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RHODIUM-CATALYZED SYNTHESIS OF 3-METHYL-9,9A-DIHYDRO-1*H*-CYCLOPENTA[*B*]QUINOLIN-2(4*H*)-ONE

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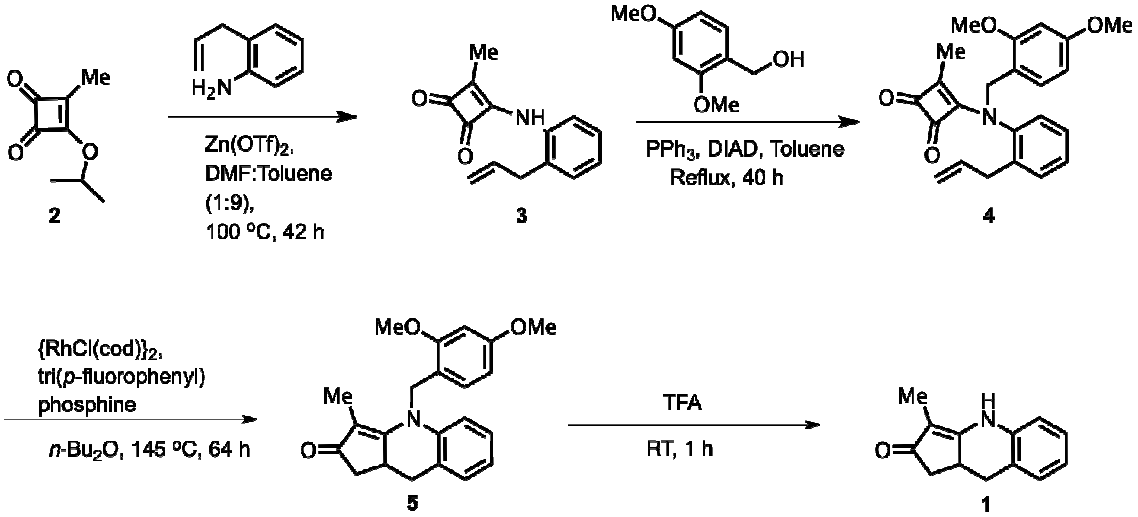
Abstract: 3-Methyl-9,9a-dihydro-1*H*-cyclopenta[*b*]quinolin-2(4*H*)-one **1** was synthesized from squaric acid diisopropoxy ester. Key reactions involved the Pauson Khand-type rhodium-catalyzed decarbonylative cycloaddition of cyclobutenediones with a pendant alkene, and the Mitsunobu reaction.

Keywords: Pauson Khand type reaction, Rhodium catalysis, Vinylogous amide

Introduction

The Pauson-Khand (PK) reaction involves a cobalt-mediated cycloaddition of an alkyne, an alkene, and CO leading to form a cyclopentenone.[1] Yamamoto et al.[2] developed Rhodium-catalyzed PK-type reactions, that avoid the use of harmful CO gas, by using squaric acid as a platform. We have extended this method to the synthesis of a novel 5,6,6-tricyclic ring system - 3-methyl-9,9a-dihydro-1*H*-cyclopenta[*b*]quinolin-2(4*H*)-one **1** (Scheme 1). This system is of interest for its novelty and drug-like properties (Molecular weight: 199.25, tPSA: 29.1, CLogP: 2.614).



Scheme 1

The synthesis commenced with the preparation of monoisopropoxycyclobutanedione **2** from a commercially available diisopropoxy ester of squaric acid via a known procedure.[3]

Compound **3** was synthesized from 3-isopropoxy-4-methylcyclobut-3-ene-1,2-dione **2** and 2-allyl aniline[4] by a zinc triflate catalyzed displacement reaction in 41% yield. Mitsunobu reaction of **3** with 2,4-dimethoxybenzyl alcohol afforded crude **4** which on rhodium (I)-catalyzed decarbonylative ring expansion[2] of yielded cyclopenta[*b*]quinolin-2(4*H*)-one **5**. Trifluoracetic acid induced deprotection of **5** furnished target **1** in 16% yield over three steps from **3**. Rhodium (I)-catalyzed decarbonylative ring expansion of **3** to give **1** directly was unsuccessful presumably due to poisoning of the rhodium catalyst via the unprotected nitrogen lone pair. Hence protection of the vinylogous nitrogen with the 2,4-dimethoxybenzyl group was critical.

