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REACTIONS OF 5-[1-(2-PHENYL)METHYLIDENE]-3-PHENYLIMIDAZOLIDINE-2,4-DIONES WITH SOME ORGANOMETALLIC REAGENTS

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ABSTRACT. The reaction of Grignard reagents with 5-[1-(2-chlorophenyl)methylidene]-3-phenylimidazolidine-2,4-dione, **4**, and 5-[1-(2-bromophenyl)methylidene]-3-phenylimidazolidine-2,4-dione, **5**, gave exclusively 1,2-addition products, **6-8**, in 70-80% yields. Lithium dibutylcuprate reacted with **4** to yield exclusively 1,2-addition product **9** (92%). No conjugate or 1,4-addition products were obtained. These results indicate that 5-[1-(2-phenyl)methylidene]-3-phenylimidazolidine-2,4-diones do not react like normal unsaturated carbonyl compounds.

KEY WORDS: Imidazolidine-2,4-diones, α,β-Unsaturated carbonyl compounds, 1,2-Addition, conjugate addition, Grignard reagents, Lithium dibutylcuprate

INTRODUCTION

The properties of the α,β-unsaturated carbonyl group and the double bond at 1'-position in the 5-[1-(2-phenyl)methylidene]-3-phenylimidazolidine-2,4-diones, derived from aldehydes, is unclear. The carbonyl group should withdraw electrons from the double bond, making the bond electrophillic and hence susceptible to nucleophilic attack. On the other hand, the imidazolidine-2,4-dione amide nitrogen will contribute electrons to the more electronegative oxygen atom making it somewhat nucleophilic and hence susceptible to electrophillic attack.

Grignard reagents are known to add to α,β-unsaturated carbonyl compounds either through 1,2- or 1,4-addition, but in the presence of copper(I) salts the 1,4-addition predominates [1]. Further organocuprates have been used as stochiometric 1,4-addition reagents instead of Grignard reagents [2]. It is believed that these reagents proceed through radical or single electron transfer mechanisms. We hereby report a set of reactions designed to determine whether 1,2- or 1,4-addition of nucleophiles, at the olefinic position of imidazolidine-2,4-dione could give the much desired intermediates for the synthesis of compounds related to the physiologically active lysergic acid diethylamide.

RESULTS AND DISCUSSION

Imidazolidine-2,4-diones, **4** and **5**, were synthesised from condensation of respective benzaldehydes (**1** and **2**) and 3-phenylimidazolidine-2,4-dione **3**, according to the procedure by Hoofman and Wheeler, (Scheme **1**) [3]; they were further purified and reacted with the respective Grignard reagents or organocuprate [4].

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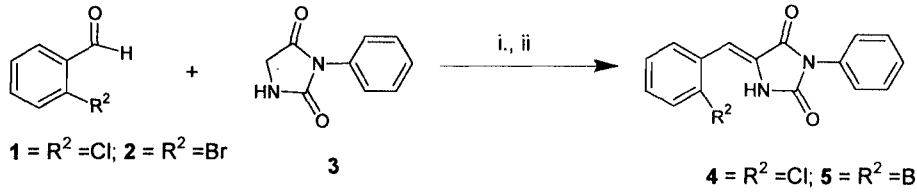
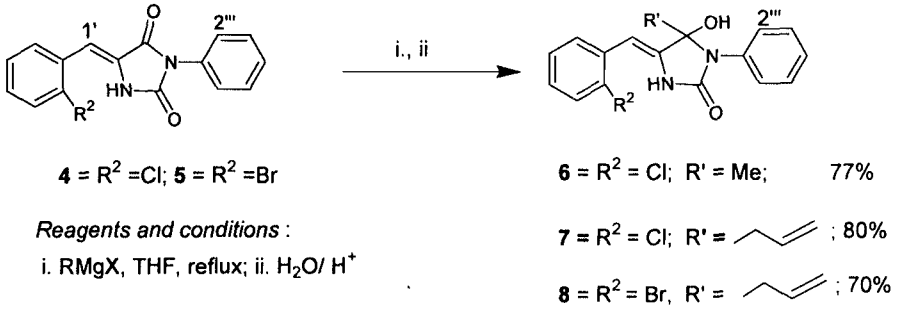


