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Synthesis of poly-substituted tetrahydropyridines from Baylis–Hillman adducts modified with *N*-allylamino group via radical cyclization

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ABSTRACT

An expedient method was developed for the synthesis of 1,4,5,6-tetrahydropyridines by radical cyclization protocol involving consecutive 1,5-hydrogen transfer and double bond isomerization process starting from Baylis–Hillman adducts.

Radical cyclizations have been used for the synthesis of various cyclic compounds. In some instances initial radical species underwent 1,*n*-H transfer to form another radical before cyclization reaction.[1,2] Among the 1,*n*-H transfers, 1,5- and 1,6-H transfers are the most common.[1,2] Very recently we observed an interesting radical cyclization procedure for the synthesis of tricyclic lactam derivatives involving 1,5-H transfer and concomitant isomerization.[1a]

Suitably substituted dihydro- and tetrahydropyridine derivatives have been regarded as important synthetic intermediates for the synthesis of various important compounds.[3] Especially, 1,4,5,6-tetrahydropyridine derivative **A** has been used for the synthesis of antidepressant drug paroxetine (**B**)[4] and many paroxetine-like PSSRIs (phenylpiperidine selective Serotonin reuptake inhibitors) including femoxetine (**B′**).[4,5] In addition, many 1,2,5,6-tetrahydropyridine derivatives **C** have been reported as renin inhibitors (Fig. 1).[5] During our recent studies on the chemical transformations of Baylis–Hillman adducts,[6,7] we imagined that we could synthesize tetrahydropyridine skeleton[4,5] *via* the radical cyclization of **4a–e** as in Scheme 1. *N*-Tosyl-*N*-allyl derivatives **4a–e** were prepared in good to moderate yields from the acetates of Baylis–Hillman adducts **1a** and **1b** as summarized in Scheme 2 in two steps.[7,8]

With the substrates **4a–e** we examined the radical cyclization reaction under the conditions of *n*-Bu_3SnH (1.2 equiv)/AIBN in refluxing benzene.[7] As expected, we obtained 1,4,5,6-tetrahydropyridines **5a–e** in good to moderate yields (56–82%) in short time (Table 1).[9] Compounds having two stereogenic centers including **5a**, **5c,** and **5d** were isolated as their *syn/anti* diastereomeric mixture in a ratio of 3:2–4:1. However, we could not separate each isomer in their pure form. The mechanism for the formation of **5** could be regarded as in Scheme 1: (i) 1,5-hydrogen transfer from the initial radical (**I**) to form (**II**),[1a] isomerization to more stable benzylic radical (**III**), the following cyclization in a 6-*exo*-*trig* mode to (**IV**), and final hydrogen radical abstraction to **5**.

However, the reaction of *N*-benzyl derivative **4f** showed low yield of product **5f** (38%) under the same conditions (1.2 equiv of *n*-Bu_3SnH) due to the formation of many intractable side products. Fortunately, we obtained **5f** in an improved yield (76%) when we used *n*-Bu_3SnH in excess amounts (2.5 equiv) presumably due to rapid hydrogen abstraction of the corresponding radical intermediate (**IV**) from *n*-Bu_3SnH (Scheme 3). Similarly, the reaction of *N*-phenyl derivative **4g** showed similar pattern. When we used 1.2–1.5 equiv of *n*-Bu_3SnH, pyrrolidine derivative **6** was formed in appreciable amounts with low yield of **5g**. The desired compound **5g** was isolated in moderate yield (50%) with 2.5 equiv of *n*-Bu_3SnH, together with pyrrolidine derivative **6** in 21% yield as a *syn/anti* (1:1) mixture (Scheme 4). The formation of **6** could be explained as sequential hydrostannylation at the allyl group[10] and following radical cyclization in a *5-exo-trig* mode. The reduction of bromophenyl moiety might occur independently with excess Bu_3SnH. Compound **6** was also prepared from **4g′** under the same conditions (2.5 equiv of *n*-Bu_3SnH) in good yield (77%). We obtained compounds **5h** (31%) and **7** (24%) from the reaction of *N*-methallyl derivative **4h**, similarly. In the reaction, two minor compounds **8** (12%) and **9** (28%) were isolated together as side products and we did not confirm the geometry of double bond Scheme 5.

