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1,3-Cycloaddition of Chiral Azomethine Ylides Generated from 2-(tert-butyl)-3-methylimidazolidin-4-one.

Jean-François Peyronel * [a], Serge Grisoni [a]

[a] *Rhône Poulenc Rorer, Centre de Recherches de Vitry, 13, Quai Jules Guesdes,BP 14, 94403 Vitry sur Seine, France.*

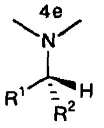
Bertrand Carboni * [b], Thierry Courgeon [b] and Robert Carrié [b]

[b] *GRPS, URA CNRS. n° 704, Université de Rennes I, Avenue du Général Leclerc, 35042 Rennes Cédex, France.*

Key Words *: azomethine ylides ; 1,3-dipolar cycloaddition ; imidazolidin-4-one ; diastereoselectivity ; pyrrolidines*

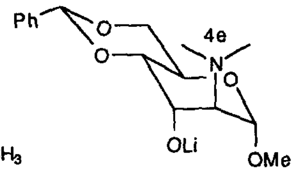
Abstract : Chiral azomethine ylides, easily generated from 2-(tert-butyl)-3-methyl-imidazolidin-4-one and aldehydes, undergo 1,3-dipolar cycloadditions to activated alkenes. These reactions proceed with complete facial stereoselection. In the case of benzaldehyde and hexanal, the configurations of the 1,3-dipoles are also controlled and these ylides display high diastereoselectivity in their reactions with N-phenylmaleimide.

Azomethine ylides are powerful building blocks for pyrrolidine synthesis. Although a number of reports have been devoted to the cycloaddition reactions of these attractive 1,3 dipoles [1], only little attention has been paid to the incorporation of a chiral directing element in the dipole moiety. A. Pawda et al. observed 40 to 60% diastereoisomeric excess in the reactions of azomethine ylide **1**, generated from N-cyanomethyl-N-trimethylsilylmethylamines with β-nitrostyrene [2a], but 1 : 1 mixtures of diastereoisomers were obtained if similar ylides are opposed to 5,6-dihydropyran-2-one [2b]. The deprotonation of a β-hydroxyamine N-oxyde and an aminosugar N-oxide gave very reactive ylides **2** and **3** which added to stilbene in a 85/15 diastereoisomer ratio [3]. Very high diastereofacial and endo/exo stereoselectivities (d.e. > 95%) have been measured in the cycloaddition of the ylide **4**, generated from 4-phenyloxazolidine acetic acid (-)-8-phenylmenthyl ester, with N-phenylmaleimide [4]. Ylides **5** [5] and **6** [6], derived from substituted morpholin-2-ones, gave good to excellent levels of diastereoselection. Double asymmetric induction has recently been explored by A.J. Meyers and A.M. Fray in the reaction of **1** with chiral unsaturated bicyclic lactams [7] and by P. Garner *et al* in the addition of ylide **7** with chiral acrylates and acrylamides [8].



1 $R^1 = Ph$ $R^2 = CH_2OCH_3$

2 $R^1 = Et$ $R^2 = CH_2OLi$



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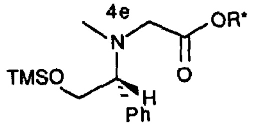

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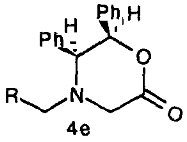

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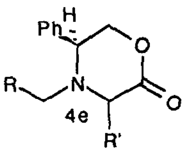

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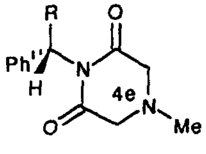