Reagents and conditions : i. base/Ac_2O/AcOH; ii. reflux

Scheme 1

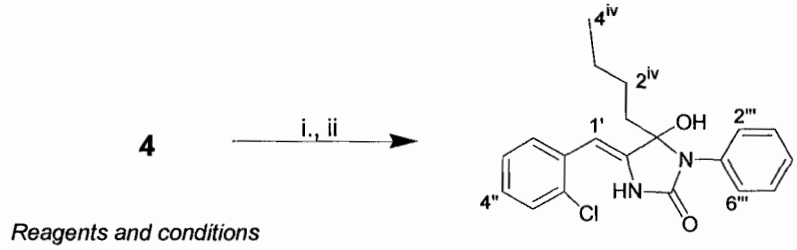
Imidazolidine-2,4-dione **4** was directly treated with methylmagnesium chloride to yield product **6**, (Scheme 2), which exhibited broad absorption band between 3500-3000 cm^{-1}, indicating the presence of a hydroxyl group. Their ^1H NMR spectra, showed a new three proton singlet at δ 1.44, indicating that the introduced methyl group was attached to a quartenary carbon and not the methine carbon. The appearance of a nine proton multiplet at δ 7.53-7.63 supported the retention of the *N*-phenyl and four aromatic protons. Three sharp, one proton singlets resonated at δ 5.77, 6.81 and 9.85. An HSQC (H-C correlation) experiment indicated that the proton giving rise to the signal at δ 5.77 was attached to a carbon whose nucleus resonated at δ 94.3, consistent with a shielded olefinic position. In contrast, there was no correlation for the proton signal at δ 6.18 and 9.85. This indicated that the signals were due to an NH or OH proton. The chemical shift of the singlet at δ 9.85 was almost consistent with an amide-like NH proton, so the signal at δ 6.18 was assigned to an OH proton. Thus, product **6** must have arisen through 1,2-addition of the nucleophile. The neighboring position of the protons from the methyl (δ 1.47), olefinic (δ 5.77) and hydroxyl (δ 6.18) were confirmed through strong cross peaks in the NOESY spectrum.

Similarly, treatment of **4** and **5** with allylmagnesium bromide, each gave the corresponding 1,2-addition products **7** and **8** (Scheme 2).



Scheme 2

Lithium dibutylcuprate was prepared according to literature procedure [5] and was reacted immediately with an equimolar amount of imidazolidine-2,4-dione **4** (Scheme 3) to give **9**, whose structure was similarly confirmed by NMR studies.



Reagents and conditions
i. n-BuLi, CuI, THF; ii. sat. aqu.NH_4Cl

Scheme 3

CONCLUSION

The fact that 1,2-addition occurs, even when an organocuprate is used, indicates that 5-[1-(2-phenyl)methylidene]imidazolidine-2,4-diones do not behave like normal α,β-unsaturated carbonyl compounds. This is probably due to the enamine character of the double bond, which should be investigated further in order to obtain imidazolidine-2,4-diones that can be used as intermediates to indole derivatives of lysergic acid

EXPERIMENTAL

General

Melting points were measured on a Richert microscope and are uncorrected. Microanalyses were performed by Dr. H.P. Pham, Microanalytical Unit, The University of New South Wales, Dr. R. Bergman and Dr. V. Withers, Microanalytical Unit, Australian National University. Ultraviolet spectra were recorded on a Hitachi U-3200 spectrophotometer and refer to solutions in absolute MeOH. Infrared spectra were recorded on a Perkin-Elmer 298 IR spectrophotometer and refer to Nujol mulls. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker AC300F (300 MHz) or on a Bruker DMX 500 (500 MHz) Avance instrument. Data are reported as follows: chemical shift (δ) in ppm downfield from tetramethylsilane (TMS), multiplicity, observed coupling constant(s) (*J* in Hz) and proton assignment. The ^{13}C NMR spectra were also recorded on a Bruker AC 300F spectrometer at 75.06 MHz and are reported in ppm downfield from TMS. The correlated two dimensional spectra (COSY, DEPT, NOESY, HSQC, HMBC) experiments were recorded on a Bruker DMX500 (500 MHz) Avance instrument.

