Facile Synthesis of 1,2,3,4-Tetrasubstituted Pyrroles from Baylis-Hillman Adducts

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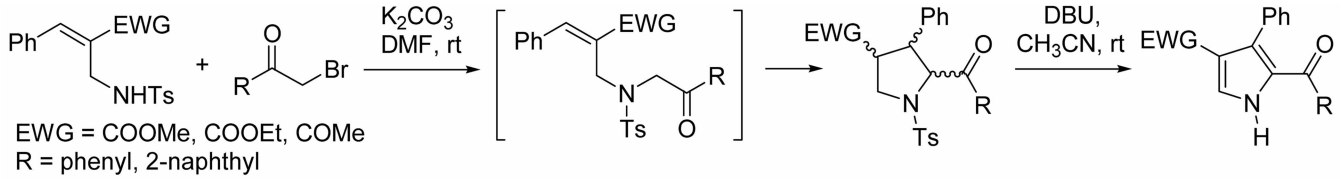
Suitably functionalized pyrroles are the basic skeleton of many biologically important substances and numerous synthetic methods of pyrroles have been investigated extensively.[1,2] However, the synthesis of pyrrole derivatives from Baylis-Hillman adducts was not developed much.[2] Recently, we reported the synthesis of 2,3,4-trisubstituted pyrroles starting from the rearranged *aza*-Baylis-Hillman adducts (Scheme 1).[3]

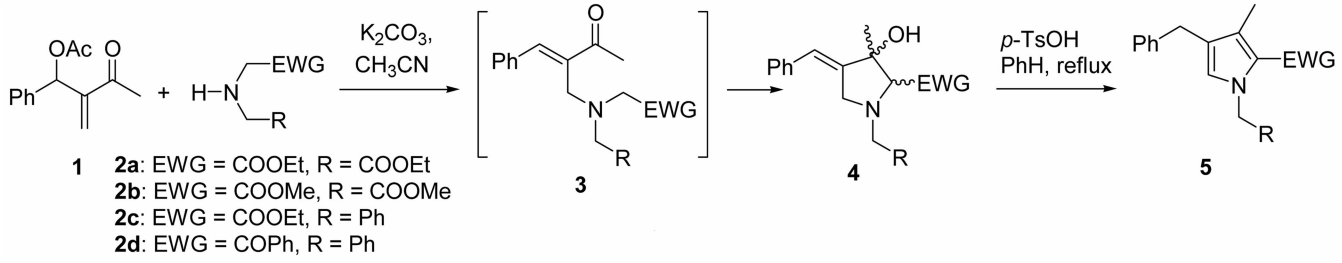
Meantime we presumed that we could synthesize 1,2,3,4-tetrasubstituted pyrrole derivatives by using the synthetic approach in Scheme 2. As shown in Scheme 2, we imagined that the reaction of Baylis-Hillman acetate **1**, as the representative example, and secondary amine derivatives **2a-d** could give the corresponding S_N2' product **3a-d**, which could be cyclized to **4a-d** under basic conditions. The following acid-catalyzed dehydration and concomitant double bond isomerization of **4a-d** would provide desired pyrroles **5a-d**.

Among the examined conditions the use of K_2CO_3 in CH_3CN gave the best results for the preparation of **4a-d**. As expected we could not observe the formation of **3** (except for **3c**, entry 3 in Table 1),[4] instead we obtained **4a-d** directly in 50-74% yields as inseparable *syn/anti* mixtures in a one-pot reaction. Based on the ^1H NMR spectra of **4a-d** the ratio of *syn/anti* was 4:1 to 2:1 (footnotes b-d in Table 1), however, we did not confirm which isomer is the major one. For the reaction of **1** and **2c** we isolated **3c** in 34% yield (entry 3 in Table 1) together with **4c** in 50% yield. For the synthesis of compound **4d** (entry 4) we used **2d**[5] in slightly excess amount (footnote e in Table 1). The following dehydration step of **4a-d** was carried out under the influence of *p*-TsOH (20-40 mol%) in benzene and we obtained the desired compounds **5a-d** in 41-64% yields. Isomerization of double bond occurred during the dehydration stage simultaneously to afford pyrroles directly. The results are summarized in Table 1.

