

An Expeditious Synthesis of Substituted Pyrrolidines and Tetrahydrofurans Starting from Baylis-Hillman Adducts

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Suitably substituted pyrrolidines¹ and tetrahydrofurans² constitute important moieties of many biologically important natural and non-natural substances. Various synthetic methodologies for these compounds have been examined.¹⁻⁴ Among them one of the expeditious route is the catalytic hydrogenation of the corresponding *exo*- or *endo*-double bond-containing precursors.^{3,4}

Recently, we reported the synthesis of 2,5-dihydropyrroles and furans *via* the ring-closing metathesis (RCM) reaction of suitably modified Baylis-Hillman adducts.⁵ In addition, we reported the synthesis of *exo*-methylene tetrahydropyrroles and furans by using the radical cyclization of suitably modified Baylis-Hillman adducts.⁶ With these *endo*-⁵ and *exo*-methylene⁶ compounds we examined the feasibility for the synthesis of substituted pyrrolidines and tetrahydrofuran derivatives under various catalytic hydrogenation conditions (Scheme 1).⁷

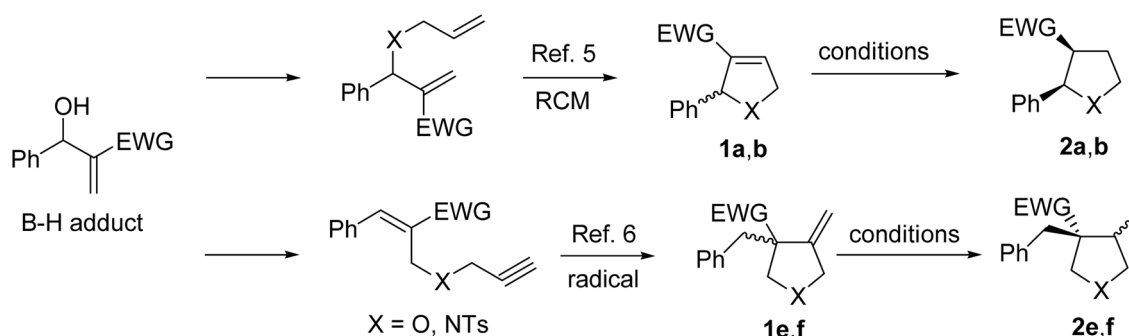
Required starting materials, **1a-d**, were synthesized according to the previous paper from the Baylis-Hillman adducts or *aza*-Baylis-Hillman adducts *via* the sequential allylation and RCM reaction with second generation Grubbs catalyst.⁵ With these compounds we examined the hydrogenation toward tetrahydrofuran **2a** and pyrrolidines **2b-d** under typical catalytic hydrogenation conditions (EtOH, Pd/C, H₂ balloon) and we obtained the desired compounds **2a-d** in good to excellent yields with complete stereocontrol at room temperature or at elevated temperature depending upon the substrates (entries 1-4, Table 1). The stereochemistry of products **2a** and **2b** is *cis* based on the references^{3,4} and NOE experimental results of **2a** (*vide infra*, Figure 1).

As a next trial we examined the hydrogenation of *exo*-

methylene compounds **1e** and **1f**, which were prepared *via* the radical cyclization from the suitably modified Baylis-Hillman adducts as reported.⁶ The hydrogenation of **1e** under similar conditions (Pd/C, EtOH) at room temperature or at around 40-50 °C did not produce the tetrahydrofuran derivative **2e** in appreciable amounts. When we carried out the reaction at elevated temperature (Pd/C, EtOH, reflux, 20 h, entry 5) we could obtain the reduction product **2e** in 63% yield as a diastereomeric mixture (3:1). In the reaction we isolated trace amounts of 2,3-dihydrofuran derivative **3** (2%)^{3a} and recovered remaining starting material **1e** in 25% yield. The yield and stereoselectivity of **2e** was not improved with Adam's catalyst (PtO₂, EtOH, reflux, 30 h, entry 6). However, when we replaced the solvent to EtOAc and carried out the reaction at around 50 °C we could isolate the compound **3** in an increased yield (15%, entry 7).^{3a} It is interesting to note that the yield of **3** could be increased to 97% under the conditions of Pd/C in EtOAc at room temperature (entry 8).

