Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4119–4122

Synthesis of poly-substituted pyrroles starting from the Baylis–Hillman adducts

Hyun Seung Lee, Jeong Mi Kim and Jae Nyoung Kim*

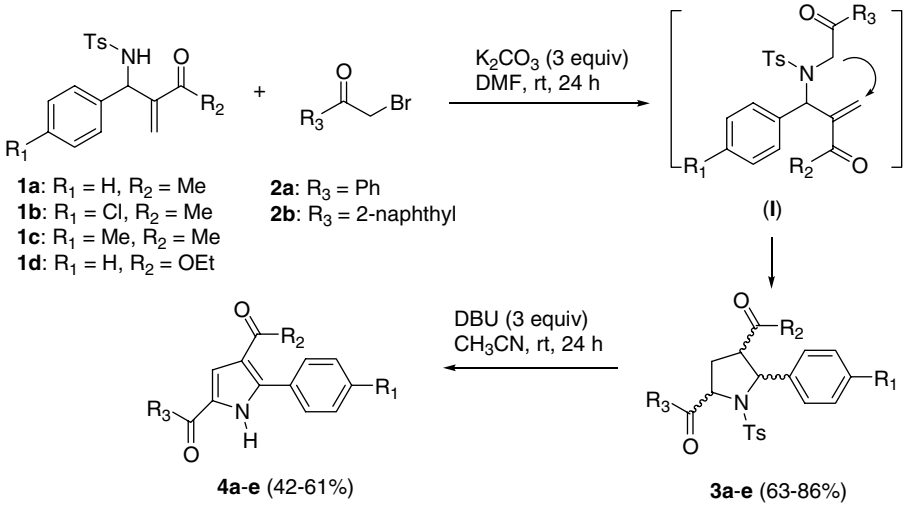
Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea

Received 12 March 2007; revised 30 March 2007; accepted 2 April 2007
Available online 11 April 2007

Abstract—We synthesized poly-substituted pyrrole derivatives **4a–e**, **7a–c** and **10a–d** from the reaction of phenacyl bromide and the *aza*-Baylis–Hillman adducts **1a–d** or their rearranged derivatives **5a–e**. The pyrroles were synthesized via the successive N-alkylation, Michael addition, elimination of *p*-toluenesulfinic acid and oxidative aromatization processes.

A variety of aromatic and heterocyclic compounds have been synthesized by using suitable chemical transformations starting from the Baylis–Hillman adducts.[1] Pyrroles are the basic skeleton of many biologically important substances and numerous synthetic methods of pyrroles have been investigated extensively.[2,3] However, the synthesis of pyrrole derivatives from Baylis–Hillman adducts was not developed much.[3] During the chemical transformations of Baylis–Hillman adducts[4] we were interested in the synthesis of poly-substituted pyrrole derivatives.

Our initial synthetic pathway is depicted in Scheme 1. We thought that trisubstituted tetrahydropyrrole derivatives **3** could be synthesized from *aza*-Baylis–Hillman adducts **1**[5] by sequential N-alkylation with phenacyl bromide (**2a**) and Michael addition at the conjugated vinyl moiety of the corresponding intermediate.[6] Elimination of



Scheme 1.

Keywords: Poly-substituted pyrroles; Baylis–Hillman adducts; Michael addition; DBU.
* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389; e-mail: kimjn@chonnam.ac.kr

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.022

Table 1. Synthesis of 2,3,5-trisubstituted pyrroles

Entry	1 + 2	3 (%)	4 (%)
1	**1a** + **2a**	**3a** (70)	**4a** (54)
2	**1a** + **2b**	**3b** (86)	**4b** (48)
3	**1b** + **2a**	**3c** (68)	**4c** (52)
4	**1c** + **2a**	**3d** (63)	**4d** (61)
5	**1d** + **2a**	**3e** (74)	**4e** (42)

p-toluenesulfinic acid from **3** and the following oxidation would give 2,3,5-trisubstituted pyrroles **4** (Scheme 1).