However, the reaction of **1** and **2e** showed somewhat different reactivity as compared with those of **2a-d** (Scheme 3). When we carried out the reaction of **1** and **2e** in CH_3CN at room temperature the reaction did not show the formation of any new compounds in appreciable amounts presumably due to the limited solubility of **2e** in CH_3CN. Thus we elevated the temperature to refluxing, however, rearranged acetate was the major product in this case. After many trials we could obtain **3e** in 74% yield in aqueous CH_3CN at room temperature. In aqueous CH_3CN the compound **2e** was dissolved completely and the rearrangement of acetate group of **1** to the primary position was minimized at room temperature. With this compound **3e** in our hand we prepared **4e** under the same conditions of Table 1 (CH_3CN,



Scheme 1

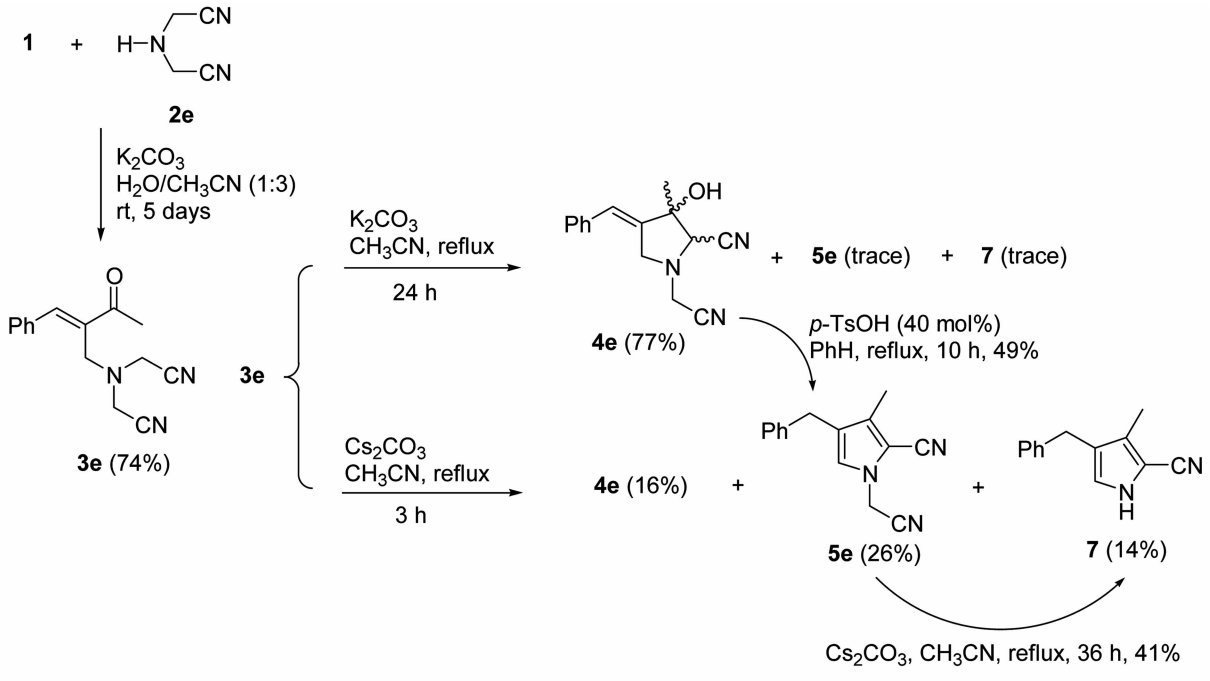


Scheme 2

Table 1. Synthesis of 1,2,3,4-tetrasubstituted pyrroles

Entry	1 + 2	Conditions	3 (%) / 4 (%)	Conditions	5 (%)[f]
1	**1** + **2a**	K_2CO_3 (1.1 equiv) CH_3CN, reflux, 27 h	**3a** (nd)[a] / **4a** (69)[b]	*p*-TsOH (20 mol%) PhH, reflux, 10 h	**5a** (64)
2	**1** + **2b**	K_2CO_3 (1.1 equiv) CH_3CN, reflux, 26 h	**3b** (nd)[a] / **4b** (71)[c]	*p*-TsOH (20 mol%) PhH, reflux, 12 h	**5b** (47)
3	**1** + **2c**	K_2CO_3 (2.2 equiv) CH_3CN, reflux, 7 days	**3c** (34) / **4c** (50)[d]	*p*-TsOH (40 mol%) PhH, reflux, 2 days	**5c** (56)
4	**1** – **2d**[e]	K_2CO_3 (1.1 equiv) CH_3CN, rt, 1 h	**3d** (nd)[a] / **4d** (74)[d]	*p*-TsOH (20 mol%) PhH, reflux, 12 h	**5d** (41)

[a]Nd means not detected. [b]The ratio is 2:1 (*syn anti* mixture). [c]The ratio is 4:1 (*syn anti* mixture). [d]The ratio is 3:1 (*syn anti* mixture). [e]Starting material **2d** was prepared by the reaction of benzylamine and phenacyl bromide according to the reference.[5] [f]The compound **2d** was unstable thus we used this compound in a crude state and we used 0.91 equiv of **1**. [f]Isolated yield.

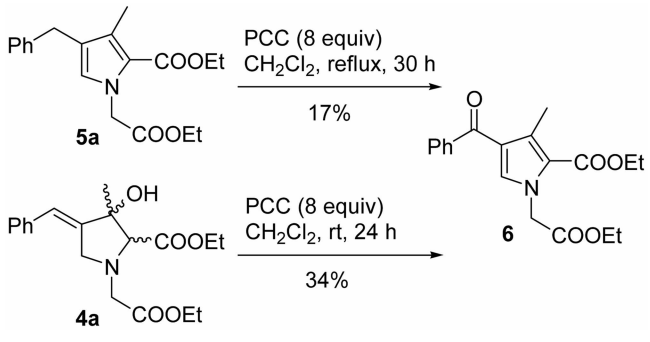


