SYNTHESIS OF NEW SPIROHETEROCYCLES WITH CYCLOOCTANE FRAGMENT

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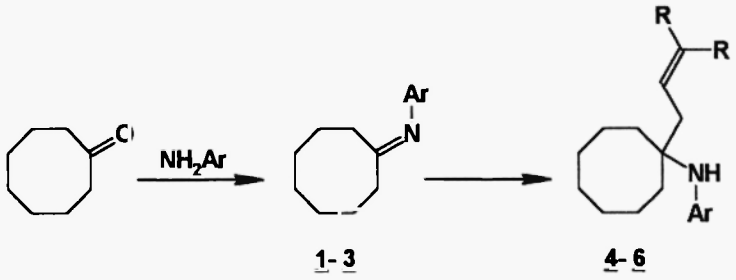
Abstract: New spiro[pyrrolidine- and 1-(2-)benzazepine- cyclooctane] were prepared from the same starting materials, - homoallylamines derived from N-cyclooctylidene-aryl(benzyl)amines and allyl(prenyl)magnesium bromide.

Introduction

Many of nitrogen-containing saturated heterocycles have been found to play fundamental roles in biological processes. Included among these are isomeric benzazepine and pyrrolidine derivatives (1,2). Cyclization processes are a quite 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 ring formation. We consider that homoallylic amines, readily accessible from the corresponding imines and allylorganometalic compounds, could be very suitable for preparing these heterocycles. On the other hand, a growing family of cyclooctane-containing natural product shows interesting biological activities (3). Nevertheless, the spirocyclooctanes annulated with nitrogen-containing heterocycles are still unknown in nature. Our idea was unit such heterocycles as 1-benzazepine (2-benzazepine) or pyrrolidine with a cyclooctane ring via spirocarbon atom in order to study biological activity of these compounds. Herein, we wish to report on a useful transformation of *gem*-alkenyl-N-phenyl(benzyl)aminocyclooctanes into new spiroheterocycles with cyclooctane fragment.

Results and Discussion

The N-cyclooctylidene-arylamines 1-3 readily available from cyclooctanone and corresponding primary amines, were taken as basic precursors. These imines were transformed into the corresponding homoallylic amines 4-6 through Grignard procedure using allyl- and prenyl-magnesium bromides as organometalic reagents (scheme 1). We performed this nucleophilic addition in ether at 20 °C. After stirring for 4 hours the reaction mixture was treated with saturated NH_4Cl solution, organic products were extracted and then distilled at reduced pressure affording *gem*-alkenyl-N-phenyl(benzyl)aminocyclooctanes 4-6 in 58-65% yield.

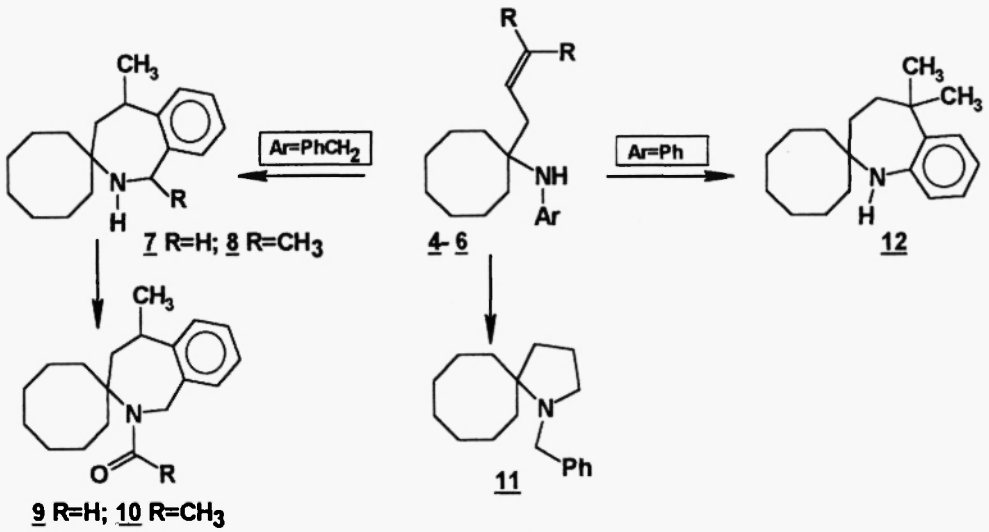


1-3 4-6

1,4 Ar= $PhCH_2$, R=H; 2,5 Ar=$Ph(CH_3)CH$, R=H;
3,6 Ar=Ph, R=CH_3

Scheme 1

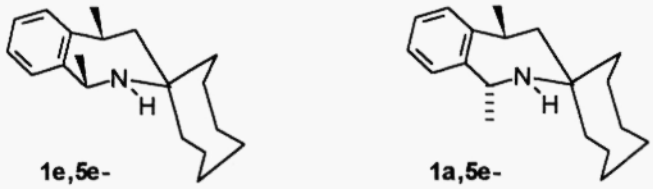
In continuation of our studies on functionalized 2-benzazepines (4,5), we synthesized 1,2,4,5-tetrahydrospiro[3H-2-benzazepine-3,1'-cyclooctanes] 7,8 from the corresponding homoallylamines 4,5 under acidic conditions (scheme 2).