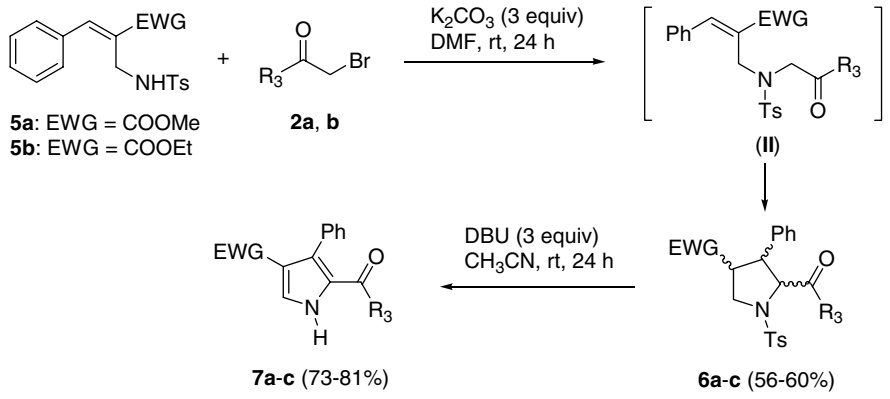
The reaction of **1a**–**d** and phenacyl bromide (**2a**) or 2-bromo-2′-acetonaphthone (**2b**) under the influence of K_2CO_3 in DMF gave the corresponding diastereomeric mixtures of tetrahydropyrroles **3a**–**e** in moderate yields (63–86%) via the intermediate (**I**). Actually we observed the formation of several isomers of **3** having similar R_f values on TLC. We separated them together by using a short path silica column and used them together in the next elimination reaction. The elimination of *p*-toluenesulfinic acid was examined with DBU in CH_3CN. However, to our surprise, we obtained 2,3,5-trisubstituted pyrroles **4** directly under the conditions in moderate yields (42–61%) and the results are summarized in Table 1.[7] Although the mechanism for the dehydrogenative oxidation process is unclear at this stage[8] we could prepare our desired pyrroles very easily in two steps.

Table 2. Synthesis of 2,3,4-trisubstituted pyrroles

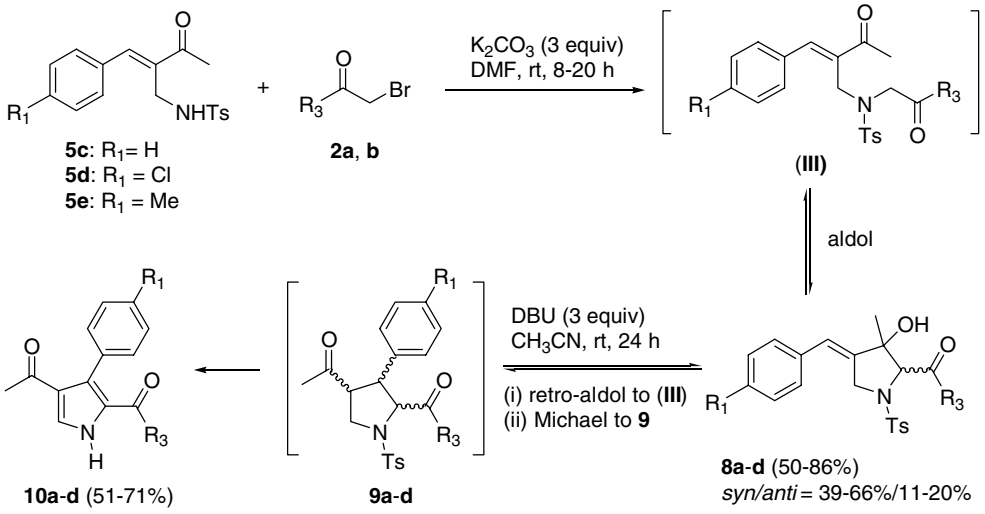
Entry	5 + 2	6 (%)	7 (%)
1	**5a** + **2a**	**6a** (60)	**7a** (81)
2	**5a** + **2b**	**6b** (56)	**7b** (77)
3	**5b** + **2a**	**6c** (58)	**7c** (73)

