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SYNTHESIS OF NEW SPIRO-*N*-HETEROCYCLES WITH CYCLO-OCTANE FRAGMENT FROM *N*-(1-ALKENYLCYCLOOCTYL)-*N*-ARYL(BENZYL) AMINES

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Abstract – The homoallylic amines (**6**-**10**) derived from *N*-cyclooctylidenearyl (benzyl)amines and allyl- or prenylmagnesium bromides as organometallic reagents have been used for synthesis of spiro-*N*-heterocycles. The tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclooctanes] (**11** and **12**) have been obtained from the homoallylamines (**6** and **7**) under acidic conditions. The tetrahydro-1-benzazepine (**15**) spiroannulated with a cyclooctane moiety has been prepared by treating the homoallylic amine (**9**) with conc. sulfuric acid. Treatment of the homoallylmine (**6**) with 92% sulfuric acid in chloroform at reflux afforded tetrahydrospiro[1,2,3-oxathiazine-2,2-dioxide-4,1'-cyclooctane] (**17**). The latter has been converted into 1-benzyl-4-methylspiro[azetidine-2,1'-cyclooctane] (**18**). The homoallylamine (**6**) has been cyclized into the 1-benzylspiro[pyrrolidine-2,1'-cyclooctane] (**19**).

INTRODUCTION

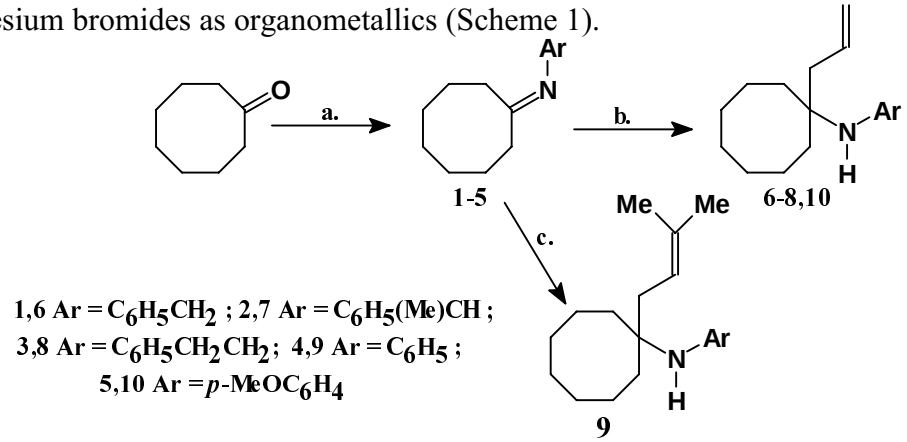
Substituted benzazepines and five- or four-membered ring *N*-heterocycles have attracted the attention of synthetic organic chemists for many years. Among the reasons for the interest in these heterocycles, the two more important are the following: *i*) isolated pyrrolidines and 1-, 2-, 3-benzazepine rings are contained in many molecules of natural origin, especially alkaloids,[1-3] *ii*) a big number of synthetic substituted pyrrolidines[4] and azetidines[5] or benzazepines[6] (included spiroannulated derivatives) possess significant biological activity, ranging from effective antidepressants[7] or neuroexcitory[8] agents for pyrrolidines to anticonvulsant, antiarrhythmic, anti-inflammatory and analgesic properties for several 1-, 2- and 3-benzazepines.[9] Consequently, the development of general methods for the synthesis of these heterocycles has been an active field of research.[10-12] The cyclization process is an attractive entry for ring

construction of these heterocycles, however, there are few examples where the same starting materials are used both in benzazepine and pyrrolidine or azetidine ring formation. We consider that homoallylic amines, readily available from the corresponding imines and allylorganometalic reagents, could be very suitable for forming nitrogen-containing saturated heterocycles. To our knowledge, the synthetic potential of such homoallylamines has not been explored. On the other hand, growing families of cyclooctane-containing natural products have been isolated. These products extracted from the basidiomycetes *Pleurotus mutilus*,[13] the red seaweed *Laurencia Poitei*[14]or the soft coral *Capnella imbricata*[15] and the plant *Steganotaenia araliacea*,[16] show interesting biological activities. Nevertheless, the cyclooctanes spiroannulated with nitrogen-containing heterocycles are still unknown in nature. Our motive in undertaking this work is the hope that the combination of such heterocycles as 1-benzazepine (2-benzazepine) or pyrrolidine and azetidine with a cyclooctane ring *via* spirocarbon atom may modify or even improve the biological potency of this class of compounds. As part of our research program on the chemistry of homoallylamines, we wish to report here a useful transformation of *N*-(1-alkenylcyclooctyl)anilines(benzylamines) (homoallylamines) into new spiro-*N*-heterocycles.