In summary, we disclosed an efficient synthetic way for 1,4,5,6-tetrahydropyridines by radical cyclization protocol involving

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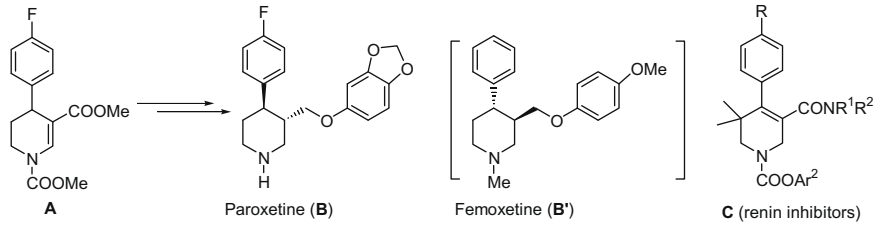
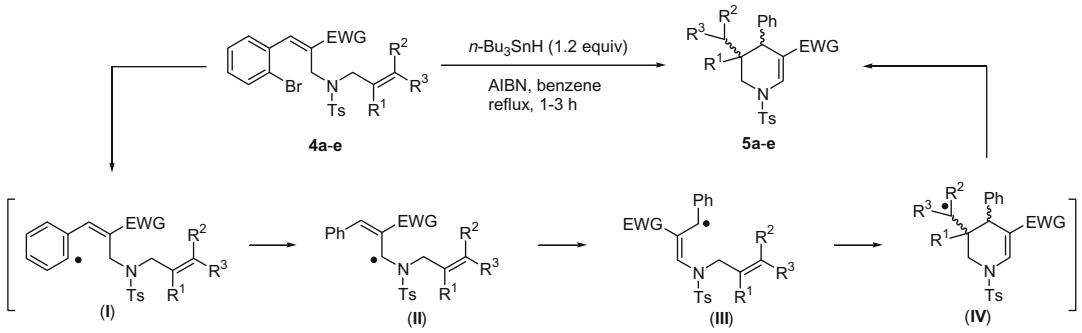


Figure 1.

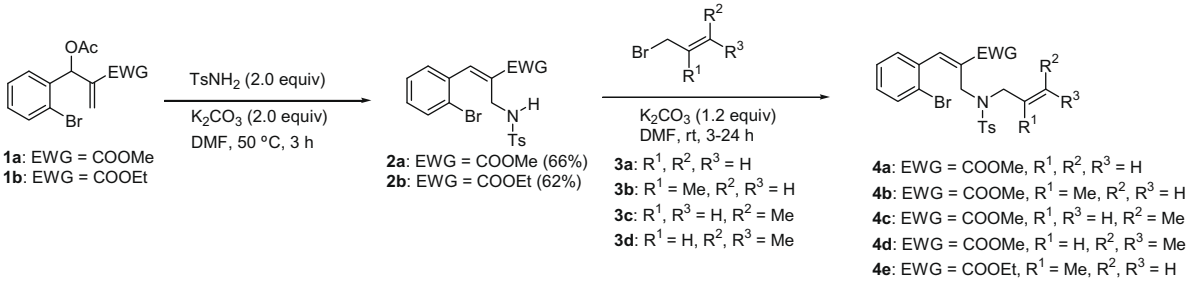


Scheme 1.

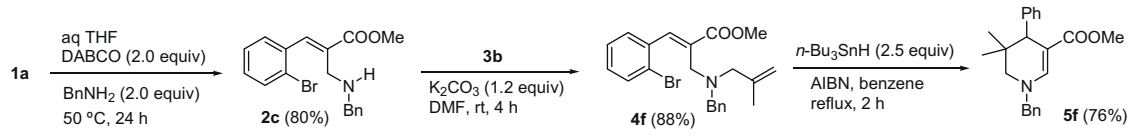
Table 1
Synthesis of tetrahydropyridine derivatives