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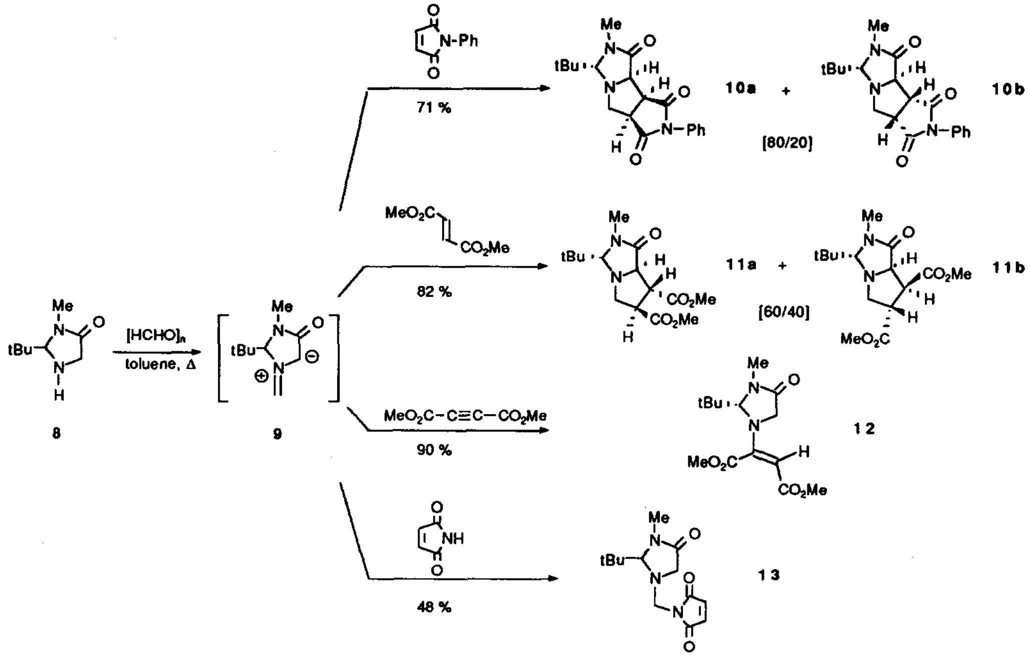
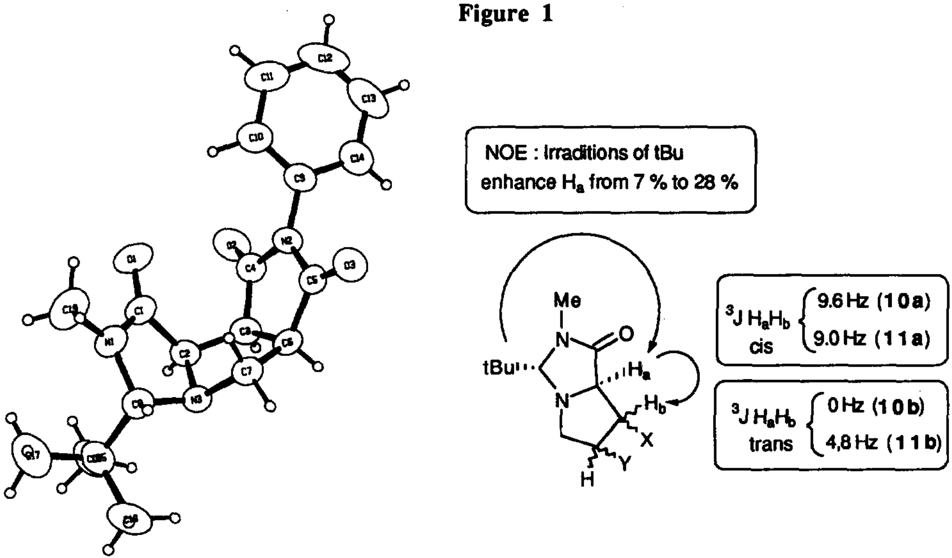
D. Seebach *et al.* have extensively demonstrated the synthetic usefulness of 2-(tert-butyl)-3-imidazolidin-4-one **8** as chiral glycine enolate precursor [9]. **8** was easily obtained enantiomerically pure in scales up to one mole [10] and was shown to be an excellent structural element for determining the stereochemical course of various reactions. To the best of our knowledge, no development involving this heterocycle as chirality controller has been reported in the field of 1,3-dipolar cycloaddition. We here describe the results of our preliminary investigations concerning the generation and the highly stereoselective trapping of a new azomethine ylide **9** [11]. Heating 2-(tert-butyl)-3-imidazolidin-4-one **8** in refluxing toluene in the presence of paraformaldehyde and dipolarophiles led to various adducts (Scheme 1).