RESULTS AND DISCUSSION

In the organometallic field, the addition of allylmetal compounds to ald- or ketimines to give homoallylic amines is of particular interest, due to the many possible transformations of the C=C double bond of the allyl group. Thus, diastereoselective and enantioselective addition of allylmetal derivatives to aldimines have received many attention recently.[17-19] However, the ketimines have not been studied systematically in this reaction and the products obtained have not been used for heterocycle synthesis. To fill this gap, in this work, the *N*-cyclooctylidenearyl(benzyl)imines (**1-5**) readily available from cyclooctanone and the corresponding primary amines were taken as basic precursors. These imines were transformed into the corresponding homoallylic amines (**6-10**) through addition of the Grignard reagent using allyl- and prenylmagnesium bromides as organometallics (Scheme 1).

Scheme 1



Conditions: **a.** $ArNH_2$/ C_6H_6, Δ; **b.** $BrMgCH_2CH=CH_2/Et_2O$;
c. $BrMgCH_2CH=CMe_2/Et_2O$.

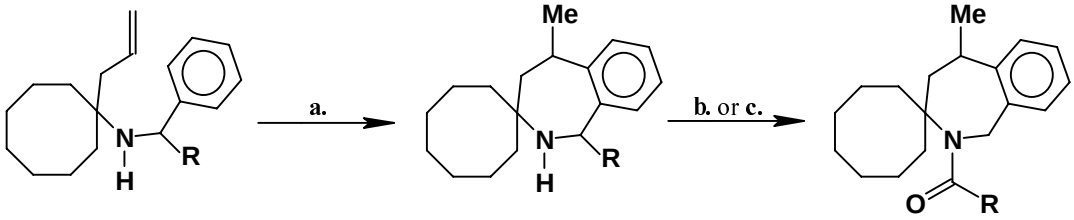
We performed this nucleophilic addition in ether at 20 °C. After stirring for 4 h the reaction mixture was treated with saturated NH_4Cl solution, the organic products were extracted and then distilled at reduced pressure affording the *N*-(1-alkenylcyclooctyl)-*N*-aryl(benzyl)amines (**6**-**10**) in 40 - 70% yields.

These homoallylic amines, possessing an π-electron rich aromatic ring, a basic nitrogen atom and an allyl (electrophilic C_3 synthon) or prenyl (electrophilic C_4 synthon) fragments, represent versatile starting materials that can afford different heterocycles.

Cyclization on the aromatic ring.

The synthesis of partially hydrogenated 1- or 2-benzazepine derivatives is an important step in the conception of more complex benzazepine compounds or natural products. As a continuation of our studies on functionalized benzazepines,[20,21] we synthesized 1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclooctanes] (**11** and **12**) from the homoallylamines (**6** and **7**) under acidic conditions (Scheme 2). This cationic cyclization of **6** and **7** was achieved through heating at 95 °C for 3 h in 92% sulfuric acid and can be considered as a *7-exo-trig* process where an allyl group acts as an internal electrophilic C_3 synthon. Compounds (**11**,**12**) were isolated by column chromatography as pale yellow oils in 52 and 42% yields, respectively. The tetrahydro-2-benzazepine (**11**) has been obtained previously.[22] According to the ^{1}H NMR and GC-MS spectra, the cyclization of **7** affords a mixture of the two geometric isomers (*cis-trans* : 1-Me/5-Me) of the tetrahydro-2-benzazepine (**12**), as we have demonstrated in a series of 1,5-dimethyl-1,2,3,4-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclohexanes].[20]

Scheme 2



6,7 **11 R = H; 12 R = Me** **13R = H; 14 R = Me**

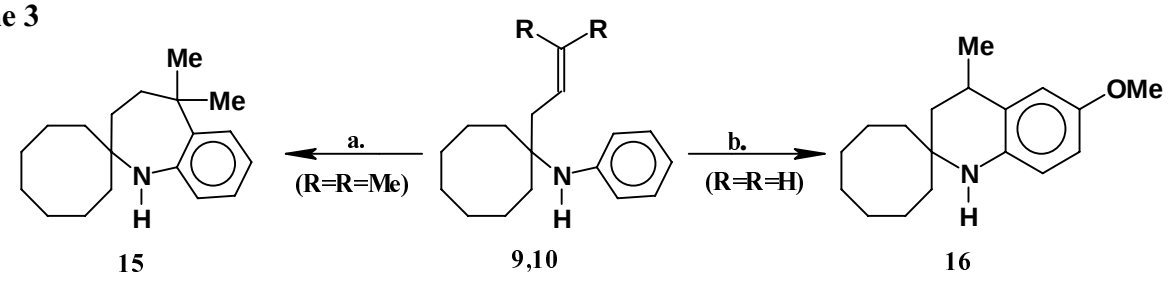
Conditions: **a.** 92% H_2SO_4, 95 °C, 3 h; **b.** HCOOH/Ac_2O/Py, 0 °C, 4 h; **c.** Ac_2O/Et_3N, Δ, 6 h.