Encouraged by the results we examined the reaction of rearranged tosylamide derivatives **5a** and **5b**, which could be easily synthesized from the corresponding Baylis–Hillman acetates and tosylamide in an S_N2' manner.[5] The reactions of **5a** and **5b** showed the same reactivity as those of **1a**–**d** and we synthesized 2,3,4-trisubstituted pyrroles **7a**–**c** in good yields (73–81%) under the same conditions. The results are summarized in Scheme 2 and in Table 2.

However, the reactions of **5c**–**e** were somewhat different from those of the cases of Schemes 1 and 2. The reac-



Scheme 2.



Scheme 3.

Table 3. Synthesis of 2,3,4-trisubstituted pyrroles

Entry	5 + 2	Time (h)	8 (%, *syn*/*anti*)[a]	10 (%)
1	**5c** + **2a**	8	**8a** (86, 66/20)	**10a** (71)
2	**5c** + **2b**	8	**8b** (73, 56/17)	**10b** (51)
3	**5d** + **2a**	10	**8c** (79, 59/20)	**10c** (67)
4	**5e** + **2a**	20	**8d** (50, 39/11)[b]	**10d** (67)

[a] Isolated yields of *syn* and *anti* isomers.
[b] The yield of **8d** was relatively low due to low reactivity of **5e**.

tions of **5c–e** and **2** under the same conditions (K_2CO_3/DMF) produced **8a–d** as the major products as separable *syn*/*anti* mixtures.[9] The formation of **8** can be explained by an intramolecular aldol reaction of intermediate (**III**). However, when we subjected **8** under the conditions of DBU in CH_3CN we could obtain 2,3,4-trisubstituted pyrroles **10a–d** in moderate yields (51–71%), fortunately. Compounds **8a–d** could be converted to intermediate (**III**) by the retro-aldol pathway and intermediate (**III**) was slowly transformed to **9a–d** via the Michael addition pathway. The last step for the formation of **10** from **9** could be explained as in Schemes 1 and 2. The results are summarized in Scheme 3 and in Table 3.

In summary, we developed an expeditious synthetic method of poly-substituted pyrrole derivatives from the reaction of phenacyl bromide and the *aza*-Baylis–Hillman adducts or their rearranged derivatives via successive N-alkylation, Michael addition, elimination of *p*-toluenesulfinic acid and oxidative aromatization processes. The studies on DBU-mediated interesting oxidation process are underway.

Acknowledgments

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, KRF-2006-311-C00384). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