The electron impact (EI) mass spectra were recorded on a VG Quattro mass spectrometer with an ionising potential of 70 eV and an ion source temperature of 220 °C. The principal ion peaks, *m/z,* are reported together with their percentage intensities relative to the base peak.

3-Phenyl-1,3-diazolidine-2,4-dione ***3***

Following the method of Finkbeiner [6], glycine (7.50 g, 0.13 mol) was dissolved in a solution of KOH (6.80 g) in water (40 mL) and the mixture was cooled in ice. Phenylisocyanate (13.20 g, 0.11 mol) was then added dropwise to the stirred solution. Upon standing overnight, the mixture deposited a precipitate (2.00 g) which was collected and identified as diphenyl urea m.p. 235-237 °C, (lit. [7] m.p. 239-241°C). The filtrate was acidified to yield another precipitate which

was collected, drained at the pump, and then refluxed with a mixture of water (20 mL) and concentrated HCl (20 mL) for 1 h. The resulting solution was cooled to room temperature and the crystalline precipitate was collected. Further recrystallization from ethanol gave **3** as white needles (11.60 g, 66%), m.p. 153-154 °C (lit. [3] m.p. 154-155 °C). ^{1}H NMR (DMSO-d_6): δ 4.05, s, H5; 7.32-7.48, m, H2'-H6'; 8.27, br s, NH. Mass spectrum: *m/z*: 177 (M+1, 5%), 176 (M^+, 43), 120 (36), 119 (100), 118 (3), 104 (6), 93 (8), 92 (13), 91 (36), 90 (4), 77 (17), 64 (14), 63 (9), 56 (5), 51 (5), 41 (4).

Condensation of 3 with aldehydes

General procedure

Following the method of Hoffman and Wheeler, [3] molar equivalents of compound **3** and the aldehydes, anhydrous KOAc, and glacial ACOH were dissolved together at room temperature and the mixture warmed to reflux. Reactions were monitored by thin layer chromatographic analysis until all the aldehyde had reacted. Upon cooling, the mixture gave a precipitate which was collected and recrystallized.

5-[1-(2-Chlorophenyl)methylidene]-3-phenylimidazolidine-2,4-dione 4

2-Chlorobenzaldehyde (5.00 g, 36 mmol), reacted to give a yellow solid (4.90 g). Recrystallization from ethanol gave a 90:10 mixture of (*Z*) and (*E*) **4** as white needles (4.73 g, 64%), m.p. 250-252 °C (lit. [8] m.p. 251-253 °C). Found: C, 64.20; H, 3.98; N, 9.14; calc. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38%). λ_{max} (MeOH): 206 (ε 9.5 x 10^4), 313 nm (9.2 x 10^4). ν_{max}: 3170, 1760, 1725, 1660, 1585, 1450, 1370, 1225, 1175, 1110, 1030, 920, 850, 750 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.60, s, H1' (*E*-isomer); 6.75, s, H1' (*Z*-isomer); δ: 7.30-7.81, m, H3"- H5" and H2'"-H6'"; 7.79, dd, *J* 7.2, 2.0 Hz, H6"; 11.19, br s, NH. ^{13}C NMR (DMSO-d_6): δ 104.8, C1'; 127.2, C2'" and C6'"; 127.9, C5; 128.4, C4'"; 129.2, C3'" and C5'"; 129.4, C4"; 130.0, C5"; 130.4, C3"; 130.6, C6"; 131.2, C1'", 132.1, C1", 133.5, C2"; 154.5, C2; 163.4, C4. Mass spectrum: *m/z* 298 (M^+, 3%), 264 (15), 263 (100), 176 (12), 151 (8), 119 (24), 115 (13), 91 (27), 84 (27), 49 (92).