Formylation of **11** was performed with acetic formic anhydride prepared *in situ* from acetic anhydride and formic acid in the presence of pyridine to give **13**. The amide (**14**) was prepared by refluxing compound (**11**) in acetic anhydride with catalytic amounts of Et_3N.

The tetrahydro-1-benzazepine (**15**) spiroannulated with a cyclooctane moiety was obtained by treating the homoallylic amine (**9**) with conc. sulfuric acid at 80 °C for 3 h (Scheme 3). Although, the Friedel-Crafts intramolecular acylation proved to be of less value in the synthesis of tetrahydro-1-benzazepines,[5] we suppose that in this case the cyclization occurs through a more stable tertiary carbocation (C_4 synthon)

formed from the prenyl fragment that leads to 1-benzazepine ring formation *via* a *7-endo-trig* process as an electrophilic Friedel-Crafts intramolecular alkylation. Compound (**15**) was purified by column chromatography and isolated in 62% yield.

Scheme 3



Conditions: **a.** conc. H_2SO_4, 80 ^oC, 3 h; **b.** conc. H_2SO_4, 70 ^oC, 2.5 h.

Moreover, using homoallylamine (**10**) as a starting material in the same manner (conc. sulfuric acid, 70 ^oC, 2.5 h) we obtained the 3,4-dihydrospiro[1*H*-quinoline-2,1'-cyclooctane] (**16**) in 72% yield (S cheme 3). In this case, *6-exo-trig* cyclization leads to quinoline derivatives.[23]

Cyclization on the nitrogen atom.

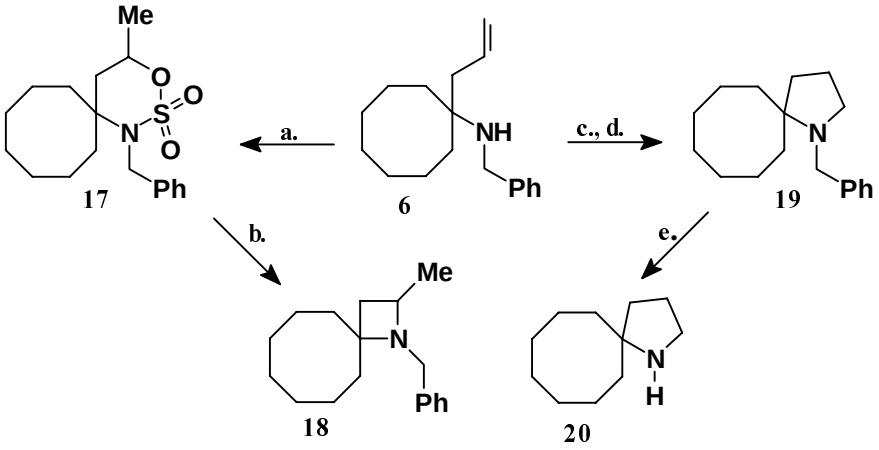
This type of cyclization could be achieved through radicals.[24,25] In contrast, cationic cyclization of an allyl group on a nitrogen atom has been less explored.[26,27] Treatment of the homoallylmine (**6**) with 92% sulfuric acid in chloroform at reflux for 7 h afforded **17** in 18% yield. We suppose that this heterocycle is a product of *Markovnikov* addition of a sulfuric acid molecule to the allyl double bond of **6** to give an internal ammonium salt, which can lose a molecule of water and cyclize into the oxatiazine derivative (**17**). Further basic hydrolysis employing NaOH-EtOH afforded 1-benzyl-4-methylspiro[azetidine-2,1'-cyclooctane] (**18**) (60 %) (Scheme 4).

Furthermore, the homoallylamine (**6**) was cyclized into the 1-benzylspiro[pyrrolidine-2,1'-cyclooctane] (**19**) in 62% yield. This *5-endo-trig* cyclization was achieved through an aminomercuration reaction.[27] The structure of this "*anti-Markovnikov*" product was strongly confirmed by ^1H-, ^{13}C- NMR, IR and MS spectra. Removement of the benzyl moiety of **19** by catalytic hydrogenation gave the pyrrolidine derivative (**20**).

