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SYNTHESIS OF 2-(3-INDOLYL)-4-METHYLENEPIPERIDINES VIA INTRAMOLECULAR CYCLIZATION OF ALLYLSILANES

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Abstract: The synthesis of 2-(3-indolyl)-4-methylenepiperidines using an efficient formation of the piperidine ring by intramolecular reaction between an allylsilane group and an iminium ion is reported.

The synthesis of protected 2-aryl-4-piperidones by an intramolecular Mannich type cyclization of iminoacetals has been studied extensively in the last decade[1-3] as has their application as intermediates to the synthesis of polycyclic compounds with potential therapeutical activity[4-6]. In previous work, we have prepared 2-aryl-4-methylenepiperidines from the corresponding 2-aryl-4-piperidones[7-8]; however, the direct synthesis of methylenepiperidines has been recently described using allylsilanes[9-13] and vinylsilanes[14].

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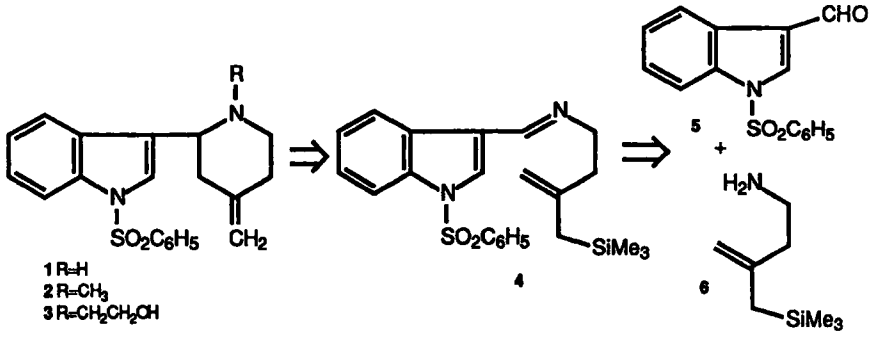
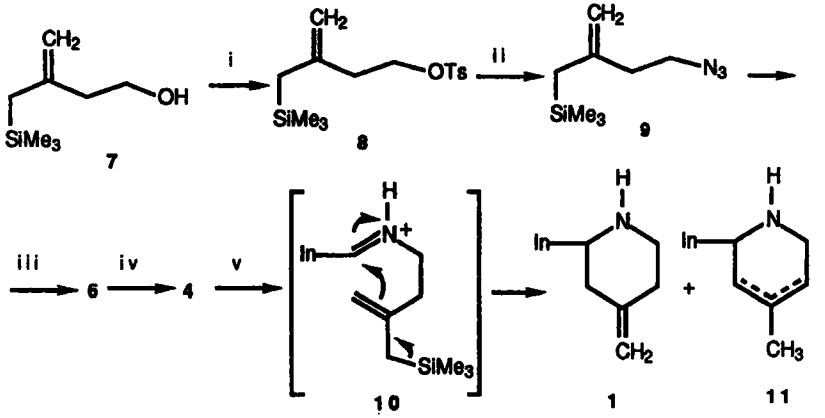


Scheme 1

In the present paper we describe the usefulness of amino allylsilane **6** and an aromatic aldehyde (*i.e.* **5**) condensation, and the subsequent acid catalyzed intramolecular cyclization of the resulting imine **4** to obtain 2-(3-indolyl)-4-methylenepiperidine **1**.

Amino allylsilane **6**, required as the key compound, was prepared from alcohol **7**[15,16] by initial tosylation, transformation into azide **9** by treatment with sodium azide in DMF, and final reduction[17] with Ph_3P in THF.

Condensation between 1-(phenylsulfonyl)indole-3-carbaldehyde (**5**)[18] and amino allylsilane **6** in dry benzene afforded imine **4** which was cyclized with dry *p*-TsOH without any purification[19]. The cyclization process led to the expected 4-methylenepiperidine **1** as the major product (51% yield), accompanied by tetrahydropyridines **11** (10%), resulting from the double bond isomerization in the acid reaction conditions. Thus, the ^{1}H-NMR spectrum of **1** showed a broad signal at δ 4.78 and a doublet of doublets (J=12 and 3 Hz) at δ 3.92, characteristic of the olefinic protons and the angular 2-H proton, respectively, while the



Reagents and conditions: (i) TsCl, pyridine, 0°C overnight. (ii) NaN_3, DMF, r.t., 24 h. (iii) Ph_3P, H_2O THF, r.t. 6 h., (iv) 1-(phenylsulfonyl)-indole-3-carbaldehyde, dry benzene, 30 min at 0°C, 45 min. at r.t., Δ, 4 h, and Dean-Stark overnight. (v) dry *p*-TsOH, benzene, Δ, 2 h.