Entry	Conditions[a]	Substrate **4** (%)	Conditions[b] (h)	Product **5** (%)
1	**2a** + **3a** ,6 h	**4a** (80)	2	**5a** (72, *syn*/*anti* = 2:3)[c]
2	**2a** + **3b**, 4 h	**4b** (93)	1	**5b** (70)
3	**2a** + **3c**, 3 h	**4c** (80)	2	**5c** (82, *syn*/*anti* = 2:3)[c]
4	**2a** + **3d**, 24 h	**4d** (87)	2	**5d** (80, *syn*/*anti* = 1:4)[c]
5	**2b** + **3b**, 4 h	**4e** (92)	3	**5e** (56)

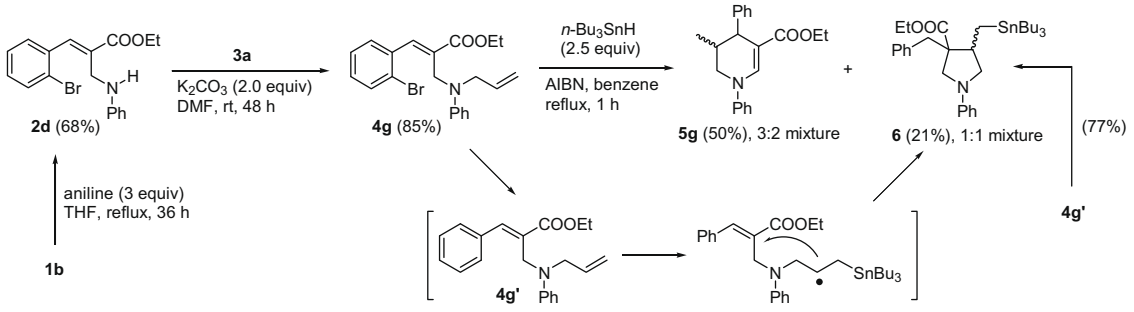
[a] Conditions: Compound **2** (1.0 mmol), compound **3** (1.5 mmol), K_2CO_3 (1.2 equiv), DMF, rt.
[b] Conditions: Substrate **4** (0.5 mmol), *n*-Bu_3SnH (0.6 mmol), AIBN (cat) benzene, reflux.
[c] The ratio of *syn*/*anti* was determined in ^1H NMR and is arbitrary.



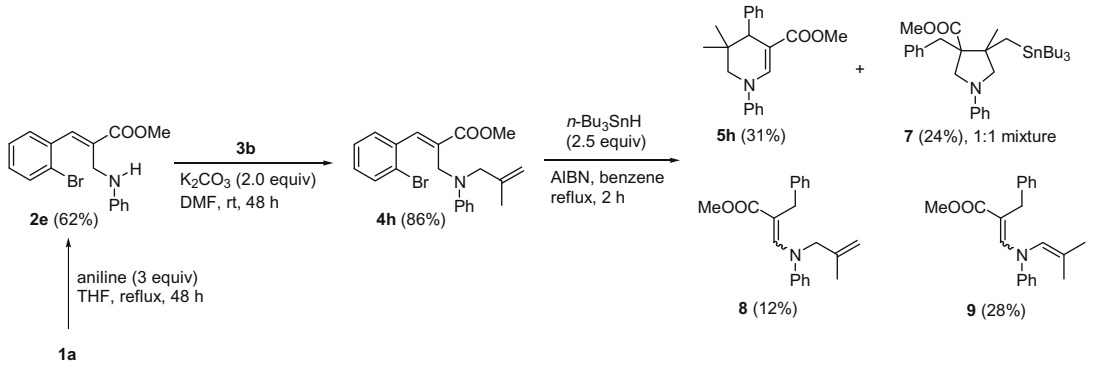
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

consecutive 1,5-hydrogen transfer and double bond isomerization process. Applications of this methodology are currently underway for the synthesis of paroxetine derivatives having 5-alkyls.