CONCLUSION

We have demonstrated the usefulness of homoallylamine precursors in the synthesis of diverse nitrogen-containing heterocycles in a straight way *via* different cyclization processes. It should be pointed out the easy synthetic procedures to prepare these precursors as well as the final products.

Scheme 4



Conditions: **a.** 92%H_2SO_4/$CHCl_3$, Δ, 7 h; **b.** EtOH/NaOH, Δ, 24 h; **c**. $Hg(OAc)_2$,THF/H_2O, rt, 10 h; **d.** $NaBH_4$/NaOH, 0°C; **e.** Pd/C/$HCOONH_4$, MeOH, Δ, 5 h.

EXPERIMENTAL

The purity of the substances and the composition of the reaction mixtures were controlled by TLC on chromatoplates of Alufol 60 and Silufol UV-254. The separation was carried out by column chromatography on Al_2O_3 (Brockmann activity 2), using mixtures of ethyl acetate - heptane with gradual increase of polarity (1:30, 1:20 and 1:15) as eluents. The IR spectra were obtained on a Perkin Elmer 599B-FT spectrophotometer in KBr unless otherwise indicated. The ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL 300 or on a Bruker AC-200 spectrometers, and are reported in ppm on the δ scale. $CDCl_3$ was used as a solvent and TMS as internal reference. Data are reported as follows: chemical shift (integral intensity, multiplicity, coupling constants and group). A Hewlett Packard 5890A Series II Gas Chromatograph interfaced to an ChemStation Data system was used for MS identification at 70 eV. Elemental analyses were performed on a Leco CHN-600 analyzer. The diffraction indexes were measured in a Schmidt Haensch 17452 apparatus. The melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. Solvents and common reagents were obtained from Merck and Aldrich and were reagent grade. Imines (**1-5**) were prepared using known procedures.[22,23]

Homoallylic amines (6-10). General Procedure

Imines (**1-5**) (0.05 mol) were dissolved in 15 mL of dry ether and added slowly at 10 °C to a magnetically stirred solution (100 mL of Et_2O) of allylmagnesium bromide, prepared from allyl bromide (19.2 g, 0.16 mol) and magnesium (7.7 g, 0.32 mol) (for compounds **1-3** and **5**) or to a solution of prenylmagnesium bromide obtained from prenyl bromide (11.05 g, 0.075 mol) and magnesium (4.0 g, 0.16 mol) (for compound **4**). The mixture was heated to 30-35 °C during 4 h, cooled to 0 °C and treated with water and then with saturated ammonium chloride solution. The organic layer was separated and the aqueous layer

was extracted with ether (3×40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was fractionated under reduced pressure.

***N*-(1-Allylcyclooctyl)benzylamine (6)**

Following the general procedure, this compound was obtained in 65% yield and its spectral and physical properties were in agreement with those reported in literature.[22]

***N*-(1-Allylcyclooctyl)-α-phenylethylamine (7)**

General procedure applied to the imine (**2**) (30.5 g) gave 20.9 g (58%) of **7** as a pale liquid, bp 174-175 ^oC/ 7 mm Hg, n_D^{20} 1.5349; *Anal*. Calcd for $C_{19}H_{29}N$: C, 84.13; H, 10.70; N, 5.16. Found : C, 84.20; H, 10.73; N, 5.05. IR (neat) : 3350, 1640 (ν NH), 1602, 1585 (ν C=C arom) cm^{-1}. ^{1}H-NMR (300 MHz) : δ 7.37 (2H, d, J = 7.2 Hz, *o*-H Ph), 7.26 (2H, dd, J = 7.2 and 7.5 Hz, *m*-H Ph), 7.15 (1H, d, J = 7.2 Hz, *p*-H Ph), 5.75 (1H, ddd, J = 17.7, 9.3 and 7.8 Hz, =CH-), 5.06 (1H, m, $=CH_2$), 5.00 (1H, m, $=CH_2$), 3.85 (1H, q, J = 6.3 Hz, -CH-N), 2.25 (1H, dd, J = 14.1 and 7.6 Hz, $-CH_A$-C=), 2.03 (1H, dd, J = 14.1 and 7.2 Hz, $-CH_B$-C=), 1.32 – 1.65 (14H, m, cyclooctane H), 1.29 (3H, d, J = 6.3 Hz, CH_3). ^{13}C-NMR (75 MHz) : δ 149.14, 135.16, 127.98, 126.51, 126.33, 126.06, 117.35, 116.49, 58.52, 51.27, 41.19, 34.17, 33.38, 27.80, 27.39, 27.30, 25.15, 22.39, 21.95. MS(EI) m/z : 230 $(M - 41)^+$.