Scheme 2

trimethylsilyl (δ 0.00) and the imine (δ 8.44) signals had disappeared. The ^{13}C-NMR spectrum showed characteristic signals for C-2 at δ 54.7, and for the methylenic and quaternary olefinic carbons at δ 109.1 and 144.0, respectively. For tetrahydropyridines **11**, the most significant ^{1}H-NMR signals corresponded to 2-H (δ 4.10 for the Δ^4-piperideine **11a** and 4.70 for its Δ^3-isomer **11b**) and the olefinic 5-H (δ 5.45) in **11a** or 3-H (δ 5.20) in **11b**, as well as a singlet at δ1.70 due to the methyl group on C-4, which was observed at δ 23.1 in its ^{13}C-NMR spectrum. It is worth mentionning that in some cases the obtention of compounds resulting from the desilylation or from the hydrolysis of the intermediate iminium ion has been described[20], which we have not observed.

Further alkylation of piperidine **1** was accomplished by treatment with methyl iodide in dry acetone or 2-bromoethanol in ethanol, both in

the presence of anhydrous K_2CO_3, yielding piperidines 2 and 3, respectively, in moderate yields.

We have thus shown that *p*-TsOH induced intramolecular cyclization is an efficient method to prepare 2-aryl-4-methylene-piperidines, and we also report a new route to amino allylsilane 6[11] in three steps from alcohol 7 and 65% overall yield.

Experimental

General. ^1H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-200 spectrometer using TMS as internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS. IR spectra were registered with a Perkin-Elmer 1430 spectrophotometer. Tlc was carried out on SiO_2 (silica gel 60, Merck 0.0063-0.200 mm), and the spots were located with UV light or iodoplatinate reagent. Microanalyses were performed on a Carlo-Erba 1106 analyzer by Departament de Química Orgànica Biològica, Barcelona.

4-Amino-2-(trimethylsilylmethyl)butene (6). A solution of alcohol 7 (2.3 g, 14.5 mmol), tosyl chloride (3 g, 15.9 mmol) and pyridine (35 ml) was stirred at 0°C overnight. The mixture was poured into ice and aqueous $NaHCO_3$ and the resulting solution was extracted with CH_2Cl_2. The extract was dried and evaporated to give tosylate 8 (4.2 g, 93%) which was rapidly used without purification in the next step.

A mixture of tosylate 8 (4.2 g, 13.5 mmol) and sodium azide (7 g, 107.7 mmol) in DMF was stirred at room temperature for 24 h. The solvent was evaporated in vacuo and the residue was partitioned between Et_2O/CH_2Cl_2 (3:1) and H_2O. The aqueous layer was extracted

with Et_2O/CH_2Cl_2 and the combined organic extracts were washed with aqueous Na_2HPO_4 and dried. Removal of the solvent afforded crude **9** which was purified by flash chromatography (hexane-ethyl acetate 95:5) to give pure azide **9** (1,2 g, 50 %): IR (CCl_4) 2096 cm^{-1}; ^1H-NMR 1.55 (s, 2H,$SiCH_2$), 2.22 (t, J=7 Hz, 2H, $=CCH_2$), 3.40 (t, J=7 Hz, 2H, NCH_2), 4.70 (m, 2H, $=CH_2$).

To a solution of azide **9** (1.2 g, 6.55 mmol) in THF (50 ml), Ph_3P (1.7 g, 6.55 mmol) was added and the mixture stirred at room temperature for 6 h. Then H_2O (1.5 eq) was added and the solution stirred at room temperature overnight. The solvent was distilled and the residue taken up in ether/petroleum ether (1:1). After filtration and careful distillation of the solvents amino allylsilane **6** (bp 110°C/4 mm; 0.8 g, 80%) was obtained; IR (CCl_4) 1635 cm^{-1}; ^1H-NMR 0.00 (s, 9H, $SiCH_3$), 1.51 (s, 2H, $SiCH_2$), 1.68 (s, 2H, NH_2), 2.12 (t, J=7 Hz, 2H, $=CCH_2$), 2.81 (t, J=7 Hz, 2H, NCH_2), 4.60 (AB system, J_{AB}=8 Hz, $\Delta\nu$=39 Hz, 2H, $=CH_2$); ^{13}C-NMR -0.8 ($SiCH_3$), 28.6 ($SiCH_2$), 39.6 ($NCH_2\underline{C}H_2$), 60.0 (NCH_2), 108.6 ($=CH_2$), 143.8 (=C).

