A NEW SPIRO-Δ^3-(1,3,4) OXADIAZOLE FROM 2-DIAZOPROPANE AND 2,5-DIBENZYLIDENECYCLOPENTANONE

L. Gouiaa[a], N. Boukamcha[b]*, M.-T. Martin[c] and A. Khemiss[a]

[a] *Laboratoire de Synthèse Hétérocyclique et de Photochimie, Faculte des Sciences, 5000, Monastir, Tunisie.*

[b] *Institut Préparatoire aux Etudes d'Ingenieur de Monastir, 5000, Monastir, Tunisie.*

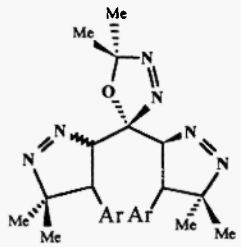
[c] *Service de RMN, Institut de Chimie des Substances Naturelles, C.N.R.S, 91190, Gif-Sur-Yvette, France.*

Abstarct

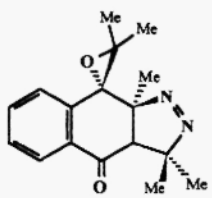
The 1,3-cycloaddition of 2-diazopropane **1** on 2,5-dibenzylidenecyclopentanone **2** leads, beside the expected diastereoisomers bis-spiro-Δ^1-pyrazolines **3** and **4**, to a new spiro-Δ^3-(1,3,4)oxadiazole bearing two spiro-Δ^1-pyrazolinyl rests **6**. The photolysis of the major diastereoisomer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

Introduction

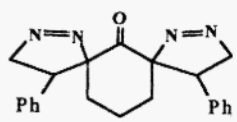
We have recently described[1] a diasteroselective synthesis of a new Δ^3-(1,3,4)oxadiazoles[2] structures **1'** by 1,3-cycloaddition of 2-diazopropane[3,4] on an acyclic dienone, the diarylidenacetone. In order to generalize our approach, we focus on the exocyclic 2,5-diarylidenecyclopentanone, dienone **2**. The simultaneous addition of 2-diazopropane on the carbonyl and the ethylenic double bond was rarely mentioned. Only Dean et al.[5] have obtained a *gem*-dimethyl spiro-oxirane **2'** by treating the 2-methyl-1,4-naphtoquinone 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.[6] 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.[7]



1'



2'



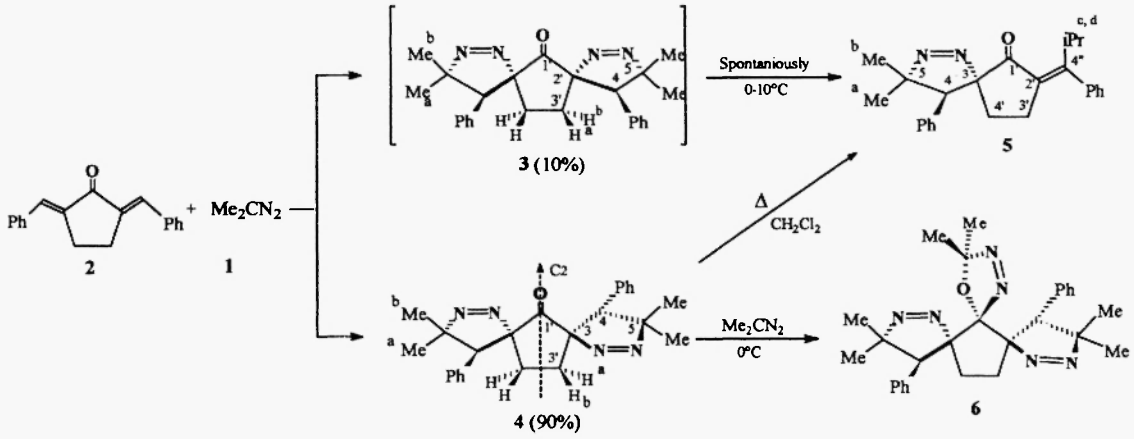
3'