***N*-(1-Allylcyclooctyl)-β-phenylethylamine (8)**

Following the procedure to imine (**3**) (12.65 g) provided 6.01 g (40%) of **8** as brownish oil, n_D^{20} 1.5250. *Anal*. Calcd for $C_{19}H_{29}N$: C, 84.13; H, 10.70; N, 5.17. Found : C, 84.26; H, 10.82; N, 5.02. IR (neat): 3390 (ν NH), 1605, 1560 (ν C=C arom) cm^{-1}. ^{1}H-NMR (200 MHz) : δ 7.29 - 7.15 (5H, m, Ar), 5.11-5.25 (1H, m, -CH=), 4.98 (1H, m, $=CH_2$), 4.89 (1H, m, $=CH_2$), 2.37 (2H, t, J = 7.7 Hz $-CH_2$-N), 2.08 (2H, d, J = 7.7 Hz, $-CH_2$-C=), 1.85 (2H, t, J = 7.7 Hz, $-CH_2$Ph), 1.35-1.55 (14H, m, cyclooctane H). ^{13}C-NMR (75 MHz) : δ 140.37, 134.64, 128.67, 128.50, 128.28, 125.99, 117.28, 57.25, 42.96, 41.85, 41.17, 37.08, 33.23, 28.52, 27.12, 25.59, 24.67, 21.93. MS (EI) m/z : 230 $(M^+ - 41)$.

***N*-(1-Prenylcyclooctyl)aniline (9)**

Following the procedure to imine (**4**) (10.00 g) afforded 7.05 g (52%) of **9** as brownish oil, n_D^{20} 1.5240. *Anal*. Calcd for $C_{19}H_{29}N$: C, 84.13; H, 10.70; N, 5.17. Found : C, 84.22; H, 10.76; N, 5.19. IR (neat) : 3394, 1604 (ν NH), 1505 (ν C=C arom) cm^{-1}. ^{1}H-NMR (200 MHz) : δ 7.71 - 6.80 (5H, m, Ar), 5.42 (1H, t, J = 3.4 Hz, =CH-), 3.58 (2H, d, J = 3.4 Hz, $-CH_2C$=), 2.45 (4H, t, J = 6.9 Hz, cyclooctane H-2'and H-8'), 1.95 (4H, m, cyclooctane H-3'and H-7'), 1.84 (3H, s, $-CH_3$), 1.78 (3H, s, $-CH_3$), 1.65 (4H, m, cyclooctane H-4'and H-6'), 1.45 (2H, t, J = 6.9 Hz, cyclooctane H-5'). MS(EI) m/z : 230 $(M - 41)^+$.

***N*-(1-Allylcyclooctyl)-*p*-methoxyphenylamine (10)**

Following the general procedure, compound (**10**) was prepared in 70 % yield from the imine (**5**). The spectral data of this compound coincided with those reported previously.[23]

5-Methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclooctane] (11)

This spiro-compound was obtained in 52 % yield from the homoallylamine **(6)**. The spectral data of this compound coincided with those reported previously.[22]

1,5-Dimethyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclooctane] (12)

92% Sulfuric acid (6.0 mL) was added dropwise at 0 ^{o}C to the homoallylamine (**7**) (2.0g, 7.38 mmol) and the resulting mixture was heated at 95 ^{o}C for 3 h while stirring vigorously. The reaction progress was monitored *via* TLC. At the end of the reaction the mixture was cooled down to rt and concentrated ammonium hydroxide solution was added to pH 10. Three 20 mL extractions with ether were performed. The organic layers were combined, dried (Na_2SO_4) and concentrated. The oily residue was purified by column chromatography over alumina with heptane and ethyl acetate (20 : 1) to give 0.84 g (42%) of **12** as a pale yellow oil. *Anal*. Calcd for $C_{19}H_{29}N$: C, 84.13; H, 10.70; N, 5.17. Found : C, 84.23; H, 10.68; N, 5.20. IR (neat) : 3318, 1639 (ν NH), 1601 (ν C=C arom) cm^{-1}. ^{1}H-NMR (200 MHz) : δ 7.10-7.30 (4H, m, Ar), 4.30 (2H, q, J = 6.7 Hz, H-1), 3.35 and 3.40 (1H, m, H-5), 1.65 (1H, m, H_e-4), 1.49 and 1.51 (3H, d, J = 6.7 Hz, 1-CH_3), 1.40 (1H, m, H_a-4), 1.35 and 1.37 (3H, d, J = 7.0 Hz, 5-CH_3), 1.30-1.60 (14H, m, cyclooctane H). GC-MS(EI) m/z (%) : an isomer with t_R 28.50 min : 271 (M^+, 13), 256 (33), 242 (28), 228 (17), 214 (9), 200 (49), 186 (8), 172 (68), 160 (18), 146 (39), 131 (100), 115 (22), 105 (10), 91 (39), 84 (2), 77 (12), 67 (9), 55 (14). Other isomer with t_R 34.31 min : 271 (M^+, 33), 256 (28), 242 (4), 228 (7), 214 (9), 200 (100), 187 (25), 159 (33), 147 (61), 131 (57), 115 (11), 103 (32), 91 (11), 84 (1), 77 (25), 67 (8), 57 (22).

