Synthesis of Murrayaquinone-A

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Murrayaquinone-A, one of the carbazolequinone alkaloids isolated from Murraya euchrestifolia HAYATA (Rutaceae), was prepared starting from 1,2,3,4-tetrahydrocarbazol-4(9H)-one in good overall yield.

Keywords carbazolequinone alkaloid; murrayaquinone-A; cardiotoxic activity; synthesis; debenzylolation; Fremy’s salt

In the course of our synthetic studies on biologically active natural products, we planned to synthesize murrayaquinone-A (1), which is one of the carbazolequinone alkaloids isolated from the root bark of Murraya euchrestifolia HAYATA (Rutaceae). Murrayaquinone-A has a cardiotoxic activity on guinea-pig papillary muscle. Some synthetic studies of this alkaloid have already been reported.

Our synthetic approach to the title compound started with 1,2,3,4-tetrahydrocarbazol-4(9H)-one (2), which had been prepared in several ways, i.e., by the Fischer indole synthesis of 1,3-cyclohexanedione monophenylhydrazine by treatment of 3-(2-iodophenyl)amino-2-cyclohexen-1-one with sodium hydride-copper(I) iodide in hexamethylphosphoramide (HMPA), and also by photocyclization or palladium-catalyzed cyclization of 3-(2-bromophenyl)amino-2-cyclohexen-1-one.

Protection of the NH group of 2 with 4-methoxybenzyl chloride (MPMCI) in N,N-dimethylformamide (DMF) at room temperature in the presence of sodium hydride followed by methylation of the 3-position of 3 with methyl iodide in tetrahydrofuran (THF) in the presence of lithium cyclohexylisopropylamide (LCIA) gave 4 in 70% overall yield. In order to introduce a double bond into the

Chart 1

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2—3-position of 4, the enone (4) was successfully treated with LCIA and phenylselenenyl chloride in THF in the presence of HMPA. After work-up with 2N HCl, a phenylselenenylated compound (5) and an aromatized compound (6) were obtained in 38 and 30% yields, respectively. Oxidative work-up (NaIO₄) of the above selenenylated reaction mixture resulted in the isolation of 5 and 6 in 21 and 23% yields, respectively. The selenenylated compound (5) was converted into the aromatized compound (6) in 49% yield by means of peracetic acid oxidation and concomitant elimination reaction.

Oxidation of the phenol ring of 6 to the quinone ring was then examined. Treatment of 6 with F remedy’s salt in the presence of potassium dihydrogen phosphate (KH₂PO₄) in acetonitrile—water (1:1) at room temperature gave the quinone (7) in 84% yield. An attempt to remove the protecting group in 7 with trifluoroacetic acid in methylene chloride at room temperature⁶⁹ resulted only in the recovery of the starting material (80%). Therefore, we tried to apply the method developed recently by Murakami et al. for debenzylolation of indole derivatives.⁷⁰ Thus, when 5 was treated with anhydrous aluminum chloride in anisole at 0°C for 10 min, a conjugate addition product of anisole to 7, in which the protecting group still remained, was isolated in 89% yield. These observations led us to change the reaction sequence, and removal of the protecting group in 6 was examined. Treatment in 6 with anhydrous aluminum chloride (3 eq) in benzene at 7—10°C for 1.5 h resulted only in the isolation of the rearranged compounds 9 and 10 in 54 and 14% yields, respectively. These results probably reflect the fact that the benzene rings of 6 were more nucleophilic than benzene used as the solvent. Therefore, benzene was replaced by anisole and the hydroxyl group of 6 was converted into an acetyl group to reduce the nucleophilicity of the phenol ring. The acetate (11) was prepared by the usual method (acetyl chloride and triethylamine in methylene chloride). Treatment of 11 with anhydrous aluminum chloride (5 eq) in anisole at 0—3°C for 10 min afforded the desired deprotected compound 12 in 82% yield. Hydrolysis of the ester group of 12 was performed with aqueous HCl in methanol to give 13 in 81% yield. Finally, oxidation of 13 with F remedy’s salt in acetonitrile—water (1:1) at room temperature in the presence of KH₂PO₄ (20 mol%) cleanly gave the title compound (14) in 84% yield. Ammonium cerium(IV) nitrate oxidation of 13 gave 1 in 34% yield.⁸ IR, ¹H-NMR and MS spectra of the synthesized 1 were identical with those reported for natural 1.⁹ In summary, murraqui none-A (1) was synthesized starting from 1,2,3,4-tetrahydro carbazol-4(9H)-one (2) through 8 steps in good overall yield.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. IR spectra were measured with a Hitachi 260-30 IR spectrometer, and ¹H-NMR spectra were recorded on a JEOL JNM-FX270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. MS were taken with a JEOL LMS-HX100 instrument.

