

# A NEW SPIRO- $\Delta^3$ -(1,3,4) OXADIAZOLE FROM 2-DIAZOPROPANE AND 2,5-DIBENZYLIDENECYCLOPENTANONE

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## Abstract

The 1,3-cycloaddition of 2-diazopropane **1** on 2,5-dibenzylidenecyclopentanone **2** leads, beside the expected diastereoisomers bis-spiro- $\Delta^1$ -pyrazolines **3** and **4**, to a new spiro- $\Delta^3$ -(1,3,4)oxadiazole bearing two spiro- $\Delta^1$ -pyrazolinyl rests **6**. The photolysis of the major diastereoisomer **4** gives the stereospecific *gem*-dimethyl bis-spiro-cyclopropanes **8** via **7** in high yields.

## Introduction

We have recently described<sup>(1)</sup> a diastereoselective synthesis of a new  $\Delta^3$ -(1,3,4)oxadiazoles<sup>(2)</sup> structures **1'** by 1,3-cycloaddition of 2-diazopropane<sup>(3,4)</sup> on an acyclic dienone, the diarylidenacetone. In order to generalize our approach, we focus on the exocyclic 2,5-diarylidenecyclopentanone, dienone **2**. The simultaneous addition of 2-diazopropane on the carbonyl and the ethylenic double bond was rarely mentioned. Only Dean et al.<sup>(5)</sup> have obtained a *gem*-dimethyl spiro-oxirane **2'** by treating the 2-methyl-1,4-naphthoquinone by 2-diazopropane at low temperature. To our knowledge, the dienone **2** has not been opposed to any 1,3-dipole. Furthermore, T.-Y. Lin et al.<sup>(6)</sup> described the addition of diazomethane on the 2,6-dibenzylidenecyclohexanone as stereospecific reaction (obtaining of a unique bis-adduct **3'** and wich has been shown to possess a mutagenic activity). These results are quite surprising, because one can predict the formation of a diastereoisomeric mixture of two bis-pyrazolines resulting from different approach of the dienone by 2-diazopropane.<sup>(7)</sup>

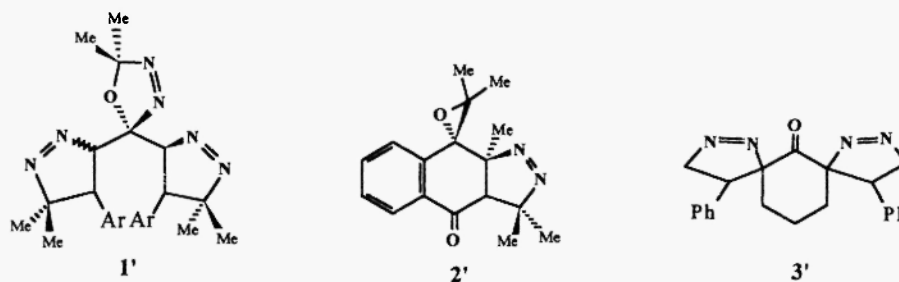
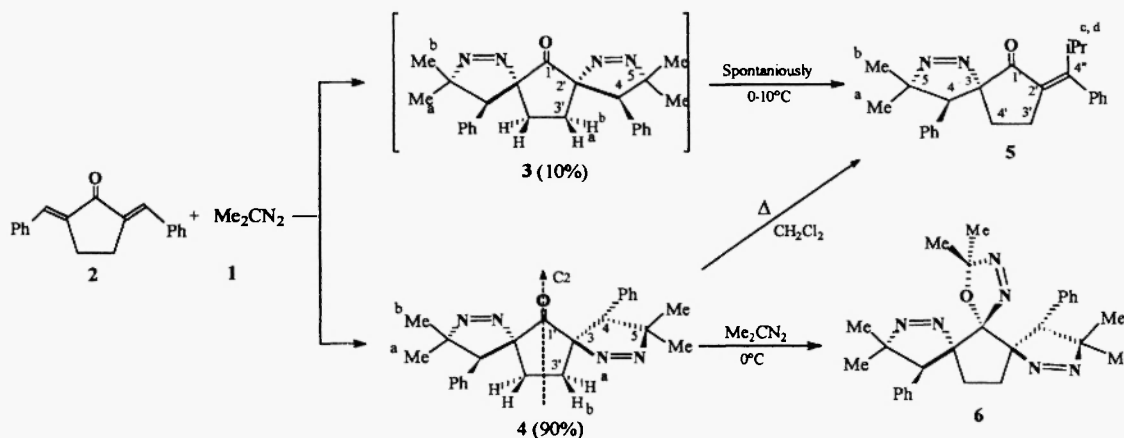