2-Formyl-5-methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclooctane] (13)

The spiro-compound (**11**) (0.3 g; 1.2 mmol) was added to a mixture of formic acid (0.15 mL, 3.8 mmol) and acetic anhydride (0.15 mL, 2.6 mmol) at 0 ^{o}C. A few drops of pyridine were then added to the resulting mixture and the mixture was stirred at 0 ^{o}C for 4 h. At the end of the reaction the mixture was treated with sodium bicarbonate and extracted with ether (3×10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (alumina) with ethyl acetate and heptane (1 : 5) to yield 0.25 g (74%) of **13** as a pale yellow powder, mp 72-74 ^{o}C (heptane). *Anal*. Calcd for $C_{19}H_{27}NO$: C, 80.00; H, 9.47; N, 4.91. Found : C, 79.94; H, 9.55; N, 5.10. IR (KBr) : 1651(ν CO), 1583 (ν C=C arom) cm^{-1}. ^{1}H-NMR (200 MHz) : δ 8.33 (1H, s, H-C=O), 7.01-7.45 (4H, m,

Ar), 4.70, 4.50 (2H, AB, J = 15.1 Hz, H-1), 3.25 (1H, m, H-5), 1.80 (1H, d, J = 14.0 Hz, H_e-4), 1.49-1.86 (14H, m, cyclooctane H), 1.40 (3H, d, J = 7.0 Hz, 5-CH_3), 1.30 (1H, dd, J = 14.0 and 10.5 Hz, H_a-4). ^{13}C-NMR (75 MHz) : δ 161.25, 144.04, 136.89, 129.81, 127.34, 126.10, 125.45, 63.38, 47.05, 42.73, 35.64, 31.17, 29.15, 28.92, 27.42, 25.41, 22.80, 22.73, 21.82. MS(EI) m/z : 285 (M^+)

2-Acetyl-5-methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclooctane] (14)

The spiro-compound (**11**) (0.3 g, 1.2 mmol) was heated under reflux for 6 h in acetic anhydride (0.3 mL, 3.18 mmol) in the presence of Et_3N (0.1 mL 0.72 mmol). The reaction was monitored *via* TLC. At the end of the reaction the pH was brought to 7-8 with sodium bicarbonate. The organic products were extracted with ether (3×10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The oily residue was purified by column chromatography (silica gel) with ethyl acetate and heptane (1 : 10) to give 0.3 g (86%) of **14** as a viscous pale yellow liquid. *Anal*. Calcd for $C_{20}H_{29}NO$: C, 80.27; H, 9.70; N, 4.68. Found : C, 80.35; H, 9.87; N, 4.40. IR (neat) : 1641(ν CO), 1490 (ν C=C arom) cm^{-1}. ^{1}H-NMR (200 MHz) : δ 7.00-7.30 (4H, m, Ar), 4.88, 4.25 (2H, AB, J = 15.1 Hz, H-1), 3.23 (1H, m, H-5), 2.10 (3H, s, CH_3), 1.70 (1H, m, H_e-4), 1.48 (1H, m, H_a-4), 1.40-1.65 (14H, m, cyclooctane H), 1.38 (3H, d, J = 7.1 Hz, 5-CH_3). ^{13}C-NMR (75 MHz) : δ 171.8, 143.55, 135.83, 129.05, 128.76, 127.22, 125.87, 66.15, 49.53, 43.38, 34.92, 33.73, 29.71, 28.84, 28.79, 26.02, 25.05, 24.13, 23.33, 23.09. MS(EI) m/z : 299 (M^+).

