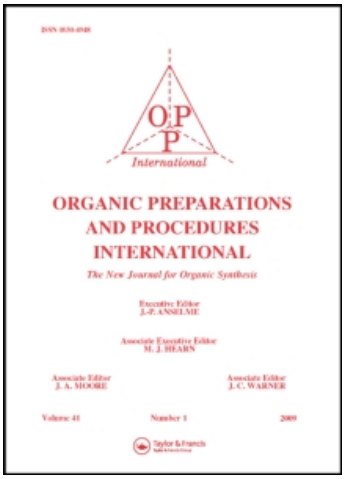

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UNEXPECTED DIECKMANN CONDENSATION IN THE SYNTHESIS OF METHYL 6-(6-METHOXY-2-NAPHTHYL)-6-OXOHEXANOATE WITH AN ARYLCADMIUM REAGENT

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OPPI BRIEFS

UNEXPECTED DIECKMANN CONDENSATION IN THE SYNTHESIS OF METHYL 6-(6-METHOXY-2-NAPHTHYL)-6-OXOHEXANOATE WITH AN ARYLCADMIUM REAGENT

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(04/21/00)

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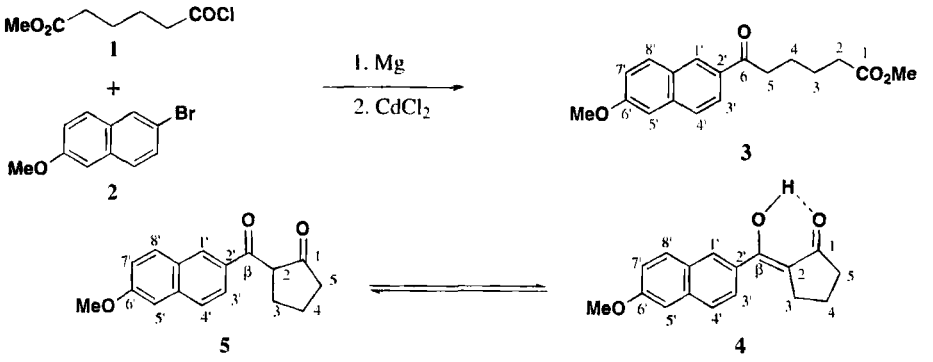
Methyl 6-(6-methoxy-2-naphthyl)-6-oxohexanoate (**3**) exhibits anti-inflammatory properties,[1] and has been used both as a fluorescent probe[2] and as an intermediate in the synthesis of other fluorescent molecules used for the study of the polarity of lipid bilayers in biological membranes.[3] The synthesis of this useful molecule in moderate yields (40%) by a Friedel-Crafts reaction has been reported recently.[4] The present work was undertaken in an attempt to improve the synthesis of **3** by reaction of a weakly ionic naphthalene organocadmium derivative with methyl adipoyl chloride (methyl 6-chloro-6-oxohexanoate, **1**) in the hope that addition would occur selectively at the most electrophilic carbonyl group.

The reaction of an excess of the cadmium reagent of **2** with **1** gave, in addition to 6,6'-dimethoxy-2,2'-binaphthyl (4%) and adipic acid (10%), the desired product **3** and a yellow solid **4**, whose structure was established as described below.

Compound **4** showed a highly deshielded D_2O-exchangeable signal at δ 14.73 in its ^1H NMR spectrum and reacted with diazomethane to afford a derivative **6**, with an additional signal for a methoxy group at δ 3.60. However, neither the IR spectrum of **4** nor that of **6** were compatible with these compounds being an acid and its methyl ester respectively. In fact, an authentic sample of 6-(6-methoxy-2-naphthyl)-oxohexanoic acid (**7**), obtained by saponification of **3**, had IR and ^1H NMR spectra very different from those of **4**. A close inspection of their spectroscopic data led us to assign the structures of 2-[hydroxy(6-methoxy-2-naphthyl)methylene]cyclopentanone to **4** and that of its methyl ether to **6**.