Figure 1

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## Results and discussion

The 1,3-dipolar cycloaddition reaction of 2-diazopropane (DAP) **1** on the dienone **2**<sup>(8)</sup>, done at 0°C, leads to the bis-spiro- $\Delta^1$ -pyrazolines **3** and **4** in 1: 9 ratios respectively. The minor bis-adduct **3**, which's the consequence of a *syn* approach of two DAP unit, is very instable and evolves spontaneously in solution at room temperature, to the ethylenic derivative **5**. The latter, can be also obtained by heating **4** in anhydrous dichloromethane, (Scheme 1).



Scheme 1

When an excess of DAP is added to the main diastereoisomer **4**, a new adduct **6** is formed. The FAB-MS ( $\text{MH}^+$  peaks) shows that **6** results from the addition of a third DAP unit compared to **3** and **4**. Moreover, IR and  $^{13}\text{C}$  NMR experiments showed the absence of the C=O function. The third DAP unit must have been added on the carbonyl. The  $^1\text{H}$  NMR spectrum of this adduct show six methyl singlets between 0.97 and 1.78ppm and two singlets at 1.98 and 3.48 ppm corresponding to  $\text{H}_{4'}$  and  $\text{H}_{4''}$  respectively. Furthermore, the 2D-HMBC experiment has enabled us to establish the oxadiazole ring regiochemistry. Thus, methyl (c) and (f) correlate only with a new quaternary carbon at 123.5 ppm which is C5 when carbon C2 (133.5ppm) correlates with  $\text{H}_{4'}$ ,  $\text{H}_{4''}$  and  $\text{H}_{6,7}$ , (figure 2). The high chemical shifts of these two carbons indicates that each one of them is linked to a heteroatom<sup>(9)</sup>. All these data are in agreements with a spiro- $\Delta^3$ -(1,3,4)-oxadiazole structure bearing two spiro- $\Delta^1$ -pyrazoliny rests and which correspond to an "inverse"<sup>(10)</sup> addition of 2-diazopropane on the carbonyl group. Other correlations confirming this structure were also established.

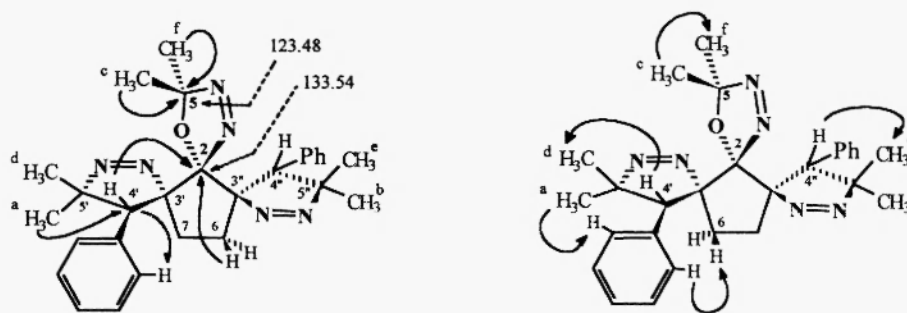
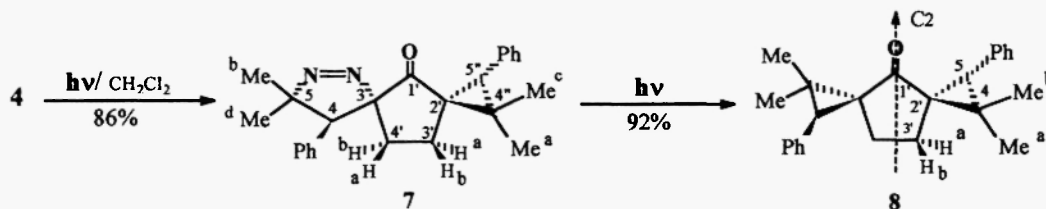


Figure 2: HMBC and NOESY correlations for **6**

The *gem*-dimethyl cyclopropane unit, fused or not to a carbocycle, is a commonly displayed architectural feature of natural products such as aristolone, phorobol and chrysantemic acids<sup>(11-15)</sup>. A *gem*-dimethyl  $\Delta^1$ -pyrazoline is a suitable precursor by a photochemical nitrogen extrusion.