5-[1-(2-Bromophenyl)methylidene]-3-phenylimidazolidine-2,4-dione 5

2-Bromobenzaldehyde (4.00 g, 21.6 mmol) reacted to give a yellow solid (5.00 g) that was shown by ^{1}H NMR to be isomerically pure. Recrystallized from AcOH gave **5** as white needles (2.44 g, 32%), m.p. 240-242 °C. Found: C, 56.11; H, 2.96; N, 8.11.$C_{16}H_{11}N_2BrO_2$ requires: C, 56.00; H, 3.23; N, 8.16%). λ_{max} (MeOH): 208 (ε 6.3 x 10^3), 277 nm (6.1 x 10^3). ν_{max}: 3250, 1760, 1720, 1660, 1450, 1380, 1210, 1110, 910 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.70, s, H1'; 7.29, dd, *J* 8.2, 2.0 Hz, H4" and H5"; 7.40-7.50, m, H2'"-H6'"; 7.75, dd, *J* 8.2, 2.0 Hz, H3" and H6"; 11.13, br s, NH. ^{13}C NMR (DMSO-d_6): δ 107.6, C1'; 124.5 C2"; 127.2, C2'" and C6'"; 128.4, C5; 128.5, C4'"; 129.0, C5"; 129.2, C3'" and C5'"; 130.6, C6"; 130.8, C1"[132.9, C4'"; 133.3, C1'"; 132.9, C3"; 154.4, C2; 163.4, C4. Mass spectrum: *m/z* 345 (M^+, ^{81}Br, 4%), 343 (4), 265 (4), 264 (22), 263 (100), 262 (6), 195 (6), 144 (3), 132 (5), 119 (24), 115 (39), 114 (16), 89 (40), 77 (17), 65 (7), 63 (16), 51 (4).

General preparation of Grignard reagents

Grignard reagents were prepared according to the literature methods [9], except MeMgCl which was purchased from Aldrich. Freshly distilled and dry alkyl halide was added, in portions by means of a syringe, to pre-oven dried Mg turnings in THF. The mixture was heated at reflux until the magnesium turnings dissolved. A suspension of the 5-[1-(2-phenyl)methylidene]-3-phenylimidazolidine-2,4-dione in THF was added through a pressure equalizing funnel and the reaction warmed to reflux. Upon completion of the reaction the mixture was poured into water and the resulting solid recrystallized from EtOH.

5-[1-(2-Chlorophenyl)-1-hydroxyethyl]-3-phenylimidazolidine-2,4-dione ***6***

Imidazolidine-2,4-dione **4** (2.00 g, 6.71 mmol) was dissolved in dry THF (50 mL) under argon and MeMgCl in THF (17.8 mL of 0.1 M, 13.4 mmol) was added dropwise. The mixture was heated to reflux for 8 h then cooled and poured into aqueous HCl (2 M, 50 mL). The resulting white solid (1.70 g) was collected at the pump and was recrystallized from EtOH to afford **6** as white needles (1.60 g, 77%), m.p. 120-122 °C. Found: C, 64.70, H, 4.75; N, 8.88. $C_{17}H_{15}ClN_2O_2$ requires: C, 64.87; H, 4.80, N, 8.90%). λ_{max} (MeOH): 206 nm (ε 1.4 x 10^4), 234 (1.1 x 10^4), 278 (1.8 x 10^4). ν_{max} (Nujol): 3500-3000, 1705, 1655, 1450, 1400, 1110, 1090, 950, 850 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.44, s, CH_3; 5.77, s, H1'; 6.81, s, OH; 7.57-7.63, m, H3"-H6" and H2"'-H6"'; 9.85, s, NH. ^{13}C NMR (DMSO-d_6): δ 26.5, CH_3; 89.0, C5; 93.8, C1'; 127.0, C4"'; 127.5, C3"; 127.6, C2"' and C6"'; 128.2, C5"; 128.7, C4"; 129.3, C3"' and C5"'; 130.0, C6"; 130.3, C2"; 135.5, C1"; 135.9, C1"', 141.0, C1; 155.8, C3. Mass spectrum: *m/z* 316 ($M(^{37}Cl)^+$, 1%), 314 ($M(^{35}Cl)^+$, 5), 299 (6), 279 (4), 261 (19), 217 (4), 203 (5), 161 (4), 160 (35), 152 (15), 125 (15), 119 (13), 91 (27), 89 (39), 77 (100), 63 (29), 51 (53), 43 (98).