Experimental Details

3-((2-allylphenyl)amino)-4-methylcyclobut-3-ene-1,2-dione (3). To a solution of 3-isopropoxy-4-methylcyclobut-3-ene-1, 2-dione **2** (0.200 g, 1.29 mmol) and 2-allylaniline (0.207 g, 1.55 mmol) in DMF: toluene (0.4 mL: 4 mL), zinc triflate (0.046 g, 0.233 mmol) was added and the reaction was stirred at 100 °C for 42 h. The solvent was removed under reduced pressure. The residue was purified by combiflash (SiO_2, 33% ethylacetate in hexanes). All fractions were pooled together to give 3-(but-3-en-1-yl(2,4-dimethoxybenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione (0.120 g, 41%) as a dark green oil.

^{1}H NMR (600 MHz, CD_3OD) δ 7.35 (2H, bs), 7.27 (2H, bs), 5.95-5.88 (1H, m), 5.03 (1H, d, *J* = 9.6 Hz), 4.97 (1H, d, *J* = 16.8 Hz), 3.46 (2H, bs), 1.70 (3H, bs); LCMS *m/z* 228.1097 ([M + H^+], $C_{14}H_{14}NO_2$ requires 228.1019); Purity >96.0% (HPLC).

3-methyl-9,9a-dihydro-1*H*-cyclopenta[*b*]quinolin-2(4*H*)-one (1).

To a solution of 3-((2-allylphenyl)amino)-4-methylcyclobut-3-ene-1,2-dione **3** (0.300 g, 1.45 mmol) in dry toluene (7.2 mL) was added triphenyl phosphine (0.570 g, 2.17 mmol) and (2,4-dimethoxyphenyl)methanol (0.366 g, 2.17 mmol) in this sequence. The mixture was cooled to 0 °C. Then a solution of diisopropyl azodicarboxylate (0.429 mL, 2.17 mmol) in toluene (7.2 mL) was added drop wise with stirring over 10 min. The reaction mixture was stirred at 110 ^oC for 40 h. Solvent removed in vacuo and the residue purified by combiflash (SiO_2, 50 g, 1%-4% MeOH in DCM) to get 3-((2-allylphenyl)(2,4-dimethoxybenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione **4** (0.395 g, crude 72 %) which was taken to the next step without further purification. LCMS *m/z* 378.1837 ([M + H^+], $C_{23}H_{24}NO_4$ requires 378.1700).

To a solution of 3-((2-allylphenyl)(2,4-dimethoxybenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione (0.290 g, 0.768 mmol) in dry degassed *n*-Bu_2O (7.3 mL) was added chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.038 g, 0.076 mmol) and tris(4-fluorophenyl)phosphine (0.098 g, 0.308 mmol) and the resultant mixture was degassed in liquid nitrogen and stirred at 145 °C for 64 h. The solvent was removed under reduced pressure, and the residue was attempted to be purified by combiflash (SiO_2, 25%-66% ethylacetate in hexanes) to get 4-(2,4-dimethoxybenzyl)-3-methyl-9,9a-dihydro-1*H*-cyclopenta[*b*]quinolin-2(4*H*)-one **5** (0.141 g, crude 53%) which was taken to the next step without further purification. LCMS *m/z* 350.1892 ([M + H^+], $C_{22}H_{24}NO_3$ requires 350.1751).

Trifluoroacetic acid (1 mL, 13.1 mmol) was added to 4-(2,4-dimethoxybenzyl)-3-methyl-9,9a-dihydro-1*H*-cyclopenta[*b*]quinolin-2(4*H*)-one **5** (0.141 g, 0.403 mmol) and the mixture was stirred at RT for 1 h. Dichloromethane (5 mL) was added and the solvent was removed on rotavapor. The residue was purified by combiflash (SiO2, 66%-90% ethylacetate in

hexanes) to afford 3-methyl-9,9a-dihydro-1*H*-cyclopenta[*b*]quinolin-2(4*H*)-one **1** (0.019 g, 16% yield over three steps).
^{1}H NMR (600 MHz, CD_3OD) δ 7.19-7.14 (2H, m), 7.04 (1H, d, *J* = 7.8 Hz), 6.94 (1H, t, *J* = 7.2 Hz), 3.03 (1H, dd, *J* = 6, 15.6 Hz), 2.84-2.81 (1H, m), 2.69 (1H, dd, *J* = 6.6, 16.2 Hz), 2.47 (1H, t, *J* = 15 Hz), 2.09 (1H, dd, *J* = 3.6, 15.6 Hz), 1.72 (3H, s); ^{13}C NMR (150 MHz, CD_3OD) δ 204.1, 170.9, 137.5, 128.6, 127.6, 125.1, 122.4, 116.2, 107.2, 39.5, 33.2, 31.1, 4.9; HRMS *m/z* 200.1069 ([M + H^+], $C_{13}H_{14}NO$ requires 200.1070); Purity >99.5% (HPLC).

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