Additional support for the structure proposed for compound **4** came from the interesting observation that in $CDCl_3$ solution, it gave rise to a new molecular species (**5**), easily detected in both the ^1H and ^{13}C NMR spectra. The concentration of this new species increased slowly and stabilized after 14 days at a **4/5** ratio of 56:44 (± 2; from ^1H NMR integrals). Although not all the spectral parameters of **5** could be determined, ^1H and ^{13}C NMR data obtained were sufficient for tentative characterization of this compound as 2-(6-methoxy-2-naphthoyl)cyclopentanone. Thus **4**, the only species detected in the solid state (IR), is transformed into an equilibrium mixture of tautomers **4** and **5** soon after dissolved in $CDCl_3$.

The formation of the unexpected side-product is attributable to compound **3** having undergone a Dieckmann condensation, *via* the formation of a carbanion at the methylene α to the ketone group, due to the strongly basic medium in which **3** was initially formed. The isolation of **4** in such noteworthy yield (32%, as against 40% for the target compound **3**) is especially surprising given the fact that no analogous cyclized side-products have been detected in similar syntheses of its higher or lower side-chain homologues.[7] A plausible explanation for this particular behavior is that Dieckmann condensation of **3** leads to an easy to generate, stable five-membered ring.

Thus, the yield of the coupling reaction between the ester-chloride **1** and the organocadmium derivative of **2** should have been at least 72%. However, attempts made to improve the yield of **3** were unsuccessful. Decreasing the time or the temperature of reaction led to an increase in the isolated amounts of 6-methoxynaphthalene and adipic acid; on the other hand, extending reaction time led to an increase in the Dieckmann condensation side product. Production of **4** in 80% yield was achieved when **3** was refluxed for 4 h in methanolic sodium methoxide.

EXPERIMENTAL SECTION

Melting points (uncorrected): Reichert Kofler Thermopan. IR (in KBr discs, for solids, or films between NaCl plates, for oils): Perkin Elmer FT-IR 1640. NMR (in $CDCl_3$ with TMS as internal standard): Bruker AMX-300 (300 MHz for ^1H and 75 MHz for ^{13}C NMR). EIMS (at 70 eV): Kratos MS-50. Microanalyses: Perkin-Elmer 240B Elemental Analyser. Silica gel 60 (70-230 mesh) for chromatography was from Merck. Reagents and solvents were of commercial grade and were used as received.

Methyl 6-Chloro-6-oxohexanoate (1).- Thionyl chloride (27 mL, 370 mmol) was slowly added to monomethyl adipate (10.0 g, 60 mmol) at 0° and the mixture was heated at 70° for 1 h. The excess thionyl chloride was removed by warming the mixture *in vacuo* until the oily liquid residue had constant mass (12 g). IR: 1799 (acid chloride C=O), 1732 (ester C=O) cm^{-1}.

Reaction of *bis*(6-Methoxy-2-naphthyl)cadmium with 1.- Magnesium (3.75 g, 154 mmol) was placed in a flask and the apparatus was flame dried under argon. A solution of **2** (10.0 g, 42.2 mmol) in dry THF (35 mL) was added, followed by an iodine crystal and 3 drops of CH_3I, and the stirred mixture spontaneously began to reflux. While stirring the mixture, further **2** (21.0 g, 88.6 mmol) in dry THF (75 mL) was added at a rate to maintain the reflux. The mixture was vigorously stirred and heated at reflux for an additional 35 min, and the formation of the Grignard reagent was confirmed by the Gilman test.[8] The reaction mixture was then cooled to 0° in an ice-bath, and finely powdered, oven-dried (110°) $CdCl_2$ (16.0 g, 87.3 mmol) was added at once and the mixture was vigorously stirred until it gave a negative result in the Gilman test (*ca.* 30 min). The THF was distilled off and residual solvent was removed by co-distillation with dry toluene (50 mL). Additional dry toluene (50 mL) was added to the crude arylcadmium reagent, and ester-chloride **1** (11.5 g, 64.4 mmol) was slowly dripped into the mixture. The reaction was successively heated at reflux for 1 h, cooled to 0° and acidified with 2 N H_2SO_4. The organic layer was separated, washed with water and dried (Na_2SO_4). The solvent was eliminated to afford a yellow paste which was chromatographed on silica gel, with 8:2 toluene/EtOAc as eluent, to afford 2-methoxynaphthalene (7.8 g) and a complex mixture of other products (16.5 g). Further chromatography of the latter mixture, with DCM as eluent, gave a spectroscopically pure (^1H NMR) yellow solid which was identified as **4** (5.46 g, 32%). An analytical sample of **4** was obtained by recrystallization from EtOAc. Subsequent elution of the chromatographic column with 8:2 DCM/EtOAc gave a white solid identified as **3** (7.67g, 40%). An analytical sample of **3** was obtained by triple recrystallization from toluene. Further elution of the column with EtOAc left a solid residue from which alkaline extraction allowed the isolation of adipic acid (0.90 g), while recrystallization of the neutral fraction from DCM led to isolation of 6,6'-dimethoxy-2,2'-binaphthyl (0.81 g).