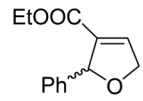
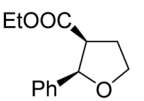
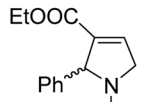
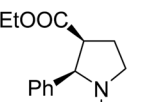
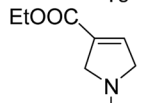
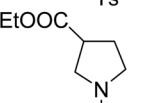
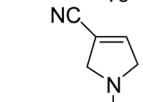
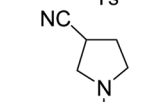
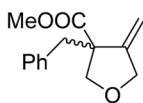
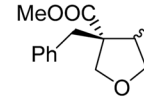
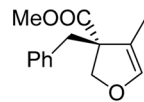
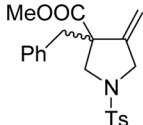
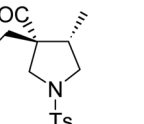
The reaction of **1f** under typical conditions (Pd/C, EtOH, 50 °C, 10 h) did not produce any new compounds in appreciable amounts and the starting material **1f** was recovered in 87% yield. However, when we changed the conditions (PtO₂, EtOAc, 50 °C, 12 h) desired reduction product **2f** was obtained in 70% yield (9:1 mixture). The major isomer was separated in pure state and the stereochemistry was determined by NOE experiments (Fig. 1). However, unfortunately, we could not synthesize the double bond-isomerized compound, 2,3-dihydropyrrole, in this case under various conditions.

In summary, we disclosed an expeditious route for the synthesis of pyrrolidines and tetrahydrofurans starting from

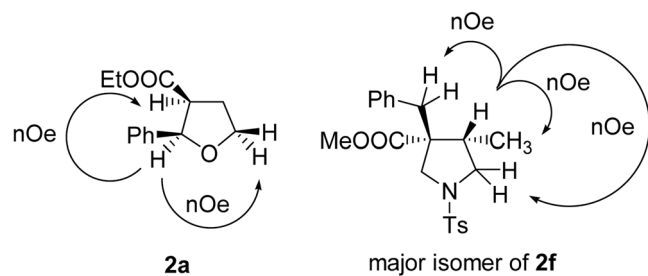


Scheme 1

Table 1. Synthesis of tetrahydrofuran and pyrrolidine derivatives

Entry	Substrate	Conditions ^a	Products (%)
1	 1a ⁵	Pd/C, EtOH rt, 5 h	 2a (88)
2	 1b ⁵	Pd/C, EtOH 50 °C, 7 h	 2b (94)
3	 1c ⁵	Pd/C, EtOH 50 °C, 8 h	 2c (92)
4	 1d ⁵	Pd/C, EtOH 50 °C, 2 h	 2d (99)
5	 1e ⁶	Pd/C, EtOH reflux, 20 h	 2e ^b (63%, 3:1) + 1e (25%) + 3 (2%)
6		PtO ₂ , EtOH reflux, 30 h	2e (70%, 3:1) + 1e (12%)
7		PtO ₂ , EtOAc 50 °C, 12 h	1e (82%) + 3 (15%)
8		Pd/C, EtOAc rt, 4 h	 3 (97)
9 ^c	 1f ⁶	Pd/C, EtOH 50 °C, 10 h	1f (87%)
10		PtO ₂ , EtOAc 50 °C, 12 h	 2f ^d (70%, 9:1) + 1f (10%)

^aAll reactions were carried out under H₂ balloon. ^bThe ratio of **2e** was determined based on ¹H NMR, but we did not confirm the stereochemistry. ^cIsomerized compound (2,3-dihydropyrrole derivative) as not formed under any conditions. ^dThe ratio of **2f** was determined based on ¹H NMR, and the major isomer was isolated and the stereochemistry as confirmed by NOE experiments (Fig. 1).

**Figure 1**

the suitably modified Baylis-Hillman adducts *via* RCM/hydrogenation or radical cyclization/hydrogenation protocols.

Experimental Section

Synthesis of starting materials **1a-f**, was carried out according to the previous papers.^{5,6}

Typical procedure for the synthesis of 2a: A solution of **1a** (109 mg, 0.5 mmol), 5 mol% Pd/C (20 mg) in ethanol (5 mL) was stirred at room temperature for 5 h under H₂ balloon. The reaction mixture was filtered through a pad of Celite and washed with dichloromethane. After removal of solvent and column chromatographic purification process (hexanes/ether, 6:4) we obtained **2a** as colorless oil, 97 mg (88%). Spectroscopic data of prepared compounds, **2a-f** and **3** are as follows.