9-(4-Methoxybenzyl)-1,2,3,4-tetrahydrocarbazol-4(9H)-one (3) NaN₃ (0.77 g, 60% in oil, 19.3 mmol) was added to a solution of 2 (3.24 g, 17.5 mmol) in dry DMF (25 ml) and the resulting solution was stirred at room temperature under N₂ for 1 h. A solution of PMPCl (2.6 ml, 19.2 mmol) in dry DMF (5 ml) was added to the above solution, and the whole was stirred at room temperature for 2 h. After the addition of 3N HCl under ice-cooling, the mixture was washed with H₂O, and the extract was washed successively with water and brine. Drying over anhydrous Na₂SO₄ and concentration of the organic layer under reduced pressure gave a brown oil, which was purified by SiO₂ column chromatography (CHCl₃) to furnish 3 (4.29 g, 80%) as brown plates after crystallization from MeOH; mp 115—116°C. IR (Nujol) cm⁻¹: 1640, 1610, 1515. ¹H-NMR (CDCl₃); δ: 2.16—2.30 (2H, m, CH₂=CH₂), 2.58 (2H, dd, J=7, 6 Hz, COCH₂CH₃), 2.88 (2H, t, J=6 Hz, CCH₃CH₂), 3.77 (3H, s, OCH₃), 5.27 (2H, s, NCH₂), 6.82 (2H, dt, J=9, 2 Hz, ArH), 6.97 (2H, dt, J=9, 2 Hz, ArH), 7.18—7.32 (3H, m, ArH), 8.26—8.32 (1H, m, ArH). MS m/z: Calcd for C₂₃H₂₉NO₃: 360.1416. Found: 359.1416.

6 from 5 Acetic acid (0.31 ml) and 30% H₂O₂ (1.5 ml) were added successively to a solution of 5 (0.976 g, 2.06 mmol) in dry THF (40 ml) at —2—0°C, and the whole was stirred at the same temperature for 1 h.
After the addition of a saturated NaHCO₃ solution (20 ml), the reaction mixture was warmed to room temperature and extracted with AcOEt. The combined organic layer was washed with 5% NaHCO₃ and brine successively. After drying over anhydrous Na₂SO₄, Removal of the solvent under reduced pressure gave an oil (0.786 g), which was purified by SiO₂ column chromatography (CHCl₃) to furnish 6 (0.317 g, 49%), after crystallization from MeOH; mp 137–138 °C. The IR, 1H-NMR, and mass spectral data were identical with those of the compound obtained above.

4-Acetoxy-3-methyl-9H-carbazole (11) A solution of 11 (220 mg, 0.61 mmol) in dry anisole (5 ml) was added dropwise to a stirred suspension of AlCl₃ (408 mg, 3.06 mmol) in dry anisole (3 ml) at 0 °C and the resulting mixture was stirred at 0 °C for 10 min. After the addition of water, the mixture was extracted with AcOEt and the combined organic layers were washed with 5% NaHCO₃ and brine successively, and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to give an oil (284 mg), which was purified by SiO₂ column chromatography (hexane: AcOEt = 4:1) to yield 12 (120 mg, 82%) and the acetate of 10 (10 mg, 5%). 12: mp 151–152 °C (MeOH, colorless crystalline powder). IR (Nujol) cm⁻¹: 3340, 1740, 1510, 1630, 1260, 1230. 1H-NMR (CDCl₃) δ: 3.72 (3H, s, CH₃), 7.31–7.50 (3H, m, ArH), 7.17–7.72 (3H, m, ArH), 7.87–8.42 (2H, m, ArH), 5.55 (1H, m, ArH). MS m/z: Caled for C₂₃H₁₈NO₂: 329.0946. Found: 329.0946.

4-Hydroxy-3-methyl-9H-carbazole (13) A reaction mixture obtained by the addition of dilute HCl (12 ml) to a solution of 12 (80 mg, 0.38 mmol) in MeOH (15 ml) was refluxed for 4 h. Removal of MeOH gave crystals, which were collected by filtration and washed with water. Recrystallization of the crude product from acetone gave 13 (40 mg, 85%) as a colorless crystalline powder; mp 237–239 °C (lit. mp 239–240 °C).[19] IR (Nujol) cm⁻¹: 3330, 1580. 1H-NMR (CDCl₃) δ: 3.94 (3H, s, CH₃), 5.90 (1H, brs, OH), 7.17–7.50 (3H, m, ArH), 7.73–7.90 (3H, m, ArH), 8.22–8.30 (1H, m, ArH). MS m/z: Caled for C₂₃H₁₈NO₂: 329.0946. Found: 329.0946.

References