SYNTHESIS OF NOVEL 4-(DIARYLMETHYLENE)PIPERIDINES

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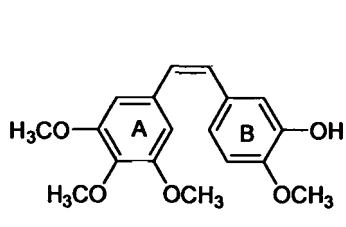
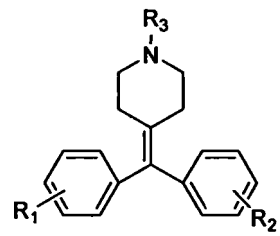
Abstract: An efficient sequence to the seven novel 4-(diarylmethylene)piperidines starting from the commercially available 1-acetylpiperidine-4-carboxylic acid is reported.

Introduction

4-(Diarylmethylene)piperidines analogues are useful as antiemetic, antihistamine, antidopamine, antiserotonin, pulmonary, antiallergy, antiinflammatory, and antispasmodic agents.[1] The potent antitumor drug combretastatin A4 (CA-4) has served as the lead molecule for a large number of vicinal and geminal diaryl heterocycles which have been studied as antitumor agents [2] SAR studies showed that the cisoid orientation of the two aryl rings is required and that



Combretastatin A4



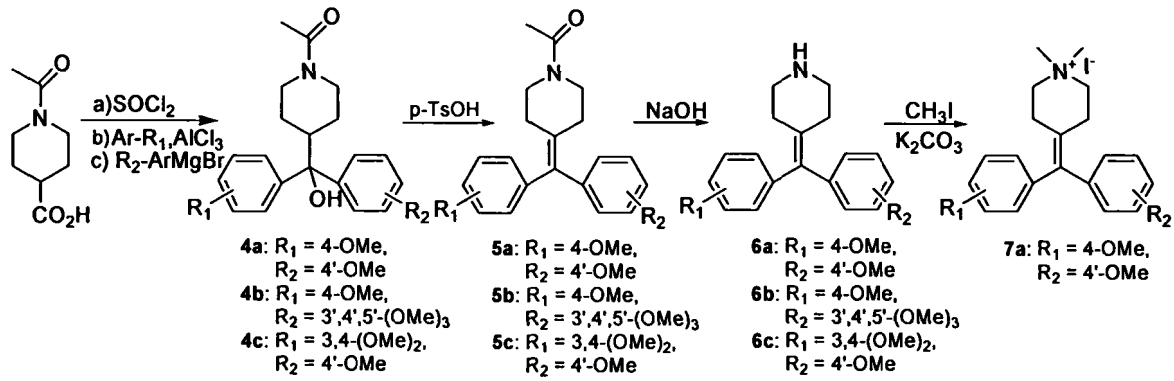
4-(diarylmethylene)piperidines

3,4,5-trimethoxy substituents on the A-ring of CA-4 are essential for potent cytotoxicity.[2f, 2h] Numerous studies have focused on synthesis of CA-4 analogues in which the linker of the two aryl units has been widely altered. Various heterocyclic rings have been extensively used as linkers. Here we report the preparation of 4-(diarylmethylene) piperidines analogues of CA-4. We have also synthesized analogues with variations on the A-ring, B-ring and with substitution on the piperidine nitrogen.

Results and Discussion

The synthetic approach employed is presented in Scheme 1. Treatment of 1-acetylpiperidine-4-carboxylic acid with thionyl chloride afforded the acid chloride **2**, which on treatment with substituted benzenes under Friedel-Crafts acylation conditions yielded 1-acetyl-4-aroylpiperidines **3**.[3] Furthermore, system **3** was easily converted into 1-acetyl-α,α-diaryl-4-piperidinemethanols **4a-4c** via addition of arylmagnesium bromide reagents in THF. Dehydration of **4a-4c** to give the 1-acetyl-4-(diarylmethylene)piperidines **5a-5c** occurred on heating at reflux in toluene in the presence of *p*-TsOH [4] The acetyl group of **5a-5c** was removed by treatment with base to give 4-(diarylmethylene) piperidines **6a-6c**.[5] Compound **6a** reacted with iodomethane to afford the 1,1-dimethylpiperidinium **7a**.[6] In conclusion, an efficient sequence to the 4-(diarylmethylene)piperidines starting from 1-acetylpiperidine-4-carboxylic acid was developed.

