Synthesis of *N*-Benzyl 3,5-Disubstituted Piperidines via Double Michael Addition Strategy

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Recently, Basavaiah and co-workers have reported the facile synthesis of functionalized 1,4-pentadienes from Baylis-Hillman type reaction from cinnamyl bromide derivatives (vide infra, Scheme 1).[1a-c] However, the usefulness of the 1,4-pentadienes has not been studied extensively.[1d,1e] We thought that we could prepare 3,5-disubstituted piperidine skeleton from these compounds *via* double Michael addition reaction strategy.[2-4]

3,5-Disubstituted piperidines are important fundamental backbones for alkaloids,[5a] high affinity agonists of human GABA-A receptors,[5b] farnesyl-protein transferase inhibitors[5c] and continue to be basic moieties in pharmaceutical research.[2,6,7] Due to their unique biological properties, the piperidines have been target molecules in organic synthesis.[2,6,7]

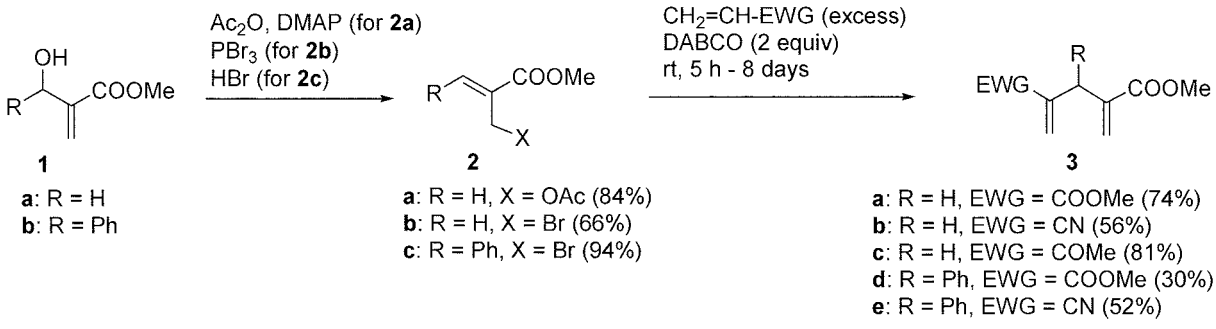
The starting materials **3a-e** were synthesized according to the reported methods[1] from the corresponding bromides or acetates **2a-c** as shown in Scheme 1. With the 1,4-dienes in our hands, we first tried the reaction of **3a** and benzylamine without solvent. As expected, 3,5-disubstituted piperidine **4a** was obtained. As shown in Table 1 (entry 1), **4a**-*cis* (28%) and **4a**-*trans* (25%) were isolated. In the reaction, small amount of piperidone derivative **5a** was also isolated (16%). The structures of piperidines **4a** were easily assigned based on their ^{1}H NMR spectra. As reported in a similar system,[8] the benzylic protons appear as a singlet for **4a**-*cis* whereas as a typical AB quartet for **4a**-*trans*. However, long reaction time was required to complete the reaction at room temperature (5 days). When we elevated the temperature of the reaction mixture, somewhat complex mixtures were observed on TLC. Thus, we tried the same reaction in CH_3CN at refluxing temperature. Long reaction time was required in this case also (entry 2, 60 h) to get similar yields of products. In order to reduce the reaction time we used $LiClO_4$ (2 equiv) in refluxing CH_3CN, and we obtained similar results (entry 3, 24 h) in relatively shorter reaction time.[4c] Similarly, the corresponding piperidines **4b-e** were synthesized in moderate yields from **3b-e** and the results are summarized in Table 1.

The reaction mechanism for the formation of piperidine **4** and piperidone **5** is depicted in Scheme 2. Intermolecular Michael type addition of benzylamine to 1,4-pentadiene **3** gave the corresponding intermediate **I**. Intramolecular consecutive Michael type reaction (pathway a) gave the piperidine **4**. Piperidone derivative **5** was formed by amide bond formation pathway (pathway b). As mentioned above, the benzylic protons of four *cis*-isomers (**4a**, **4c-e**) appear as a singlet. The benzylic protons of all *trans*-isomers appear as AB quartets ($\Delta\delta J$ = 2.4-5.3). Exceptionally, the benzylic protons of **4b**-*cis* showed a typical AB quartet pattern with a relatively small $\Delta\delta J$ value ($\Delta\delta J$ = 1.6). For the synthesis of **4c**, the use of $LiClO_4$ gave unsatisfactory results. Thus, in this case, we used the neat condition (entry 5).

In summary, we disclosed the facile synthesis of 3,5-disubstituted piperidines from the easily available 1,4-pentadienes via double Michael addition reactions. Further studies on the selective formation of one-isomer and the chemical transformations of the synthesized piperidines are underway.

