Pergamon

Tetrahedron 55 (1999) 449–460

TETRAHEDRON

Stereo- and Chemoselectivity in 1,3-Dipolar Cycloaddition Reaction of 2-Diazopropane with Diarylidenacetones

N. Boukamcha[a], R. Gharbi[a], M.-T. Martin[b]#, A. Chiaroni[b] Z. Mighri[a] and A. Khemiss[a]*

[a] Laboratoire de Chimie des Substances Naturelles et de Synthèse Organique
Faculté des Sciences, 5000, Monastir, Tunisie.

[b] Institut de Chimie des Substances Naturelles, CNRS,
91190, Gif-Sur-Yvette, France

Received 20 February 1998; accepted 5 November 1998

Abstract: 1,3-Dipolar cycloaddition reaction of 2-diazopropane **1** with diarylideneacetones **2** carried out at 0°C led to a minor Δ^2-pyrazoline monocycloadduct **4** and two diastereoisomeric bicycloadducts **5** and **6**. The same addition realised at -60°C has enabled us to observe, beside bis-Δ^2-pyrazolines **5** and **6**, the formation of unexpected Δ^3-(1,3,4)oxadiazoline derivatives **9** and **10**. These two diastereoisomers result from the addition of 2-diazopropane on the carbonyl of unstable Δ^1-pyrazoline intermediates **3'** and **3''** with an unusual regiochemical way. Oxidation of **5** and **6** gave 3H-pyrazoles **7** and **8**.

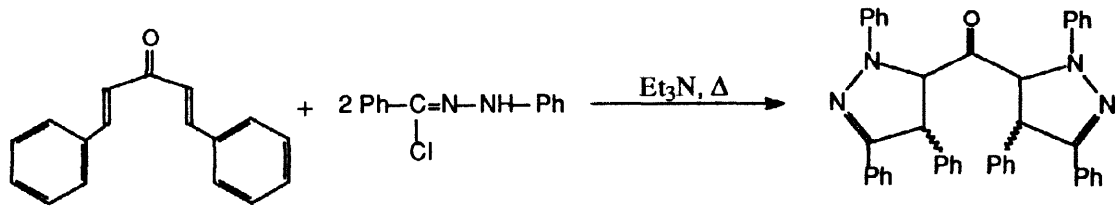
INTRODUCTION

The present work is part of a larger project studying the 1,3-dipolar cycloaddition reactions of 2-diazopropane[1] (DAP) **1** with α,β-ethylenic ketones. The chemical reactivity of diazoalkanes according to α,β-unsaturated ketones, as well as the regio- and stereoselectivity of these reactions have been thoroughly studied.[3-6] However, the simultaneous addition of 2-diazopropane on the carbonyl and the ethylenic double bond is rarely and scantily mentioned before in the literature.[7] To study the different aspects of the reaction: diastereo-, regio- and chemoselectivity (site selectivity) we are interested in diarylidenacetones[2] **2**, which are considered as suitable dipolarophiles.

Tsatsaroni et al.[8] described the addition of diphenylnitrile imine on dibenzylidenacetone as both a regio- and diastereospecific reaction. These results are quite surprising because one can predict the formation of bis-pyrazoline diastereoisomers resulting from different approaches of dibenzylideneacetone by diphenylnitrile imine (Scheme 1).

Email : mtm@icsn.cnrs-gif.fr ; Fax : 33 01 69 07 72 47

0040-4020/99/$ - see front matter
PII: S0040-4020(98)01056-4



Scheme 1

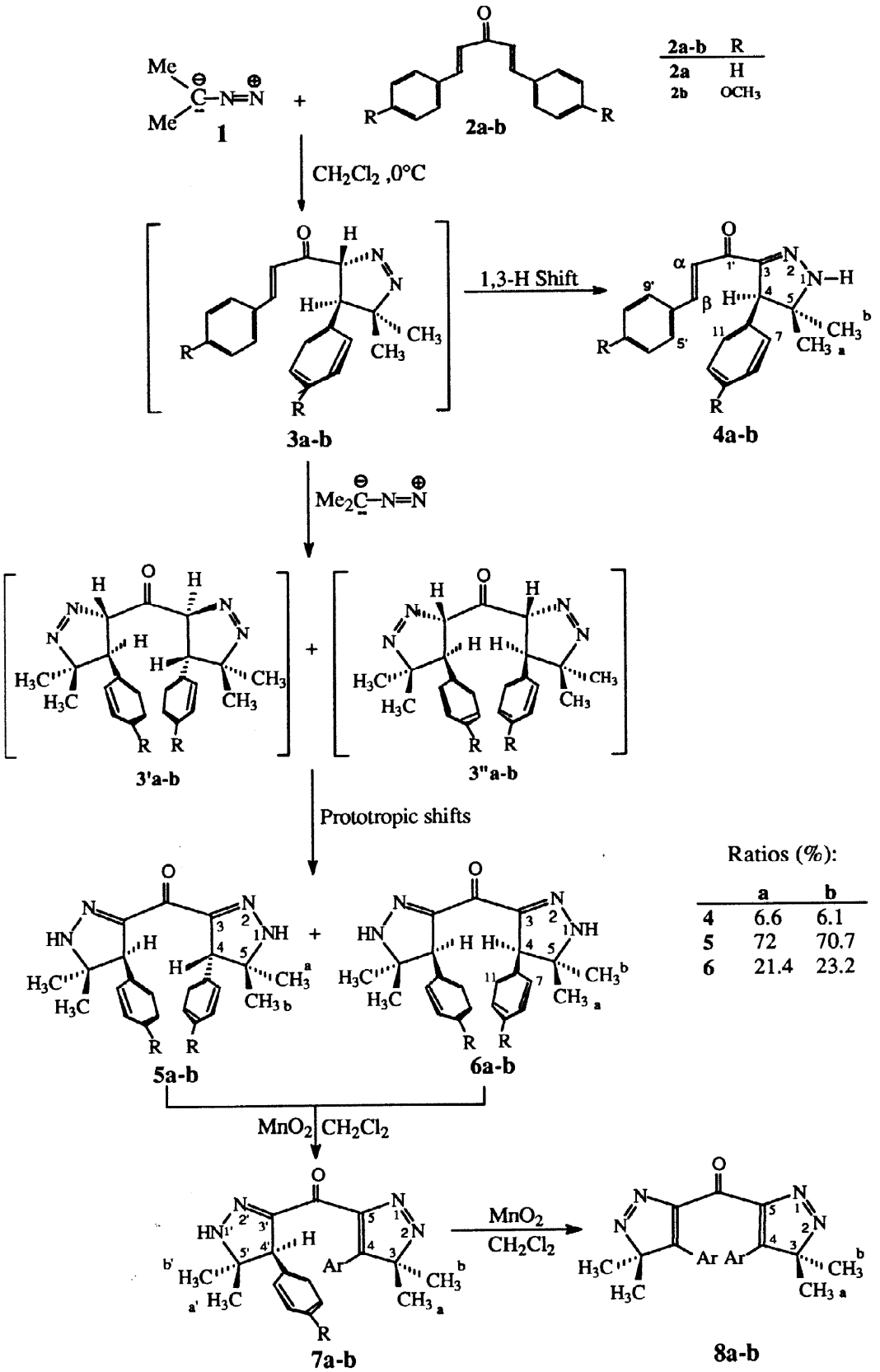
We recently noticed that the chemoselectivity of the addition of 2-diazopropane with acyclic α,β-ethylenic ketones is temperature dependent[9] and in order to better elucidate this aspect, all the addition reactions were carried out at two extreme temperatures, 0°C and -60°C.