Scheme 1



Experimental

Melting points were recorded using a Mel-Temp 3.0 capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded employing a Bruker 400 Ultrashield™ instrument; chemical shifts (δ) are in ppm relative to internal TMS. Mass spectra were recorded on a VG analytical 70-SE spectrometer. Elemental analyses were obtained from Atlantic Microlab, Inc. (Norcross, GA).

General procedure for the preparation of 1-acetyl-α,α-diaryl-4-piperidinemethanols 4a-4c. A mixture of 1-acetylpiperidine-4-carboxylic acid (18 mmol) and $SOCl_2$ (15 ml) was stirred at rt for 2 h, petroleum ether (60 ml) was added to the mixture, stirred for 10 min, filtered, the solid was washed with petroleum ether to give 1-acetyl-4-piperidylcarbonyl chloride **2** as white solid (88%), which was used directly in the next step. A substituted benzene (70 mmol) was added dropwise to a mixture of **2** (15 mmol) and $AlCl_3$ (35 mmol) in dry 1,2-dichloroethane (5 ml) cooled in an ice bath. The reaction mixture was heated at reflux for 2.5 h, cooled, and poured onto ice-water. After stirring for 30 min, the mixture was extracted (CH_2Cl_2), the organic layer washed with brine, dried (Na_2SO_4), filtered and evaporated. Ethyl ether (5 ml) was then added to the residue, filtered and washed with hexane to give the 1-acetyl-4-aroylpiperidines **3** as white solid, which were used directly in the next step. A 0.5 M solution of Grignard reagent (24 ml, 12 mmol) was added dropwise to a solution of **3** (10 mmol) in anhydrous THF (12 ml) at 0°C. After addition was complete, the solution was stirred at rt for 2 h. A saturated NH_4Cl solution (20 ml) was slowly added to the reaction mixture at 0°C and followed by Et_2O, the phases were separated, and the aqueous layer was extracted with Et_2O (20 ml× 3). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel to furnish target compounds **4a-4c**.

1-Acetyl-α,α-di(4-methoxyphenyl)-4-piperidinemethanol (4a): White solid , 66% yield, m.p. 169-170 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (m, 3H), 1.62 (t, J = 14 Hz, 2H), 2.05 (S, 3H), 2.13 (s, 1H), 2.55 (t, J = 13.2 Hz, 2H), 3.06 (t, J = 13.2 Hz, 1H), 3.80 (s, 6H), 4.68 (d, J = 11.6 Hz, 1H), 6.86 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 4H), 7.36 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.4, 26.4, 27.2, 41.9, 44.6, 46.8, 55.2, 79.0, 113.5, 127.1, 127.2, 137.9, 138.0, 158.2, 158.3, 168.8; MS: (ESI, M^++1) 370.2.

1-Acetyl-α-(4-methoxyphenyl)- α-(3,4,5-trimethoxyphenyl)-4-piperidinemethanol (4b): White solid , 70% yield, m.p. 150-152 ℃; ^{1}H NMR ($CDCl_3$) δ 1.32 (m, 3H), 1.60 (m, 2H), 2.07 (s, 3H), 2.16 (d, J = 7.2 Hz, 1H), 2.54 (t, J = 12.0 Hz, 2H), 3.05 (t, J = 12.0 Hz, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 3.84 (s, 6H), 4.70 (d, J = 13.2 Hz, 1H), 6.67 (s, 2H), 6.88 (dd, J_1 = 3.6 Hz, J_2 = 8.8 Hz, 2H), 7.41 (dd, J_1 = 3.6 Hz, J_2 = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.1, 26.4, 27.2, 41.9, 44.8, 46.8, 55.2, 56.4, 60.7, 79.3, 104.1, 104.3, 113.7, 127.0, 137.7, 141.5, 153.0, 158.5, 168.6; MS: (ESI, M^++1) 430.2.