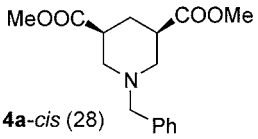
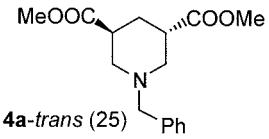
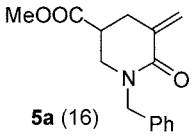
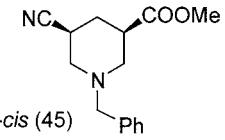
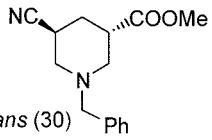
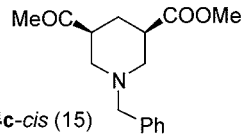
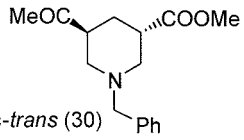
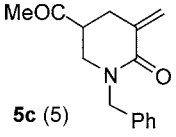
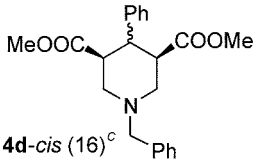
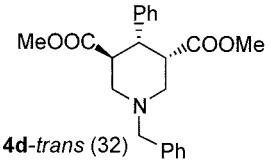
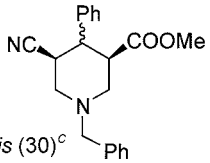
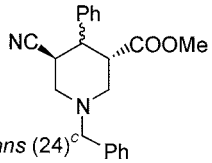
Experimental Section

Synthesis of starting materials **2a-c** was performed according to the literature methods[1] from the corresponding

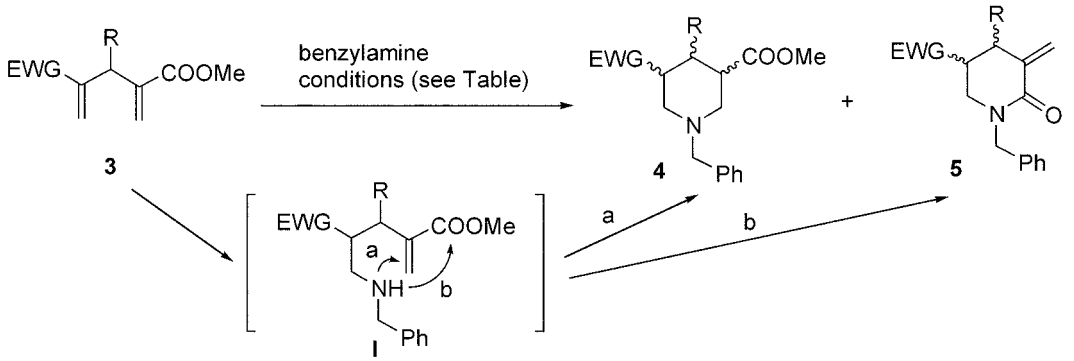


Scheme 1

Table 1. Synthesis of piperidines **4** and piperidones **5** from **3** and benzylamine

Entry	3	Conditions	Products (%)		
1	**3a**	$BnNH_2$ (1.5 equiv) no solvent rt, 5 days	 **4a**-*cis* (28)	 **4a**-*trans* (25)	 **5a** (16)
2	**3a**	$BnNH_2$ (1.5 equiv) CH_3CN reflux, 60 h	**4a**-*cis* (40)	**4a**-*trans* (28)	**5a** (7)
3	**3a**	$BnNH_2$ (1.5 equiv) CH_3CN $LiClO_4$ (2 equiv) reflux, 24 h	**4a**-*cis* (35)	**4a**-*trans* (23)	**5a** (trace)
4	**3b**	$BnNH_2$ (1.5 equiv) CH_3CN $LiClO_4$ (2 equiv) reflux, 40 h	 **4b**-*cis* (45)	 **4b**-*trans* (30)	*b*
5	**3c**	$BnNH_2$ (1.5 equiv) no solvent[a] rt, 22 h	 **4c**-*cis* (15)	 **4c**-*trans* (30)	 **5c** (5)
6	**3d**	$BnNH_2$ (1.5 equiv) CH_3CN $LiClO_4$ (2 equiv) reflux, 3 days	 **4d**-*cis* (16)[c]	 **4d**-*trans* (32)	*b*
7	**3e**	$BnNH_2$ (1.5 equiv) CH_3CN $LiClO_4$ (2 equiv) reflux, 3 days	 **4e**-*cis* (30)[c]	 **4e**-*trans* (24)[c]	*b*

[a]The use of typical reaction conditions (CH_3CN, $LiClO_4$, reflux) gave more complex mixtures of intractable mixtures. [b]The corresponding piperidone was not isolated. [c]The stereochemistry of phenyl group was not determined.