Methyl 6-(6-Methoxy-2-naphthyl)-6-oxohexanoate (3): white solid, mp 81-82° (toluene), (*lit.*[4] 81-83°). Spectral data as previously described.[4]

Anal. Calcd for $C_{18}H_{20}O_4$ (300.3): C, 71.98; H, 6.71. Found: C, 72.06; H, 6.92

6,6'-Dimethoxy-2,2'-binaphthyl: white solid, mp 180-181° (DCM). IR: 1624 and 1591 (aromatic C=C) cm^{-1}. ^1H NMR: δ 8.26 (1 H, d, J = 1.6 Hz, 1-H); 7.83 (1 H, d, J = 9.0 Hz, 8-H); 7.74 (1 H, d, J = 8.7 Hz, 4-H); 7.47 (1 H, dd, J = 8.7, 1.6 Hz, 3-H); 7.23 (1 H, dd, J = 9.0, 2.5 Hz, 7-H); 7.12 (1 H, d, J = 2.5 Hz, 5-H); 3.92 (3 H, s, OCH_3). EIMS: *m/z* (%) 102 (13), 114 (27), 145 (32), 173 (43), 189 (25), 271 (14), 299 (25), 314 (100, M).

Anal. Calcd for $C_{22}H_{18}O_2$ (314.4): C, 84.05; H, 5.77. Found: C, 83.90; H, 5.88

2-[Hydroxy(6-methoxy-2-naphthyl)methylene]cyclopentanone (4): yellow solid, mp 123-124° (EtOAc). IR: 1626 (C=O), 1585 (C=C) cm^{-1}. ^1H NMR: δ 14.73 (1 H, br s, OH); 8.21 (1 H, s, 1'-H);

7.84 (1 H, dd, J = 8.7, 1.7 Hz, 3'-H); 7.80 (1 H, d, J = 9.0 Hz, 8'-H); 7.77 (1 H, d, J = 8.7 Hz, 4'-H); 7.19 (1 H, dd, J = 9.0, 2.3 Hz, 7'-H); 7.14 (1 H, d, J = 2.3 Hz, 5'-H); 3.94 (3 H, s, 6'-OCH_3); 2.98 (2 H, t, J = 7.1 Hz, 3-H_2); 2.52 (2 H, t, J = 7.9 Hz, 5-H_2); 2.00 (2 H, quintet, J = 7.5 Hz, 4-H_2). ^{13}C NMR: δ 210.35, 169.31, 159.48, 136.15, 130.87, 129.91, 129.14, 128.27, 127.07, 125.28, 119.87, 109.31, 105.86, 55.69, 37.79, 28.90, 21.58.

Anal. Calcd for $C_{17}H_{16}O_3$ (268.3): C, 76.10; H, 6.01. Found: C, 75.89; H, 5.86

2-(6-Methoxy-2-naphthoyl)cyclopentanone (5): tautomeric form of **4**, detected by ^{1}H and ^{13}C NMR. Equilibrium between **5** and **4**, at a 44:56 ratio, is reached after 14 days in $CDCl_3$ solution at rt. ^{1}H NMR (only signals clearly distinguishable from those corresponding to **4**): δ 8.45 (1 H, s, 1'-H); 8.02 (1 H, dd, J = 8.7, 1.8 Hz, 3'-H); 7.87 (1 H, d, J = 8.9 Hz, 8'-H); 7.20 (1 H, dd, J = 8.9, 2.4 Hz, 7'-H); 4.39 (1 H, t, J = 7.9 Hz, 2-H); 2.70-2.18 (4 H, m, 3-H_2 + 5-H_2). ^{13}C NMR: δ 214.08, 195.49, 160.24, 137.74, 132.18, 132.04, 131.70, 128.05, 127.36, 125.51, 119.97, 105.94, 57.29, 55.69, 39.34, 27.63, 21.44.