Compound 2a: 88%; colorless oil; IR (film) 2981, 1731,

1178 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.25 (t, $J = 7.2$ Hz, 3H), 2.27-2.36 (m, 2H), 2.91-2.99 (m, 1H), 4.05 (dd, $J = 7.2$ and 6.9 Hz, 1H), 4.13-4.23 (m, 3H), 5.05 (d, $J = 7.2$ Hz, 1H), 7.27-7.38 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 14.18, 30.66, 52.34, 60.89, 68.39, 83.33, 125.75, 127.68, 128.40, 141.40, 173.33; FAB Mass 221 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$: C, 70.89; H, 7.32. Found: C, 70.97; H, 7.44.

Compound 2b: 94%; colorless oil; IR (film) 2971, 1731, 1349, 1153 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.13 (t, $J = 7.2$ Hz, 3H), 1.90-1.98 (m, 1H), 2.00-2.13 (m, 1H), 2.40 (s, 3H), 2.86-2.92 (m, 1H), 3.51-3.59 (m, 1H), 3.64-3.71 (m, 1H), 3.87-3.93 (m, 2H), 5.06 (d, $J = 4.2$ Hz, 1H), 7.20-7.38 (m, 7H), 7.67 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 13.84, 21.37, 27.03, 48.55, 53.40, 60.96, 65.65, 125.94, 127.32, 127.49, 128.34, 129.37, 134.50, 141.92, 143.32, 171.71; FAB Mass 374 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_4$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.51; H, 6.08; N, 3.59.

Compound 2c: 92%; colorless oil; IR (film) 2971, 1731, 1345, 1160 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.20 (t, $J = 7.2$ Hz, 3H), 2.00-2.10 (m, 2H), 2.44 (s, 3H), 2.94 (quintet, $J = 7.5$ Hz, 1H), 3.28-3.34 (m, 2H), 3.38 (dd, $J = 10.2$ and 6.9 Hz, 1H), 3.58 (dd, $J = 10.2$ and 8.1 Hz, 1H), 4.06 (q, $J = 7.2$ Hz, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.72 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 13.99, 21.45, 28.29, 42.73, 47.32, 49.84, 61.01, 127.56, 129.64, 133.38, 143.56, 172.24.

Compound 2d: 99%; colorless oil; IR (film) 2245, 1338, 1156, 1094 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 2.03-2.14 (m, 1H), 2.18-2.29 (m, 1H), 2.45 (s, 3H), 3.00 (quintet, $J = 7.5$ Hz, 1H), 3.31-3.46 (m, 3H), 3.67 (dd, $J = 10.5$ and 7.5 Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.72 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 21.55, 27.74, 29.76, 46.62, 50.57, 119.12, 127.56, 129.98, 132.95, 144.29.

Compound 2e (major isomer): colorless oil; IR (film) 2952, 1731, 1206 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.0 (d, $J = 7.2$ Hz, 3H), 2.32 (sextet, $J = 7.2$ Hz, 1H), 2.75 (d, $J = 13.8$ Hz, 1H), 3.30 (d, $J = 13.8$ Hz, 1H), 3.47-3.53 (m, 1H), 3.69 (s, 3H), 3.83 (d, $J = 9.3$ Hz, 1H), 4.04 (d, $J = 9.3$ Hz, 1H), 4.12-4.17 (m, 1H), 7.11-7.14 (m, 2H), 7.23-7.26 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 14.48, 41.32, 43.20, 51.46, 58.63, 71.59, 74.31, 126.71, 128.31, 129.66, 137.46, 173.41.

Compound 2f (major isomer): colorless oil; IR (film) 2952, 1731, 1454, 1344, 1164 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.80 (d, $J = 6.9$ Hz, 3H), 2.26 (sextet, $J = 6.9$ Hz, 1H), 2.43 (s, 3H), 2.67 (d, $J = 13.5$ Hz, 1H), 2.92 (dd, $J = 9.9$ and 6.3 Hz, 1H), 3.18 (d, $J = 13.5$ Hz, 1H), 3.37-3.45 (m, 2H), 3.48 (s, 3H), 3.70 (dd, $J = 9.9$ and 6.9 Hz, 1H), 7.00-7.03 (m, 2H), 7.20-7.25 (m, 3H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 14.67, 21.49, 41.02, 41.41, 51.03, 51.50, 53.39, 57.76, 126.95, 127.49, 128.41, 129.56, 129.72, 134.12, 136.45, 143.30, 172.56.