5,5-Dimethyl-1,2,3,4-tetrahydrospiro[5*H*-1-benzazepine-2,1'-cyclooctane] (15)

Conc. sulfuric acid (2 mL) was added dropwise at 0 °C to the homoallylamine (**9**) (1.0 g, 3.7 mmol) and the resulting mixture was heated at 80 °C for 3 h. The reaction progress was monitored *via* TLC. Then the mixture was cooled down to rt and concentrated ammonium hydroxide solution was added to pH 10 and the mixture was extracted with ether. After removal of the solvent of the combined extracts, the oily residue was chromatographed by alumina column with heptane and ethyl acetate (20 : 1) to give 0.62 g (62%) of **15** as an oil, n_D^{20} 1.5412. *Anal*. Calcd for $C_{19}H_{29}N$: C, 84.13; H, 10.70; N, 5.17. Found : C, 84.21; H, 10.73; N, 5.06. IR (neat) : 3400, 1607 (ν NH), 1580 (ν C=C arom) cm^{-1}. ^{1}H-NMR (200 MHz) : δ 6.45 - 7.18 (4H, m, Ar), 3.38 (1H, br s, N-H), 3.30 (2H, t, J = 6.9 Hz, cyclooctane H-2'), 2.40 (2H, t, J = 6.9 Hz, cyclooctane H-8'), 1.92 (2H, m, H-3), 1.75 (2H, t, J = 5.8 Hz, H-4), 1.60-1.35 (10H, m, cyclooctane H-3'- H-7'), 1.31 (3H, s, CH_3), 1.29 (3H, s, CH_3). MS(EI) m/z : 271 (M^+).

6-Methoxy-4-methyl-3,4-dihydrospiro[1*H*-quinoline-2,1'-cyclooctane] (16)

Conc. sulfuric acid (2 mL) was added dropwise at 0 °C to compound (**10**) (0.5 g, 0.18 mmol). The mixture was heated at 70 °C for 2.5 h with vigorous stirring. The reaction progress was monitored *via* TLC. Then the mixture was cooled down to rt and was basified with saturated ammonium hydroxide

solution and extracted with ether. The residue from the ether extract was chromatographed (alumina) with ether and heptane (1 : 2) to give 0.36 g (72%) of **16** as a brownish oil. *Anal*. Calcd for $C_{18}H_{27}NO$: C, 79.12; H, 9.89; N, 5.13, Found : C, 79.20; H, 9.75; N, 5.10. IR (neat) : 3370 (ν NH), 1511 (ν C=C arom) cm^{-1}. ^{1}H-NMR (300 MHz) : δ 6.75 (1H, d, J = 2.3 Hz, H-5), 6.58 (1H, dd, J = 8.0 and 2.30 Hz, H-7), 6.41 (1H, d, J = 8.0 Hz, H-8), 3.74 (3H, s, OCH_3), 2.84 (1H, m, H-4), 1.92 (1H, dd, J = 13.0 and 5.6 Hz, H_e-3), 1.90-0.91 (14, m, cyclooctane H), 1.29 (3H, d, J = 6.7 Hz, 4-CH_3), 1.17 (1H, dd, J = 13.0 and 12.7 Hz, H_a-3). ^{13}C- NMR (75 MHz) : δ 151.75, 137.71, 127.43; 115.34, 113.16, 112.52, 55.90, 53.88, 42.69, 38.61, 31.98, 29.79, 28.75, 28.42, 27.48, 25.33, 22.17, 20.77. MS(EI) m/z : 273 (M^+).

3-Benzyl-6-methyl-3,4,5,6-tetrahydrospiro[1,2,3-oxatiazine-2,2-dioxide-4,1'-cyclooctane] (17)

The homoallylamine (**6**) (2.5 g, 9.73 mmol) in chloroform (12.5 mL) was added to a mixture of chloroform (20 mL) and 92% sulfuric acid (2.5 mL). The resulting mixture was refluxed for 7 h. At the end of the reaction the mixture was cooled down to 0 ^{o}C and a few pellets of sodium hydroxide in water (10 mL) was added to pH 14. The organic products were extracted with chloroform (3×10 mL) to give a precipitate. The latter was filtered and washed with chloroform to afford 0.6 g (18%) of **17** as a colorless amorphous solid, mp 237-239 ^{o}C. *Anal*. Calcd for $C_{18}H_{27}NO_3S$: C, 64.09; H, 8.01; N, 4.15. Found : C, 64.15; H, 8.10; N, 4.13. IR (KBr) : 1588 (ν C=C arom), 1296, 1194 (ν SO_2) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) : δ 7.41 – 7.61 (5H, m, Ar), 4.58 (1H, br s, H-6), 4.24, 4.09 (2H, AB, J = 12.6 Hz, CH_2-N), 2.05-1.26 (16H, m, cyclooctane H and H-5), 1.45 (3H, d, J = 6.2 Hz, CH_3). MS(EI) m/z : 257 $(M - SO_3)^+$.