The photolysis of **4** in anhydrous dichloromethane afforded first the correspondent *gem*-dimethyl cyclopropane derivatives **7**. The HMBC spectrum of this compound shows correlations of methyls **a** and **c** with carbons C2', C4'' and C5'' respectively at 43.0, 36.4 and 35.2 ppm and which constitute the cyclopropane unit.

When **7** was irradiated in similar conditions, the stereospecific<sup>(16)</sup> *gem*-dimethyl bis-spiro-cyclopropane **8** which is being determined by XR diffraction, was obtained in 92% yield (Scheme 2).



Scheme 2

## Conclusion

In conclusion, both carbonyl and the ethylenic double bond can be, *a priori*, subjected to 1,3-dipolar attack during the 1,3-cycloaddition process of diazoalkanes with  $\alpha,\beta$ -ethylenic ketones. The regiochemistry of the reaction can be discussed in term of HO(dipole)-LU(dipolarophile) favored interaction<sup>(17-20)</sup>. Further generalization of these results and the photochemistry<sup>(21)</sup> of these new spiro-oxadiazole structures are under investigations.

## Experimental

NMR spectra were recorded on a BRUKER AC-300 ( $^1\text{H}$  and  $^{13}\text{C}$ ) and AM-400 ( $^1\text{H}$ ,  $^{13}\text{C}$  and 2D-spectra) with TMS as an internal standard. Infrared spectra were run on a BIORAD FTS-6000 infrared spectrometer. Mass spectra were determined on a Nier-Johnson Kratos MS-80 Rf mass spectrometer with LSIMS technique (positive mode),  $\text{Cs}^+$  as a bombardment ion in a thioglycerol matrix. Melting points were determined on a BUCHI-510 capillary melting point apparatus. 2-Diazopropane **1** was prepared according to the Staudinger method and conserved in ethereal solutions at  $-78^\circ\text{C}$ . Dibenzylidene-cyclopentanones **2** was easily obtained by a basic aldolic condensation of benzaldehyde with cyclopentanone.<sup>(8)</sup> Thin Layer Chromatography (TLC) was performed on silica gel 60F-254 plates (Merck) with UV (254 nm) visualisation whereas chromatographic separations were conducted on silica gel Si-60-7734 Merck using water-jacketed columns. Microanalyses were performed at the "Service de Microanalyses de l'Institut de Chimie des Substances Naturelles", CNRS, Gif-Sur-Yvette, France.

### Preparation and characteristic data of **3** and **4**:

An ethereal solution of 2-diazopropane, prepared at  $-78^\circ\text{C}$ , was added, in small fractions, to a solution of **2** (7.7 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$ . The reaction was discontinued when the dienone **2** was completely consumed (TLC). The crude was chromatographed on silica gel water-jacketed column (8:2 hexane:AcOEt elution) to provide 0.64 mmol (9.88%) of the very instable **3** and 5.90 mmol (90.12%) of **4** as colorless crystals, mp.  $68$  and  $129^\circ\text{C}$  resp. Total yield 85%.

**Rel-(2'R,6'R)-Bis-dispiro(4-phenyl-5,5-dimethyl-dihydro-3H-pyrazol-3:2',5'-cyclopentan-1'-one) 3:**

IR v: 1760(C=O), 1543(C=C)<sub>arom</sub>, 2978(C-H); L.SIMS<sup>+</sup> m/z(%): 401(MH<sup>+</sup>, 43), 373(MH<sup>+</sup>-N<sub>2</sub>, 37), 345(MH<sup>+</sup>-2N<sub>2</sub>, 26); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta_{ppm}$ : 1.22(s, 6H, CH<sub>3</sub><sup>a</sup>), 1.54(s, 3H, CH<sub>3</sub><sup>b</sup>), 1.72(m, 2H, H3'a), 2.66(m, 2H, H3'b), 2.84(s, 2H, H4), 6.65-7.19(m, 10H, Ph); <sup>13</sup>C NMR (100 MHz)  $\delta$ : 23.7(Ca), 27.7(Cb), 28.5(C3'), 55.0(C4), 93.8(C5), 102.3(C3), 127.4, 128.2, 130.5, 134.8(Carom), 208.0 (C=O).

