The First Synthesis of 3,5-Dimethylene-4-phenylpiperidine-2,6-dione from Baylis-Hillman Adduct

Mi Jung Lee, Seung Chan Kim, and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
**E-mail: kimjn@chonnam.ac.kr*
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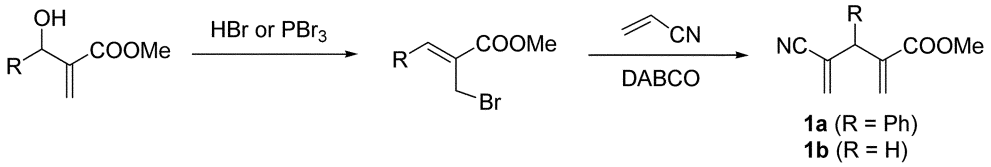
Recently we reported the synthesis of *N*-benzyl 3,5-disubstituted piperidines *via* double Michael addition strategy from the 1,4-pentadiene derivatives.[1] During the investigations we found the formation of 3-methylene-piperidin-2-one derivatives in low yields.[1] Lee and co-workers also reported the synthesis of benzylidenesuccinimide from methyl 2-cyanomethylcinnamates under $FeCl_3$/AcOH conditions.[2]

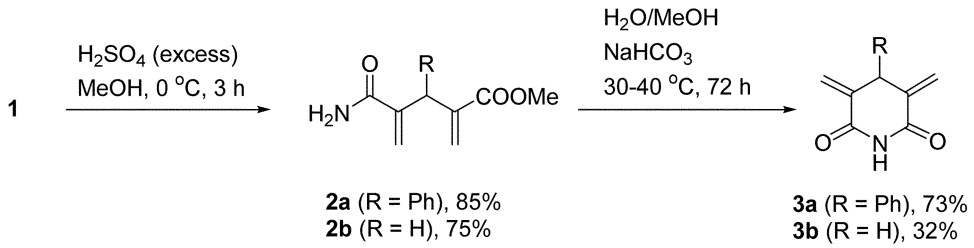
Many compounds containing piperidine-2,6-dione moiety (simply as glutarimide) have been found in a variety of biologically important compounds.[3,4] The synthesis of methylene- or alkylideneglutarimide derivatives has been studied by Koomen and co-workers.[4] In these respects, we intended to prepare 3,5-dimethylenepiperidine-2,6-dione derivatives, which could be used as Michael acceptors for further transformations.

The requisite starting materials **1a** and **1b** were prepared according to the previous paper from the corresponding Baylis-Hillman adducts (Scheme 1).[1,5] In order to hydrolyze the nitrile group of **1** into amide functionality of **2**, we examined a variety of conditions.[6] Among the conditions the use of excess amounts of H_2SO_4 in MeOH at low temperature gave the best yields of **2** (75-85%). With **2a** and **2b** in our hands, we tried the cyclization toward the desired glutarimide derivatives **3**. Fortunately we found that the use of $NaHCO_3$ in aqueous MeOH could afford the products **3a** and **3b** in reasonable yields (Scheme 2).[7] However, due to the low nucleophilicity of the amide group of **2a** and **2b** the reaction rate for the cyclization reaction was slow.

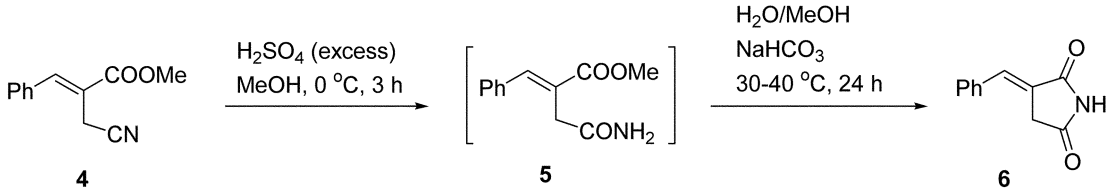
In addition, when we subjected methyl 3-phenyl-2-cyanomethyl-2-propenoate (**4**)[2] under the same reaction conditions, we could obtain the benzylidenesuccinimide **6** *via* the corresponding amide derivative **5** in a slightly improved yield (51%) than the reported one (Scheme 3).[2]