Scheme 2

Baylis-Hillman adducts **1** by using HBr, PBr_3, or Ac_2O/DMAP conditions (Scheme 1) in 66-94% isolated yields. Synthesis of starting materials (**3a**,[1c] **3b**,[1c] **3c**,[1c] **3e**[1a]) was carried out according to the reported procedures (Scheme 1)

in 52-81%.[1] The compound **3d** was also prepared (**2c**, methyl acrylate, DABCO, rt, 8 days, 30%) by following the reported method[1] and the IR and ^{1}H NMR spectrum of **3d** is as follows: IR (KBr) 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 6H), 5.32 (s, 1H), 5.35 (s, 2H), 6.40 (s, 2H), 7.15-7.34 (m, 5H).

Typical procedure for the reaction of 3a and benzylamine in CH_3CN in the presence of $LiClO_4$ (entry 3 in Table 1): A stirred mixture of **3a** (184 mg, 1 mmol), benzylamine (160 mg, 1.5 mmol), and $LiClO_4$ (212 mg, 2 mmol) in CH_3CN (3 mL) was heated to reflux for 24 h. After usual workup and column chromatographic purification process (hexanes/EtOAc, 10 : 1) we obtained **4a**-*cis* (102 mg) and **4a**-*trans* (67 mg) as clear oils in 35% and 23%, respectively. Spectroscopic data of synthesized compounds are as follows.

4a-*cis*[6c]: clear oil; IR (KBr) 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (q, *J* = 13.2 Hz, 1H), 2.03 (t, *J* = 11.4 Hz, 2H), 2.30-2.37 (m, 1H), 2.64 (tt, *J* = 12.0 and 3.9 Hz, 2H), 3.08-3.14 (m, 2H), 3.57 (s, 2H), 3.65 (s, 6H), 7.22-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.86, 41.44, 51.93, 54.86, 62.95, 127.38, 128.50, 129.16, 137.99, 173.95; Mass (70 eV) *m/z* (rel intensity) 91 (100), 168 (16), 200 (15), 260 (4), 291 (M^+, 4).

4a-*trans*: clear oil; IR (KBr) 1732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (t, *J* = 5.7 Hz, 2H), 2.59-2.71 (m, 4H), 2.81-2.89 (m, 2H), 3.41 (d, *J* = 13.5 Hz, 1H), 3.59 (d, *J* = 13.5 Hz, 1H), 3.67 (s, 6H), 7.20-7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.41, 39.25, 51.81, 55.15, 62.81, 127.25, 128.28, 128.92, 138.29, 174.34; Mass (70 eV) *m/z* (rel intensity) 91 (100), 168 (33), 200 (18), 260 (8), 291 (M^+, 11).

5a: clear oil; IR (KBr) 1736, 1658, 1616 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72-2.95 (m, 3H), 3.44-3.58 (m, 2H), 3.65 (s, 3H), 4.61 (d, *J* = 14.7 Hz, 1H), 4.75 (d, *J* = 14.7 Hz, 1H), 5.42-5.43 (m, 1H), 6.34-6.36 (m, 1H), 7.24-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.41, 38.99, 48.49, 50.80, 52.14, 123.82, 127.53, 128.17, 128.63, 135.18, 136.71, 163.51, 172.01; Mass (70 eV) *m/z* (rel intensity) 41 (31), 65 (36), 91 (100), 259 (M^+, 4).

4b-*cis*: clear oil; IR (KBr) 2241, 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (q, *J* = 12.6 Hz, 1H), 2.09-2.19 (m, 2H), 2.36-2.43 (m, 1H), 2.61 (tt, *J* = 11.6 and 3.9 Hz, 1H), 2.74 (tt, *J* = 11.6 and 3.9 Hz, 1H), 3.06-3.15 (m, 2H), 3.54 (d, *J* = 13.2 Hz, 1H), 3.61 (d, *J* = 13.2 Hz, 1H), 3.68 (s, 3H), 7.26-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.34, 30.28, 40.86, 52.20, 54.46, 54.70, 62.52, 120.25, 127.73, 128.66, 129.12, 137.20, 172.75.

4b-*trans*: clear oil; IR (KBr) 2241, 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01-2.07 (m, 2H), 2.50-2.60 (m, 2H), 2.70-2.93 (m, 3H), 3.02-3.09 (m, 1H), 3.51 (d, *J* = 13.5 Hz, 1H), 3.63 (d, *J* = 13.5 Hz, 1H), 3.68 (s, 3H), 7.23-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.56, 29.08, 39.07, 52.10, 54.52, 54.70, 62.37, 120.93, 127.58, 128.58, 128.89, 137.50, 173.31.