**Rel-(2'R,6'R)-bis-dispiro(4-phenyl-5,5-dimethyl-dihydro-3H-pyrazol-3:2',5'-cyclopentan-1'-one) 4:**

IR v: 1627(C=O), 1490(C=C)<sub>arom</sub>, 2954(C-H); L.SIMS<sup>+</sup> m/z(%): 401(MH<sup>+</sup>, 2), 373(MH<sup>+</sup>-N<sub>2</sub>, 4), 345(MH<sup>+</sup>-2N<sub>2</sub>, 100); <sup>1</sup>H NMR(400MHz, CDCl<sub>3</sub>)  $\delta_{ppm}$ : 1.20(s, 6H, CH<sub>3</sub><sup>a</sup>), 1.58(s, 3H, CH<sub>3</sub><sup>b</sup>), 2.36(m, 2H, H3'a), 2.45(m, 2H, H3'b), 3.26(s, 2H, H4), 6.92(m, 10H, Ph); <sup>13</sup>C NMR(100 MHz)  $\delta$ : 23.7 (Ca), 27.8 (Cb), 28.6(C3'), 55.0(C4), 93.8(C5), 102.3(C3), 127.3, 128.1, 130.6, 135.5 (Carom), 206.5 (C=O).

**Preparation and characteristic data of 5:**

A solution of 4 (0.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was refluxed, under N<sub>2</sub>, for 30 min. The crude product was purified by a silica gel column chromatography to give 0.43 mmol of 5 as yellow crystals, mp. 138°C, 57% yield.

**Rel-(3S,4S)-spiro(4-phenyl-5,5-dimethyl-4,5-dihydro-3H-pyrazol-3:5'-2'-(4"-isopropyl-4"phenyl)cyclopentanone 5:**

IR v: 1697(C=O), 1612(C=C)<sub>alky</sub>, 1592(C=C)<sub>arom</sub>, 2964(C-H); L.SIMS<sup>+</sup> m/z(%): 373(MH<sup>+</sup>, 28), 345(MH<sup>+</sup>-N<sub>2</sub>, 20); <sup>1</sup>H NMR(400MHz, CDCl<sub>3</sub>)  $\delta_{ppm}$ : 0.84 and 0.87(d, 6.8 and d, 6.9 Hz, CH<sub>3</sub><sup>c</sup>, iPr), 1.12(s, 3H, CH<sub>3</sub><sup>a</sup>), 1.59(s, 3H, CH<sub>3</sub><sup>b</sup>), 2.06(m, 2H, H3'b, H4'b), 2.60(m, 1H, H4'a), 2.81(m, 1H, H3'a), 3.31(s, 1H, H4), 4.28(m, 1H, H5'', iPr), 6.81-7.40(m, 10H, Harom); <sup>13</sup>C-NMR (100 MHz):  $\delta$ : 20.9(Cc), 21.0(Cd), 23.9(Ca), 27.9(Cb), 27.9(C3'), 28.8(C5''), 30.3(C4'), 52.5(C4), 94.1(C5), 107.8 (C3), 126.9 (C2'), 163.6(C4''), 199.5(C1'), 122.2-139.8(7 signals, Carom). Assignments through CHCORR, HMBC, COSY and NOESY experiments.

**Preparation and characteristic data of 6:**

An excess of DAP was added to a solution of 0.5 mmol of 4 in dry dichloromethane. After consumption of the starting material(TLC) and removal of the solvent, the product was purified by a silica gel column chromatography using n-hexane:AcOEt (8:2) as an eluant. 6 was obtained as colorless crystals, mp 133°C in 74% yield.

**Rel-(3'S,4'S,3''R,4''R)-2',5'-bis-(5,5-dimethyl-4-phenyl-4,5-dihydro-3H-pyrazol-3:2')-5,5-dimethyl-2,5-dihydro-(1,3,4)oxadiazole 6:**