RESULTS AND DISCUSSION

The 1,3-dipolar cycloaddition reaction of 2-diazopropane **1** with diarylidenacetones **2** realized at 0°C led first to unstable mono-Δ^1-pyrazoline intermediate **3** which undergoes a subsequent prototropic shift[10,11] to yield the Δ^2-pyrazoline monocycloadduct **4**. The reaction was followed by Thin Layer Chromatography which showed the formation of the bis-Δ^2-pyrazolines **5** and **6** whereas the enone **2** has not totally reacted. Moreover, the very small ratios (~ 6,3 %) of the monocycloadduct **4** made us think that there is a competition between the formation of the later derivative, via the Δ^1-pyrazoline intermediate **3**, and a second DAP addition to give bicycloadducts **5** and **6** (Scheme 2). Intermediate **3** is probably more reactive towards 2-diazopropane than enone **2**.

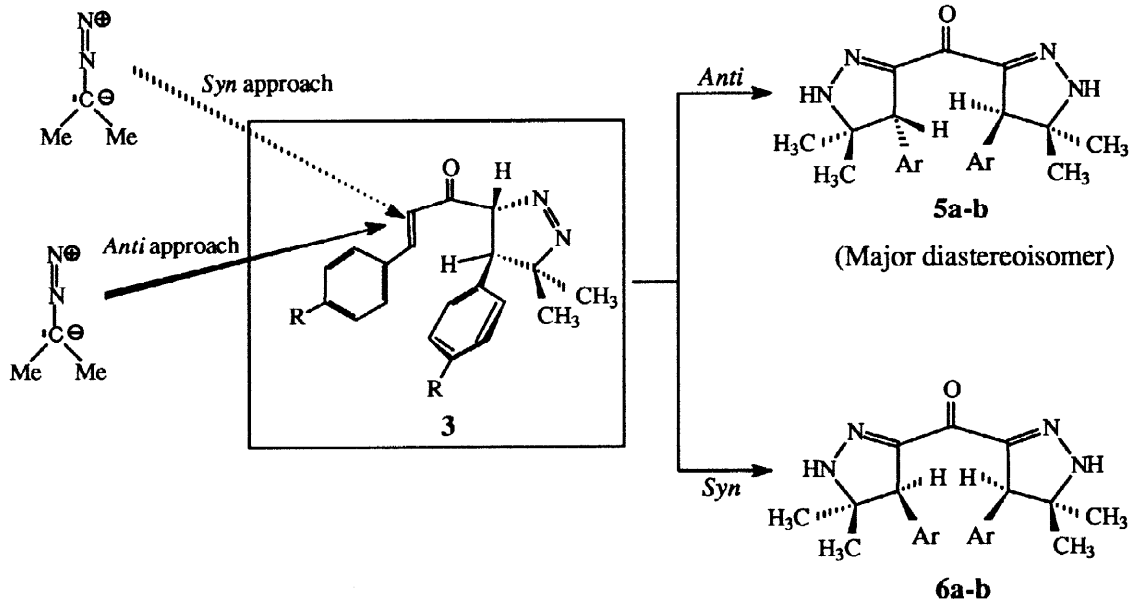
The proton NMR spectra of **5** and **6** showed symmetric structures because of the reduced number of signals. The FAB mass and two-dimensional NMR spectra of these adducts are identical and correspond to diastereoisomeric structures indiscernible by spectroscopic analyses. However, regiochemical assignments of all adducts were deduced from their HMBC 2D-NMR spectra. Methyl protons (a) and (b) correlate only with two carbon atoms C_4 and C_5 and each other suggesting that they are directly linked to the quaternary carbon C_5. In a similar manner, aromatic protons H_7 and H_{11} correlate with the carbon C_4 which is directly bonded to the aryl group. Consequently, this latter correlation shows Ar—C_4—C_5—(Me(a),Me(b)) linkages indicative of a "normal" regiochemistry which is generally observed in 1,3-dipolar cycloaddition reactions of simple diazoalkanes with α,β-unsaturated ketones.[12]

In the same way, a whole set of linkages that confirm these structures was also established. Assignement of the (a) and (b) methyls in all adducts, was deduced from their NOESY spectra. An observed nOe cross peak between both H_7 and H_{11} and methyl (a) placed these three units on the same side of the average pyrazole ring plane. H_4 and methyl (b) are therefore, on the other side of this plane.


2a-b R
2a H
2b OCH3
1
2a-b
CH2Cl2 ,0°C
3a-b
1,3-H Shift
4a-b
Me2C–N=N
3'a-b
3"a-b
Prototropic shifts
Ratios (%):
a b
4 6.6 6.1
5 72 70.7
6 21.4 23.2
5a-b
6a-b
MnO2 CH2Cl2
7a-b
MnO2
CH2Cl2
8a-b

Scheme 2

The observed diastereoselectivity between **5** and **6**, which can be explained by steric considerations, may lead us to distinguish them. As a matter of fact, during formation of these adducts, the two faces of precursor dipolarophilic intermediates **3** are not equivalent i.e. diastereotopic. So the second 2-diazopropane unit preferentially attacks from the *anti* side relative to the first one already added (scheme 3).



Scheme 3

Oxidation of bis-Δ^2-pyrazolines **5** and **6** led first to (dihydro-1H-pyrazolyl)(3H-pyrazolyl)ketones **7** and then to bis-3H-pyrazoles **8** which can be considered as suitable precursors to gem-dimethylcyclopropenes after photochemical nitrogen extrusion[13-15] (scheme 2).

The same 1,3-dipolar cycloaddition reaction done at -60°C was slower and led, beside expected bicycloadducts **5** and **6** to two new products **9** and **10** with a ratio of 8:2. Microanalyses and FAB mass spectrometry (MH^+ peaks) indicate that **9** and **10** result from addition of a third DAP equivalent compared with **5** and **6**. IR spectra of these two new adducts show a total absence of N-H and C=O bands. Moreover, there are no carbonyl signals in the ^{13}C NMR spectra, so the third DAP unit, must have added to the carbonyl function. On the other hand, ^1H NMR spectra of adducts **9** shows six methyl singlets and four doublets (1H) each relative to two AX patterns with average coupling constants of 8.8Hz. However, ^1H NMR spectra of adducts **10** show fewer signals compared to those of **9** (only three methyl singlets and one AX pattern). Adducts **10** have therefore, symmetrical structures.

Regiochemistry of these two adducts could be also established from their HMBC spectra. The assignment procedure for the Δ^1-pyrazoline rings is analogous to that for **4**, **5** and **6**. The C_4-, C_4-H_{arom} correlations showed the same addition mode of 2-diazopropane on the ethylenic double bonds (Fig. 1).