5-[1-(2-Chlorophenyl)-1-hydroxybut-3-enyl]-3-phenylimidazolidine-2,4-dione ***7***

Imidazolidine-2,4-dione **4** (1.50 g, 5.03 mol) reacted with AllylMgBr to afford, after recrystallization, **7** as white needles (1.36 g, 80%), m.p. 125-127 °C. Found: C, 66.88; H, 5.01; N, 8.11. $C_{19}H_{17}ClN_2O_2$ requires: C, 66.96; H, 5.03; N, 8.22%). λ_{max} (MeOH): 206 nm (ε 4.2 x 10^5), 230 (2.5 x 10^5), 283 (4.6 x 10^5). ν_{max}: (Nujol) 3500-3300, 1680, 1450, 1280, 1050 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.48, m, H_a1^{iv} and H_b1^{iv}; 4.90, dd, *J* 17.3, 2.0 Hz, H_a3^{iv}; 5.03, dd, *J* 10.2, 2.0 Hz, H_b3^{iv}; 5.35, m, $H2^{iv}$; 5.72, s, H1'; 7.15, s, OH; 7.24-8.11, m, H3"-H6" and H2"'-H6"'; 9.96, s, NH. ^{13}C NMR (DMSO-d_6): δ 41.9, $C1^{iv}$; 91.4, C5; 97.8, C1'; 125.9, C2"' and C6"'; 120.6, $C3^{iv}$; 127.2, $C2^{iv}$; 127.9, C4"'; 128.5, C5"; 128.9, C3"' and C5"'; 130.1, C4"; 129.9, C6"; 133.2, C3"; 133.4, C2"; C1"; 134.9, C1"; 139.4, C1"'; 144.4, C1; 155.9, C3. Mass spectrum: *m/z* 342 ($M(^{37}Cl)^+$, 4%), 340 ($M(^{35}Cl)^+$, 11), 324 (16), 322 (40), 302 (10), 301 (54), 299 (100), 287 (11), 244 (5), 211 (55), 186 (13), 154 (23), 152 (74), 150 (55), 127 (31), 125 (78), 115 (41), 89 (52), 77 (84), 55 (35), 43 (51).

5-[1-(2-Bromophenyl)-1-hydroxybut-3-enyl]-3-phenylimidazolidine-2,4-dione ***8***

Imidazolidine-2,4-dione **2** (2.50 g, 7.30 mol), reacted with allylMgBr to afford, after recrystallization, **8** as white needles (1.36 g, 70%), m.p. 180-182 °C. Found: C, 59.70; H, 4.14; N, 7.42. $C_{19}H_{17}BrN_2O_2$ requires: C, 59.38; H, 4.43; N, 7.29%). λ_{max} (MeOH): 207 nm (ε 8.9 x 10^5), 238 (6.3 x 10^5), 280 (5.1 x 10^5). ^1H NMR (DMSO-d_6): δ 2.48, m, H_a1^{iv} and H_b1^{iv}; 4.94, dd, *J* 17.2, 1.7 Hz, H_a3^{iv}; 5.03, dd, *J*1 10.2, 1.7 Hz, H_b3^{iv}; 5.54, m, $H2^{iv}$; 5.67, s, H1'; 7.06-7.62, m, OH, H3"-H5" and H2"'-H6"'; 9.95, br s NH. ^{13}C NMR (DMSO-d_6): δ 42.7, $C1^{iv}$; 90.8, C5; 97.5,