Scheme 3

K_2CO_3, reflux, 24 h) in 77% yield (*syn/anti*, 3:2). Dehydration of **4e** under the same conditions (*p*-TsOH/benzene/reflux) afforded **5e** in 49% yield. During the synthesis of **4e** we observed the formation of trace amounts of **5e** and **7**. It is interesting to note that the yields of **5e** and **7** were increased with concomitant decrease of **4e** when we used Cs_2CO_3 (CH_3CN, reflux, 3 h). The formation of pyrrole derivative **7** can be explained by decyanomethylation of **5e**,[6] and we confirmed the conversion experimentally by transforming **5e** into **7** under the same conditions (41% and recovered **5e** in 10%).

Finally, we examined the possibility for the oxidation of **5a** into 4-benzoylpyrrole derivative **6** as in our previous oxidation involving PCC (pyridinium chlorochromate) in a similar syatem.[7] However, the yield of oxidized compound **6** was very low to be useful in a synthetic point of view. It is interesting to note that the oxidation with the precursor **4a** instead of **5a** showed somewhat improved yield.

In summary, we disclosed the synthesis of poly-substituted



Scheme 4

pyrrole derivatives from the reaction of Baylis-Hillman acetate and some secondary amine compounds.[8]

Experimental Section

Typical experimental procedure for the synthesis of compounds 4a and 5a, and the spectroscopic data of 3c,

3e, 4a-e, 5a-e, 6, and 7 are as follows. A stirred mixture of **1** (218 mg, 1.0 mmol), **2a** (189 mg, 1.0 mmol), and K_2CO_3 (152 mg, 1.1 mmol) in CH_3CN (5 mL) was heated to reflux for 27 h. After the usual aqueous workup procedure and column chromatographic purification process (hexanes/EtOAc, 3:1) we obtained **4a** as colorless oil, 240 mg (69%). A solution of **4a** (174 mg, 0.5 mmol) and *p*-TsOH (19 mg, 0.1 mmol) in benzene (4 mL) was heated to reflux for 10 h. After the usual aqueous workup procedure and column chromatographic purification process (hexanes/EtOAc, 6:1) we obtained **5a** as a white solid, 105 mg (64%).