Scheme 1



Reaction of **9** with N-phenyl maleimide yielded the cycloadducts as a mixture of two diastereoisomers **10a/10b** (80/20) in a 71% yield and dimethyl fumarate furnished the bicyclic substances **11a** and **11b** (60/40) in 82% yield. The structure of the major isomer **10a** was established by crystallographic analysis [12]. NOE difference experiments and ^1H NMR data secured the other proposed structures for **10b**, **11a** and **11b** (Figure 1).

Figure 1



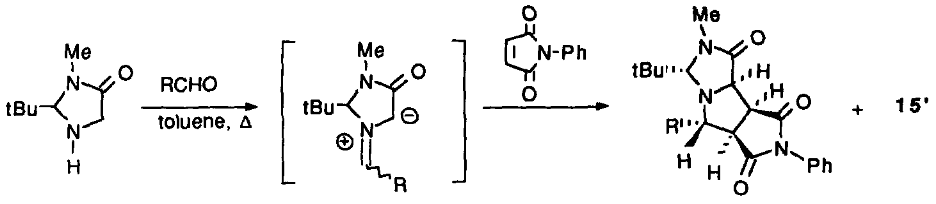
Selected ^1H NMR data of adducts **10** and **11**

Crystal structure of **10a** [12]

Under the same experimental conditions, ethyl acrylate furnished mixtures of isomers in a 50 % yield. We were unable to separate these products and to determine their configuration. In the case of dimethyl acetylenedicarboxylate and maleimide, no cycloaddition occured and the Michael type adduct **12** and the amidoalkylation product **13** were the only isolated compounds in 90% and 48% yield, respectively.

We then decided to investigate the outcome of the reaction of ylides **14**, prepared from imidazolidinone **8** and other aldehydes. Following the same procedure as above, we generated **14a** (R = Ph) and **14b** (R = nC_5H_{11}) by heating **8** with benzaldehyde or hexanal in the presence of N-phenyl maleimide. Five stereogenic centers were thus created with high preference since the examination of the crude mixtures by ^1H and ^{13}C NMR spectroscopy revealed the presence of only two diastereoisomers **15** and **15'** (**a**, R = Ph, 63% yield, **15a/15'a** = 80/20 and **b**, R = nC_5H_{11}, 61% yield, **15b/15'b** = 85/15) [13] (Scheme 2).

Scheme 2



8 **14** **15**

a R = Ph ,63% [80/20] **b** R = nC_5H_{11} ,61% [85/15]

The structure of the cycloadduct **15a** was determined by crystal structure analysis [14] (Figure 2). The proposed stereochemistry of **15b** was in agreement with ^1H and ^{13}C NMR data of **15a**. Attemps to isolate **15'a** and **15'b** in order to elucidate their configurations were unsuccessful.

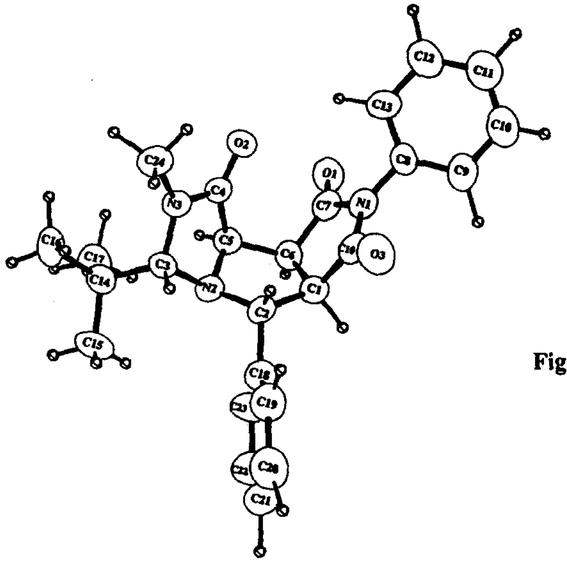
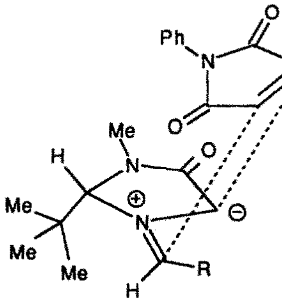