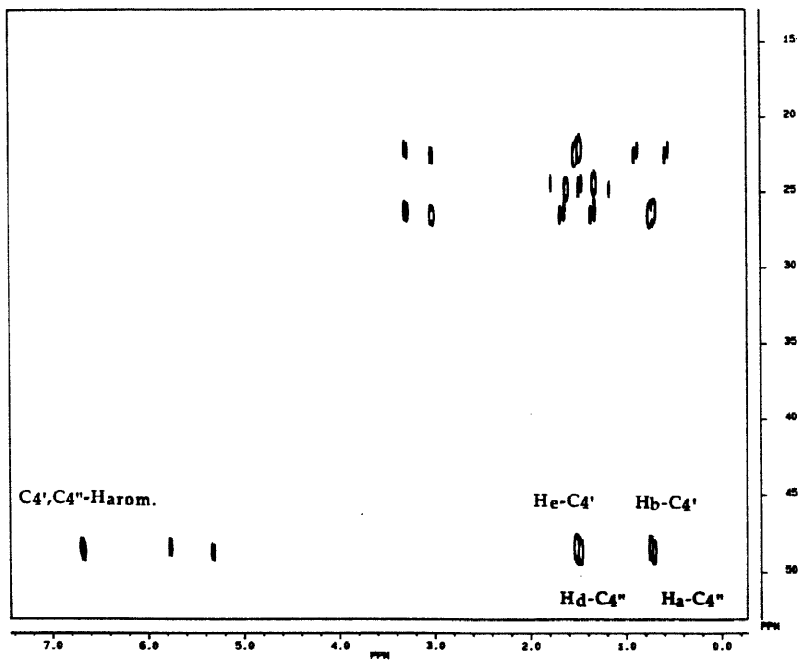


Fig. 1. 12.8-53.0 ppm enlargement of HMBC spectrum of adduct **9b**.

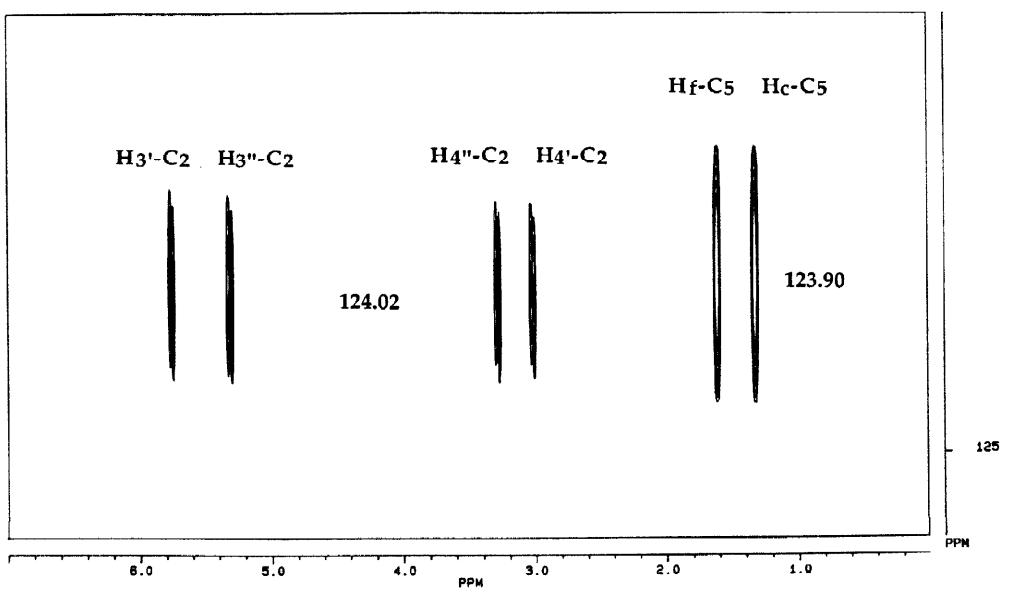
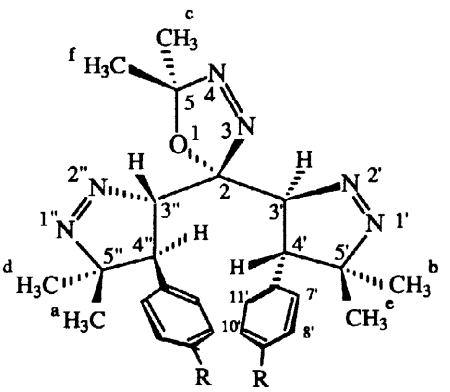
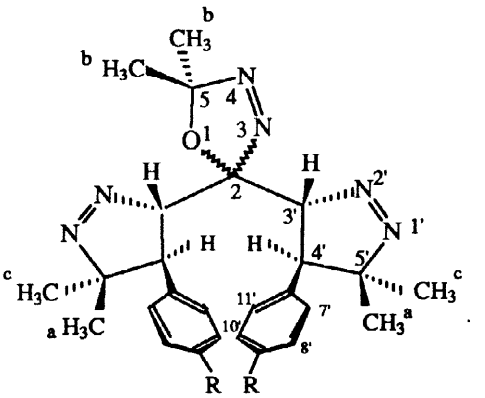


Fig. 2. 122.0-125.6 ppm enlargement of HMBC spectrum of adduct **9b**.

For the oxadiazole ring which is the consequence of the third DAP addition, the 122.0-125.6 ppm enlargement of the HMBC spectrum of adduct **9b** shows correlations of pyrazoline protons $H_{3'}$, $H_{3''}$ and $H_{4'}$, $H_{4''}$ with a new quaternary carbon at 124.02 ppm which is C_2. Methyl protons (c) and (f), correlate with each other and with only the quaternary carbon at 123.9 ppm: C_5 (Fig.2). Moreover, the high and very similar chemical shifts of C_2 and C_5 indicate that each of these two carbons is linked to heteroatoms. For adduct **10b** the 120.70-125.87 ppm enlargement of its HMBC spectrum demonstrate the same 2D-structure. All these data are in agreement with Δ^3-(1,3,4)oxadiazoline structures bearing two Δ^1-pyrazoline rings which are diastereoisomers and correspond to an "inverse" addition of 2-diazopropane on the carbonyl function (Fig. 3).



9a-b



10a-b

Fig. 3.

The relative positions of the pyrazole methyls (a, b, d and e or a and c) were established from NOESY maps. However, from these maps one cannot establish the stereochemistry of the oxadiazole ring in respect of the pyrazole ones in the case of adducts **10**. A single crystal X-ray analysis was therefore indispensable to establish the exact relative configuration of the oxadiazole ring. This study has unambiguously demonstrated the configuration corresponding to minimal steric hindrance.

