Synthesis of 4-Benzylidene-2,5-dimethyl-3,4-dihydro-2H-pyrrole Derivatives from Baylis-Hillman Adducts and Their Chemical Transformations

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Recently, Basavaiah and Rao reported the synthesis of substituted γ-lactams by the reductive cyclization of γ-nitrocycarbonyl compounds, which were prepared from the reaction of the acetates of Baylis-Hillman adducts and nitro compounds. γ-Nitrocycarbonyl compounds could be transformed into cyclic nitrones or pyrroline derivatives depending upon the reduction conditions and the nature of the carbonyl groups. Various reduction conditions have been used for the reductive cyclization of γ-nitrocycarbonyl compounds including Fe/AcOH, Zn/NH₄Cl, and catalytic hydrogenation.

Suitably substituted pyrrolines or cyclic nitrone derivatives have been prepared and used as important synthetic intermediates. During the investigation on the chemical transformations of Baylis-Hillman adducts, we intended to examine the reductive cyclization of γ-nitrocycarbonyl derivatives derived from the acetates of Baylis-Hillman adducts as shown in Scheme 1. The starting materials 2a-e were easily prepared by the S_{N}2 reaction of primary nitroalkanes and the acetates of the Baylis-Hillman adducts according to the previous method. We tried the reductive cyclization of 2a under various conditions and the results are summarized in Table 1 (entries 1-3). As shown in Table 1, we obtained mixtures of 4-benzylidene-2,5-dimethyl-3,4-dihydro-2H-pyrrole (5a) and cyclic nitrone derivative 6a in variable yields. The use of Fe/AcOH gave the pyrrole derivative 5a as the major product under refluxing conditions (entry 1). Whereas, we obtained the cyclic nitrone derivative 6a as the major product when we use Zn/NH₄Cl at lower temperature (entry 3). The use of Fe/AcOH (entry 2) at lower temperature and Zn/NH₄Cl at room temperature (not shown) showed diminished selectivity. In spite of our extensive efforts we failed to obtain higher selectivity. Similarly, we synthesized 5b-e and 6b-e from the reaction of 2b-e under Fe/AcOH/reflux conditions and the results are summarized in Table 1.

For the substrates 2b-d, pyrrole derivatives 5b-d were isolated as the major products. However, nitrone 6e was obtained as the major product in the case of dimethyl-substituted starting material 2e (entry 7). Structure identification of the synthesized products was carried out by their ¹H and ¹³C NMR, IR, mass, and chemical transformations (vide infra). The stereochemistry of the double bond of 5a and 6a was confirmed as E based on NOE experiments (shown in Table 1). The mechanism for the formation of 5 and 6 was proposed as in Scheme 2 with 5a and 6a as the representative examples. Reduction of the nitrile group into amino group to form 3a and the following condensation gave 5a. Partial reduction to hydroxylamine derivative 4a and the following cyclization and dehydration afforded 6a.

In order to verify the usefulness of the prepared pyrrole compounds 5, we examined the Michael addition reaction of the acidic methyl group at the 5-position of 5a toward acrylonitrile or methyl acrylate (Scheme 3). The reaction of pyrrole 5a and acrylonitrile in THF in the presence of catalytic amounts of base (DBU or NaOMe) produced intractable mixtures of products. Fortunately, we could obtain 8a in moderate yield (59%) by refluxing 5a in acrylonitrile without any base and solvent for long time (60 h). First introduction of acrylonitrile to the methyl group of 5a produced the corresponding mono adduct (1), which reacted once more with acrylonitrile to produce 8a. But, the third introduction of acrylonitrile to 8a did not occur presumably due to the steric hindrance. The Michael addition reaction was thought to occur via the imine-enamine tautomerization as shown. Similarly, we obtained 7a from the reaction of 5a and methyl acrylate in 58% yield. The

Scheme 1
compound 7a could be transformed to bicyclic lactam derivative 9a in refluxing toluene in the presence of acetic acid in 48% yield. We also tried the reactions of 5e and 5c and obtained the corresponding tetrahydroindolizinone derivatives 9b and 9c via the corresponding intermediates 7b and 7c although the yields were relatively low (Schemes 4 and 5).

In summary, we disclosed the reductive cyclization of γ-nitrocarbonyl compounds derived from Baylis-Hillman adducts into cyclic nitronate and pyrroline derivatives.
Selective double Michael addition reaction of the pyrroline compounds was observed for the first time. Further studies on the synthesis of bicyclic lactam derivatives and transformation into natural alkaloid derivatives are underway.