2-[1-(Phenylsulfonyl)-3-indolyl]-4-methylenepiperidine(**1**).A solution of amine **6** (0.5 g, 3.22 mmol) and aldehyde **5** (1.01g, 3.54 mmol) in dry C_6H_6 (100 ml) was stirred at 0°C for 30 min, at room temperature for 45 min, and under reflux for 2.5 h. After 16 h of additional refluxing with removal of water by a Dean-Stark trap, the solvent was evaporated to give imine **4** (1.32 g, 86%): IR (NaCl) 1680, 1650 cm^{-1}; ^1H-NMR 0.05 (s, 9H, $SiCH_3$), 1.60 (s, 2H, $SiCH_2$), 2.37 (t, J=7 Hz, 2H, $=CCH_2$), 3.74 (t, J=7 Hz, 2H, $=NCH_2$), 4.61 and 4.69 (2 apparent s, 1H each, $=CH_2$), 7.20-8.30 (m, 10H, ArH), 8.44 (s, 1H, N=CH); ^{13}C-NMR -1.7 ($SiCH_3$), 26.8 ($SiCH_2$), 39.4

(=C<u>C</u>H_2), 60.8 (=N<u>C</u>H_2), 108.2 (In-C3), 113.1 (In-C7), 123.1 (In-C4), 124.1 (In-C5), 125.7 (In-C6), 126.7 (Ar-<u>ortho</u>), 128.3 (In-C3a), 129.3 (Ar-<u>meta</u>), 134.1 (Ar-<u>para</u>), 136.9 and 138.0 (In-C7a and Ar-<u>ipso</u>), 145.0 (In-C2), 153.9 (N=CH); CIMS (relative intensity) 425 (M^++1, 10), 353 (3), 285 (15), 232 (9), 178 (11), 136 (41), 134 (49), 69 (100).

A stirred mixture of the imino allylsilane 4 (749 mg, 1.76 mmol) and anhydrous *p*-TsOH (362 mg, 2.1 mmol) in dry C_6H_6 (100 ml) was refluxed under N_2 for 2h 30min. The cooled mixture was washed with aqueous Na_2CO_3 and extracted with CH_2Cl_2. The extract was dried and evaporated to give 4-methylenepiperidine 1 (315 mg, 51%) and a mixture of tetrahydropyridines 11 (62 mg, 10%) after flash chromatography (95:5 CH_2Cl_2-CH_3OH).

1 (Higher Rf): ^{1}H-NMR 2.10-2.40 (m, 4H, 3-Hax, 5-H and NH), 2.59 (dd, <u>J</u>=12 and 3 Hz, 1H, 3-Heq), 2.80 (ddd, <u>J</u>=13, 9 and 5.6 Hz, 1H, 6-Hax), 3.26 (dt, <u>J</u>=13 and 4 Hz, 1H, 6-Heq), 3.92 (dd, <u>J</u>=12 and 3 Hz, 1H, 2-Hax), 4.78 (s, 2H, =CH2), 7.15-7.60 (m, 8H, ArH), 7.80 (d, <u>J</u>=7 Hz, 1H, ArH), 7.91 (d, <u>J</u>=7 Hz, 1H, ArH); ^{13}C-NMR 35.0 (C-5), 42.2 (C-3), 47.7 (C-6), 54.7 (C-2), 109.1 (=CH_2), 113.9 (In-C7), 120.2 (In-C5), 122.4 (In-C4), 123.3 (In-C6), 125.0 (In-C2), 127.0 (Ar-<u>ortho</u>), 129.5 (Ar-<u>meta</u>), 134.0 (Ar-<u>para</u>), 137.0 and 138.0 (In-C7a and Ar-ipso), 144.0 (=C); CIMS (relative intensity) 370 (M^++18, 4), 353 (M^++1, 12), 299 (1), 209 (8), 181 (8), 163 (29), 137 (18), 69 (100). Anal. Calcd for $C_{20}H_{20}N_2O_2S$.3/4 H_2O: C, 65.66; H, 5.88; N, 7.66. Found: C, 66.05; H, 6.19; N, 7.42. The hydrochloride melted at 204-205°C (acetone).