A perspective view of the molecule appears in figure 4 showing in the crystal, the non symmetrical arrangement of the two moieties with respect to the

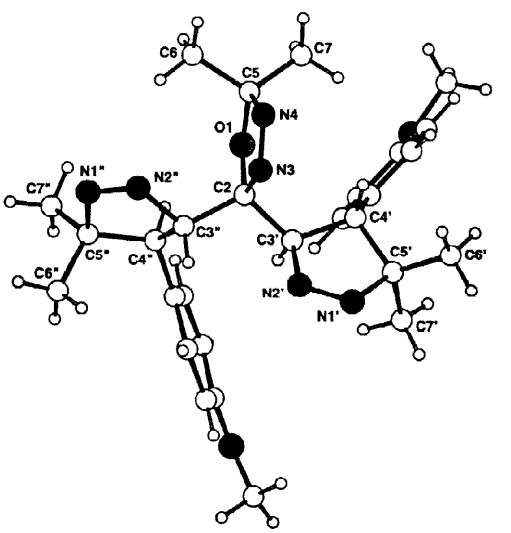
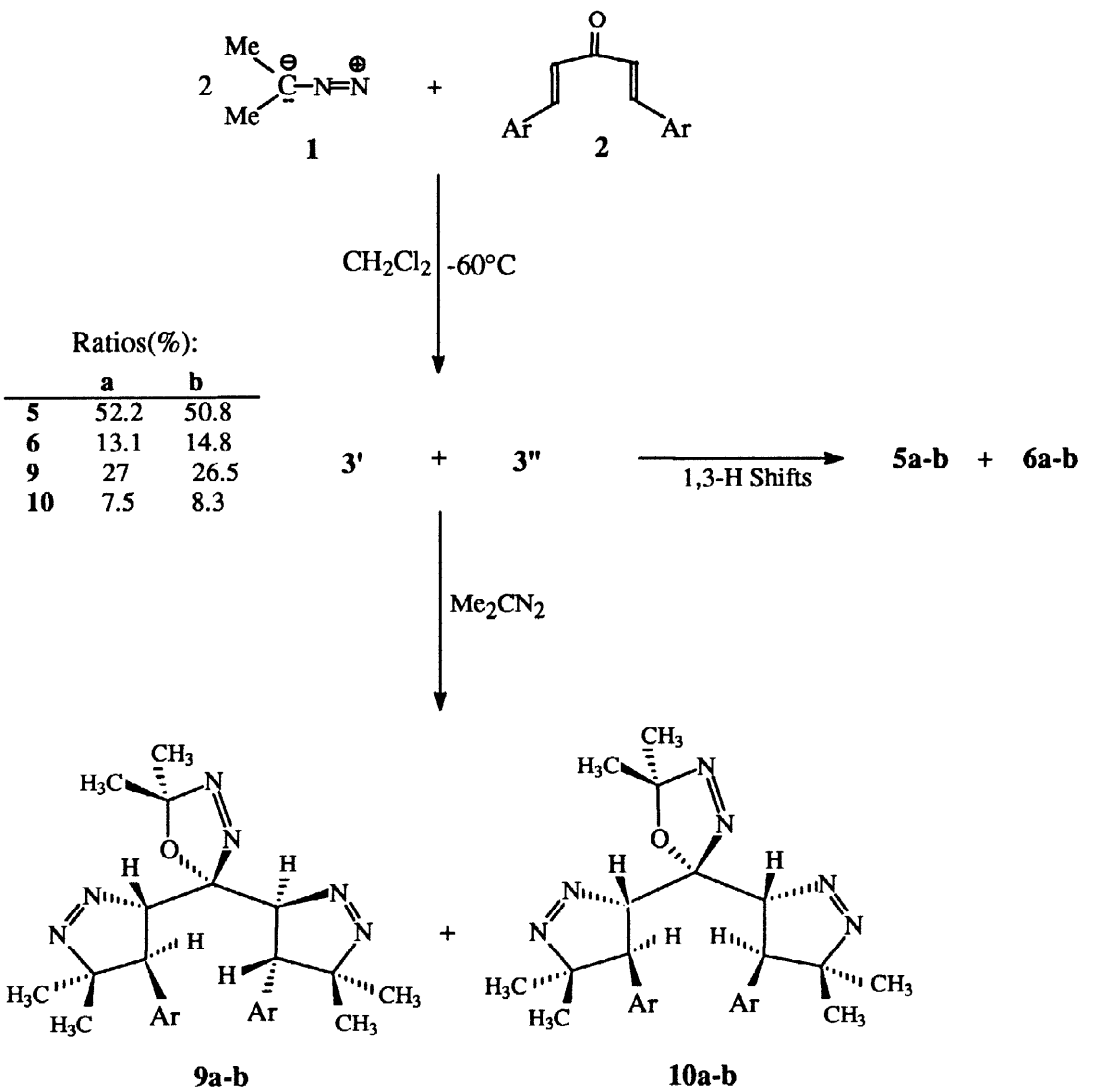


Fig. 4. X-Ray crystal structure of diastereisomer **10b**

oxadiazole ring and that the three five-membered rings are perpendicular to each other. The " inverse" mode addition of DAP on carbonyl was also easily confirmed.

Oxadiazolines **9** and **10** probably result from Δ^1-pyrazoline transient species **3'** and **3''** which are relatively stable at low temperature so that, they can be attacked by a third 2-diazopropane unit (scheme 4). The "inverse" regiochemical sense in cycloaddition of 2-diazopropane on the carbonyl function seems to be essentially conditioned by steric factors. (Steric hindrance of C_2 leads to its attack by the terminal nitrogen atom of 2-diazopropane, instead of C_5 bearing the two methyls).



Scheme 4

CONCLUSION

During the 1,3-dipolar cycloaddition of 2-diazopropane with α,β-ethylenic ketones, both carbonyl and ethylenic double bond can be *a priori*, subjected to 1,3-dipolar attack. The regiochemistry of these reactions can be discussed in term of HO(1,3-dipole)-LU(dipolarophile) favored interaction.[16-19]

Further generalisation of these results, their implication for the synthesis of various heterocyclic compounds and the photochemistry of the 3H-pyrazole and the oxadiazole structures are under investigations.

EXPERIMENTAL SECTION

NMR spectra were recorded on a BRUKER AC-300 (^1H and ^{13}C) and AM-400 (^1H, ^{13}C and 2D-spectra) with TMS as an internal standard. Signal assignments were based on HMBC and NOESY experiments. Infrared spectra were run on a PERKIN-ELMER IR-197 infrared spectrometer. Mass spectra were determined on a Nier-Johnson Kratos MS-80 Rf mass spectrometer with FAB technique (positive mode), xenon as a bombardment gas 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[1] method and conserved in etheral solutions at -78°C. Diarylidenacetones **2** were easily obtained by basic aldolic condensations of benzaldehydes with acetone.[2] 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.

Cycloaddition reaction at 0°C of 2-diazopropane with enones 2a-b.
General procedure for cycloadducts 4a-b, 5a-b and 6a-b.