Figure 1

* Corresponding author. Fax: 216 73 500 512. E. mail: Najeh.Boukamcha@ipeiss.rnu.tn

Results and discussion

The 1,3-dipolar cycloaddition reaction of 2-diazopropane (DAP) **1** on the dienone **2**[8], done at O°C, leads to the bis-spiro-Δ¹-pyrazolines **3** an **4** in 1: 9 ratios repectively. The minor bis-adduct **3**, which's the consequence of a *syn* approach of two DAP unit, is very instable and evolutes 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 (MH^+ peaks) shows that **6** results from the addition of a third DAP unit compared to **3** and **4**. Moreover, IR and ^{13}C NMR experiments showed the absence of the C=O function. The third DAP unit must have been added on the carbonyl. The ^1H 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 H4' and H4'' 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 H4',4'' and H6,7, (figure 2). The high chemical shifts of these two carbons indicates that each one of them is linked to an heteroatom[9]. All these data are in agreements with a spiro-Δ³- (1,3,4)-oxadiazole structure bearing two spiro-Δ¹-pyrazolinyl rests and which correspond to an "inverse"[10] addition of 2-diazopropane on the carbonyl group. Other correlations confirming this structure were also established.

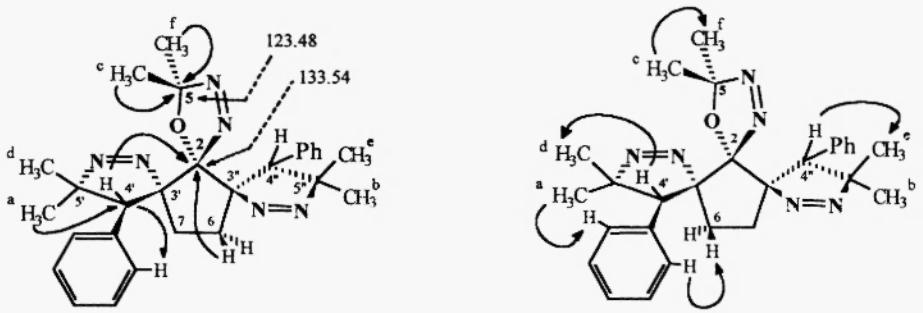
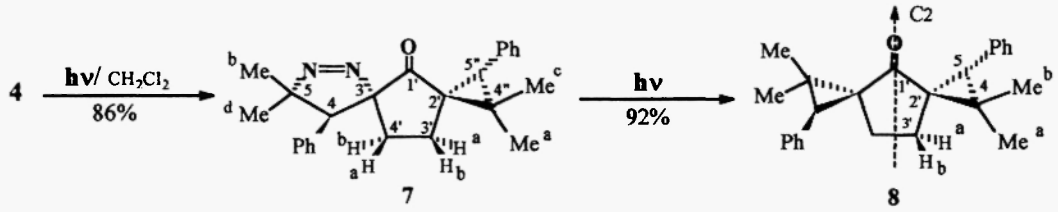


Figure 2: HMBC and NOESY correlations for **6**

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[11-15]. A *gem*-dimethyl Δ^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 wich constitute the cyclopropane unit.

When 7 was irradiated in similar conditions, the stereospecific[16] *gem*-dimethyl bis-spiro-cyclopropane 8 wich 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 α,β-ethylenic ketones. The regiochemistry of the reaction can be discussed in term of HO(dipole)-LU(dipolarophile) favored interaction[17-20]. Further generalization of these results and the photochemistry[21] of these new spiro-oxadiazole structures are under investigations.