1-Benzyl-4-methylspiro[azetidine-2,1'-cyclooctane] (18)

A mixture of compound (**17**) (0.16 g, 0.47 mmol) and powdered NaOH (0.25 g, 6.25 mmol) in ethanol (4 mL) was refluxed for 24 h. After cooling, water (5 mL) was added and the organic products were extracted with ether (3×5 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The oily residue was purified by column chromatography (alumina) with ethyl acetate and heptane (1 : 25) to give 0.07 g (60%) of **18** as a viscous pale yellow liquid. *Anal*. Calcd for $C_{18}H_{27}N$: C, 84.04; H, 10.50; N, 5.45. Found : C, 84.12; H, 10.58; N, 5.50. IR (neat) : 1605 (ν C=C arom), 731, 698 (δ =C-H arom) cm^{-1}. ^{1}H-NMR (300 MHz) : δ 7.20 - 7.40 (5H, m, Ar), 3.81, 3.44 (2H, AB, J = 13.1 Hz, CH_2-N), 3.18 (1H, tq, J = 7.6 and 5.8 Hz, H-4), 1.90 (1H, dd, J = 7.6 and 10.2 Hz, H_a-3), 1.36–1.57 (14H, m, cyclooctane H), 1.41 (1H, dd, J = 7.6 and 10.2 Hz, H_e-3), 0.86 (3H, d, J = 5.8 Hz, CH_3). ^{13}C-NMR (75 MHz) : δ 140.95, 128.92, 127.80, 126.37, 65.21, 56.46, 54.62, 39.73, 38.31, 30.86, 28.94, 28.66, 27.41, 24.29, 22.73, 22.43, 21.98. MS(EI) m/z : 257(M^+).

1-Benzylspiro[pyrrolidine-2,1'-cyclooctane] (19)

To a solution of homoallylamine (**6**) (1.78 g, 7.0 mmol) in THF (5 mL) was added dropwise a solution of mercury acetate (4.4 g, 13.8 mmol) in THF/H_2O (15 mL, 1:1). The mixture was stirred at rt for 10 h. Then, a solution of $NaBH_4$ (0.5 g, 14.0 mmol) in 2.5 N NaOH (10 mL) was added slowly to the resulting reaction mixture, cooled down to 0 ^oC. The inorganic precipitates were filtered and THF was evaporated. The aqueous layer was extracted with ether (3×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The crude organic concentrate was purified by alumina column chromatography (heptane) to afford 0.93 g (62%) of analytically pure **18** as an oil. *Anal*. Calcd for $C_{18}H_{27}N$: C, 84.04; H, 10.50; N, 5.45. Found : C, 84.00; H, 10.56; N, 5.57. IR (neat) : 1604 (ν C=C arom), 735, 699 (δ =C-H arom) cm^{-1}. ^{1}H-NMR (300 MHz) : δ 7.18-7.36 (5H, m, Ar), 3.64 (2H, s, -CH_2-N), 2.58 (2H, t, J = 6.2 Hz, H-5), 1.85-1.91 (2H, m, H-4), 1.42-1.72 (16H, m, cyclooctane H and 3-CH_2). ^{13}C-NMR (75 MHz) : δ 141.42, 128.45, 128.06, 128.06, 126.45, 126.39, 65.12, 53.57, 50.68, 37.28, 32.19, 32.00, 28.68, 28.50, 24.67, 23.89, 23.80, 20.76. MS(EI) m/z : 257 (M^+).

Spiro[pyrrolidine-2,1'-cyclooctane] (20)

The spiro-compound (**19**) (0.28 g, 1.09 mmol) and ammonium formate (0.24 g, 3.8 mmol) was heated to reflux in methanol (25 mL) for 5 h in the presence of 10% Pd/C (0.031 g). The reaction was monitored *via* TLC. The inorganic precipitates were filtered and methanol was evaporated. Then, a solution of 0.5 N NaOH (5 mL) was added slowly to the resulting mixture and the solution was extracted with CH_2Cl_2 (3×5 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The oily residue was purified by alumina column chromatography with ethyl acetate and heptane (1 : 3) to afford 0.16 g (88%) of **20** as a pale yellow liquid. *Anal*. Calcd for $C_{11}H_{21}N$: C, 79.04; H, 12.57; N, 8.38. Found : C, 79.00; H, 12.66; N, 8.40. IR (neat) : 3294 and 1604 cm^{-1} (ν NH). ^{1}H-NMR (300 MHz) : δ 3.37 (2H, t, J = 5.8 Hz, H-5), 2.36 (2H, t, J = 6.0 Hz, H-3), 2.17 (2H, m, H-4), 1.80- 2.06 (14H, m, cyclooctane- H). MS(EI) m/z : 167 (M^+).

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