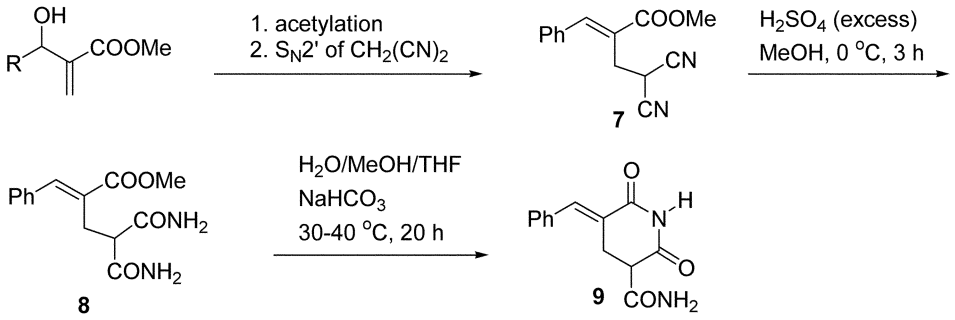
Scheme 1



Scheme 2



Scheme 3



Scheme 4

In order to examine the possibility for the synthesis of mono-alkylidene glutarimide we introduced malononitrile at the primary position of the Baylis-Hillman adduct and obtained **7** in 61% yield.[8] This compound **7** was subjected under the similar conditions (hydrolysis followed by cyclization), and we obtained the desired compound **9** successfully although the yield was low (48%) as in Scheme 4.

In summary, we synthesized two dimethylene glutarimides and two benzylideneimide derivatives from Baylis-Hillman adducts. We are currently studying the usefulness of these compounds as Michael acceptors toward a variety of nucleophiles.

Experimental Section

Typical procedure for the synthesis of 2a and 3a. To a stirred solution of **1a** (227 mg, 1.0 mmol) in MeOH (3 mL) was added H_2SO_4 (2 mL) cautiously at 0 °C and the reaction mixture was stirred at room temperature for 3 h. After usual workup and column chromatographic purification process (hexanes/EtOAc, 1 : 1) we obtained **2a** as a white solid, 209 mg (85%). A mixture of **2a** (123 mg, 0.5 mmol) and $NaHCO_3$ (210 mg, 2.5 mmol) in aq MeOH (3 mL) was maintained at 30-40 °C for 72 h. After usual workup and column chromatographic purification process (hexanes/EtOAc, 4 : 1) we obtained **3a** as a white solid, 78 mg (73%). Spectroscopic data of **2a-3b** are as follows.

Compound **2a**: 85%; white solid, mp 80-82 °C; IR (KBr) 3321, 3186, 1720, 1670, 1631, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ3.72 (s, 3H), 5.17 (s, 1H), 5.26 (s, 1H), 5.38 (s, 1H), 5.88 (br s, 2H), 6.01 (s, 1H), 6.42 (s, 1H), 7.17-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.87, 52.08, 121.90, 127.08, 127.25, 128.55, 128.90, 138.57, 141.43, 145.09, 166.88, 169.85.

Compound **2b**: 75%; white solid, mp 61-63 °C; IR (KBr) 3336, 3201, 1720, 1670, 1631 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ3.34 (s, 2H), 3.76 (s, 3H), 5.42 (s, 1H), 5.67 (s, 1H), 5.88 (s, 1H), 6.16 (br s, 2H), 6.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.95, 52.00, 121.71, 127.36, 137.44, 141.28, 167.28, 169.94.

Compound **3a**: 73%; white solid, mp 177-178 °C; IR (KBr) 1701, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ4.78 (s, 1H), 5.72 (s, 2H), 6.53 (s, 2H), 7.21-7.42 (m, 5H), 7.93 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.18, 127.37, 127.71, 128.00, 129.25, 137.43, 138.22, 165.22; ESIMS *m/z* 214.1 (M^++H).

Compound **3b**:[4a,4c] 32%; white solid, mp 148-150 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ3.53 (s, 2H), 5.66 (s, 2H), 6.33 (s, 2H), 8.70 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ34.72, 125.30, 133.42, 165.48.