Experimental

NMR spectra were recorded on a BRUKER AC-300 (^{1}H and ^{13}C) and AM-400 (^{1}H, ^{13}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), 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 etheral solutions at -78°C. Dibenzylidecyclopentanones 2 was easily obtained by a basic aldolic condensation of benzaldehyde with cyclopentanone.[8] 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°C, was added, in small fractions, to a solution of 2 (7.7 mmol) in anhydrous CH_2Cl_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°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 ν: 1760(C=O), 1543(C=C)$_{arom}$, 2978(C-H); L.SIMS$^+$ m/z(%): 401(MH^+,43), 373(MH^+-N_2, 37), 345(MH^+-2N_2, 26); ^{1}H NMR (400MHz, $CDCl_3$) δ_{ppm}: 1.22(s, 6H, CH_3^a), 1.54(s, 3H, CH_3^b), 1.72(m, 2H, H3'a), 2.66(m, 2H, H3'b), 2.84(s, 2H, H4), 6.65-7.19(m, 10H, Ph) ; ^{13}C NMR (100 MHz) δ: 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-diméthyl-dihydro-3H-pyrazol-3:2',5'-cyclopentan-1'-one) 4:

IR ν: 1627(C=O), 1490(C=C)$_{arom}$ 2954(C-H); L.SIMS$^+$ m/z(%): 401(MH^+,2), 373(MH^+-N_2, 4), 345(MH^+-2N_2, 100); ^{1}H NMR(400MHz, $CDCl_3$) δ_{ppm}: 1.20(s, 6H, CH_3^a), 1.58(s, 3H, CH_3^b), 2.36(m, 2H, H3'a), 2.45(m, 2H, H3'b), 3.26(s, 2H, H4), 6.92(m, 10H, Ph) ;^{13}C NMR(100 MHz) δ: 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_2Cl_2 was refluxed, under N_2, for 30 min. The crude product was purified by a silica gel column chromatography to give 0.43 mmol of **5** as yellow cristals, 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 ν: 1697(C=O), 1612(C=C)$_{ethy}$, 1592(C=C)$_{arom}$, 2964(C-H); L.SIMS$^+$ m/z(%): 373(MH^+,28), 345(MH^+-N_2, 20); ^{1}H NMR(400MHz, $CDCl_3$) δ_{ppm}: 0.84 and 0.87(d, 6.8 and d, 6.9 Hz, $CH_3^{c,c'}$, iPr), 1.12(s, 3H, CH_3^a), 1.59(s, 3H, CH_3^b), 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); ^{13}C-NMR (100 MHz): δ: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 us 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: ν: 1089(C-O), 1577(C=C)$_{arom}$, 2973(C-H); L.SIMS$^+$, m/z(%): 471(MH^+,8), 343(MH^+-N_2, 90), 345(MH^+-2N_2, 88), 387(MH^+-3N_2, 100), 401(MH^+-Me_2CN_2, 10); ^{1}H NMR(400MHz, $CDCl_3$) δ_{ppm}: 0.97(s, 3H, CH_3^a), 1.18 (s, 3H, CH_3^b), 1.32(s, 6H, CH_3^c), 1.34(s, 3H, CH_3^d), 1.47(s, 3H, CH_3^e), 1.78(s, 3H, CH_3^f), 1.98(s, 1H, H4'), 2.79(m, 4H, H6,7), 3.48(s,1H, H4"), 6.85-7.22(m, 10H, Ph); ^{13}C-NMR(100MHz) δ: 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 caracteristic 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 provide160mg (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: v: 1627(C=O), 1490(C=C)$_{arom}$, 2954(C-H); L.SIMS$^+$ m/z(%): 373(MH^+,100), 345(MH^+-N_2, 80); ^{1}H NMR (400MHz, $CDCl_3$) δ_{ppm}: 1.00(s, 3H, CH_3^a), 1.27(s, 3H, CH_3^b), 1.34(s, 3H, CH_3^c), 1.54(m, 1H, H3'a), 1.60(s, 3H, CH_3^d), 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); ^{13}C-NMR (100 MHz): δ: 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. v: 1627(C=O), 1490(C=C)$_{arom}$, 2954(C-H); ELMS m/z(%): 344(M^+, 20), 213(40), 91(100); ^{1}H NMR (300MHz, $CDCl_3$) δ_{ppm}: 1.10(s, 6H, CH_3^a), 1.40(s, 6H, CH_3^b), 1.80(m, 2H, H3'a), 1.90(m, 2H, H3'b), 2.71(s, 2H, H4), 7.06-7.20(m, 10H,Ph);^{13}C-NMR (75MHz): δ: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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