C1'; 120.2, $C3^{iv}$; 123.1, $C2^{iv}$ 126.4, C4'''; 126.9, C2''' and C6'''; 128.0, C5"; 128.3, C3''' and C5'''; 128.9, C4"; 129.8, C6"; 131.5, C3"; 132.9, C2"; 135.6, C1"; 136.3, C1'''; 142.3, C1; 155.7, C3. Mass spectrum: *m/z* 386 (M^+, absent), 369 (11%), 366 (54), 365 (17), 288 (4), 256 (9), 244 (8), 242 (5), 211 (35), 209 (6), 181 (13), 168 (19), 167 (26), 166 (16), 140 (16), 129 (16), 128 (25), 115 (26), 102 (11), 89 (11), 77 (100), 76 (12), 63 (7), 51 (41).

5-[1-(2-Chlorophenyl)-1-hydroxybutyl]-3-phenylimidazolidine-2,4-dione **9**

Following the method of Grieco and Finkelhor [5], *n*-BuLi (5 mL of 1.5 M, 7.5 mmol) was added to a cooled (0 °C) stirred suspension of CuI (0.72 g, 3.79 mmol) in dry THF (10 mL), under argon. The resulting blood red solution was stirred at 0 °C for 15 min after which imidazolidine-2,4-dione **4** (1.00 g, 3.36 mmol) in THF (10 mL) was added dropwise and the mixture stirred at 0 °C for 1 h. The reaction mixture was poured into saturated aqueous NH_4Cl (20 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The resulting solid (1.25 g) was recrystallized from ethanol to afford **9** as white needles (1.12 g, 92%), m.p. 158-160 °C. Found: C, 67.09; H, 5.82; N, 7.79. $C_{20}H_{21}N_2ClO_2$ requires: C, 67.32; H, 5.93; N, 7.85%). λ_{max} (MeOH): 212 (ε 7.98 x 10^5), 234 (5.80 x 10^5), 282 nm (1.00 x 10^6). ν_{max} (Nujol): 3500-3300, 2200, 2000, 1690, 1500, 1400, 1380, 1050 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.69, t, *J* 6.7 Hz, $H4^{iv}$; 1.09, m, $H3^{iv}$ and $H2^{iv}$; 1.72, tt, *J* 10.8, 13.4 Hz, $H1^{iv}$; 5.68, s, H1'; 6.64, s, OH; 7.00-7.60, m, H3"-H6" and H2'''-H6'''; 9.96, s, NH. ^{13}C NMR (DMSO-d_6): δ 14.0, $C4^{iv}$; 22.1, $C3^{iv}$; 25.3, $C2^{iv}$; 37.3, $C1^{iv}$; 91.6, C5; 93.9, C1'; 126.1, C4'''; 126.4, C2''' and C6'''; 126.6, C5"; 127.6, C3''' and C5'''; 127.6, C4", 128.9, C6"; 129.5, C3"; 131.7, C2"; 133.8, C1"; 136.2, C1'''; 142.8, C4; 155.7, C2. Mass spectrum: *m/z* 358 (M $(^{37}Cl)^+$, 3%), 356 (M $(^{35}Cl)^+$, 7), 338 (11), 311 (6), 309 (19), 299 (100), 295 (7), 274 (3), 273 (10), 263 (14), 245 (6), 231 (16), 217 (6), 202 (16), 187 (18), 178 (16), 159 (6), 153 (21), 150 (61), 141 (15).

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