), 7.07–7.12 (m, 1H), 7.19–7.43 (m, 10H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 34.63, 50.04, 51.50, 58.56, 62.08, 126.85, 127.43, 127.78, 128.22, 128.56, 128.63, 128.74, 137.27, 138.92, 142.27, 166.21; ESIMS *m/z* 308 $[M+H]^+$. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.34; H, 6.97; N, 4.31.

**Methyl 1-(4-methoxybenzyl)-6-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2b):** 53%; pale yellow oil; IR (film) 1714, 1511, 1258 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.54–2.62 (m, 2H), 2.97–3.09 (m, 1H), 3.05 (d, *J* = 12.9 Hz, 1H), 3.43–3.54 (m, 1H), 3.58 (t, *J* = 6.3 Hz, 1H), 3.69 (d, *J* = 12.9 Hz, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 6.83 (d, *J* = 8.4 Hz, 2H), 7.05–7.10 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.24–7.31 (m, 1H), 7.32–7.42 (m, 4H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 34.68, 49.85, 51.53, 55.21, 57.94, 62.04, 113.63, 127.42, 127.81, 128.63, 128.78, 129.76, 130.81, 137.29, 142.34, 158.58, 166.27; ESIMS *m/z* 338 $[M+H]^+$. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.49; H, 6.82; N, 4.03.

**Methyl 1-benzyl-5-methyl-6-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (2h, major):** 47%; pale yellow oil; IR (film) 1739, 1453, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 3H), 2.54–2.64 (m, 1H), 3.09–3.20 (m, 2H), 3.27 (d, *J* = 13.5 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 3.66 (s, 3H), 3.84 (s, 1H), 5.71 (s, 1H), 7.17–7.41 (m, 10H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 21.32, 41.09, 47.96, 51.68, 58.12, 69.06, 118.51, 126.84, 127.33, 127.97, 128.19, 128.60, 129.39, 137.61, 139.12, 141.00, 173.93; ESIMS *m/z* 322 $[M+H]^+$. Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.76; H, 7.50; N, 4.23.

**Methyl 1-benzyl-5-methyl-6-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (2h, minor):** 32%; pale yellow oil; IR (film) 1739, 1453, 1171 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 3H), 2.48 (t, *J* = 10.5 Hz, 1H), 3.14 (dd, *J* = 11.4 and 5.1 Hz, 1H), 3.19 (d, *J* = 13.5 Hz, 1H), 3.34–3.48 (m, 1H), 3.66 (s, 3H), 3.71 (d, *J* = 13.5 Hz, 1H), 3.81 (s, 1H), 5.71 (s, 1H), 7.14–7.44 (m, 10H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 21.25, 42.12, 48.88, 51.79, 58.46, 69.61, 118.93, 126.82, 127.41, 128.10, 128.24, 128.58, 129.17, 137.43, 139.10, 141.70, 173.53; ESIMS *m/z* 322 $[M+H]^+$.

**Methyl 1-benzyl-6-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (3):** 54%; colorless oil; IR (film) 1681, 1620, 1296, 1152 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.88–2.06 (m, 3H), 2.32–2.50 (m, 1H), 3.74 (s, 3H), 4.20 (d, *J* = 15.3 Hz, 1H), 4.28 (t, *J* = 3.9 Hz, 1H), 4.43 (d, *J* = 15.3 Hz, 1H), 7.12–7.24 (m, 4H), 7.26–7.42 (m, 6H), 7.82 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 16.21, 28.76, 50.64, 57.45, 57.66, 95.12, 126.37, 127.34, 127.41, 127.76, 128.58, 128.73, 137.02, 141.48, 146.52, 168.88; ESIMS *m/z* 308 $[M+H]^+$. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.44; H, 7.03; N, 4.61.

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**Supporting Information.** Additional supporting information is available in the online version of this article.

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11. NOE experiment was carried out with both stereoisomers of **2h**; however, a significant NOE increment of the proton at C5-position (–CHCOOMe) was not observed for both isomers by irradiation of the proton at C2-position (–CHPh). Thus the cis/trans stereochemistry could not be confirmed by NOE experiment (see, Supporting Information).
12. The 1:2 adduct of **1e** and benzylamine was obtained in appreciable yield (37%) when we separate it before treating with $K_2CO_3$ in a separate experiment.
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