To a stirred solution containing 3g (12.8-10.2 mmol) of diarylideneacetone **2a-b** in 50 ml of anhydrous dichloromethane at 0°C was added in small fractions a 2.6M etheral solution of 2-diazopropane prepared at -78°C. The progress of the reaction was monitored by a TLC control (60-40 hexane-ethyl acetate elution) and the reaction was discontinued when enone **2a-b** had totally reacted. The solution was allowed to react 12h at 0°C and the solvent was evaporated under reduced pressure. The resulting crude oil was chromatographed on a silica gel column using hexane, progressively enriched until 50% with ethyl acetate, as the eluant. Monoadduct **4a-b**, (180-130mg ,0.6-0.35mmol) was eluted first, and then successively the bisadducts **5a-b**, (2.46-1.76g, 6.57-4.05 mmol) and **6a-b**, (720-580mg, 0.60-0.35 mmol). Total yields, 70-57%. Structures of all adducts were assigned by their analytical and spectral properties as follows:

Rel-(4R)-(5,5-dimethyl-4-phenyl-4,5-dihydro-1H-pyrazolyl-3yl-)(2-phenylethenyl)ketone (4a). Green-yellow solid; mp 162°C. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.94; H, 6.57; N, 5.26. Found: C, 78.28; H, 6.75; N, 5.58. IR (KBr) ν_{cm-1}: 1580 (C=N), 1600 $(C=C)_{arom}$, 1620 (C=C), 1640 (C=O), 2950 (C-H), 3300 (N-H); FAB-MS m/z(%): 305 (MH^+, 100), 217 (45), 201 (Ph-$C_5N_2H_8$-C≡O^+, 30), 131 (Ph-C_2H_2-C≡O^+, 30); ^1H-NMR (300 MHz, C_6D_6) δ: 0.62 (s, 3H, CH_3(a)), 0.95 (s, 3H, CH_3(b)), 4.00 (s, 1H, H_4), 5.62 (s, 1H, exchangeable, H_1), 7.10-7.40 (m, 10H, H_{arom}); 7.80 and 8.04 (m, 2H,

H_α,H_β): AB patt. J=16.5 Hz; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.7 (CH_3(a)), 29.3 (CH3(b)), 58.0 (C_4), 68.2 (C_5), 121.1 (C_β), 127.3-136.6 (8 signals, C_{arom}), 141.7 (C_α),153.5 (C_3), 184.3 ($C_{1'}$).

Rel-(4R)-(4-anisyl-5,5-dimethyl-4,5-dihydro-1H-pyrazolyl-3yl-)(2-anisylethenyl)ketone (4b). Green-yellow solid; mp 124°C. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.52; H, 6.59; N, 13.18. Found: C, 73.08; H, 7.05; N, 13.56. IR (KBr) ν_{cm-1}: 1570 (C=N), 1590 (C=C)$_{arom}$, 1610 (C=C), 1630 (C=O), 2900 (C-H), 3350 (N-H); FAB-MS m/z(%): 365 MH^+, 100), 217 (45), 231(p-CH_3OPh-$C_5N_2H_8$-C≡O^+, 25), 161(p-CH_3OPh -C_2H_2-C≡O^+, 46); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (s, 3H, CH_3(a)), 1.33 (s, 3H, CH_3(b)), 3.75 (s, 3H, OCH_3, pyrazol), 3.82 (s, 3H, OCH_3, anisyl), 4.00 (s, 1H, H_4), 6.11 (s, 1H, exchangeable, H_1), 6.80 (m, 2H, $H_{8,10}$) and 6.95 (m, 2H, $H_{7,11}$): AA'BB' patt. J=8.4 Hz, 6.88 (m, 2H, $H_{6',8'}$) and 7.55 (m, 2H, $H_{5',9'}$): AA'BB' patt. J=8.6 Hz, 7.62 (s, 2H, H_α, H_β); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.5 (CH_3(a)), 29.0 (CH_3(b)), 55.1 (OCH_3, pyrazol), 55.9 (OCH_3, anisyl), 57.2 (C_4), 67.2 (C_5), 113.9 ($C_{8,10}$), 114.2 ($C_{6',8'}$), 119.7 (C_α), 127.5 ($C_{4'}$), 128.7 (C_6), 129.2 ($C_{7,11}$), 130.7 ($C_{5',9'}$), 141.4 (C_β), 158.6 (C_3), 161.2 ($C_{7'}$), 162.1 (C_9), 184.1 ($C_{1'}$).

Rel-(4S,4'S)-bis-(5,5-dimethyl-4-phenyl-4,5-dihydro-1H-pyrazol-3yl)ketone (5a). Pale-yellow solid; mp 240°C. Anal. Calcd for $C_{23}H_{26}N_4O$: C, 73.79; H, 6.95; N, 14.97. Found: C, 73.82; H, 6.99; N, 15.02. IR (KBr) ν_{cm-1}: 1540 (C=N), 1620 (C=O), 3000 C-H), 3350 (N-H); FAB-MS m/z(%): 375 (MH^+, 100), 201 (Ph-$C_5N_2H_8$-C≡O^+, 57); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.70 (s, 6H, CH_3(a)), 1.30 (s, 6H, CH_3(b), 4.10 (s, 2H, H_4), 6.15 (s, 2H, exchangeable, H_1), 6.85-7.20 (m, 10H, H_{arom}); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.7 (CH_3(a)), 28.0 (CH_3(b)), 58.4 (C_4), 66.2 (C_5), 126.3-137.5 (4 signals, C_{arom}), 152.3 (C_3), 182.4 (C=O).

Rel-(4S,4'S)-bis-(4-anisyl-5,5-dimethyl-4,5-dihydro-1H-pyrazol-3yl-)ketone (5b). Pale-yellow solid; mp 215°C. Anal. Calcd for $C_{25}H_{30}N_4O_3$: C, 69.84; H, 6.91; N, 11.06. Found: C, 69.84; H, 7.71; N, 11.52. IR (KBr) ν_{cm-1}: 1550 (C=N), 1640 (C=O), 3000 (C-H), 3400 (N-H); FAB-MS m/z(%): 435 (MH^+, 100), 231 (p-CH_3OPh-$C_5N_2H_8$-C≡O^+, 35); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.85 (s, 6H, CH_3(a)), 1.35 (s, 6H, CH_3(b)), 3.80 (s, 6H, OCH_3), 4.05 (s, 2H, H_4), 6.20 (s, 2H, exchangeable, H_1), 6.69 (m, 4H, $H_{8,10}$) and 6.87 (m, 4H, $H_{7,11}$,): AA'BB' patt. J=8.7 Hz; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.7 (CH_3(a)), 28.8 (CH_3(b)), 52.2 (OCH_3), 58.5 (C_4), 66.8 (C_5), 113.9 ($C_{8,10}$), 128.9 (C_6), 129.4 ($C_{7,11}$), 151.8 (C_3), 158.4 (C_9), 184.2 (C=O).