Figure 2 . Crystal structure of **15a** [14]

The relative configurations of the cycloadducts **10**, **11** and **15** can be rationalized by envisaging *endo*/*exo* approaches of the dipolarophile to predominantly one face of the ylides **9** or **14**, the conformation of the imidazolidinone ring being essentially planar. When benzaldehyde or hexanal were used, the major cycloadducts **15a** and **15b** also resulted from an *endo* addition to the side *anti* to the tBu group. Furthermore, it must be concluded that this bulky substituent forced the ylide **14** to adopt an E configuration (Figure 3).

Figure 3



sterically and electronically preferred approach of **14** to N-phenylmaleimide

In summary, 1,3-dipolar cycloadditions of readily available azomethine ylides **9** and **14**, derived from 2-(tert-butyl)-3-imidazolidin-4-one, to activated alkenes occur with high diastereofacial and good to moderate endo stereoselectivities. Results obtained with these ylides clearly indicate that they should be interesting precursors of substituted pyrrolidines. Additional examples of ylides derived from similar imidazolidinones and aldehydes and studies of transformations of the cycloadducts are currently in progress.

Acknowledgement : X-ray analyses were performed at the University of Rennes I (Département de Physique Cristalline, URA CNRS 804) by Dr. L. Toupet who is gratefully acknowledged.

Experimental

^1H and ^{13}C spectra were recorded on a Bruker AM 300 Spectrometer (75.5 MHz for ^{13}C). Chemical shifts are reported in δ (ppm) and coupling constants are given in Hz. Deuterochloroform was used as the solvent. Elemental analyses were performed by the "Laboratoire Central d'Analyses du CNRS", Lyon. All melting points were determined with a Kofler apparatus and were uncorrected. Flash chromatography was carried out using E. Merck 60 silica gel (250-400 mesh).

General procedure : Paraformaldehyde (10.0 mmol) (1.0 mmol when PhCHO or $C_5H_{11}CHO$ was used) was added to a solution of dipolarophile (2.0 mmol) and 2-(tert-butyl)-3-imidazolin-4-one (1.0 mmol) **8** in sodium dried toluene. The flask was fitted with a Dean-Stark apparatus and the mixture heated 15 h with stirring to reflux. After cooling to room temperature and removal of solvent *in vacuo*, the residue was purified by silica gel column chromatography.

Reaction of 8 with formaldehyde and N-phenyl maleimide : major adduct **10a**, 59 % yield, m.p. 173°C. Rf = 0.45 (ethyl acetate - hexane 60/40). ^1H NMR : δ 0.88 (s, 9H) ; 2.78 (s, 3H) ; 3.32 - 3.54 (m, 3H) ; 3.58 - 3.71 (m, 2H) ; 4.18 (d, 1H, J = 9.6) ; 7.15 - 7.47 (m, 5H). ^{13}C NMR : δ : 25.6 ; 31.3 ; 38.2 ; 47.9 ; 49.9 ; 57.5 ; 66.3 ; 91.3 ; 126.0 ; 128.5 ; 129.1 ; 131.8 ; 170.2 ; 173.1 ; 176.8 (Found : C, 66.6 ; H, 6.7 ; N, 12.1. Calc. for $C_{19}H_{23}N_3O_3$: C, 66.86 ; H, 6.74 ; N 12.32). Minor adduct **10b**, 12 % yield, m.p. 138-141°C. Rf = 0.3, ethyl acetate-hexane 60/40. ^1H NMR : δ 0.98 (s, 9H) ; 2.77 (dd, 1H, J = 8.7 and 8.7) ; 3.01 (s, 3H) ; 3.37 (dd, 1H, J = 8.7 and 8.7) ; 3.61 (s, 1H) ; 3.76 (d, 2H, J = 8.7) ; 4.09 (s, 1H) ; 7.23 - 7.53 (m, 5H). ^{13}C NMR : δ : 26.3 ; 32.6 ; 38.1 ; 44.0 ; 45.7 ; 58.4 ; 68.1 ; 91.5 ; 126.3 ; 128.8 ; 129.2 131.7 ; 172.8 ; 176.4 ; 177.1 (Found : C, 66.9 ; H, 6.8 ; N, 12.0. Calc. for $C_{19}H_{23}N_3O_3$: C, 66.86 ; H, 6.74 ; N 12.32).