**Experimental Section**

**Typical procedure for the synthesis of starting material 2a:** A solution of Baylis-Hillman acetate 1a (436 mg, 2 mmol), nitroethane (300 mg, 4 mmol), and K$_2$CO$_3$ (830 mg, 6 mmol) in DMF (5 mL) was stirred at room temperature for 3 h. After the normal aqueous workup and column chromatographic purification process (hexanes/ether, 10:1) we obtained 2a, 370 mg (79%). Other starting materials 2b-e were synthesized similarly and the spectroscopic data are as follows.

- **Compound 2a:** 79%; oil; IR (neat) 1550 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.44 (d, $J = 6.6$ Hz, 3H), 2.48 (s, 3H), 2.93 (ddd, $J = 14.1$, 5.7, and 0.9 Hz, 1H), 3.15 (dd, $J = 14.1$ and 9.0 Hz, 1H), 4.77-4.89 (m, 1H), 7.27-7.46 (m, 5H), 7.70 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 18.80, 25.84, 31.92, 81.45, 128.65, 128.73, 129.01, 134.48, 137.00, 143.85, 199.64.

- **Compound 2b:** 61%; oil; IR (neat) 1547 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 0.88 (t, $J = 7.2$ Hz, 3H), 1.67-1.76 (m, 1H), 1.86-1.97 (m, 1H), 2.47 (s, 3H), 2.93 (dd, $J = 14.1$ and 4.5 Hz, 1H), 3.13 (dd, $J = 14.1$ and 9.6 Hz, 1H), 4.60-4.71 (m, 1H), 7.28-7.44 (m, 5H), 7.69 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 10.12, 25.84, 26.77, 30.52, 88.27, 128.63, 128.66, 128.94, 134.47, 136.98, 143.80, 199.63.

- **Compound 2c:** 82%; oil; IR (neat) 1666, 1547 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.18 (t, $J = 7.2$ Hz, 3H), 1.43 (d, $J = 6.7$ Hz, 3H), 2.77-2.96 (m, 3H), 3.11-3.19 (m, 1H), 4.78-4.88 (m, 1H), 7.26-7.45 (m, 5H), 7.71 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 8.65, 18.87, 30.74, 32.23, 81.57, 128.65,
1H NMR (CDCl₃, 300 MHz) δ 1.28 (d, J = 6.9 Hz, 3H), 1.31 (d, J = 6.9 Hz, 3H), 2.43 (dt, J = 17.4 and 2.7 Hz, 1H), 2.57 (qd, J = 7.5 and 1.5 Hz, 2H), 3.07 (dd, J = 17.4, 6.9, and 2.7 Hz, 1H), 4.19–4.28 (m, 1H), 6.71 (t, J = 2.7 Hz, 1H), 7.24–7.47 (m, 5H); ¹⁳C NMR (CDCl₃, 75 MHz) δ 11.26, 22.59, 22.69, 38.01, 65.31, 124.21, 127.60, 128.50, 128.69, 136.99, 142.34, 174.99.

Compound 6c: 21%; oil; IR (neat) 1539, 1273 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.20 (t, J = 7.5 Hz, 3H), 1.52 (d, J = 6.6 Hz, 3H), 2.66 (q, J = 7.5 Hz, 2H), 2.71–2.79 (m, 1H), 3.35 (ddd, J = 16.5, 8.4, and 2.7 Hz, 1H), 4.17–4.25 (m, 1H), 6.53 (t, J = 2.7 Hz, 1H), 7.22–7.45 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 9.66, 16.67, 19.59, 33.40, 66.56, 121.91, 127.24, 128.52, 128.66, 134.06, 136.59, 149.70.

Compound 5d: 34%; IR (neat) 2954, 2927, 1601 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.92 (t, J = 6.9 Hz, 3H), 1.33–1.47 (m, 5H), 1.72–1.83 (m, 1H), 2.24 (d, J = 1.8 Hz, 3H), 2.49 (dt, J = 17.4 and 2.7 Hz, 1H), 3.01 (ddd, J = 17.4, 7.2, and 2.7 Hz, 1H), 4.10–4.19 (m, 1H), 6.72 (t, J = 2.7 Hz, 1H), 7.20–7.48 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 13.98, 15.70, 22.72, 28.49, 35.36, 36.37, 69.71, 125.48, 127.84, 128.55, 128.76, 136.71, 142.56, 171.69.