Rel-(4S,4'R)-bis-(5,5-dimethyl-4-phenyl-4,5-dihydro-1H-pyrazol-3yl-)ketone (6a). Yellow solid; mp 212°C. Anal. Calcd for $C_{23}H_{26}N_4O$: C, 73.79; H, 6.95; N, 14.97. Found: C, 73.82; H, 6.99; N, 15.02. IR (KBr) ν_{cm-1}: 1540 (C=N), 1620 (C=O), 3000, (C-H), 3350 (N-H); FAB-MS m/z(%): 375 (MH^+, 100), 201 (Ph-$C_5N_2H_8$-C≡O^+, 57); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 (s, 6H, CH_3(a)), 1.30 (s, 6H, CH_3(b)), 4.05 (s, 2H, H_4), 6.15 (s, 2H, exchangeable, H_1), 6.85-7.20 (m, 10H, H_{arom}); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.7 (CH_3(a)), 28.8 (CH_3(b)), 59.3 (C_4), 67.0 (C_5), 126.9-136.4 (4 signals, C_{arom}), 151.8 (C_3), 181.0 (C=O).

Rel-(4S,4'R)-bis-(4-anisyl-5,5-dimethyl-4,5-dihydro-1H-pyrazol-3yl-)ketone (6b). Yellow solid; mp 208°C. Anal. Calcd for $C_{25}H_{30}N_4O_3$: C, 69.12; H, 6.91; N, 11.06. Found: C, 69.84; H, 7.71; N, 11.08. IR (KBr) ν_{cm-1}: 1550 (C=N), 1640 (C=O), 3000 (C-H), 3400 (N-H); FAB-MS m/z(%): 435 (MH^+, 100), 231 (p-CH_3OPh -$C_5N_2H_8$-C≡O^+, 35); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.85 (s, 6H, CH_3(a)), 1.35 (s, 6H, CH_3(b)), 3.75 (s, 6H, OCH_3), 3.96 (s, 2H, H_4), 6.20 (s, 2H, exchangeable, H_1), 6.69 (m, 4H, $H_{8,10}$) and 6.87 (m, 4H, $H_{7,11}$): AA'BB' patt. J=8.7 Hz; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.6 (CH_3(a)), 28.8 (CH_3(b)), 55.1 (OCH_3), 58.5 (C_4), 66.8 (C_5), 113.7 ($C_{8,10}$), 128.7 (C_6), 129.1 ($C_{7,11}$), 151.9 (C_3), 158.4 (C_9), 184.2 (C=O).

Oxidation of adducts 5a-b and 6a-b.
Preparation of 3H-pyrazoles 7a-b and 8a-b.

To a suspension of MnO_2 (30g) in 100 ml of anhydrous dichloromethane was added, under dry atmosphere via an addition funnel, a solution containing 1g (2.67-2.30 mmol) of **5a-b** or **6a-b** in 120 ml of dry dichloromethane. Vigorous stirring was maintained for 30 min at which time the suspension was filtered and the solvent was evaporated under reduced pressure. The residue was chromatographed on 50g of silica gel using a 40% hexane-ethyl acetate mixture as the eluant. (1H-Pyrazolyl)(3H-pyrazolyl)ketones **7a-b** were crystallized again at -30°C from a 50:50 petroleum ether-diethyl ether mixture (48.7-44% yields). The same treatment for products **7a-b** affords bis-3H-pyrazoles **8a-b** (48-41% yields). The structures of all products were assigned by their analytical and spectral properties.

(3,3-Dimethyl-4-phenyl-3H-pyrazol-5-yl)(5,5-dimethyl-4-phenyl-4,5-dihydro-1H-pyrazol-3-yl) ketone (7a)
Yellow solid; mp 170°C. Anal. Calcd for $C_{23}H_{24}N_4O$: C, 74.19; H, 6.45; N, 14.05. Found: C, 74.38; H, 6.43; N, 14.52. IR (KBr) ν_{cm-1}: 1540 (C=N), 1615 (C=C-C=N), 1640 (C=O), 2900 (C-H), 3400 (N-H); FAB-MS m/z(%): 373 (MH^+, 55); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 (s, 3H, CH_3(a')), 1.32 (s, 3H, CH_3(b')), 1.50 (s, 3H) and 1.52 (s, 3H): CH_3 (a),(b), 4.07 (s, 1H, $H_{4'}$), 6.64 (s, 1H, exchangeable, H_1), 6.96-7.86 (m, 10H, H_{arom}); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.3 and 20.7 (CH_3(a),(b)), 22.5 (CH_3(a')), 29.0 (CH_3(b')), 57.6 ($C_{4'}$), 68.5 ($C_{5'}$), 95.7 (C_3), 127.2-128.9 (5 signals, C_{arom}), 136.2 (C_4), 151.1 ($C_{3'}$), 152.1 (C_5), 182.4 (C=O).

(4-Anisyl-3,3-dimethyl-3H-pyrazol-5-yl)(4-anisyl-5,5-dimethyl-4,5-dihydro-1H-pyrazol-3-yl) ketone (7b)
Bright-yellow solid; mp 130°C. Anal. Calcd for $C_{23}H_{28}N_4O_3$: C, 69.60; H, 6.26; N, 12.99. Found: C, 70.20; H, 6.77; N, 13.57. IR (KBr) ν_{cm-1}: 1540 (C=N), 1615 (C=C-C=N), 1640 (C=O), 3000 (C-H), 3400 (N-H); FAB-MS m/z(%): 433 (MH^+, 62); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (s, 3H, CH_3(a')), 1.34 (s, 3H, CH_3(b')), 1.52 (s, 3H) and 1.56 (s, 3H) :CH_3 (a),(b), 3.75 (s, 3H, OCH_3) and 3.82 (s, 3H, OCH_3), 4.09 (s, 1H, $H_{4'}$), 6.40 (s, 1H, exchangeable, H_1), 6.80 (m, 2H) and 6.94 (m, 2H): AA'BB' patt. J=7.8 Hz, 6.87 (m, 2H) and 7.34 (m, 2H): AA'BB' patt. J=7.8 Hz; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.9 and 21.0 (CH_3(a),(b)), 22.6 (CH_3(a')), 29.0 (CH_3(b')), 55.3 and 55.5 (OCH_3), 57.1 ($C_{4'}$), 68.6 ($C_{5'}$), 95.2 (C_3), 113.9-129.8 (4 signals, C_{arom}), 134.1 (C_4), 152.1 (C_5), 152.2 ($C_{3'}$), 182.6 (C=O).

bis-(4-Phenyl-3,3-dimethyl-3H-pyrazol-5-yl)ketone (8a). Yellow solid; mp 118°C. Anal. Calcd for $C_{25}H_{22}N_4O$: C, 74.59; H, 5.94; N, 15.13. Found: C, 75.08; H, 6.31; N, 15.59. IR (KBr) ν_{cm-1}: 1615 (C=C-C=N), 1630 (C=O), 2900 (C-H); FAB-MS m/z(%): 371(MH^+,55), 201(100); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 12H, CH_3(a),(b)), 7.05-7.40 (m, 10H, H_{arom}); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.5 (CH_3(a),(b)), 96.9 (C_3), 125.2-129.4(5 signals, C_{arom}), 148.7 (C_4), 164.1 (C_5), 183.7 (C=O).

bis-(4-Anisyl-3,3-dimethyl-3H-pyrazol-5-yl)ketone (8b). Bright-yellow solid; mp 98°C. Anal. Calcd for $C_{25}H_{26}N_4O_3$: C, 74.59; H, 5.94; N, 15.13. Found: C, 75.08; H, 6.31; N, 15.59. IR (KBr) ν_{cm-1}: 1620 (C=C-C=N), 1640 (C=O), 2900 (C-H); FAB-MS m/z(%): 431 (MH^+, 73), 215 (100); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 12H, CH_3(a),(b)), 3.80 (s, 6H, OCH_3), 6.87-7.09 (m, 8H, $H_{8,10}$,$H_{7,11}$): AA'BB' patt. J=8.2 Hz; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.6 (CH_3(a),(b)) 55.5 (OCH_3), 95.7 (C_3), 147.7 (C_4), 163.3 (C_5), 114.2-128.4 (4 signals, C_{arom}), 184.8 (C=O).

