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Short Note

Dimethyl 7-(dimethylamino)-3,4-dihydro-1-(2-oxopropyl)-4-phenylnaphthalene-2,2(1*H*)-dicarboxylate

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Abstract: A Friedel-Crafts–type ring-opening/intramolecular Michael addition cascade reaction of (*E*)-4-(3-(dimethylamino)phenyl)but-3-en-2-one with dimethyl 2-phenylcyclopropane-1,1-dicarboxylate catalyzed by $Yb(OTf)_3$ has produced a new compound, dimethyl 7-(dimethylamino)-3,4-dihydro-1-(2-oxopropyl)-4-phenylnaphthalene-2,2(1*H*)-dicarboxylate. This reaction provided diastereoslective *trans* tetralin (7:3 dr) on the cyclohexyl ring. The structure of the newly synthesized compound was determined using ^{1}H-, ^{13}C-NMR, IR and mass spectral data.

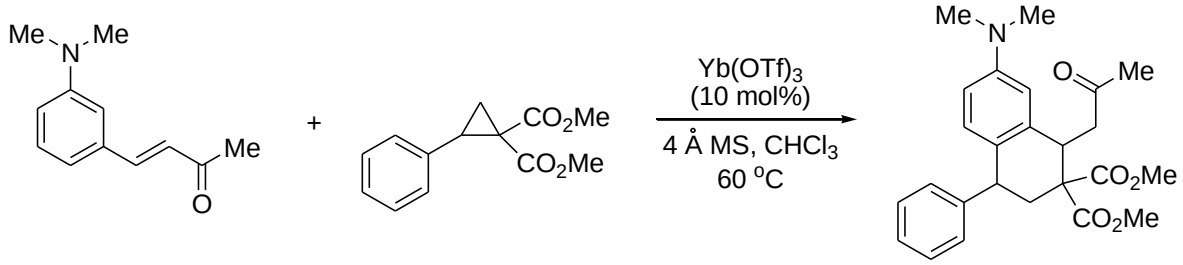
Keywords: tetralin; Friedel-Crafts reaction; Michael addition; cascade reaction

1. Introduction

Tetralin is structurally essential scaffold in biologically active natural products and synthetic pharmaceutical compounds [1–3]. Especially the 1-aryltetralin is widely found in natural cyclolignans and synthetic derivatives with a broad spectrum of biological activities including antimalarial, antifungal, antibacterial, anti-inflammatory, antitumor, anti-HIV, and antidepressant activities [4–6]. In view of the significance of the aryltetralin structure in medicinal and organic chemistry, numerous synthetic methods for aryltetralines have been developed [7,8]. Based on our previous results of the cascade reaction for the synthesis of 1-aryltetralin compounds [9], we have successfully obtained a novel dimethyl 7-(dimethylamino)-3,4-dihydro-1-(2-oxopropyl)-4-phenyl-naphthalene-2,2(1*H*)-dicarboxylate.

2. Results

The synthesis of dimethyl 7-(dimethylamino)-3,4-dihydro-1-(2-oxopropyl)-4-phenylnaphthalene-2,2(1*H*)-dicarboxylate (**3**) was achieved in one step, as presented in Scheme 1, which was performed by a Friedel-Crafts–type ring-opening/intramolecular Michael addition cascade reaction of (*E*)-4-(3-(dimethylamino)phenyl)but-3-en-2-one (**1**) [10] with dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**2**) [11]. The reaction was carried out in $CHCl_3$ in the presence of 10 mol % of $Yb(OTf)_3$ as a catalyst and 4 Å molecular sieve as an additive at 60 °C. The desired product **3** was obtained in 72% yield with moderate diastereoselectivity (7:3 dr) via the ring-opening/Michael cascade reaction. The structure of compound **3** was confirmed by ^{1}H- and ^{13}C-NMR, IR, mass spectral data, and all data are in accordance with the proposed structure.



1 **2** **3** (72%)

Scheme 1. Synthesis of dimethyl 7-(dimethylamino)-3,4-dihydro-1-(2-oxopropyl)-4-phenylnaphtha-lene-2, 2(1*H*)-dicarboxylate (**3**).

3. Experimental Section

3.1. General Information

All reagents were used as received without further purification. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. Chromatographic purification of the title compound **3** was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates (Merck, Darmstadt, Germany, 70–230 mesh). Developed chromatograms were visualized by fluorescence quenching (254 nm) and anisaldehyde stain. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance 400 spectrometer (Bruker BioSpin GmbH, Karlsruhe, Germany) in $CDCl_3$. Chemical shifts are internally referenced to residual protio solvent signals (δ 7.26 ppm for ^{1}H; δ 77.16 ppm for ^{13}C). Data for ^{1}H-NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C-NMR are reported in terms of chemical shift. IR spectra were recorded on ALPHA FT-IR spectrometer (Bruker Optics GmbH, Ettlingen, Germany), and reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectrometry data was recorded on a JEOL JMS-700 MStation mass spectrometer (JEOL, Tokyo, Japan).

3.1.1. Synthesis of (*E*)-4-(3-(Dimethylamino)phenyl)but-3-en-2-one (**1**)

To a solution of 3-dimethylaminobenzaldehyde [12] (149 mg, 1.0 mmol) in THF (5 mL) was added 1-(triphenylphosphoranylidene)-2-propane (382 mg, 1.2 mmol) at room temperature. The resulting mixture was refluxed for 72 h until complete consumption of 3-dimethylaminobenzaldehyde was observed as determined by TLC. The resulting mixture was cooled to room temperature and concentrated in vacuo. The crude residue was purified by flash silica gel column chromatography using EtOAc/hexane (1/10) as eluent to afford the desired title compound **1** (89%, 169 mg).