Compound 3: 97%; colorless oil; IR (film) 2950, 1731 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.73 (d, $J = 1.5$ Hz, 1H), 2.81 (d, $J = 13.8$ Hz, 1H), 3.40 (d, $J = 13.8$ Hz, 1H), 3.73 (s, 3H), 4.22 (d, $J = 9.6$ Hz, 1H), 4.67 (d, $J = 9.6$ Hz, 1H), 6.10 (q, $J = 1.5$ Hz, 1H), 7.09-7.12 (m, 2H), 7.22-7.29 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 8.30, 40.20, 52.09, 59.91, 75.60, 112.11, 126.75, 128.37, 129.45, 136.92, 142.60, 173.35.

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References and Notes

- For the synthesis and biological activities of pyrrolidine derivatives, see: (a) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484-4517. (b) Najera, C.; de Gracia retamosa, M.; Sansano, J. M. *Tetrahedron: Asymmetry* **2006**, *17*, 1985-1989. (c) Berlin, S.; Engman, L. *Tetrahedron Lett.* **2000**, *41*, 3701-3704. (d) Felluga, F.; Pitacco, G.; Prodan, M.; Pricl, S.; Visintin, M.; Valentin, E. *Tetrahedron: Asymmetry* **2001**, *12*, 3241-3249. (e) Cimarelli, C.; Palmieri, G. *J. Org. Chem.* **1996**, *61*, 5557-5563. (f) Denes, F.; Perez-Luna, A.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 398-406. (g) Declerck, V.; Allouchi, H.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2007**, *72*, 1518-1521. (h) Evans, P. *J. Org. Chem.* **2007**, *72*, 1830-1833.
- For the synthesis and biological activities of tetrahydrofuran derivatives, see: (a) Majumdar, K. C.; Basu, P. K.; Chattopadhyay, S. K. *Tetrahedron* **2007**, *63*, 793-826. (b) Makosza, M.; Przyborowski, J.; Klajn, R.; Kwast, A. *Synlett* **2000**, 1773-1774. (c) Makosza, M.; Judka, M. *Chem. Eur. J.* **2002**, *8*, 4234-4240. (d) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887-3890. (e) Jana, S.; Guin, C.; Roy, S. C. *Tetrahedron Lett.* **2005**, *46*, 1155-1157. (f) Dunach, E.; Esteves, A. P.; Medeiros, M. J.; Olivero, S. *Tetrahedron Lett.* **2004**, *45*, 7935-7937. (g) Esteves, A. P.; Goken, D. M.; Klein, L. J.; Leite, L. F. M.; Medeiros, M. J.; Peters, D. G. *Eur. J. Org. Chem.* **2005**, 4852-4859.
- For the catalytic hydrogenation of *exo*-double bond-containing precursors for the synthesis of tetrahydrofurans and pyrrolidines, see: (a) Bueno, J. M.; Coteron, J. M.; Chiara, J. L.; Fernandez-Mayoralas, A.; Fianor, J. M.; Valle, N. *Tetrahedron Lett.* **2000**, *41*, 4379-4382. (b) Gurjar, M. K.; Mohapatra, S.; Phalgune, U. D.; Puranik, V. G.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 7899-7902. (c) Ferrie, L.; Bouyssi, D.; Balme, G. *Org. Lett.* **2005**, *7*, 3143-3246. (d) Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773-1776. (e) Langlois, N.; Rakotonrandany, F. *Tetrahedron* **2000**, *56*, 2437-2448. (f) Del Valle, J. R.; Goodman, M. *J. Org. Chem.* **2003**, *68*, 3923-3931. (g) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412-4428. (h) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808-12809.
- For the catalytic hydrogenation of *endo*-double bond-containing precursors for the synthesis of tetrahydrofurans and pyrrolidines, see: (a) Pohmakotr, M.; Issaree, A.; Sampaogoen, L.; Tuchinda, P.; Reutrakul, V. *Tetrahedron Lett.* **2003**, *44*, 7937-7940. (b) Yoon-Miller, S. J. P.; Opalka, S. M.; Pelkey, E. T. *Tetrahedron Lett.* **2007**, *48*, 827-830.
- Kim, J. M.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 2805-2808.
- Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859-4863.
- For our recent papers on the synthesis of pyrrolidine and tetrahydrofuran moiety-containing compounds, see: (a) Lee, K. Y.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 2007-2011. (b) Gowrisankar, S.; Kim, S. J.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 289-292. (c) Lee, K. Y.; Lee, Y. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28*, 143-146. (d) Lee, K. Y.; Seo, J.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 3913-3917. (e) Kim, S. C.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 3463-3466. (f) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 4052-4058. (g) Lee, K. Y.; Park, D. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 1489-1492. (h) Lee, H. S.; Kim, S. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 1063-1066. (i) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 929-932.