Cycloaddition reaction at -60°C.

Preparation of adducts 9a-b and 10a-b.

To a 2.5g (10.6-8.5 mmol) of enone **2a-b** in 100 ml of dry dichloromethane at -60°C was added in small fractions a 2.8M etheral solution of 2-diazopropane at -78°C. The TLC controls (40:60 ethyl acetate-hexane elution) indicated the apparition of two new products beside bis-pyrazolines **5** and **6** and the addition was stopped when enone **2** had totally reacted. After 12h at 0°C, removal of the solvent under reduced pressure left an oil, which was chromatographed, on 200g of silica gel eluting with hexane progressively enriched, until 50% with ethyl acetate. We recovered, in order of elution, a mixture of adducts **9** and **10** then successively bis-adducts **5a-b**(1.1-1.2g, 2.94-2.76 mmol) and **6a-b** (280-340mg, 0.74-0.78 mmol). Fractional crystallisation from 10% n-pentane-diethyl ether mixture afforded pure

diastereoisomers **9a-b** (680-730mg, 1.53-1.44 mmol). Isomers **10a-b** (190-230mg, 0.42-0.45 mmol) were crystallized again from n-pentane. Total yields, 53-54%.

Rel-(3'S,4'R,3''S,4''R)-2,2-bis-(5,5-dimethyl-4-phenyl-4,5-dihydro-3H-pyrazol-3-yl)-5,5-dimethyl-2,5-dihydro-(1,3,4) oxadiazole (9a) .Colourless crystals; mp 144°C (decomp). Anal. Calcd for $C_{26}H_{32}N_6O$: C, 69.44; H, 7.40; N, 19.44. Found: C, 70.16; H, 7.86; N, 19.32. IR (KBr) ν_{cm-1}: 980-1090 (C-O), 1530 (N=N), 2950 (C-H); FAB-MS m/z(%): 445 (MH^+, 46); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.68 (s, 3H, CH_3(a)), 0.76 (s, 3H, CH_3(b)), 1.34 (s, 3H, CH_3(c)), 1.43 (s, 3H, CH_3(d)), 1.51 (s, 3H, CH_3(e)), 1.65 (s, 3H, CH_3(f)), 3.06 (d, 1H, $H_{4'}$) and 5.89 (d, 1H, $H_{3'}$): AX patt. $J_{3'-4'}$=9.2 Hz, 3.13 (d, 1H, $H_{4''}$) and 5.41(d, 1H,$H_{3''}$): AX patt. $J_{3''-4''}$=9.5 Hz, 6.80-7.92 (m, 10H, H_{arom}); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.6 (CH_3(a)), 22.8 (CH_3(b)), 24.7 (CH_3(f)), 25.0 (CH_3(c)), 26.5 (CH_3(d)), 26.8 (CH_3(e)), 48.7 ($C_{4'}$), 48.8 ($C_{4''}$), 91.6 and 91.7 ($C_{5'}$, $C_{5''}$), 94.4 and 94.5 ($C_{3'}$, $C_{3''}$), 124.3 (C_5), 124.5 (C2), 127.4-136.3 (4 signals, C_{arom}).

Rel-(3'S,4'R,3''S,4''R)-2,2-bis-(4-anisyl-5,5-dimethyl-4,5-dihydro-3H-pyrazol-3-yl)-5,5-dimethyl-2,5-dihydro-(1,3,4) oxadiazole (9b). Colourless crystals; mp 142°C (decomp). Anal. Calcd for $C_{28}H_{36}N_6O_3$: C, 66.66; H, 7.14; N, 16.66. Found: C, 66.49; H, 7.05; N, 16.93. IR (KBr) ν_{cm-1}: 1300 (C-O), 1560 (N=N); FAB-MS m/z(%): 505 (MH^+, 46); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.70 (s, 3H, CH_3(a)), 0.74 (s, 3H, CH_3(b)), 1.32 (s, 3H, CH_3(c)), 1.47 (s, 3H, CH_3(d)), 1.52 (s, 3H, CH_3(e)), 1.66 (s, 3H, CH_3(f)), 3.76 (s, 3H, OCH_3), 3.01 (d, 1H, $H_{4'}$) and 5.76 (d, 1H, $H_{3'}$): AX patt. $J_{3'-4'}$=8.0 Hz, 3.28 (d, 1H, $H_{4''}$) and 5.30 (d, 1H, $H_{3''}$): AX patt. $J_{3''-4''}$=8.5 Hz, 6.56-6.69 (m, 8H, H_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.3 (CH_3(a)), 22.7 (CH_3(b)), 24.6 (CH_3(f)), 25.0 (CH_3(c)), 26.4 (CH_3(d)), 26.7 (CH_3(e)), 48.5 ($C_{4'}$), 48.8 ($C_{4''}$), 54.9 (OCH_3), 92.7 and 92.8 ($C_{5'}$, $C_{5''}$), 94.2 and 94.4 ($C_{3'}$, $C_{3''}$), 113.7 and 113.8 ($C_{8',10'}$, $C_{8'',10''}$), 123.9 (C_5), 124.0 (C_2), 128.3 and 128.6 ($C_{7',11'}$, $C_{7'',11''}$), 158.2 and 158.4 ($C_{9'}$, $C_{9''}$).

Rel-(3'R,4'S,3''S,4''R)-2,2-bis-(5,5-dimethyl-4-phenyl-4,5-dihydro-3H-pyrazol-3-yl)-5,5-dimethyl-2,5-dihydro-(1,3,4) oxadiazole (10a). Colourless crystals; mp 172°C (decomp). Anal. Calcd for $C_{26}H_{32}N_6O$: C, 69.44; H, 7.40; N, 19.44. Found: C, 70.35; H, 8.05; N, 19.56. IR (KBr) ν_{cm-1}: 990-1095 (C-O), 1560 (N=N); FAB-MS m/z(%): 444 (MH^+, 35); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.65 (s, 6H, CH_3(a)), 1.24 (s, 6H, CH_3(b)), 1.52 (s,6H, CH_3(c)), 2.60 (d, 2H, $H_{4'}$) and 5.63 (d, 2H, $H_{3'}$): AX patt. $J_{3'-4'}$=9.5 Hz, 7.02-7.28 (m, 10H, H_{arom}); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.9 (CH_3(a)), 24.7 (CH_3(b)), 25.9 (CH_3(c)), 50.6 ($C_{4'}$), 90.7 ($C_{3'}$), 90.9 ($C_{5'}$), 123.0 (C_5), 123.1 (C_2), 127.3-136.4 (4 signals, C_{arom}).