References and notes

1. For the review articles on Baylis–Hillman reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891; (b) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, pp 201–350; (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062; (d) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645; (e) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490, and further references cited therein.
2. For the synthesis of poly-substituted pyrroles and their biological activities, see: (a) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213–7256; (b) Knight, D. W.; Sharland, C. M. *Synlett* **2004**, 119–121; (c) Singh, V.; Kanojiya, S.; Batra, S. *Tetrahedron* **2006**, *62*, 10100–10110; (d) Knight, D. W.; Sharland, C. M. *Synlett* **2003**, 2258–2260; (e) Magnus, N. A.; Staszak, M. A.; Udodong, U. E.; Wepsiec, J. P. *Org. Proc. Res. Dev.* **2006**, *10*, 899–904; (f) Zen, S.; Harada, K. *Chem. Pharm. Bull.* **1982**, *30*, 366–369; (g) Chen, Q.; Wang, T.; Zhang, Y.; Wang, Q.; Ma, J. *Synth. Commun.* **2002**, *32*, 1051–1058; (h) Nicolaou, I.; Demopoulos, V. J. *J. Med. Chem.* **2003**, *46*, 417–426; (i) Gupton, J. T.; Banner, E. J.; Scharf, A. B.; Norwood, B. K.; Kanters, R. P. F.; Dominey, R. N.; Hempel, J. E.; Kharlamova, A.; Bluhn-Chertudi, I.; Hickenboth, C. R.; Little, B. A.; Sartin, M. D.; Coppock, M. B.; Krumpe, K. E.; Burnham, B. S.; Holt, H.; Du, K. X.; Keertikar, K. M.; Diebes, A.; Ghassemi, S.; Sikorski, J. A. *Tetrahedron* **2006**, *62*, 8243–8255; (j) Cadamuro, S.; Degani, I.; Dughera, S.; Fochi, R.; Gatti, A.; Piscopo, L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 273–283; (k) Cohnen, E.; Dewald, R. *Synthesis* **1987**, 566–568; (l) Misra, N. C.; Panda, K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 1246–1251.
3. For the examples on the synthesis of pyrroles from Baylis–Hillman adducts, see: (a) Declerck, V.; Ribiere, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372–8381; (b) Shi, M.; Xu, Y.-M. *Eur. J. Org. Chem.* **2002**, 696–701; (c) Roy, A. K.; Pathak, R.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2006**, 1021–1027.
4. For our recent papers on chemical transformations involving the Baylis–Hillman adducts, see: (a) Gowrisankar, S.; Lee, K. Y.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 5785–5788; (b) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 4052–4058; (c) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859–4863; (d) Lee, K. Y.; Gowrisankar, S.; Lee, Y. J.; Kim, J. N. *Tetrahedron* **2006**, *62*, 8798–8804; (e) Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 6641–6645; (f) Park, D. Y.; Kim, S. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 6315–6319; (g) Gowrisankar, S.; Kim, S. J.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 289–292; (h) Park, D. Y.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 1633–1636; (i) Kim, S. J.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 1069–1072, and further references cited therein.
5. For the synthesis of *aza*-Baylis–Hillman adducts and the rearranged compounds, see: (a) Park, D. Y.; Lee, M. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 8799–8803; (b) Lee, M. J.; Kim, S. C.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 439–442; (c) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Gong, J. H. *Synlett* **2002**, 173–175; (d) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2001**, *66*, 6498–6501; (e) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2002**, *67*, 2329–2334; (f) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2004**, *45*, 3089–3092.
6. For the synthesis of indole derivatives by using the similar approach, N-alkylation with phenacyl bromide and the following Michael type reaction, please see: Caron, S.; Vazquez, E.; Stevens, R. W.; Nakao, K.; Koike, H.; Murata, Y. *J. Org. Chem.* **2003**, *68*, 4104–4107.
7. *Typical procedure for the synthesis of compound* **4a** *and some selected spectroscopic data of* **4a**, **7a**, **8a**-*syn*, **8a**-*anti and* **10a** *are as follows*: A solution of **1a** (329 mg, 1.0 mmol), K_2CO_3 (415 mg, 3.0 mmol) and **2a** (300 mg, 1.5 mmol) in DMF (2 mL) was stirred at room temperature for 24 h. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/ether, 4:1:1) we obtained compound **3a** (313 mg, 70%) as a yellow solid (R_f value of the major diastereoisomer on TLC is 0.25 in hexanes/ether = 1:3). Compound **3a** (224 mg, 0.5 mmol) was dissolved in CH_3CN (2 mL) and DBU (228 mg, 1.5 mmol) was added and stirred at room temperature for 24 h. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/ether, 2:1:1) we obtained compound **4a** (79 mg, 54%) as a white solid.
Compound **4a**: 54%; white solid, 178–180 °C; IR (film) 3259, 1674, 1616, 1468, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H), 7.33 (d, $J = 2.7$ Hz, 1H), 7.46–7.55

(m, 5H), 7.60–7.65 (m, 3H), 7.89 (d, $J = 7.2$ Hz, 2H), 10.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.01, 121.12, 123.96, 128.54, 128.56, 128.97, 129.28, 129.68, 129.81, 130.89, 132.47, 137.43, 141.72, 184.94, 193.96; LCMS m/z 289 (M^+). Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.65; H, 5.37; N, 4.79.