Compound **3c**: 34%; colorless oil; IR (film) 2924, 1737, 1666, 1231, 1189, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, J = 7.2 Hz, 3H), 2.42 (s, 3H), 3.22 (s, 2H), 3.76 (s, 2H), 3.81 (s, 2H), 4.04 (q, J = 7.2 Hz, 2H), 7.19-7.27 (m, 5H), 7.32-7.42 (m, 3H), 7.55-7.58 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.14, 26.70, 49.21, 53.37, 57.85, 60.07, 127.10, 128.18, 128.37, 128.83, 129.11, 130.05, 135.11, 138.59, 139.04, 141.62, 171.18, 200.85.

Compound **3e**: 74%; colorless oil; IR (film) 2246, 1664, 1421, 1230, 1132 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.51 (s, 3H), 3.55 (s, 4H), 3.64 (s, 2H), 7.42-7.49 (m, 5H), 7.85 (s, 1H).

Compound **4a**: 69% (*syn*:*anti*, 2:1); colorless oil; IR (film) 3446, 2981, 1738, 1448, 1195, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer) δ 1.27 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.64 (s, 3H), 2.80 (br s, 1H), 3.51-3.84 (m, 4H), 4.11-4.36 (m, 5H), 6.61 (t, J = 2.4 Hz, 1H), 7.20-7.24 (m, 3H), 7.28-7.36 (m, 2H).

Compound **4b**: 71% (*syn*:*anti*, 4:1); colorless oil; IR (film) 3452, 2954, 1747, 1693, 1442, 1213, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer) δ 1.63 (s, 3H), 3.51-3.90 (m, 6H), 3.70 (s, 3H), 3.77 (s, 3H), 6.61 (t, J = 2.4 Hz, 1H), 7.20-7.26 (m, 3H), 7.27-7.36 (m, 2H).

Compound **4c**: 50% (*syn*:*anti*, 3:1); colorless oil; IR (film) 3454, 2981, 1739, 1448, 1261, 1196 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer) δ 1.32 (t, J = 7.5 Hz, 3H), 1.60 (s, 3H), 2.75 (br s, 1H), 3.34-3.65 (m, 3H), 3.94-4.05 (m, 2H), 4.21-4.31 (m, 2H), 6.56 (t, J = 2.4 Hz, 1H), 7.15-7.21 (m, 3H), 7.24-7.39 (m, 2H).

Compound **4d**: 74% (*syn*:*anti*, 3:1); colorless oil; IR (film) 3438, 1676, 1448, 1228, 1180, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer) δ 1.55 (s, 3H), 2.68 (br s, 1H), 3.38-4.23 (m, 4H), 4.38 (s, 1H), 6.53 (t, J = 2.4 Hz, 1H), 7.17-7.34 (m, 10H), 7.43-7.49 (m, 2H), 7.54-7.60 (m, 1H), 7.93-7.97 (m, 2H).

Compound **4e**: 77% (*syn*:*anti*, 3:2); colorless oil; IR (film) 3429, 2925, 2222, 1448, 1261, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer) δ 1.66 (s, 3H), 2.60 (br s, 1H), 3.69 (s, 1H), 3.80-3.97 (m, 4H), 6.70 (t, J = 2.4 Hz, 1H), 7.21-7.46 (m, 5H) and ^1H NMR ($CDCl_3$, 300 MHz, minor isomer) δ 1.71 (s, 3H), 2.54 (br s, 1H), 3.78 (s, 1H), 3.81 (s, 1H), 3.87 (s, 1H), 3.91 (d, J = 2.4 Hz, 2H), 6.60 (t, J = 2.4 Hz, 1H), 7.21-7.42 (m, 5H).

