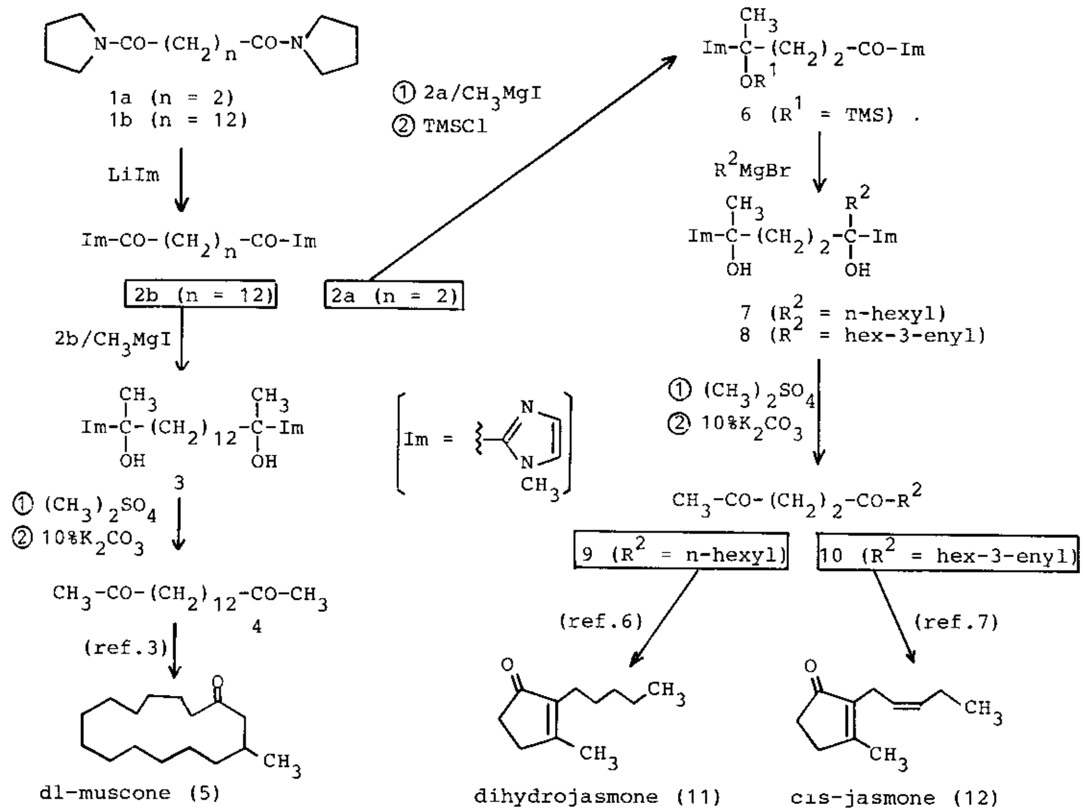
SYNTHESES OF DIKETONIC INTERMEDIATES FOR THE TOTAL SYNTHESES OF DIHYDROJASMONE, cis-JASMONE AND dl-MUSCONE STARTING FROM 1,n-DI(1-METHYL-1H-IMIDAZOL-2-YL)-1,n-ALKANEDIONE

Shunsaku Ohta, Satoshi Hayakawa, Yoshimi Tamai, Teruyuki Yuasa,
and Masao Okamoto*
Kyoto Pharmaceutical University
Misasagi-Nakauchicho 5, Yamashina-ku, Kyoto 607, Japan

Abstract —— 2,15-Dihydroxy-2,15-di(1-methyl-1H-imidazol-2-yl)hexadecane (3) was obtained by treating 1,14-(1-methyl-1H-imidazol-2-yl)-1,14-tetradecadione (2b) with an excess of CH_3MgI, while 1,4-di(1-methyl-1H-imidazol-2-yl)-4-trimethylsilyloxy-2-pentanone (6; R^1 = TMS) was obtained by the similar treatment of 1,4-(1-methyl-1H-imidazol-2-yl)-1,4-butadione (2a) followed by trimethylsilylation. These products (3 and 6) were convertible into the known diketonic intermediates for the synthesis of dl-muscone, dihydrojasmone and cis-jasmone.