Scheme 2

This cationic cyclization was achieved through heating compounds 4,5 in 85% sulfuric acid and can be considered as a *7-exo-trig* process. Compounds 7,8 were isolated by column chromatography as yellowish oil in 52 and 42% yield respectively.

Compound 7 had been obtained previously (5). According to the ^{1}H NMR spectrum of 2-benzazepine 8 (6) this compound is formed as a mixture of two geometric *cis-trans* isomers: 1e,5e-8a and 1a,5e-8b in 1:1 ratio. The semi-chair conformation for the tetrahydrobenzazepine ring was predicted by calculation methods (4). Studies of cyclooctane conformation indicate that the most stable conformation is that of the boat-chair (7). According to this information we assigned the structure for these isomers as indicated in fig.1.



1e,5e-**8a** 1a,5e-**8b**

Fig.1

Seeking substances with potential bioactivity, we prepared N-formyl-9 and N-acetyl-10 derivatives from 2-benzazepine 7. Formylation was performed with formyl-acetyl anhydride prepared *in situ* from acetic anhydride and formic acid in the presence of pyridine. Amide 10 was obtained by refluxing compound 7 in acetic anhydride with catalytic amounts of Et_3N. We confirmed these amidation reactions by IR: ν_{CO} 1651 and 1640 cm^{-1}, respectively for 2-benzazepines 9 and 10. The ^{13}C spectra of these amides exhibit a characteristic signal in low fields at 161,2 and 171,8 ppm (C=O).

The homoallylamine 4 was then cyclized into spiro[pyrrolidine-2,1'-cyclooctane] 11 in 52% yield. This *5-endo-trig* cyclization was achieved through aminomercuration reaction (1.$Hg(OAc)_2$/THF/H_2O, 2.$NaBH_4$/NaOH). The structure of this "*anti-Markovnikov*" product was strongly confirmed by ^{1}H and ^{13}C NMR, IR and mass spectra (8).

Finally, we obtained the cyclooctane 12 spiroannulated with tetrahydro-1-benzazepine moiety by treating homoallylic amine 7 with 85% sulfuric acid (scheme 2). We suppose that in this case the cyclization occurs via more stable tertiary carbocation formed from prenyl fragment that leads to 1-benzazpine ring formation via *7-endo-trig* process. This compound was purified by column chromatography and obtained in 62 % yield. Its spectral data are in agreed with its structure (9).

Conclusion

We have demonstrated usefulness of homoallylamine precursors in synthesis of diverse nitrogen-containing heterocycles via different cyclization processes. It should be mentioned the easy synthetic procedures to prepare these precursors as well as final products. The investigation of other cyclization of similar homoallylamines to obtain new heterocycles is in progress in our laboratory.

Acknowledgment

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References and Notes

All new compounds have fully been characterised by means of IR, NMR and MS spectroscopy.

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(6) ^{1}H NMR (200 MHz, $CDCl_3$) of 8: δ 1.30-1.60 (14H, m, cyclooctyl-H); 1.35, 1.37 (3H, d, 5-CH_3); 1.40 (1H, m, 4-Ha); 1.49, 1.51 (3H, d, 1-CH_3); 1.65 (1H, m, 4-He); 3.35, 3.40 (1H, m, 5-Ha); 4.30 (2H, c, 1-H); 7.10-7.30 (4H, m, arom-H). ^{13}C NMR (75 MHz, $CDCl_3$) of 8: δ 21.2/21.4; 21.9/22.1; 22.4/24.5; 25.1/25.3; 27.0/28.1; 28.3/28.4; 28.5/28.9; 29.8/31.8; 33.6/36.7; 41.2/41.8; 47.1/47.6; 48.8/50.5; 56.8/57.0; 123.6/125.3(2C); 125.5/125.8 (2C); 126.1/126.4; 145.2/146.1.
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(8) ^{1}H NMR (300 MHz, $CDCl_3$) of 11: δ 1.42-1.72 (16H, m, cyclooctyl-H and 3-H); 1.85-1.91 (2H, m, 4-H); 2.58 (2H, t, 5-H); 3.64 (2H, s, -CH_2-N); 7.18-7.36 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) of 11: δ 20.8; 23.9 (2C); 24.7; 28.7 (2C); 32.2 (2C); 37.3; 50.7; 53.6; 65.1; 126.4; 128.0 (2C); 128.5 (2C); 141.4.
(9) IR (KBr) of 12: 3400 (ν_{NH}), 1607 (δ_{N-H}), 745 ($\delta_{=C-H\ arom}$) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) of 12: δ 1.29 (3H, s, -CH_3); 1.31 (3H, s, -CH_3); 1.35-1.40 (6H, m, cyclooctyl-H); 1.50-1.58 (4H, m, cyclooctyl-H); 1.75 (2H, t, 4-H); 1,84-1.93 (2H, m, cyclooctyl-H); 2.40-2.45 (2H, m, cyclooctyl-H); 3.30 (2H, t, 3-H); 3.38 (1H, br s, N-H); 6.45 (1H, d, 6-H); 6.68 (1H, t, 8-H); 6.95 (1H, t, 7-H); 7.18 (1H, d, 9- H).

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