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The Synthesis of Some Novel Chromans

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The inverse-electron demanded Diels-Alder reaction of 1-N,N-dimethylaminomethyl-2-naphthol (1) with substituted styrenes were investigated. With 2-, 3-, 4-methylstyrenes, 2-(2′−, 3′- and 4′-methylphenyl)-benzo-5,6-chromans (5, 6 and 7) were obtained in 12, 18 and 53 % yields respectively. With 2-, 3- and 4-chlorostyrenes, 2-(2′−, 3′- and 4′-chlorophenyl)-benzo-5,6-chromans (8,9 and 10) were obtained in 8, 20 and 33 % yields respectively. With 4-vinyl-pyridine, 2-(4′-pyridyl)-benzo-5,6-chroman (11) was obtained in 48% yield. In all pyrolysis no quinone-methide dimer (4) was encountered.

Introduction

o-Quinone-methides give regiospecific Diels-Alder reactions with simple olefins, enol-ethers and enamines[1].

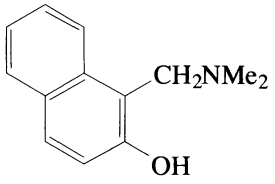
We had reported the general synthesis of polycyclic heteroaromatic compounds, by generating quinone-methides from naphthalene and phenanthrene Mannich bases with substituted aromatic amines[2].

o-Quinone-methides are reactive intermediates in the construction of chroman ring system. There are many reports concerning the use of o-quinone-methides as heterodiene compenent in cycloaddition reactions with olefins[3–5].

It is known that numbers of chroman derivatives are used as antioxidant for fats and oils[6] and some of them show weak estrogenic activity[7]. Among naturally occuring chromans that supress cellular membrane phospholipid degradation, the most powerfull is vitamine E or α-tocopherol[8].

We expected inverse-electron demanded Diels-Alder reaction of Mannich base (1) with substituted styrenes to get the chroman derivatives.

It has been reported that the inverse-electron demanded Diels-Alder reaction of 2-naphthol Mannich base (1) as the naphthalene-quinone-methide (2) precursor with styrene give 2-phenyl-benzo-5,6-chroman (3)[9] together with the dimer (4)[10]. We aimed to reinvestigate this reaction for the synthesis of 2-substituted-benzo-5,6-chromans. When 2-naphthol Mannich base (1) and styrene were heated to 200 °C, in diphenylether, under nitrogen atmosphere, 2-phenyl-benzo-5,6-chroman (3) was obtained in 52 % yield, with no dimer (4) as reported[9]. It had been reported that high temperature was necessary for the formation of quinone-methide and not necessary for Diels-Alder reaction[11].



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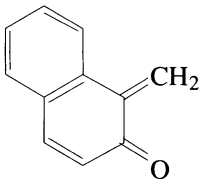

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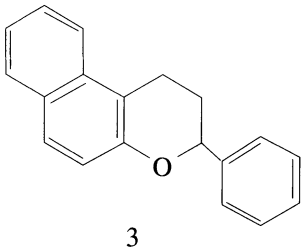

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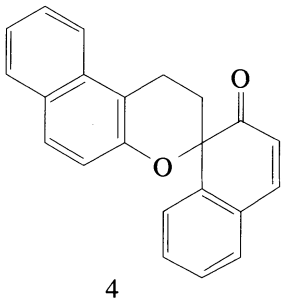

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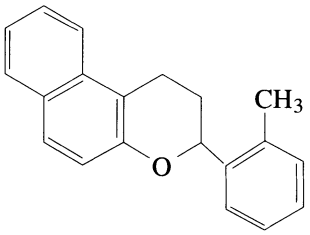

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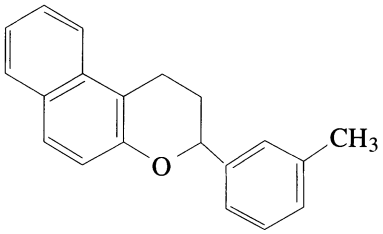

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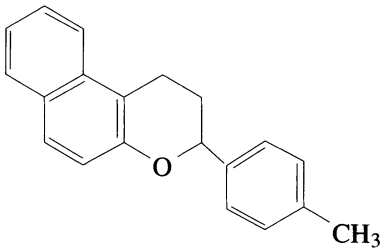

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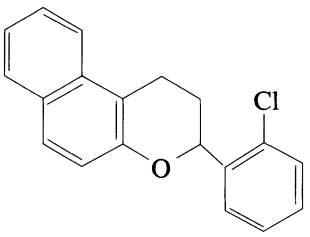