Recently the authors reported a new methodology for the synthesis and protection of various carbonyl compounds, which utilized the stability of 1-(1-methyl-1H-imidazol-2-yl)methanol system [R-C(OH)-$\overline{\text{C=N-CH=CH-N}}$($CH_3$)] and the superior leaving ability of the imidazolium group.[1] This paper deals with a further application of the methodology to prepare dicarbonyl compounds.

Succinic acid dipyrrolidine amide (1a) and 1,12-dodecanedicarboxylic acid dipyrrolidine amide (1b) were treated with two equivalents of 2-lithio-1-methyl-1H-imidazole according to the procedure in the previous report[2] to give the corresponding diimidazolyldiketones (2a and 2b), respectively. When the dicarbonyl compound (2b; n = 12) was subjected to the reaction with 2.5 equivalents of ethereal CH_3MgI at 0 ℃ to give 2,15-dihydroxy-2,15-di(1-methyl-1H-imidazol-2-



yl)hexadecane (3), which was presumed to be produced in a diastereomeric mixture and used without separation in the subsequent reaction. The Grignard reagent can be replaced with CH_3Li. According to the procedure of the previous report,[1a] the diol (3) was converted to 2,5-hexadecadione (4)[3] in 66.9 % overall yield from 2b, which was reported as an intermediate for synthesis of dl-muscone, an important perfume ingredient.[3]

On the other hand, when the diimidazolyldiketone (2a; n = 2) was treated with an excess of ethereal CH_3MgI, only one carbonyl group of 3 reacted to give the monohydroxyketone (6; R^1 = H), which was converted without purification into the corresponding trimethylsilyl (TMS) ether (6; R^1 = TMS; as a viscous oil) by the usual manner in 64.4 % overall yield from 2a. Structure of the TMS ether was confirmed by the inspection of the infrared (IR), mass (MS) and proton nuclear magnetic resonance (^{1}H-NMR) spectra as shown in the experimental section. It is noteworthy that thin-layer chromatography (TLC) hardly indicated the presence of the corresponding dihydroxy compound in the reaction mixture. The authors presumed that a negative charge on the oxygen atom of the intermediate (6; R^1 = MgI) might prohibit the further attack of the Grignard reagent on the residual carbonyl group owing to the electronic repulsion, which had no effect in the case of 2b (n = 12) due to the long distance. The silyl ether 6 (R^1 = TMS) could be successfully converted into the diol (7; R^2 = n-C_6H_{13}) by treatment with an excess of ethereal n-C_6H_{13}MgBr followed by acidic hydrolysis with hydrochloric acid. The crude diol (7; R^2 = n-C_6H_{13}) was readily converted into 2,5-undecadione (9) in 76.9 % overall yield from 6 (R^1 = TMS) according to the procedure of the previous report.[1a,b] Conversion of the diketone (9) into dihydrojasmone (11), a constituent of Bergamont oil,[4] was first reported by Stork.[5] Moreover, a Grignard reaction of the silyl ether (6; R^1 = TMS) in the similar manner as in the case of 7 furnished cis-undec-8-ene-2,5-dione (10) in 60.5 % yield from 6 (R^1 = TMS), which has also been known as a synthetic intermediate for the natural perfume component, cis-jasmone.[6]

The authors are now investigating the scope and limitation of the present methodology for preparation of various diketones.

