# A CONVENIENT SYNTHETIC ENTRY INTO 7-AZA-2,2-DIPHENYL-2-SILABICYCLO[3.3.0]OCTANE DERIVATIVES

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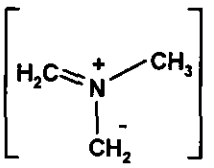
**Abstract-** 7-Aza-2,2-diphenyl-2-silabicyclo[3.3.0]octane derivatives **(5-7)** are obtained from intermolecular [3+2] cycloaddition reactions between 1,1-diphenyl-1-silacyclopent-2-enes **(3)** and **(4)** and the azomethine ylide **(2)** which was generated *in situ* from trimethylamine *N*-oxide.

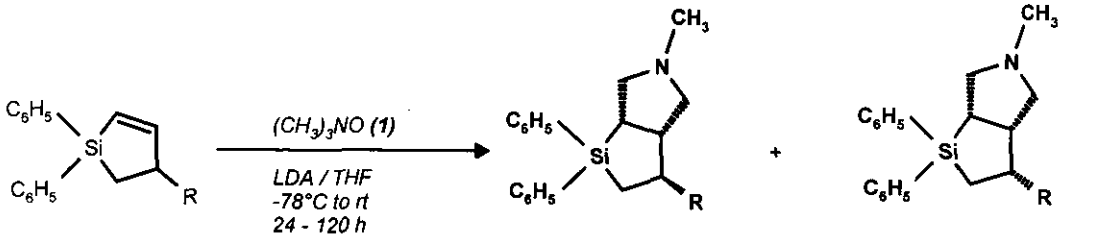
The [3+2] cycloaddition reaction of azomethine ylides to olefinic or acetylenic dipolarophiles represents a very attractive procedure for the construction of five-membered nitrogen heterocycles in which two carbon-carbon bonds are formed in a single step. Generally, this elegant synthetic pathway exhibits high chemo-, regio- and stereoselectivity, and the stereochemistry of the double bond of the dipolarophile is retained in the final adduct. [1] As an extension of our previous work, [2] directed towards the preparation of new silabicyclic derivatives, we describe herein an efficient synthesis of 7-aza-2,2-diphenyl-2-silabicyclo[3.3.0]octane derivatives *via* an analogous intermomecular [3+2] cycloaddition reaction.




(2)

Bicyclic pyrrolidine derivatives **(5-7)** were prepared by [3+2] cycloaddition of the C-unsubstituted and nonstabilized azomethine ylide **(2)** with the 4-substituted 1-silacyclopent-2-enes **(3)**[3] and **(4)**[4] as depicted in Scheme 1. Intermediate **(2)** was generated *in situ* by dehydration of trimethylamine *N*-oxide **(1)** (2-3 eq.) using a large excess of a strong base such as LDA (7-10 eq.) in THF at -78°C. [5]

**Scheme 1**




**(3)** R = -OH
**(4)** R = -N(CH$_3$)$_2$

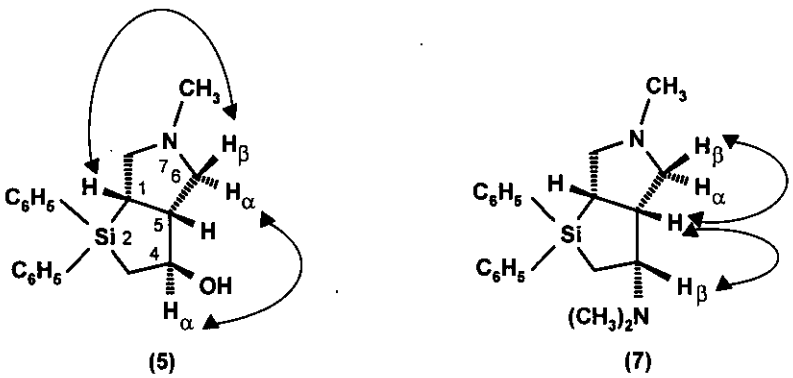
**( 5)** R = -OH (65%)

**(6)** R = -OH (21%)
**(7)** R = -N(CH$_3$)$_2$ (20%)

Surprisingly, the stereochemistry of compounds (**5-7**) depends on the nature of the substituent in position 4 in compounds (**3-4**). Thus, the cycloaddition of **2** with the allylic alcohol (**3**) mainly afforded the *trans*-isomer (**5**) in 65% yield. The minor *cis*-isomer (**6**) was also isolated in 21% yield after purification by flash chromatography on silica gel. Starting from the allylic amine (**4**), only pure *cis*-derivative (**7**) was obtained in 20% yield after purification by chromatography. Under the experimental and purification conditions employed, we did not obtain other diastereoisomer.