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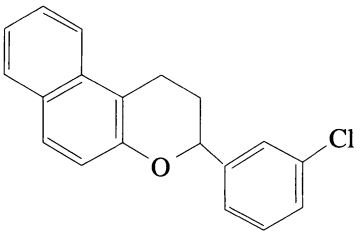

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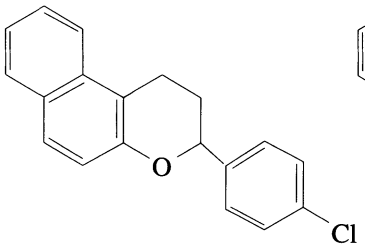

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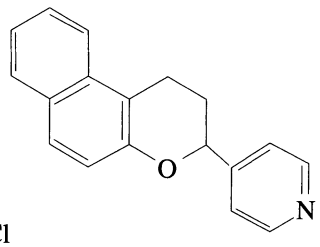

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Experimental

Mp's were determined on Electrothermal melting points apparatus. IR spectra were recorded on 1710 Perkin-Elmer Fourier Transform machine. UV spectra were recorded on PU 8720 Philips spectra. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker AMX 500 Mhz instrument. Mass spectra were recorded on VG Autospec Fisons instrument.

Merck Kieselgel F_{254} type 60 was used for tlc. Kieselgel 40-63 μm type was used for column chromatography.

2-phenyl-benzo-5,6-chroman (3)

Mannich base (1) (0.804 g, 4 mmol) and hydroquinone (20 mg) in diphenylether (20 ml) were treated with styrene (1 ml, 4 mmol) under nitrogen. This mixture was heated under nitrogen at 200 °C for 20 hours. The solvent was removed by distillation under vacuum to afford a brown oil which was chromatographed.

Elution with 50 % ethyl acetate in light petroleum afforded 2-phenyl-benzo-5,6-chroman (3) (0.416 g) (58 %) which was recrystallised from ethanol as light yellow prisms. m.p.: 85-86°C (lit. 86°C, Brugidou and Christol, 1963, 1966); (Found: C, 87.5; H, 6.2 $C_{19}H_{16}O$ requires C, 87.7; H, 6.2%); M^+: 260; IR (KBr): 1621 (aromatic), 1262 (C-O-C) cm^{-1}; UV (MeOH): 229.7, 267.3, 277.6, 289.0, 320.2 and 334.3 nm; ^{1}H-NMR ($CDCl_3$), δ: 2.29 (1H, m, J: 1.9 Hz, 3-H), 2.45 (1H, m, J: 1.9 Hz, 3-H), 3.21 (2H, m, J: 3.4 Hz, 4-H), 5.18 (1H, dd, J: 2.3 and 7.9 Hz, 2-H), 7.26-7.90 (11H, m J: 0.6 Hz, Ar-H).

2-(2′-Methylphenyl)benzo-5,6-chroman (5)

Mannich base (1) (3.216 g, 16 mmol) and hydroquinone (20 mg) in diphenylether (20 ml) were treated with 2-methylstyrene (2.1 ml, 16 mmol) under nitrogen. After being heated at 200°C for 20 hours, the solvent was removed by distillation under vacuum. A brown oil was obtained and crystallised from ethanol to give 2-(2′-methylphenyl)-benzo-5,6-chroman (5) (0.386 g) (12%). This was recrystallised from ethanol as pale white needles. m.p.: 103-104°C (Found: C, 87.1; H, 6.6 $C_{20}H_{18}O$ requires C, 87.6; H, 6.6 %); M^+: 274; IR (KBr): 1621 (aromatic), 1261 (C-O-C) cm^{-1}; UV (MeOH) : 233.5, 267.2, 277.7, 289.2 and 334.4 nm; ^{1}H-NMR ($CDCl_3$) δ: 2.21 (1H, m, J: 3.6 Hz, 3-H), 2.40 (1H, m J: 2.1 Hz, 3-H), 2.45 (3H, s, -CH_3), 3.23 (2H, m, J: 3.1 Hz, 4-H), 5.32 (1H, dd, J: 2 and 8.7 Hz, 2-H), 7.20-7.88 (10H, m, J: 5.6 Hz, Ar-H).