2-[Methoxy(6-methoxy-2-naphthyl)methylene]cyclopentanone (6).- An ethereal 0.5 M solution of CH_2N_2[9] (5 mL) was slowly added to a solution of **4** (0.49 g, 1.8 mmol) in THF, and the reaction was left for 2 h at rt. The solvent was evaporated *in vacuo,* and the residue was identified as the dimethoxy compound **6** (0.51 g , 99%), white solid, mp 107-108° (EtOAc). IR: 1650 (C=O), 1625 (exocyclic or aromatic C=C) cm^{-1}. ^{1}H NMR: δ 8.17 (1 H, s, 1'-H); 7.81 (1 H, d, J = 9.8 Hz, 8'-H); 7.79 (1 H, dd, J = 8.6, 1.6 Hz, 3'-H); 7.71 (1 H, d, J = 8.6 Hz, 4'-H); 7.19 (1 H, dd, J = 9.8, 2.3 Hz, 7'-H); 7.14 (1 H, d, J = 2.3 Hz, 5'-H), 3.94 (3 H, s, 6'-OCH_3), 3.60 (3 H, s, β-OCH_3); 2.81-2.72 (4 H, m, 3-H_2 + 5-H_2); 1.97 (2 H, quintet, J = 7.5 Hz, 4-H_2). ^{13}C NMR: δ 193.72, 166.96, 159.24, 136.72, 135.59, 131.08, 130.00, 128.14, 126.41, 126.29, 119.32, 114.04, 105.91, 57.78, 55.63, 32.07, 31.53, 19.84.

Anal. Calcd for $C_{18}H_{18}O_3$ (282.3): C, 76.57; H, 6.43. Found: C, 76.85; H, 6.65

6-(6-Methoxy-2-naphthyl)-6-oxohexanoic acid (7).- A solution of **3** (1.00 g, 3.33 mmol) in MeOH (50 mL) was treated with 5 N NaOH (5 mL) and the mixture was refluxed for 7 h. The solvent was evaporated at reduced pressure, the solid residue was dissolved in water, and the resulting solution was extracted once with Et_2O. The aqueous layer was acidified with 5 N HCl, then extracted with Et_2O. The ethereal extract was dried (Na_2SO_4) and concentrated to afford **7** (0.82 g, 86%) as a white solid, mp 134-135° (AcOH). ^{1}H NMR: δ 12.43 (1 H, br s, CO_2H); 8.40 (1 H, s, 1'-H); 8.00 (1 H, dd, J = 8.7, 1.7 Hz, 3'-H), 7.86 (1 H, d; J = 9.0 Hz, 8'-H); 7.77 (1 H, d, J = 8.7 Hz, 4'-H); 7.20 (1 H, dd, J = 9.0, 2.4 Hz, 7'-H); 7.15 (1 H, d, J = 2.4 Hz, 5'-H); 3.95 (3 H, s, 6'-OCH_3); 3.12 (2 H, t, J = 6.9 Hz, 5-H_2); 2.45 (2 H, t, J = 7.0 Hz, 2-H_2); 1.91-1.74 (4 H, m, 3-H_2 + 4-H_2). ^{13}C NMR: δ 199.90, 178.83, 160.14, 137.67, 132.75, 131.53, 129.92, 128.26, 127.53, 125.01, 120.11, 106.16, 55.82, 38.36, 34.09, 24.80, 24.19.

Anal. Calcd for $C_{17}H_{18}O_4$ (286.3): C, 71.31; H, 6.34. Found: C, 71.58; H, 6.39

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REDUCTIVE COUPLING OF KETONES WITH IMINES PROMOTED BY THE TITANIUM TETRACHLORIDE/SAMARIUM SYSTEM

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(04/18/00)

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In the early 1970's, three groups discovered that low-valent titanium abstracted oxygen from aldehydes and ketones leading to the formation of olefins.[1] Since then, a large number of coupling reactions induced by low-valent titanium reagent have been reported.[2] Recently, our group reported the intermolecular and intramolecular reductive coupling of ketone-nitrile promoted by $TiCl_4$/Sm system.[3] We now describe our preliminary results on the reductive couplings of aromatic aldimines