The relative stereochemistry of **5** and **7** was obtained after nOe experiments (NOESY, 400 MHz , τm : 250 ms). Due to the strong nOe between H-1 and H-5 the *cis* junction between the two five membered rings was postulated for both compounds. Concerning (**5**), H-1β shows an nOe correlation with H-6β but not with H-6α which allows their safe distinction. As H-4 has an nOe with H-6α and no nOe with H-1β and H-6β, we concluded on the H-4α configuration (Figure 1). On the other hand, the H-5 proton of **7** exhibits similar intense nOe's with H-4, H-1 and one of the H-6 while the correlation with the other H-6 is four times weaker. This set fits well with the inverted stereochemistry depicted in Figure 1. The relative stereochemistry of **6** was conferred from **5**.

**Figure 1.** Selected nOe connectivities for **5** and 7




To our knowledge, few syntheses of pyrrolidine cycles bearing a silyl group in position 3 have been described. They were prepared through either a direct 3-silylation of 2-pyrrolidinone followed by reduction of the amide function, [6] or by iminium ion initiated cyclization reaction of vinylsilanes. [7] Only one [3+2] cycloaddition of the azomethine ylide with 1-phenyl-2-trimethylsilylacetylene giving the corresponding 2, 5-dihydropyrrole has been reported. [8]

In conclusion, the synthesis of sila-heterocyclic derivatives (**5-7**) within an 7-aza-2,2-diphenyl-2-silabicyclo[3.3.0]octane family can be easily prepared *via* a [3+2] cycloaddition reaction.

## EXPERIMENTAL

Tetrahydrofuran was dried over 4Å molecular sieves. Commercially available reagents were used as received from suppliers. Trimethylamine *N*-oxide (**1**) was dried under *vacuo* until constant weight. The progress of the reactions was monitored by TLC on silica gel (Merck Kieselgel $60F_{254}$). Melting points were determined using a Reicher-Kofler apparatus and are uncorrected. $^{1}H$ and $^{13}C$-NMR spectra were recorded using an AC 200 or a DRX400 Bruker spectrometers. $^{1}H$ and $^{13}C$ assigments were supported by 2D homo and hetero nuclear experiments. IR spectra were recorded on a FT-IR 60SX-R Nicolet spectrophotometer. MS

were obtained on a Finnigan 4000. Elemental Analysis was performed using a Carlo Erba 1108 analyzer. Flash chromatography was performed on silica gel (Merck Kieselgel, 230-400 mesh).

**(*1R**, *4S**, *5R**)-7-Aza-2,2-diphenyl-4-hydroxy-7-methyl-2-silabicyclo[3.3.0]octane (5); (*1R**, *4R**, *5R**)-7-aza-2,2-diphenyl-4-hydroxy-7-methyl-2-silabicyclo[3.3.0]octane (6).**

To a stirred mixture of **3** (7.56 g, 0.03 mol) and **1** (4.65g, 0.062 mol) in THF (100 mL) under a nitrogen atmosphere, was added dropwise a solution of LDA (0.217 mol, prepared from 136 mL of 1.6M *n*BuLi and 31 mL of diisopropylamine) in THF (200 mL) at -78°C during 1 h. The reaction mixture was then allowed to reach rt and stirred for 120 h. The yellow solution was diluted with water (200 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layers were washed with 1N HCl (pH = 1) then with 1N $Na_2CO_3$ (pH = 9), and finally dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography using a toluene/diethylamine/ethanol mixture (90/5/5) as eluent to give 6.0 g (65%) of **5** which crystallized in isopropyl ether as white crystals (mp 60°C, $R_f$ = 0.5 in toluene/ diethylamine/ethanol mixture 90/5/5), and 2.0 g (21%) of **6** as a pale yellow oil ($R_f$ = 0.36 in toluene/diethylamine/ethanol mixture 90/5/5).

**5**: $^1$H-NMR ($CDCl_3$) δ : 1.2 (dd, J = 4 and 15 Hz, 1H, H-3β), 1.8 (dd, J = 3 and 15 Hz, 1H, H-3α), 2.2 (m, 1H, H-1β), 2.3 (s, 3H, $CH_3$), 2.4 (dd, J = 8.5 and 11.5 Hz, 1H, H-8), 2.5 (dd, J = 5.5 and 9 Hz, 1H, H-6β), 2.7 (m, 1H, H-5β), 2.8 (dd, J = 4 and 8.5 Hz, 1H, H-8), 3.2 (d, J = 9 Hz, 1H, H-6α), 4.5 (m, J = 3 , 4 and 4 Hz, 1H, H-4α), 7.3-7.7 (m, 10H, $C_6H_5$); $^{13}$C-NMR ($CDCl_3$) δ : 25.2 (C-3), 26.6 (C-1), 41.1 ($CH_3$), 51.5 (C-5), 56.5 (C-8), 59.3 (C-6), 75.9 (C-4) 126.3, 128.0, 128.3, 129.6, 129.7, 135.2 and 136.6 (CH of phenyl rings assuming superimpositions), 134.0 and 137.7 (C ipso of phenyl rings); IR (KBr) 3400 (OH), 3090, 3060, 3040, 3020, 3010 and 3000 (C-H arom.), 2930, 2920, 2900 and 2840 (C-H aliph.), 2780 (C-H aliph.), 1585, 1565, 1480 and 1425 (C=C), 1390, 1375 and 1365 (C-H aliph.), 1110 (Si-Ar and C-OH), 980 (C-O), 820 (C-H of $C_6H_5$-Si), 740 and 725 (C-H of $C_6H_5$), 700 (aromatic ring) and 505 ($C_6H_5$-Si) $cm^{-1}$; MS (EI) m/z: 309 ($M^+$), 231, 199 (100%), 181, 105, 94, 81; *Anal.* Calcd for $C_{19}H_{23}NOSi$: C, 73.73; H, 7.49; N, 4.53. Found: C, 73.5; H, 7.7; N, 4.4.