Compound **5a**: 64%; white solid, mp 42-44 °C; IR (film) 1755, 1687, 1417, 1298, 1199, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 2.24 (s, 3H), 3.76 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 4.25 (q, J = 7.2 Hz, 2H), 4.87 (s, 2H), 6.42 (s, 1H), 7.12-7.20 (m, 3H), 7.25-7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.60, 14.12, 14.34, 31.24, 51.14, 59.69, 61.30, 119.74, 122.66, 125.84, 127.65, 128.32, 128.53, 128.66, 140.81, 162.08, 169.27; LCMS m/z 329 (M^-).

Compound **5b**: 47%; colorless oil; IR (film) 1759, 1693, 1444, 1215, 1124, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.23 (s, 3H), 3.75 (s, 3H), 3.76 (s, 2H), 3.79 (s, 3H), 4.87 (s, 2H), 6.43 (s, 1H), 7.16-7.20 (m, 3H), 7.24-7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.54, 31.22, 50.80, 50.97, 52.28, 119.55, 122.77, 125.86, 127.87, 128.33, 128.52, 128.72, 140.68, 162.54, 169.69.

Compound **5c**: 56%; colorless oil; IR (film) 1693, 1452, 1421, 1386, 1297, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, J = 6.9 Hz, 3H), 2.24, (s, 3H), 3.76 (s, 2H), 4.19 (q, J = 6.9 Hz, 2H), 5.43 (s, 2H), 6.55 (s, 1H), 7.01-7.04 (m, 2H), 7.14-7.29 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.69, 14.28, 31.21, 52.44, 59.47, 119.60, 122.29, 125.76, 126.41, 127.04, 127.33, 128.28, 128.39, 128.43, 128.59, 138.96, 141.03, 161.86; LCMS m/z 333 (M^+).

Compound **5d**: 41%; colorless oil; IR (film) 1624, 1495, 1446, 1400, 1215, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.63 (s, 3H), 3.73 (s, 2H), 5.37 (s, 2H), 6.68 (s, 1H), 7.05-7.08 (m, 2H), 7.16-7.30 (m, 8H), 7.34-7.40 (m, 2H), 7.44-7.50 (m, 1H), 7.58-7.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.04, 31.30, 51.99, 122.72, 125.87, 126.80, 127.28, 128.16, 128.23, 128.34, 128.39 (2C), 128.45, 128.47, 129.00, 129.35, 131.59, 138.71, 140.73, 188.34; LCMS m/z 365 (M^+).

Compound **5e**: 49%; colorless oil; IR (film) 2208, 1493, 1425, 1390, 1372 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.11 (s, 3H), 3.73 (s, 2H), 4.82 (s, 2H), 6.58 (s, 1H), 7.13-7.16 (m, 2H), 7.19-7.33 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.32, 31.25, 35.66, 103.72, 112.38, 113.39, 124.99, 125.64, 126.42, 128.45, 128.63, 132.60, 139.28.

Compound **6**: 34%; colorless oil; IR (film) 2981, 1753, 1693, 1643, 1251, 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.5 Hz, 3H), 1.38 (t, J = 7.5 Hz, 3H), 2.64 (s, 3H), 4.24 (q, J = 7.5 Hz, 2H), 4.32 (q, J = 7.5 Hz, 2H), 4.95 (s, 2H), 7.06 (s, 1H), 7.43-7.47 (m, 2H), 7.52-7.55 (m, 1H), 7.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.55, 14.12, 14.28, 51.79, 60.47, 61.73, 121.91, 122.65, 128.26, 129.04, 131.69, 132.49, 134.92, 140.18, 168.24 (2C), 191.45; LCMS m/z 343 (M^-).

Compound **7**: 41%; pale yellow solid, mp 95-97 °C; IR (film) 3303, 2212, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.11 (s, 3H), 3.75 (s, 2H), 6.58 (d, J = 3.0 Hz, 1H), 7.14-7.22 (m, 3H), 7.26-7.31 (m, 2H), 8.45 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.96, 31.29, 100.08, 114.45, 121.97, 123.62, 126.12, 128.43, 128.46, 130.64, 140.16; LCMS m/z 196 (M^+).

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References and Notes

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