IR: v: 1089(C-O), 1577(C=C)<sub>arom</sub>, 2973(C-H); L.SIMS<sup>+</sup>, m/z(%): 471(MH<sup>+</sup>, 8), 343(MH<sup>+</sup>-N<sub>2</sub>, 90), 345(MH<sup>+</sup>-2N<sub>2</sub>, 88), 387(MH<sup>+</sup>-3N<sub>2</sub>, 100), 401(MH<sup>+</sup>-Me<sub>2</sub>CN<sub>2</sub>, 10); <sup>1</sup>H NMR(400MHz, CDCl<sub>3</sub>)  $\delta_{ppm}$ : 0.97(s, 3H, CH<sub>3</sub><sup>a</sup>), 1.18 (s, 3H, CH<sub>3</sub><sup>b</sup>), 1.32(s, 6H, CH<sub>3</sub><sup>c</sup>), 1.34(s, 3H, CH<sub>3</sub><sup>d</sup>), 1.47(s, 3H, CH<sub>3</sub><sup>e</sup>), 1.78(s, 3H, CH<sub>3</sub><sup>f</sup>), 1.98(s, 1H, H4'), 2.79(m, 4H, H6,7), 3.48(s, 1H, H4''), 6.85-7.22(m, 10H, Ph); <sup>13</sup>C-NMR(100MHz)  $\delta$ : 23.5 (Ca), 24.4(Cb), 25.6(Cf), 26.3(Ce), 26.5(Cd), 27.1(Cc), 28.8 (C6), 28.9(C7), 52.2 (C4'), 52.6(C4''), 102.5(C3''), 91.1(C5'), 91.7(C5''), 100.1(C3'), 123.5(C5), 133.5(C2), 125.2-135.9(8 signals, Carom). Assignments through HMQC, HMBC, and NOESY experiments.

**Photolysis of the bis-spiro-pyrazoline 4****Preparation and characteristic data of 7 and 8**

A solution of 3 (200mg, 0.5 mmol) in dry dichloromethane, was irradiated with a super high pressure mercury vapor lamp, in an immersion apparatus for solution phase photochemistry. After 15-20 min and removal of the solvent, the crude product was purified by a flash chromatography to provide 160mg (0.43mmol) of 7 as a colorless crystals, mp 129°C, 86% yield.

**Rel-(2'R,2S,4S)-spiro(2-phenyl-3,3-dimethylcyclopropane-1:2')-spiro(4phenyl-5,5-dimethyl-4,5-dihydro-3H-pyrazol-3:5')-cyclopentanone 7:**

IR:  $\nu$ : 1627(C=O), 1490(C=C)<sub>arom</sub>, 2954(C-H); L.SIMS<sup>+</sup>  $m/z$ (%): 373(MH<sup>+</sup>,100), 345(MH<sup>+</sup>-N<sub>2</sub>, 80); <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 1.00(s, 3H, CH<sub>3</sub><sup>a</sup>), 1.27(s, 3H, CH<sub>3</sub><sup>b</sup>), 1.34(s, 3H, CH<sub>3</sub><sup>c</sup>), 1.54(m, 1H, H3'a), 1.60(s, 3H, CH<sub>3</sub><sup>d</sup>), 1.92(m, 1H, H3'b), 2.48(m, 1H, H4'a), 2.57(m, 1H, H4'b), 2.94(s, 1H, H4''), 3.18(s, 1H, H4), 6.97-7.18(m, 10H, Ph); <sup>13</sup>C-NMR (100 MHz):  $\delta$ : 19.6(Ca), 20.0(Cc), 21.1(C4'), 23.1(C3'), 23.9(Cb), 28.1(Cd), 35.2(C5''), 43.0(C4''), 53.5(C4), 93.75(C2'), 94.1(C5), 105.3(C3), 126.0-148.9(8 signals, Carom), 200.4 (C1'). Assignments through HMQC, HMBC, COSY and NOESY experiments.

The same procedure used for 7 give 8 as colorless crystals, mp 102°C, 92% yield.

**Rel-(1R, 2S, 2''S)-bis-dispiro-(2-phenyl-3,3-dimethyl-cyclopropane-1:2')-2'-5'-cyclopentanone 8 :**

IR:  $\nu$ : 1627(C=O), 1490(C=C)<sub>arom</sub>, 2954(C-H); ELMS  $m/z$ (%): 344(M<sup>+</sup>, 20), 213(40), 91(100); <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 1.10(s, 6H, CH<sub>3</sub><sup>a</sup>), 1.40(s, 6H, CH<sub>3</sub><sup>b</sup>), 1.80(m, 2H, H3'a), 1.90(m, 2H, H3'b), 2.71(s, 2H, H4), 7.06-7.20(m, 10H, Ph); <sup>13</sup>C-NMR (75MHz):  $\delta$ : 19.7(Ca), 21.0(Cb), 25.0(C3'), 40.7(C4), 44.0(C2'), 32.6(C5), 126.3, 128.2, 130.3, 136.3 (Carom).

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