Compound **7a**: 81%; white solid, 204–206 °C; IR (film) 3319, 1703, 1622, 1389, 1281 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 3H), 6.98–7.09 (m, 7H), 7.17–7.35 (m, 3H), 7.74 (d, $J = 3.3$ Hz, 1H), 10.23 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.09, 116.32, 126.99, 127.11, 127.38, 128.78, 128.86, 129.72, 131.06, 131.34, 132.87, 133.36, 137.01, 164.14, 187.97; LCMS m/z 305 (M^+). Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.81; H, 5.01; N, 4.57.

Compound **8a**-*syn*: 66%; white solid, 98–100 °C; IR (film) 3487, 1691, 1342, 1159, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 3H), 2.12 (s, 1H), 2.38 (s, 3H), 4.57 (d, $J = 2.4$ Hz, 2H), 5.39 (s, 1H), 6.53 (s, 1H), 7.19–7.63 (m, 12H), 7.92 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.52, 28.71, 49.53, 67.85, 80.45, 122.58, 127.21, 127.59, 128.56, 128.61, 128.68, 128.73, 129.61, 133.73, 135.63, 135.72, 136.85, 142.34, 143.70, 198.60; LCMS m/z 447 (M^+).

Compound **8a**-*anti*: 20%; white solid, 158–160 °C; IR (film) 3475, 1687, 1338, 1157, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 3H), 2.37 (s, 3H), 2.54 (s, 1H), 4.54 (d, $J = 14.4$ Hz, 1H), 4.65 (d, $J = 14.4$ Hz, 1H), 5.53 (s, 1H), 6.49 (s, 1H), 7.18–7.70 (m, 12H), 7.98 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.49, 21.94, 50.10, 70.81, 80.69, 123.83, 127.47, 127.80, 128.56, 128.70 (2C), 128.89, 129.55, 133.79, 135.51 (2C), 136.59, 140.59, 143.65, 197.20; LCMS m/z 447 (M^+).

Compound **10a**: 71%; white solid, 228–230 °C; IR (film) 3213, 1658, 1620, 1377, 1281 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 6.98–7.11 (m, 7H), 7.17–7.34 (m, 3H), 7.72 (d, $J = 3.6$ Hz, 1H), 10.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.44, 126.84, 127.66, 127.71 (2C), 128.21, 128.95, 130.17, 131.20, 131.59, 132.19, 133.70, 137.31, 188.35, 194.54; LCMS m/z 289 (M^+). Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.75; H, 5.11; N, 4.92.

8. The studies on DBU-mediated interesting dehydrogenative oxidation process are actively underway in our laboratory. Some interesting base-promoted oxidations or base-induced disproportionations were reported, see: (a) Pal, M.; Swamy, N. K.; Hameed, P. S.; Padakanti, S.; Yeleswarapu, K. R. *Tetrahedron* **2004**, *60*, 3987–3997; (b) Chung, K. H.; Moon, B. C.; Lim, C. H.; Kim, J. P.; Lee, J. H.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 1203–1205; (c) Basavaiah, D.; Sharada, D. S.; Veerendhar, A. *Tetrahedron Lett.* **2006**, *47*, 5771–5774; An example of simultaneous thermal elimination of sulfinic acid and oxidation reaction was also reported, see: (d) Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1993**, *58*, 2068–2074.
9. We separated the *syn* and *anti* isomers in all cases;[7] however, we did not find any differences in their reactivity for the next reaction. The spectroscopic interpretation and the stereochemistry assignment by NOE experiment will be published in due course.