4c-*cis*: clear oil; IR (KBr) 1736, 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (q, *J* = 12.6 Hz, 1H), 1.92-2.07 (m, 2H), 2.13 (s, 3H), 2.25-2.32 (m, 1H), 2.61-2.73 (m, 2H), 3.03-3.14 (m, 2H), 3.57 (s, 2H), 3.66 (s, 3H), 7.22-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.60, 29.51, 41.61, 49.26, 51.96, 54.45, 54.89, 63.07, 127.41, 128.52, 129.18, 137.95, 173.98, 209.23; Mass (70 eV) *m/z* (rel intensity) 42 (48), 91 (100), 184 (13), 275 (M^+, 4).

4c-*trans*: clear oil; IR (KBr) 1732, 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (t, *J* = 5.4 Hz, 2H), 2.08 (s, 3H), 2.54-2.84 (m, 6H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.60 (d, *J* = 13.2 Hz, 1H), 3.67 (s, 3H), 7.22-7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.92, 28.22, 39.09, 46.94, 51.81, 54.88, 55.38, 63.09, 127.40, 128.38, 129.10, 138.25, 174.47, 209.80; Mass (70 eV) *m/z* (rel intensity) 91 (100), 184 (13), 232 (6), 275 (M^+, 4).

5c: clear oil; IR (KBr) 1712, 1658, 1612 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.62-2.72 (m, 1H), 2.83-2.94 (m, 2H), 3.35-3.54 (m, 2H), 4.55 (d, *J* = 14.4 Hz, 1H), 4.80 (d, *J* = 14.4 Hz, 1H), 5.42-5.44 (m, 1H), 6.35-6.36 (m, 1H), 7.24-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.35, 32.64, 46.76, 48.11, 51.10, 123.95, 127.83, 128.47, 128.92, 135.61, 136.96, 163.69, 206.92.

4d-*cis*: clear oil; IR (KBr) 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (t, *J* = 11.4 Hz, 2H), 2.95 (td, *J* = 11.4 and 3.6 Hz, 2H), 3.08-3.16 (m, 3H), 3.38 (s, 6H), 3.61 (s, 2H), 7.14-7.37 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.25, 48.92, 51.72, 55.85, 62.68, 127.30, 127.55, 128.03, 128.59, 128.62, 129.24, 137.74, 140.42, 173.14; Mass (70 eV) *m/z* (rel intensity) 91 (100), 118 (28), 244 (8), 276 (9), 367 (M^+, 3).

4d-*trans*: white solid, mp 88-90 °C; IR (KBr) 1739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (t, *J* = 10.8 Hz, 1H), 2.46 (dd, *J* = 11.7 and 3.6 Hz, 1H), 2.98 (dd, *J* = 7.8 and 3.3 Hz, 1H), 3.18-3.23 (m, 3H), 3.45 (d, *J* = 13.5 Hz, 1H), 3.47 (s, 3H), 3.51 (s, 3H), 3.67 (d, *J* = 13.5 Hz, 1H), 4.01 (td, *J* = 10.8 and 3.9 Hz, 1H), 7.13-7.33 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.86, 44.99, 46.65, 51.32, 51.87, 55.95, 56.58, 62.33, 126.76, 127.35, 128.32, 128.42, 128.45, 128.81, 138.23, 141.09, 172.47, 174.30.

4e-*cis*: white solid, mp 114-116 °C; IR (KBr) 2241, 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28-2.44 (m, 2H), 2.92-3.00 (m, 3H), 3.16 (dt, *J* = 11.4 and 1.2 Hz, 1H), 3.27 (dd, *J* = 11.4 and 1.2 Hz, 1H), 3.41 (s, 3H), 3.62 (s, 2H), 7.22-7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.31, 47.66, 48.51, 51.97, 55.41, 55.47, 62.29, 119.15, 127.85, 127.88, 128.24, 128.74, 129.08, 129.18, 137.00, 138.74, 172.17.

4e-*trans*: white solid, mp 135-137 °C; IR (KBr) 2245, 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (t, *J* = 10.8 Hz, 1H), 2.41 (dd, *J* = 11.7 and 2.7 Hz, 1H), 2.98-3.01 (m, 1H), 3.08 (dd, *J* = 11.7 and 4.2 Hz, 1H), 3.22 (dt, *J* = 11.4 and 2.1 Hz, 1H), 3.28 (ddd, *J* = 10.8, 3.9, and 1.8 Hz, 1H), 3.46 (s, 3H), 3.52 (dd, *J* = 11.4 and 3.9 Hz, 1H), 3.62 (d, *J* = 13.5 Hz, 1H), 3.73 (d, *J* = 13.5 Hz, 1H), 7.26-7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.51, 44.30, 45.90, 52.08, 55.06, 56.03, 62.08, 119.46, 127.69, 127.86, 128.13, 128.76, 128.94, 129.05, 137.37, 138.91, 172.72.

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