1-Acetyl-α-(4-methoxyphenyl)- α-(3,4-dimethoxyphenyl)-4-piperidinemethanol (4c): White solid , 72% yield, m.p. 124-126 ℃; ^{1}H NMR ($CDCl_3$) δ 1.29 (m, 3H), 1.64 (m, 2H), 2.05 (s, 1H), 2.07 (s, 3H), 2.55 (t, J = 12.8 Hz, 2H), 3.07 (t, J = 12.8 Hz, 1H), 3.81 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.70 (d, J = 12.4 Hz, 1H), 6.82 (dd, J_1 = 4.8 Hz, J_2 = 8.4 Hz, 1H), 6.87 (dd, J_1 = 3.6 Hz, J_2 = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 4.8 Hz, 1H), 7.38 (dd, J_1 = 3.6 Hz, J_2 = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 26.5, 27.3, 30.6, 41.9, 44.8, 46.8, 55.2, 55.9, 56.1, 79.1, 110.5, 111.2, 113.6, 118.3, 127.1, 138.0, 148.0, 149.0, 158.4, 168.6; MS: (ESI, M^++1) 400.2.

General procedure for the preparation of 1-acetyl-4-(diarylmethylene)piperidines 5a-5c. One of **4a-4c** (6 mmol) and *p*-TsOH (0.3 mmol) in toluene (60 ml) was heated at 130℃ using a Dean-Stark trap to remove water. After the reaction was finished, saturated $NaHCO_3$ was added and the solvent was evaporated. Ethyl acetate (30 ml) was added to the residue, washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to furnish target compounds **5a-5c.**

1-Acetyl-4-(di-4-methoxyphenyl)methylenepiperidine (5a): Viscous oil, 80% yield; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.41 (m, 4H), 3.48 (t, J = 6.8 Hz, 2H), 3.64 (t, J = 6.8 Hz, 2H), 3.81 (s, 6H), 6.85 (d, J = 8.0 Hz, 4H), 7.03 (d, J = 8.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.6, 31.2, 32.2, 43.0, 47.6, 55.2, 113.5, 130.8, 132.3, 134.6, 134.8, 137.0, 158.3, 169.0; Anal. Calcd. for $C_{22}H_{25}NO_3 \cdot 0.2H_2O$: C, 74.42; H, 7.21; N, 3.95. Found: C, 74.47; H, 7.12; N, 3.93; MS: (ESI, M^++1) 352.1.

1-Acetyl-4-[(4-methoxyphenyl)(3,4,5-trimethoxyphenyl)]methylenepiperidine (5b): White solid , 85% yield, m.p. 86-88 ℃; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H), 2.41 (m, 4H), 3.49 (m, 2H), 3.66 (t, J = 5.6 Hz, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 6.32 (s, 2H), 6.87 (d, J= 8.4 Hz, 2H), 7.07 (d, J= 8.4 Hz, 2H); ^{13}C NMR (DMSO-d_6, 80℃) δ 21.4, 31.8, 55.7, 56.9, 60.5, 108.4, 114.3, 130.7, 133.8, 134.6, 136.9, 137.9, 138.2, 153.3, 158.6, 168.7; Anal. Calcd. for $C_{24}H_{29}NO_5 \cdot 0.8H_2O$: C, 67.68; H, 7.24; N, 3.29. Found: C, 67.86; H, 7.47; N, 3.01; MS: (ESI, M^++1) 412.1.

1-Acetyl-4-[(4-methoxyphenyl)(3,4-dimethoxyphenyl)]methylenepiperidine (5c): White solid , 83% yield, m.p. 61-63 ℃; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H), 2.41 (m, 4H), 3.49 (m, 2H), 3.65 (t, J = 5.6 Hz, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 6.61 (s, 1H), 6.69 (d, J= 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 7.05 (d, J= 8.4 Hz, 2H);); ^{13}C NMR (DMSO-d_6, 80℃) δ 21.4, 31.7, 55.7, 56.6, 56.7, 113.5, 114.3, 115.1, 122.5, 130.7, 133.4, 135.0, 135.9, 136.7, 148.7, 149.5, 158.6, 168.7; Anal. Calcd. for $C_{23}H_{27}NO_4 \cdot 0.3H_2O$: C, 71.39; H, 7.20; N, 3.62. Found: C, 71.37; H, 7.50; N, 3.71; MS: (ESI, M^++1) 382.2.