**6**: $^1$H-NMR ($CDCl_3$) δ : 1.4 (dd, J = 9 and 14 Hz, 1H, H-3), 1.8 (dd, J = 5 and 14 Hz, 1H, H-3), 2.1 (m, 1H, H-8), 2.3 (s, 3H, $CH_3$), 2.4 (m, 1H, H-8), 2.5 (dd, J = 4 and 8 Hz, 1H, H-6), 2.6 (m, 1H, H-1), 2.8 (m, 1H, H-5), 2.9 (d, J = 8 Hz, 1H, H-6), 4.3 (ddd, J = 5 , 9.2 and 6 Hz, 1H, H-4), 7.1-7.7 (m, 10H, $C_6H_5$); $^{13}$C-NMR ($CDCl_3$) δ : 24.0 (C-3), 27.5 (C-1), 42.0 ($CH_3$), 54.0 (C-5), 58.5 (C-8), 61.0 (C-6), 77.5 (C-4), 128.2, 129.8, 129.9, 135.0 and 135.5 (CH of phenyl rings assuming some superimpositions), 134.0 and 138.0 (ipso C of phenyl rings); MS (EI) m/z: 309 ($M^+$), 231, 199, 181, 105, 94, 81.

**(*1R**, *4R**, *5R**)-7-Aza-2,2-diphenyl-4-dimethylamino-7-methyl-2-silabicyclo[3.3.0]octane (7).**

To a stirred mixture of **4** (4.2 g, 15 mmol) and **1** (3.38 g, 45 mmol) in THF (150 mL) under a nitrogen atmosphere, was added dropwise a solution of LDA (150 mmol, prepared from 93.7 mL of 1.6M *n*BuLi and 21.4 mL of diisopropylamine) in THF (150 mL) at -78°C during 1 h. The reaction mixture was then allowed to reach rt and stirred for 3 h. The yellow solution was diluted with water (500 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography using a toluene /diethylamine/ethanol mixture 90/5/5 as eluent to give 1.0 g (20%) of **7** as a viscous pale yellow liquid which was crystallized as oxalate salt in acetonile as a white needles.

(mp 192 °C, $R_f$ = 0.27 in toluene/diethylamine/ethanol mixture (90/5/5).

**7** (base form): $^1$H-NMR ($CDCl_3$) δ : 1.3 (t, J = 14 Hz, 1H, H-3β), 1.4 (dd, J = 5.5 and 14 Hz, 1H, H-3α), 2.1 (m, 2H, H-8 and H-1β), 2.2 (s, 3H, N-C$\underline{H}_3$), 2.3 (s, 6H, N(C$\underline{H}_3$)$_2$), 2.4 (m, 1H, H-4β), 2.5 (t, J = 9.5 Hz, 1H, H-6α), 2.7 (dd, J = 8.5 and 9.5 Hz, 1H, H-6β), 2.8 (m, 1H, H-4), 3.2 (m, 1H, H-5β), 7.3-7.6 (m, 10H, $C_6H_5$); $^{13}$C-NMR ($CDCl_3$) δ : 15.0 (C-3), 26.5 (C-1), 42.0 (N-$\underline{C}H_3$), 45.5 (N($\underline{C}H_3$)$_2$), 47.8 (C-5), 57.6 (C-8), 59.6 (C-6), 67.70 (C-4), 126.2, 128.2, 128.4, 129.8, 129.9, 131.1, 135.2 and 136.1 (CH of phenyl rings assuming some superimposition), 134.0 and 137.0 (ipso C of phenyl rings); IR (KBr) 3065, 3045 and 3005(C-H arom.), 2980, 2955, 2860 and 2820 (C-H aliph.), 2770 (C-H aliph.), 1590 and 1425 (C=C), 1465 (C=C), 1135 (C-N), 1110 (Si-Ar), 830 and 810 (C-H of $C_6H_5$-Si), 740 (C-H arom.), 700 (aromatic ring) 500 ($C_6H_5$-Si) cm$^{-1}$; MS (EI) m/z: 336 ($M^+$), 291, 238, 183, 162 (100%), 105, 94, 82.

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