2-(3′-Methylphenyl)-benzo-5,6-chroman (6)

Mannich base (1) (3.216 g, 16 mmol) and hydroquinone (20 mg) in diphenylether (20 ml) were treated with 3-methylstyrene (2.1 ml, 16 mmol) under nitrogen. This mixture was heated at 200°C for 20 hours. The solvent was removed by distillation under vacuum. The residue yielded a brown oil which was crystallised from light petroleum to afford 2-(3′-methylphenyl)-benzo-5,6-chroman (6) (0.579 g) (18 %). This was recrystallised from light petroleum as pale light yellow needles. m.p.: 81-82°C; (Found: C, 87.4; H, 6.6 $C_{20}H_{18}O$ requires C, 87.6; H, 6.6 %); M^+: 274; IR (KBr): 1620 (aromatic), 1263 (C-O-C) cm^{-1}; UV (MeOH) : 210.1, 228.0, 267.2, 277.6, 320.3 and 334.4 nm; ^{1}H-NMR ($CDCl_3$) δ: 2.26 (1H, m, J: 3.2 Hz, 3-H), 2.39 (1H, m J: 2.3 Hz, 3-H), 2.46 (3H, s, -CH_3), 3.18 (2H, m, J: 4.6 Hz, 4-H), 5.11 (1H, dd, J: 2.3 and 8.2 Hz, 2-H), 7.21-7.89 (10H, m, J : 5.6 Hz, Ar-H).

2-(4′-Methylphenyl)-benzo-5,6-chroman (7)

Mannich base (1) (3.216 g, 16 mmol) and hydroquinone (20 mg) in diphenylether (20 ml) were treated with 4-methylstyrene (2.1 ml, 16 mmol) under nitrogen and heated at 200°C for 20 hours. The solvent was removed by distillation under vacuum. A brown oily residue was obtained and crystallised from ethyl acetate to give 2-(4′-methylphenyl)-benzo-5,6-chroman (7) (1.705 g) (53 %). This was recrystallised from ethyl acetate as pale light yellow prisms. m.p.: 113-114°C; (Found: C, 87.4; H, 6.6 $C_{20}H_{18}O$ requires C, 87.6; H, 6.6 %); M^+: 274, IR (KBr): 1621 (aromatic), 1263 (C-O-C) cm^{-1}; UV (MeOH): 229.9, 267.5, 278.1, 289.4, 320.4 and 334.7 nm; ^{1}H-NMR ($CDCl_3$), δ: 2.43 (1H, m, J: 4.2 Hz, 3-H), 2.54 (1H, m, J: 4.2 Hz, 3-H), 2.67 (3H, s, -CH_3), 3.32 (2H, t, J: 4.5 Hz, 4-H), 5.29 (1H, d, J: 1.3 Hz, 2-H), 7.48-8.06 (10H, m, J: 7.6 Hz, Ar-H).

2-(2′-Chlorophenyl)-benzo-5,6-chroman (8)

Mannich base (1) (3.216 g, 16 mmol) and hydroquinone (20 mg) in diphenylether (20 ml) were treated with 2-chlorostyrene (2.1 ml, 16 mmol) under nitrogen. This mixture was heated at 200°C for 20 hours and the

solvent was removed by distillation under vacuum. A brown oily residue was obtained and crystallised from methanol to afford 2-(2′-chlorophenyl)-benzo-5,6-chroman (8) (0.258 g) (8 %). This was recrystallised from methanol-chloroform as light yellow prisms. m.p.: 108-109°C; (Found: C, 77.3; H, 5.1 $C_{19}H_{15}OCl$ requires C, 77.4; H, 5.1 %); M^+ 294; IR (KBr): 1622 (aromatic), 1260 (C-O-C) cm^{-1}; UV (MeOH): 232.8, 267.2, 277.3, 288.8, 319.2 and 333.2 nm; ^{1}H-Nmr ($CDCl_3$), δ: 2.09 (1H, m, J: 2.5 Hz, 3-H), 2.58 (1H, m, J: 2.3 Hz, 3-H), 3.23 (2H, m, J: 3.9 Hz, 4-H), 5.55 (1H, dd, J: 2.3 and 8 Hz, 2-H), 7.21-7.89 (10H, m, J: 5.6 Hz, Ar-H).

2-(3′-Chlorophenyl)-benzo-5,6-chroman (9)

Mannich base (1) (3.216 g, 16 mmol) and hydroquinone (20 mg) in diphenylether (20 ml) were treated with 3-chlorostyrene (2.1 ml, 16 mmol) under nitrogen. After being heated at 200°C for 20 hours, the solvent was removed by distillation under vacuum to afford a brown oil which was crystallised from light petroleum, to give white needles of a crystalline compound identified as 2-(3′-chlorophenyl)-benzo-5,6-chroman (9) (0.644 g) (20 %). m.p.: 86°C; (Found: C, 77.4; H, 5.1 $C_{19}H_{15}OCl$ requires, C, 77.4; H, 5.1 %); M^+ 294; IR (KBr): 1620 (aromatic), 1263 (C-O-C) cm^{-1}; UV (MeOH): 202.7, 233.0, 267.2, 276.9, 320.0 and 333.6 nm; ^{1}H-NMR ($CDCl_3$), δ: 2.21 (1H, m, J: 2.4 Hz, 3-H), 2.40 (1H, m, J: 2.4 Hz, 3-H), 3.17 (2H, m, J: 3.6 Hz, 4-H), 5.09 (1H, dd, J: 2.3 and 8 Hz, 2-H), 7.31-7.92 (10H, m, J: 5.6 Hz, Ar-H).