Synthesis of compound 6. The starting material **4** was prepared according to the previous paper.[2] To a stirred solution of **4** (201 mg, 1.0 mmol) in MeOH (3 mL) was added H_2SO_4 (2 mL) cautiously at 0 °C and the reaction mixture was stirred at room temperature for 3 h. After usual workup and removal of solvent we obtained **5** as crude state. We used this crude **5** for the next cyclization directly without further purification. A mixture of **5** and $NaHCO_3$ (210 mg, 2.5 mmol) in aq MeOH (3 mL) was maintained at 30-40 °C for 24 h. After usual workup and column chromatographic purification process (hexanes/EtOAc, 1 : 1) we obtained **6** as a white solid, 96 mg (51%). Spectroscopic data of **6** are as follows.

Compound **6**:[2] 51%; white solid, mp 199-200 °C; IR (KBr) 3143, 3032, 1766, 1712, 1647, 1350 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ3.64 (d, J = 2.4 Hz, 2H), 7.42-7.51 (m, 5H), 7.63 (t, J = 2.4 Hz, 1H), 8.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ35.10, 124.04, 129.18, 130.27, 130.44, 133.81, 135.30, 170.81, 173.84.

Synthesis of compound 9. To a stirred solution of Baylis-Hillman acetate (468 mg, 2.0 mmol), which was made from benzaldehyde and methyl acryalte, and malononitrile (400 mg, 6.0 mmol) in CH_3CN (7 mL) was added K_2CO_3 (00 mg, 6.0 mmol) and the reaction mixture was stirred at room temperature for 10 min. After usual workup and column chromatographic purification process (hexanes/ether, 3 : 1) we obtained **7**, 275 mg (61%). To a stirred solution of **7** (240 mg, 1.0 mmol) in MeOH (3 mL) was added H_2SO_4 (2 mL) cautiously at 0 °C and the reaction mixture was stirred at room temperature for 3 h. After usual workup and column chromatographic purification process (EtOAc) we obtained **8** as a white solid, 163 mg (59%). A mixture of **8** (138 mg, 0.5 mmol) and $NaHCO_3$ (210 mg, 2.5 mmol) in aq MeOH (3 mL, 1 mL of THF was added for the solubility) was maintained at 30-40 °C for 20 h. After usual workup and column chromatographic purification process (CH_2Cl_2/MeOH, 3 : 1) we obtained **9** as a white solid, 59 mg (48%). Spectroscopic data of **7-9** are as follows.

Compound **7**: 61%; clear oil; IR (film) 2256, 1705, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.22 (d, J = 8.1 Hz, 2H), 3.87 (s, 3H), 4.49 (t, J = 8.1 Hz, 1H), 7.34-7.50 (m, 5H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.42, 29.12, 52.60, 112.24, 124.33, 128.69, 129.01, 129.59, 133.69, 146.61, 166.91.

Compound **8**: 59%; white solid, mp 187-189 °C; IR (KBr) 3448, 3309, 3163, 1712, 1670, 1631 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.17 (d, J = 7.5 Hz, 2H), 3.46 (t, J = 7.5 Hz, 1H), 3.85 (s, 3H), 5.30 (br s, 2H), 6.58 (br s, 2H), 7.33-7.48 (m, 5H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.33, 51.08, 51.36, 127.87, 127.96, 128.76, 128.90, 134.34, 140.72, 167.60, 171.50.

Compound **9**: 48%; white solid, mp 142-143 °C; IR (KBr) 3383, 3201, 1712, 1662 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.88 (d, J = 7.2 Hz, 2H), 3.48 (t, J = 7.2 Hz, 1H), 7.03 (br s, 2H, NH_2), 7.18 (s, 1H), 7.24-7.49 (m, 5H), 7.57 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 26.61, 50.11, 127.73, 128.34, 129.02, 133.83, 134.84, 135.79, 170.07, 170.50, 171.26; ESIMS m/z 245.1 (M^++H).

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7. The formation of **3a** was observed in acidic media directly from **1a**. As an example, the reaction of **1a** and H_2SO_4 (2 equiv) in 1,2-dichloroethane at refluxing temperature for 24 h gave **2a** (31%) and **3a** (29%).
8. During the preparation of **7** from the reaction of malononitrile and the acetate of the Baylis-Hillman adduct, the use of malononitrile in excess amounts (3 equiv) was crucial. Otherwise, the formation of appreciable amounts of the corresponding 2 : 1 adduct between the Baylis-Hillman adduct and malononitrile was observed.