EXPERIMENTAL

1,4-Di(1-methyl-1H-imidazol-2-yl)-1,4-butadione (2a) : A solution of 1.55M n-BuLi in hexane (64 ml, 100 mmol) was added dropwise at -78 ℃ under N_2 to a stirred solution of 1-methylimidazole (8.20 g, 100 mmol) in tetrahydrofuran (THF; 200 ml). The whole was added to a stirred solution of the pyrrolidine amide (1a; 8.96 g, 40 mmol) in THF (80 ml) at -78 ℃ under N_2, then the mixture was stirred at room temperature for one hour. Water (20 ml) was added and the formed aqueous layer was removed by pipet followed by drying the organic layer with $MgSO_4$. Removal of the solvent under a reduced pressure to give a crystalline residue, which was refined by a silica gel chromatography (AcOEt as solvent) and subsequent recrystallization from dimethyl cellosolve to give colorless needles. mp 176 - 178 ℃. Yield, 2.21 g (22.5 %). IR ($CHCl_3$): 1660 cm^{-1} (C=O). ^{1}H-NMR (80 MHz in $CDCl_3$) δ: 3.55 (s, 4H, -($C\underline{H}_2$)$_2$-), 3.97 (s, 6H, 2 x $NC\underline{H}_3$), 7.02 and 7.14 (d each, 4H, Ar-H, J = 1 Hz each). Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found : C, 58.71; H, 5.83; N, 22.46.

1,4-Di(1-methyl-1H-imidazol-2-yl)-4-trimethylsilyloxy-1-pentanone (6; R^1 = TMS) : A Grignard reagent solution, prepared from iodomethane (1.42 g, 10 mmol), magnesium metal (486 mg, 20 mgatom) and ether (10 ml), was added dropwise at 0 ℃ under N_2

over 30 min to a stirred solution of 2a (984 mg, 4 mmol) in THF (100 ml). After being stirred for 15 min, ether and 10% HCl were added to the mixture, and the aqueous layer was basified with solid K_2CO_3 after washing the acidic layer with ether. The separated an organic material was extracted with AcOEt. The organic layer is evaporated after drying with Na_2SO_4 to give a viscous material, which was converted to the corresponding TMS ether in the usual manner (imidazole-TMSCl method). The crude product was refined by silica gel column chromatography (AcOEt : n-hexane : MeOH = 9 : 10 : 1 as an eluting solvent) to give a viscous oil. Yield, 860 mg (64.4 %). IR ($CHCl_3$) : 1678 cm^{-1} (C=O). High-resolution MS Calcd for $C_{16}H_{26}N_4O_2Si$ = 334.1823 (Found : 334.1850). ^{1}H-NMR ($CDCl_3$) δ : -0.01 (s, 9H, $(C\underline{H}_3)_3Si$), 1.79 (s, 3H, $C\underline{H}_3C$-OTMS), 2.10 ~ 3.35 (m, 4H, $-C\underline{H}_2C\underline{H}_2-$), 3.80 and 3.93 (s each, 3H each, $NC\underline{H}_3$), 6.73, 6.82, 6.97 and 7.09 (d each, 1H each, Ar-H, J = 1 Hz each).

2,5-Undecadione (9; R^2 = n-hexyl) : A Grignard reagent solution, prepared from hexyl bromide (495 mg, 3 mmol), magnesium metal (6 mgatom) and ether (3 ml), was added dropwise at 0 ℃ under N_2 to a stirred solution of 6 (R^2 = TMS; 668 mg, 2 mmol) in ether (4 ml). After being stirred for 15 min, ether and 10% HCl were added to the reaction mixture. The organic phase was extracted again with 10% HCl. The combined aqueous layer was basified with solid K_2CO_3 after washing with ether. The separated material was extracted with AcOEt followed by evaporation of the solvent after drying over Na_2SO_4. A solution of the obtained viscous residue [IR ($CHCl_3$) : no strong absorption near 1700 cm^{-1}] in AcOEt (10 ml) was refluxed for 4 h in the presence of dimethyl sulfate (630 mg, 5 mmol). Ten ml of 10% K_2CO_3 and benzene (2 ml) were added to the cooled mixture and the whole was stirred at room temperature overnight. Water and AcOEt were added to the resulting mixture followed by a further extraction of the aqueous layer with AcOEt. The combined organic layer was washed with water and 10% HCl, and dried over Na_2SO_4. The oil, which was obtained by evaporation of the solvent, was distilled in vacuo. bp 95 - 105 ℃ (1 mmHg). [Lit. bp 70 ℃ (0.2 mmHg)][7] Yield, 283 mg (76.9 %). IR ($CHCl_3$) : 1715 cm^{-1} (C=O) [Lit. 1715 cm^{-1}].[7] ^{1}H-NMR (80 MHz in $CDCl_3$) δ : 0.87 (t, 3H, $C\underline{H}_3CH_2-$, J = 8 Hz), 1.10 - 1.85 (m, 8H, $CH_3(C\underline{H}_2)_4-$), 2.10 (s, 3H, $C\underline{H}_3CO-$), 2.44 (t, 2H, $-COC\underline{H}_2(CH_2)_4-$), 2.68 (s, 4H, $-CO(C\underline{H}_2)_2CO-$). LRMS (m/z) : 184 (M). This product was identified with the previously synthesized sample by comparison of their IR spectra.[12]