11a (major isomer, Δ^4-piperideine) ^{1}H-NMR 1.70 (br s, 3H, =CCH_3), 2.20 (br, 1H, NH), 3.30 and 3.50 (2d, J_{AB}=16 Hz, 1H each, NCH_2), 4.10 (t, <u>J</u>=8 Hz, 1H, NCH), 5.45 (br s, 1H, =CH), 7.00-8.00 (m, 10H, ArH); ^{13}C-NMR 23.1

(CH_3), 36.8 (C-3), 45.2 (NCH_2), 49.6 (NCH), 113.8 (In-C7), 119.9 (=CH), 120.1 (In-C4), 122.3 (=C), 123.3 (In-C5), 124.9 (In-C6), 126.9 (Ar-ortho), 129.4 (Ar-meta), 133.9 (Ar-para), 137.0 and 138.0 (In-C7a and In-C3a).

2-[1-(Phenylsulfonyl)-3-indolyl]-4-methylene-1-methylpiperidine (2). To a solution of piperidine 1 (22 mg, 0.06 mmol) in dry acetone (5 ml), was added anhydrous K_2CO_3 (60 mg) and methyl iodide (4 µl, 0.06 mmol), under N_2 atmosphere. The mixture was stirred at room temperature for 2 h, filtered, and the solvent was evaporated to yield piperidine 2 (9 mg, 40%), after flash chromatography (95:5 CH_2Cl_2-MeOH). ^{1}H-NMR 2.01 s (NCH_3), 2.20-2.30 (m, 2H, 5-H), 2.45-2.55 (m, 2H, 3-H), 3.00-3.10 (m, 2H, 6H), 4.15 and 4.21 (2 apparent s, 1H each, =CH2), 7.20-7.60 (m, Ar-H), 7.80-8.00 (m, Ar-H); ^{13}C-NMR 34.0 (C-5), 41.9 (C-3), 43.5 (NCH_3), 57.4 (C-6), 63.0 (C-2), 108.9 (=CH_2), 113.9 (In-C7), 121.0 (In-C5), 122.5 (In-C4), 123.4 (In-C6), 125.1 (In-C2), 127.0 (Ar-ortho), 129.5 (Ar-metha), 134.0 (Ar-para), 146.6 (C-4). Anal. Calcd for $C_{21}H_{22}N_2O_2S$: C, 68.80; H, 6.00; N, 7.64. Found: C, 68.95; H, 6.09; N, 7.84.

2-[1-(Phenylsulfonyl)-3-indolyl]-4-methylene-1-(2-hydroxymethyl)-piperidine (3). 2-Bromoethanol (0.06 ml, 0.88 mmol) was added to a mixture of piperidine 1 (155 mg, 0.44 mmol) and anhydrous K_2CO_3 (200 mg) in absolute ethanol (25 ml). The resulting mixture was refluxed under N_2 for 15 h. The cooled mixture was filtered, the EtOH evaporated, and the residue, dissolved in CH_2Cl_2 was washed with water. The organic extracts were dried and evaporated to give piperidine 3 (75 mg, 43%) after flash chromatography (Al_2O_3, CH_2Cl_2-CH_3OH 95:5); IR ($CHCl_3$) 3100-3400 (OH) cm^{-1}; ^{1}H-NMR 2.10-2.50 (m, 5H), 2.55-2.70 (m, 2H, NCH_2), 3.15-

3.30 (m, 2H, CH_2OH), 3.65 (dd, J=11 and 4 Hz, 1H, 2-Hax), 4.75 (AB system, 2H, $=CH_2$), 7.00-8.00 (m, 10H, ArH); ^{13}C-NMR 33.9 (C-5), 41.2 (C-3), 52.3 (C-6), 54.8 (NCH_2), 58.2 (C-2), 60.5 (CH_2OH), 109.0 (=CH), 114.2 (In-C7), 120.3 (In-C5), 123.7 (In-C4), 124.4 (In-C6), 125.3 (In-C2), 127.0 (Ar-ortho), 129.5 (Ar-meta), 134.0 (Ar-para), 135.4 and 137.7 (In-C3a and In-C7a), 144.8 (=C). Anal. Calcd for $C_{22}H_{24}N_2O_3S.1/2H_2O$: C, 65.18; H, 6.17; N, 6.91. Found: C, 65.17; H, 6.10; N, 6.53.

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