Yellow solid; m.p. 56–58 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 15.6 Hz, 1H, C*H*CH), 7.26 (t, *J* = 7.9 Hz, 1H, Ar-H), 6.92 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.85 (d, *J* = 2.4 Hz, 1H, Ar-H), 6.78 (dd, *J* = 7.6, 2.4 Hz, 1H, Ar-H), 6.70 (d, *J* = 15.6 Hz, 1H, CHC*H*), 2.99 (s, 6H, N(CH_3)$_2$), 2.39 (s, 3H, COCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.34, 150.87, 144.07, 135.66, 129.45, 120.47, 115.90, 114.41, 112.88, 43.33, 40.52; IR (film) 2951, 2933, 2807, 1655, 1591, 1571, 1495, 1442, 1356, 1318, 1224, 1206, 1176, 1064 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{12}H_{15}NO$: 189.1154 Found: 189.1144.

3.1.2. Synthesis of Dimethyl 7-(dimethylamino)-3,4-dihydro-1-(2-oxopropyl)-4-phenylnaphthalene-2,2(1*H*)-dicarboxylate (**3**)

To a solution of (*E*)-4-(3-(dimethylamino)phenyl)but-3-en-2-one (**1**) (19 mg, 0.10 mmol), $Yb(OTf)_3$ (6.2 mg, 0.020 mmol), and 4 Å molecular sieve (20 mg) in $CHCl_3$ (0.5 mL) was added dimethyl 2-phenyl-cyclopropane-1,1-dicarboxylate (**2**) (28 mg, 0.12 mmol). The resulting mixture was stirred at 60 °C for 72 h until complete consumption of (*E*)-4-(3-(dimethylamino)phenyl)but-3-en-2-one (**1**)

was observed as determined by TLC. The resulting mixture was cooled to room temperature and was quenched with sat. $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2. The combined organic layer were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash silica gel column chromatography using EtOAc/hexane (1/10) as eluent to afford the desired title compound **3** (72%, 31 mg).

Inseparable mixture of diastereomers, colorless gum; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.2 Hz, 2H minor stereoisomer, Ar-H), 7.23 (d, *J* = 7.2 Hz, 2H major stereoisomer, Ar-H), 7.16 (d, *J* = 7.5 Hz, 1H major, Ar-H), 7.15 (t, *J* = 7.5 Hz, 1H major, Ar-H), 7.02 (d, *J* = 7.2 Hz, 1H major + 3H minor, Ar-H), 6.70 (d, *J* = 8.6 Hz, 1H major, Ar-H), 6.59 (d, *J* = 8.4 Hz, 1H minor, Ar-H), 6.52 (dd, *J* = 8.6, 2.6 Hz, 1H major, Ar-H), 6.50–6.46 (m, 1H minor, Ar-H), 6.43 (d, *J* = 2.3 Hz, 1H major, Ar-H), 4.38 (t, *J* = 5.3 Hz, 1H minor, $COCH_2CH$), 4.27 (t, *J* = 5.6 Hz, 1H major, $COCH_2CH$), 4.21 (t, *J* = 6.7 Hz, 1H major + 1H minor, CCH_2CH), 3.70 (s, 3H minor, CO_2CH_3), 3.67 (s, 3H major, CO_2CH_3), 3.66 (s, 3H minor, CO_2CH_3), 3.23 (s, 3H major, CO_2CH_3), 2.84–3.01 (m, 1H major + 1H minor $COCH_2CH$ and 1H major + 1H minor CCH_2CH), 2.90 (s, 6H major, $N(CH_3)_2$), 2.89 (s, 6H minor, $N(CH_3)_2$), 2.78 (dd, *J* = 14.2, 7.5 Hz, 1H major + 1H minor $COCH_2CH$), 2.69–2.61 (m, 1H minor CCH_2CH), 2.57 (dd, *J* = 14.1, 6.0 Hz, 1H major CCH_2CH), 2.17 (s, 3H major, $COCH_3$), 2.13 (s, 3H minor, $COCH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 206.70 (major stereoisomer), 206.04 (minor stereoisomer), 171.54 (minor), 171.45 (major), 171.04 (major), 170.69 (minor), 149.45 (major), 149.22 (minor), 146.71 (minor), 146.51 (major), 140.28 (minor), 139.66 (major), 130.81 (major), 130.44 (minor), 128.88 (major), 128.59 (minor), 128.58 (minor), 128.14 (major), 126.44 (minor), 126.07 (major), 124.37 (minor), 123.58 (major), 112.02 (minor), 111.73 (major), 111.54 (minor), 111.10 (major), 57.22 (minor), 56.63 (major), 52.82 (minor), 52.81 (minor), 52.58 (major), 52.16 (major), 49.84 (minor), 48.22 (major), 42.26 (minor), 41.32 (major), 40.63 (major), 40.54 (minor), 38.39 (major), 37.85 (minor), 35.77 (major), 34.42 (minor), 30.49 (minor), 30.34 (major); IR (film) 2952, 2928, 2869, 1731, 1702, 1611, 1512, 1451, 1351, 1260, 1193, 1122, 1067, 1014 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{25}H_{29}NO_5$: 423.2046 Found: 423.2053.

Supplementary Materials: ^{1}H- and ^{13}C-NMR spectra for compound **3** are available online.

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Conflicts of Interest: The authors declare no conflict of interest.

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