2-(4′-Chlorophenyl)-benzo-5,6-chroman (10)

Mannich base (1) (3.216 g, 16 mmol) and hydroquinone (20 mg) in diphenylether (20 ml) were treated with 4-chlorostyrene (2 ml, 16 mmol) under nitrogen and heated at 200°C for 20 hours. The solvent was removed by distillation under vacuum. The brown oil which was obtained, was crystallised from ethyl acetate, to afford 2-(4′-chlorophenyl)-benzo-5,6-chroman (10) (1.046 g) (33 %). This was recrystallised from ethyl acetate as pale light brown prisms. m.p.: 143-144°C; (Found: C, 74.7; H, 4.9 $C_{19}H_{15}OCl$ 0.5 H_2O requires C, 75.1; H, 5.3 %); M^+: 294; IR (KBr): 1621 (aromatic, 1262 (C-O-C) cm^{-1}; UV (MeOH): 233.3, 267.3, 277.6, 289.3, 320.6 and 333.9 nm; ^{1}H-NMR ($CDCl_3$), δ: 2.20 (1H, m, J: 2.3 Hz, 3-H), 2.40 (1H, m, J: 2.3 Hz, 3-H), 3.18 (2H, m, J: 3.5 Hz, 4-H), 5.10 (1H, dd, J: 2.3 and 7.9 Hz, 2-H), 7.22-7.88 (10H, m, J: 1 Hz, Ar-H).

2-(4′-Pyridyl)-benzo-5,6-chroman (11)

Mannich base (1) (1.608 g, 8 mmol) and hydroquinone (20 mg) in diphenylether (20 ml) were treated with 4-vinylpyridine (1 ml, 8 mmol) under nitrogen. This mixture was heated at 200°C for 20 hours. The solvent was removed by distillation under vacuum to afford a brown oil which was chromatographed. Elution with 50% ethyl acetate in light petroleum, afforded 2-(4′-pyridyl)-benzo-5,6-chroman (11) (0.775 g) (48%) which was recrystallised from ethyl acetate, as light yellow prisms. m.p.: 133-135°C; (Found: C, 82.6; H, 5.8; N, 5.3 $C_{18}H_{15}NO$ requires C, 82.7; H, 5.8; N, 5.4 %); M^+: 261; IR (KBr): 1622 (aromatic), 1264 (C-O-C) cm^{-1}; UV (MeOH): 224.0, 256.9, 265.2, 277.4, 288.7, 318.7 and 332.8 nm; ^{1}H-NMR ($CDCl_3$), δ: 2.12 (1H, m, J: 4.2 Hz, 3-H), 2.38 (1H, m, J: 4.2 Hz, 3-H), 3.11 (2H, m, J: 6.5 Hz, 4-H), 5.08 (1H, d, J: 9.5 Hz, 2-H), 7.23-7,85 (8H, m, J: 7.5 Hz, Ar-H), 8,68 (2H, d, J: 4.8 Hz, Ar-H).

Results and Discussions

We aimed to investigate the effect of electron-donating substituents in the benzenoid ring of the styrene to the yield in the synthesis of substituted-benzo-5,6-chromans. Therefore, 2-naphthol Mannich base (1) was reacted with 2-methylstyrene and 2-(2′-methylphenyl)-benzo-5,6-chroman (5) was obtained in 12 % yield. It was observed that the yield of the reaction was lower than that of styrene. This could be attributed to the steric effect of the methyl group in 2-position. Under same conditions, the reaction was repeated with 3-methylstyrene and 2-(3′-methylphenyl)-benzo-5,6-chroman (6) was obtained in 18 % yield. When the reaction was carried out with 4-methylstyrene, it was found that the 2-(4′-methylphenyl)-benzo-5,6-chroman (7) was formed in 53% yield. This increase in the yield was attributed to the methyl group in 4-position of the phenyl group.

To see the effect of substitutent, we tried the reaction with 2-, 3- and 4-chlorostyrenes, the yields of the chromans were in 8, 20 and 33% respectively. Except 3-chlorostyrene, there were decreases in the yields of the chromans (8 and 10). When compared with the 2- and 4-methyl-substituted styrenes these decreases could be due to the inductive effect (-I) of the chlorine atom.

To see the effect of the heteroatom in the ring, we repeated the reaction with 4-vinylpyridine. 2-(4′-Pyridyl)-benzo-5,6-chroman (11) was obtained in 48% yield.

In all pyroysis no dimer (4) was isolated from the reaction mixture.

Acknowledgement

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