Rel-(3'R,4'S,3''S,4''R)-2,2-bis-(4-anisyl-5,5-dimethyl-4,5-dihydro-3H-pyrazol-3-yl)-5,5-dimethyl-2,5-dihydro-(1,3,4) oxadiazole (10b). Colourless crystals; mp 125°C (decomp). Anal. Calcd for $C_{28}H_{36}N_6O_3$: C, 66.66; H, 7.14; N, 16.66. Found: C, 67.05; H, 7.88; N, 15.08. IR (KBr) ν_{cm-1}: 1300 (C-O), 1550 (N=N); FAB-MS m/z(%): 505(MH^+, 46); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.62 (s, 6H, CH_3(a)), 1.21 (s, 6H, CH_3(b)), 1.54 (s, 6H, CH_3(c)), 2.57 (d, 2H, $H_{4'}$) and 5.57 (d, 2H, $H_{3'}$): AX patt. $J_{3'-4'}$=10.7 Hz, 3.78 (s, 6H, OCH_3), 6.80 (m, 4H, $H_{8',10'}$), 6.92 (m, 4H, $H_{7',11'}$): AA'BB' patt. J=8.6 Hz; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 26.9 (CH_3(a)), 24.7 (CH_3(b)), 25.8 (CH_3(c)), 49.7 ($C_{4'}$), 55.2 (OCH_3), 90.5 ($C_{3'}$), 90.7 ($C_{5'}$), 113.8 ($C_{8',10'}$), 122.9 (C_5), 123.1 (C_2), 128.4 ($C_{7',11'}$), 158.7 ($C_{9'}$).

X-ray crystal structure data of diastereoisomer 10b

Crystal data. C_{28} H_{36} N_6 O_3, M_W = 504.63, monoclinic, space group $P2_1/c$, Z = 4, a = 12.383 (5), b = 15.744 (7),

c = 17.105 (8) Å, b = 94.26 (2) °, V = 3325 (3) $Å^3$, d_c =1.01 gcm^{-3}, F(000) = 1080, 1 (Cu Ka) = 1.5418 Å, m = 0.540 mm-1; 5466 intensities measured of which 5249 unique (Rint = 0.028). Correction for intensity decay of 22 %. Colorless crystal of 0.92 x 0.33 x 0.16 mm. Semi-empirical absorption correction made.

Intensity data were measured on a CAD4-Nonius diffractometer using graphite monochromated Cu Ka radiation and the (w-2q) scan technique up to q = 68° (-14 ≤ h ≤14, k : 0 to 16, l : 0 to 18). Cell parameters were refined from 25 well centered reflections with 10.2 ≤ q ≤18.9°. The structure was solved by direct methods using *SHELXS86*[20] and refined by

full matrix least-squares based upon unique F^2 with *SHELXL93*.[21] The hydrogen atoms were fitted in idealized positions (C-H 0.93 to 0.98 Å) and assigned an isotropic thermal factor equivalent to that of the bonded atom, plus 20 or 30% (in methyl groups). Thus, refinement of 342 variables converged to $R_1(F) = 0.0802$ (for 4042 Fo with $Fo \geq 4\ s(Fo)$) and $wR_2\ (F^2) = 0.2776$ (for all the 5249 data with goodness-of-fit S = 1.185). The weights of the structure factors were assumed to be $w = 1/[s^2(Fo^2) + (0.1704\ P)^2 + 0.62\ P]$ where $P = (Fo^2 + 2\ Fc^2)/3$. The residual electron density was found between -0.26 and 0.71 $eÅ^{-3}$ in the final difference map.

Lists of the fractional atomic coordinates, thermal parameters, bond distances and bond and torsion angles have been deposited at the Cambridge Crystallographic Data Center, U.K., as Supplementary Material (CIF file).

ACKNOWLEDGEMENTS We are very grateful to Professors P. Potier and B.C. Das for allowing us to carry out part of this work at the " Institut de Chimie des Substances Naturelles", C.N.R.S, Gif-Sur-Yvette, France.

REFERENCES

1. Staudinger, H.; Gaule, A. *Ber.*, **1916**, *49*, 1897.
2. Conard, C. R.; Dolliver, M. A. *Org. Synth.*, **1943**, *2*, 167; Austerweil, G. V. ; Pallaud, R. *J. Appl. Chem.* (London), **1955**, *5*, 213.
3. Huisgen, R.; Grashey, R.; Sauer, J. in *The Chemistry of Alkenes*, ed. S. Pataî, Interscience, New York, **1964**, 826.
4. Cossy, J.; Carrupt, P. A.; P. Vogel, P. in *The Chemistry of the Double Bonded Functional Groups*, part1, Wiley Interscience, New York, **1977**, 1454.
5. Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.*, **1973**, *95*, 7287.
6. Houk, K. N.; Sims, J.; Watts, C. R.; Luksus, L. J. *J. Am. Chem. Soc.*, **1973**, *95*, 7301.
7. Aldersley, M. F.; Dean, F. M.; Mann, B. E. *J. Chem. Soc. Perkin Trans* I, **1986**, 2217.
8. Tsatsaroni, E. G. *Chim. Chron.*, New Series, **1984**, *13*, 185.
9. Martin, M.-T.; Gharbi, R.; Khemiss, A.; Mighri, Z. *Magn. Res. Chem.*, **1997**, *35*, 251.
10. Huisgen, R.; Eberhard, P. *Tetrahedron Lett.*, **1971**, *45*, 4343.
11. Jones, G. W.; Chang, K. T.; Shechter, H. *J. Am. Chem. Soc.*, **1979**, *100*, 3906.
12. Regitz, M.; Heydt, H. in *1,3-Dipolar cycloaddition Chimistry*, Padwa, A. ed., Wiley Interscience, New York, **1984**, *1*, 393.
13. Pincok, J. A.; Mathur, N. C. *J. Org. Chem.*, **1982**, *47*, 3699.
14. Franck-Neumann, M.; Miesch, M. *Tetrahedron*, **1983**, *39*, 1247; *Tetrahedron Lett.*, **1984**, *25*, 2909.
15. Padwa, A.; Wannamaker, M. W. *Tetrahedron*, **1990**, *46*, 1145.
16. Sustmann, R. *Tetrahedron Lett.*, **1971**, *29*, 2717.
17. Huisgen, R. *J. Org. Chem.*, **1976**, *41*, 403.
18. Gill, G. B.; Willis, M. R. in *Pericyclic Reactions*, Chapman and Hall, London, **1974**, 164.
19. Norman, R. O. C. in *Principles of Organic Synthesis*, Chapman and Hall, London, **1978**, 288.
20. Sheldrick, G. M., **SHELXS86**. Program for the Solution of Crystal Structures. University of Göttingen, Germany, **1986**.
21. Sheldrick, G. M., **SHELXS93**. Program for the Refinement of Crystal Structures. University of Göttingen, Germany, **1993**.