cis-Undec-8-ene-2,5-dione (10) : A Grignard reaction was carried out as described in the case of the synthesis of 7 starting from 6 (R' = TMS; 668 mg, 2 mmol), cis-1-iodo-3-hexene (630 mg, 3 mmol),[8] magnesium metal (146 146mg, 6 mgatom) and ether (6 ml). An oily product was obtained. bp 112 - 120 ℃ (15 mmHg). Yield, 220 mg (60.5 %). IR ($CHCl_3$) : 1715 cm^{-1} (C=O) [Lit. IR (neat) : 1715 cm^{-1}].[6] Low-resolution MS (m/z) : 182 (M). ^1H-NMR (300 MHz in $CDCl_3$) : 0.95 (t, 3H, $C\underline{H}_3CH_2$-, J = 7 Hz), 1.95 - 2.10 and 2.31 (m and m, 2H each, allylic position), 2.19 (s, 3H, $C\underline{H}_3CO$-), 2.51 and 2.60 - 2.75 [t (J = 7 Hz) and m, 2H and 4H, adjacent methylene protons to C=O], 5.20 - 5.45 (m, 2H, -C$\underline{H}$=C$\underline{H}$-). [Lit. ^1H-NMR ($CDCl_3$) : 0.95 (t, 3H), 2.17 (s, 3H), 2.68 (s, 4H), 5.35 (m, 2H)].[7] The cis configuration was confirmed from J value between the two vinylic protons (10.75 Hz).

1,14-Di(1-methyl-1H-imidazol-2-yl)-1,14-tetradecadione (2b) : A similar reaction of 1b (8.20 g, 100 mmol) as described in the preparation of 2a afforded a crystalline product, which was recrystallized from ethanol to give colorless needles. mp 111.5 - 112 ℃. Yield, 6.96 g (45.2 %). IR ($CHCl_3$) : 1678 cm^{-1} (C=O). ^1H-NMR (80 MHz in $CDCl_3$)δ: 1.00 - 1.90 (m, 20H, -$(C\underline{H}_2)_{10}$-), 3.11 (t, 4H, -$COC\underline{H}_2$- x 2, J = 7 Hz), 3.99 (s, 6H, 2 x $NC\underline{H}_3$), 7.01 and 7.12 (d each, 2H each, Ar-H, J = 1 Hz each). Anal. Calcd for $C_{22}H_{34}N_4O_2$: C, 68.36 ; H, 8.87 ; N, 14.50. Found : C, 68.12 ; H, 9.06 ; N, 14.26.

2,15-Hexadecadione (4)[3] : i) A similar reaction starting from 2b (1.54 g, 4 mmol) and methylmagnesium iodide (10 mmol) as described in the preparation of 9 afforded a crystalline product, which was recrystallized from n-hexane. mp 77 - 79 ℃. Yield, 600 mg (59.0 %). IR ($CHCl_3$) : 1710 cm^{-1} (C=O). ^1H-NMR (80 MHz in $CDCl_3$)δ: 0.95 - 1.80 (m, 20H, -$(C\underline{H}_2)_{10}$-), 2.12 (s, 6H, $C\underline{H}_3CO$- x 2), 2.41 (t, 4H, -$C\underline{H}_2CO$- x 2, J = 7 Hz).

ii) A similar reaction as described in i) except use of 1.4M MeLi (100 mmol) in hexane instead of methylmagnesium iodide afforded the same product. Yield, 680 mg (66.9 %). TLC indicated that purity of the intermediate (3) was somewhat improved comparing with that of i).

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