Compound 6d: 20%; oil; IR (neat) 2954, 1550, 1269 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.92 (t, J = 6.9 Hz, 3H), 1.23–1.43 (m, 5H), 1.58–1.71 (m, 1H), 2.17 (d, J = 1.5 Hz, 3H), 2.82 (dt, J = 16.5 and 2.7 Hz, 1H), 3.26 (ddd, J = 16.5, 8.4, and 2.7 Hz, 1H), 4.08–4.19 (m, 1H), 6.51 (t, J = 2.7 Hz, 1H), 7.06–7.46 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 9.18, 13.91, 22.53, 26.63, 31.17, 32.52, 70.80, 122.43, 127.35, 128.59, 128.72, 135.30, 136.54, 146.23.

Compound 5e: 37%; oil; IR (neat) 2970, 1601, 1450 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.26 (t, J = 6.9 Hz, 3H), 1.30 (d, J = 6.9 Hz, 3H), 2.43 (dt, J = 17.4 and 2.7 Hz, 1H), 2.57 (qd, J = 7.5 and 1.5 Hz, 2H), 3.07 (dd, J = 17.4, 6.9, and 2.7 Hz, 1H), 4.19–4.28 (m, 1H), 6.71 (t, J = 2.7 Hz, 1H), 7.24–7.47 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 11.26, 22.59, 22.69, 38.01, 65.31, 124.21, 127.60, 128.50, 128.69, 136.99, 142.34, 174.99.

Compound 6f: 21%; oil; IR (neat) 1543, 1265 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.30 (s, J = 6.9 Hz, 3H), 2.20 (s, 3H), 2.71 (d, J = 2.7 Hz, 2H), 6.68 (t, J = 2.7 Hz, 1H), 7.25–7.46 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 15.99, 29.46, 43.81, 70.08, 125.38, 127.76, 128.53, 128.69, 136.88, 143.22, 168.84.

Compound 6g: 46%; white solid, mp 87–89 °C; IR (neat) 2974, 2931, 1543, 1265 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.49 (s, J = 6.9 Hz, 3H), 2.17 (s, 3H), 3.05 (d, J = 2.1 Hz, 2H), 6.52 (J = 2.1 Hz, 1H), 7.22–7.43 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 9.40, 26.42, 40.70, 72.25, 121.98, 127.16, 128.47, 128.64, 130.07, 136.67, 143.55.

Typical procedures for the synthesis of Michael adduct 7a and bicyclic lactam derivative 9a: A solution of 5a (185 mg, 1 mmol) in methyl acrylate (3 mL) was heated to reflux for 4 days. After removal of methyl acrylate and column chromatographic purification process (hexanes/EtOAc, 2:1) we obtained 7a, 208 mg (58%). To a stirred solution of 7a (179 mg, 0.5 mmol) in toluene (3 mL) was added AcoH (180 mg, 3 mmol) and the reaction mixture was heated to reflux for 3 days. After removal of solvent and column chromatographic purification process (hexanes/CH₂Cl₂/EtOAc, 2:1) we obtained 9a, 78 mg (48%). The compounds 7b, 7c, 8a, 9b, and 9c were synthesized analogously and the spectroscopic data are as follows.

Compound 7a: 58%; oil; IR (neat) 2954, 1736, 1439 cm⁻¹; ¹H NMR (CDCl₃) δ 1.30 (d, J = 6.8 Hz, 3H), 1.95–2.50 (m,
\[ \text{Notes} \]


9H), 2.85-3.00 (m, 1H), 3.09 (dd, J = 17.4, 7.2, and 2.7 Hz, 1H), 3.65 (s, 6H), 2.47-2.43 (m, 1H), 6.75 (t, J = 2.7 Hz, 1H), 7.26-7.49 (m, 5H) \[ \text{Compound } 7b: 28\%; \text{IR (neat) } 2958, 1736, 1169 \text{ cm}^{-1}; \text{1H NMR (CDCl}_3, 300 \text{ MHz}) \delta 1.13 (s, 6H), 1.90-2.17 (m, 4H), 2.22-2.47 (m, 4H), 2.73 (d, J = 2.7 Hz, 2H), 2.89-2.95 (m, 1H), 3.64 (s, 6H), 6.73 (t, J = 2.7 Hz, 1H), 7.20-7.47 (m, 5H); \text{13C NMR (CDCl}_3, 75 \text{ MHz}) \delta 28.24, 28.48, 31.36, 31.52, 35.95, 38.09, 51.53, 65.53, 124.62, 127.87, 128.57, 128.93, 136.81, 142.63, 173.82, 175.40; \text{EIMS m/z } 358.09 (M^+). \]

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\text{References and Notes} \[ \begin{align*}