Acknowledgments

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9. *Typical experimental procedure for the synthesis of **4b** and **5b***: To a stirred mixture of **2a** (424 mg, 1.0 mmol) and **3b** (203 mg, 1.5 mmol) in DMF (3 mL) was added K_2CO_3 (166 mg, 1.2 mmol) and stirred at room temperature for 4 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 2:1) compound **4b** was isolated as colorless oil, 445 mg (93%). A mixture of **4b** (239 mg, 0.5 mmol), Bu_3SnH (175 mg, 0.6 mmol), and AIBN (8 mg, 0.05 mmol) in benzene (3 mL) was heated to reflux for 1 h. After removal of solvent, the residue was purified by column chromatography (hexanes/ether, 4:1) to obtain compound **5b** as a white solid, 279 mg (70%). Selected spectroscopic data of compound **4b**, **5b**, **5f**, and **6** are as follows.Compound **4b**: 93%; colorless oil; IR (film) 1720, 1436, 1339, 1248, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.62 (s, 3H), 2.41 (s, 3H), 3.65 (s, 3H), 3.71 (s, 2H), 4.15 (s, 2H), 4.77 (s, 1H), 4.78 (s, 1H), 7.20–7.27 (m, 3H), 7.37 (t, J = 7.5 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.56–7.65 (m, 3H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.93, 21.46, 44.09, 52.06, 54.89, 113.58, 124.11, 127.36, 127.38, 129.40, 129.55, 130.33, 130.98, 132.81, 134.63, 136.59, 140.82, 142.32, 143.00, 167.29; ESIMS m/z 478 (M^++1), 480 (M^++3).Compound **5b**: 70%; white

solid, mp 110–112 °C; IR (KBr) 1709, 1633, 1168, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.59 (s, 3H), 0.88 (s, 3H), 2.49 (s, 3H), 2.80 (d, J = 12.0 Hz, 1H), 3.18 (d, J = 12.0 Hz, 1H), 3.37 (s, 1H), 3.61 (s, 3H), 6.70 (d, J = 5.7 Hz, 2H), 7.03–7.15 (m, 3H), 7.40 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.1 Hz, 2H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.64, 25.25, 27.03, 31.96, 48.00, 49.38, 51.43, 110.10, 126.62, 127.33, 127.76, 128.66, 130.09, 134.07, 134.44, 141.23, 144.69, 167.04; ESIMS m/z 400 (M^++1). Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.37; H, 6.13; N, 3.45.Compound **5f**: 76%; white solid, mp 123–124 °C; IR (KBr) 1682, 1620, 1167, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.54 (s, 3H), 0.99 (s, 3H), 2.36 (d, J = 12.3 Hz, 1H), 2.85 (d, J = 12.3 Hz,1H), 3.35 (s, 1H), 3.56 (s, 3H), 4.37 (d, J = 15.3 Hz, 1H), 4.44 (d, J = 15.3 Hz, 1H), 7.02 (d, J = 6.6 Hz, 2H), 7.10–7.41 (m, 8H), 7.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.51, 28.07, 31.52, 47.85, 50.51, 52.41, 60.11, 97.51, 125.91, 127.46, 127.90, 127.98, 128.71, 128.78, 136.59, 144.32, 144.55, 168.89; ESIMS m/z 336 (M^++1). Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.89; H, 7.76; N, 4.05.Compound **6** (separated pure isomer, but *syn/anti* was not determined): 21%; colorless oil; IR (film) 1726, 1598, 1507, 1374 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85–0.92 (m, 15H), 1.02–1.07 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 1.24–1.55 (m, 12H), 2.46–2.53 (m, 1H), 2.74 (d, J = 13.8 Hz, 1H), 2.94 (dd, J = 8.7 and 6.3 Hz, 1H), 3.34 (d, J = 13.8 Hz, 1H), 3.41 (d, J = 9.9 Hz, 1H), 3.58 (d, J = 9.9 Hz, 1H), 3.56–3.62 (m, 1H), 4.09–4.20 (m, 2H), 6.50 (d, J = 7.5 Hz, 2H), 6.66 (t, J = 7.5 Hz, 1H), 7.12–7.29 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.20, 9.31, 13.69, 14.30, 27.41, 29.19, 41.24, 45.70, 51.87, 54.42, 59.34, 60.44, 111.17, 115.52, 126.66, 128.26, 129.12, 129.92, 137.67, 147.39, 173.31; ESIMS m/z 613 (M^++1).

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