General procedure for the preparation of 4-(diarylmethylene)piperidines 6a-6c. One of **5a-5c** (6 mmol) in 6N NaOH (7.5 ml) and EtOH (18 ml) was heated at reflux for 8 h. The solution was diluted with water (40 ml), extracted with CH_2Cl_2 (30 ml), organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Recrystallization from Et_2O/ hexane gave **6a, 6c** as white solid. As for **6b**, the residue was dissolved in acetone (3 ml), conc. HCl (1 ml) was added and stirred for 30 min, the mixture was filtered, the solid was washed with ethyl ether to give **6b.**

4-[Bis(4-methoxyphenyl)methylene]piperidine (6a): White solid , 73% yield, m.p. 123-124 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (t, J = 5.6 Hz, 4H), 2.92 (t, J = 5.6 Hz, 4H), 3.81 (s, 6H), 6.84 (dd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, 4H), 7.04 (dd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 33.5, 48.6, 55.2, 113.3, 130.9, 134.9, 135.0, 135.3, 158.0; Anal. Calcd. for $C_{20}H_{23}NO_2 \cdot 0.3H_2O$: C, 76.31; H, 7.56; N, 4.45. Found: C, 74.26; H, 7.50; N, 4.38; MS: (ESI, M^++1) 310.2.

4-[(4-Methoxyphenyl)(3,4,5-trimethoxyphenyl)methylene]piperidine hydrochloride (6b): White solid , 70% yield, m.p. 261-262 °C; ^{1}H NMR ($CDCl_3$) δ 2.74 (t, J = 5.6 Hz, 4H), 3.24 (t, J = 5.6 Hz, 4H), 3.80 (s, 6H), 3.82 (s, 3H), 3.86 (s, 3H), 6.28 (s, 2H), 6.87 (dd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, 2H), 7.03 (dd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, 2H), 9.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.5, 45.2, 55.2, 56.2, 60.9, 106.3, 113.8, 128.1, 130.3, 133.0, 136.9, 137.1, 139.7, 153.1, 158.7; Anal. Calcd. for $C_{22}H_{27}NO_4 \cdot HCl$: C, 65.10; H, 6.95; N, 3.45. Found: C, 64.95; H, 6.87; N, 3.40; MS: (ESI, M^++1) 370.2.

4-[(3,4-Dimethoxyphenyl)(4-methoxyphenyl)methylene]piperidine (6c): oil , 68% yield; ^{1}H NMR ($CDCl_3$) δ 2.36 (t, J = 4.8 Hz, 4H), 2.93 (t, J = 4.8 Hz, 4H), 3.82 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 6.63 (d, J = 1.2 Hz, 1H), 6.69 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 33.6, 33.7, 48.6, 55.2, 55.8, 110.7, 113.2, 113.3, 122.1, 130.8, 135.0, 135.1, 135.2, 135.6, 147.5, 148.4, 158.0; Anal. Calcd. for $C_{21}H_{25}NO_3 \cdot 0.7H_2O$: C, 71.63; H, 7.56; N, 3.97. Found: C, 71.23; H, 7.17; N, 3.57; MS: (ESI, M^++1) 340.2.

Procedure for the preparation of 4-[di(4-methoxyphenyl)methylene]-1,1-dimethylpiperidinium iodide 7a. A solution of **6a** (1 mmol), CH_3I (1 mmol) and K_2CO_3 (1.03 mmol) in DMF (9 mL) was stirred for 5 h. The mixture was filtered and the solid was washed with Et_2O. The solid was dissolved in EtOH, filtered and the solvent was evaporated, ethyl ether (5 ml) was added to the residue and filtered to give **7a** in 80% yield. White solid , m.p. 172-174 °C; ^{1}H NMR (DMSO-d_6) δ 2.61 (t, J = 5.6 Hz, 4H), 3.17 (s, 6H), 3.44 (t, J = 5.6 Hz, 4H), 3.77 (s, 6H), 6.92 (d, J = 8.4 Hz, 4H), 7.05 (d, J = 8.4 Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 26.0, 51.2, 55.4, 55.6, 62.3, 114.2, 127.3, 131.0, 134.0, 138.0, 158.6; Anal. Calcd. for $C_{22}H_{28}INO_2 \cdot 0.9H_2O$: C, 54.87; H, 6.24; N, 2.91. Found: C, 54.68; H, 5.86; N, 2.88; MS: (ESI, M-HI+1) 338.2.

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