Reaction of 8 with formaldehyde and dimethyl fumarate : mixture of two diastereoisomers **11a/11b** (60/40), 82 % yield after column chromatography. Rf = 0.30 (diethylether-hexane 80/20). Major adduct **11a** (spontaneous cristallization from the mixture) m.p. 91-92°C. ^1H NMR : δ 0.94 (s, 9H) ; 2.92 (s, 3H) ; 3.13 - 3.26 (m, 2H) ; 3.36 - 3.43 (m, 1H) ; 3.60 - 3.72 (m, 2H) ; 3.71 (s, 3H) ; 3.76 (s, 3H) ; 4.12 (d, 1H, J = 9.0). ^{13}C NMR : δ 25.6 ; 31.3 ; 38.3 ; 45.8 ; 48.7 ; 52.2 ; 52.32 ; 60.2 ; 66.1 ; 92.8 ; 171.5 ; 172.0 (2C) (Found : C, 57.6 ; H, 7.8 ; N, 8.8. Calc. for $C_{15}H_{24}N_2O_5$: C, 57.69 ; H, 7.69 ; N, 8.97. Minor adduct **11b** (NMR data were measured in a 25-75 mixture of **11a** and **11b**). ^1H NMR : δ 2.89 (t, J = 8.8, 1H) ; 2.93 (s, 3H) ; 3.38 - 3.52 (m, 3H) ; 3.63 (s, 1H) ; 3.69 (s, 3H) ; 3.78 (s, 3H) ; 4.02 (d, J = 4.8, 1H). ^{13}C NMR : δ 26.7 ; 32.0 ; 38.5 ; 47.8 ; 48.8 ; 52.4 ; 52.7 ; 59.2 ; 66.9 ; 92.0 ; 172.0 ; 172.5 ; 173.9. (Found : C, 57.7 ; H, 7.8 ; N, 8.8. Calc. for $C_{15}H_{24}N_2O_5$: C, 57.69 ; H, 7.69 ; N, 8.97).

Reaction of 8 with formaldehyde and dimethyl acetylenedicarboxylate. **12** : m.p. 116-117°C. Rf = 0.50 (diethylether). ^1H NMR : δ 1.02 (s, 9H) ; 3.04 (s, 3H) ; 3.66 (s, 3H) ; 3.76 (d, 1H, J = 15.5) ; 3.92 (d, 1H, J = 15.5) ; 3.94 (s, 3H) ; 4.69 (s, 1H) ; 4.90 (s, 1H). ^{13}C NMR : δ 26.1 ; 31.9 ; 40.7 ; 51.2 ; 52.3 ; 53.2 ; 63.9 ; 90.3 ; 152.5 ; 165.0 ; 167.3 ; 169.1 (Found : C, 56.4 ; H, 7.2 ; N, 9,2. Calc. for $C_{14}H_{22}N_2O_5$: C, 56.37 ; H, 7.38 ; N, 9.40.

Reaction of 8 with formaldehyde and maleimide. **13** : 48 % yield. m.p. = 118-120°C. Rf = 0.45 (diethylether). ^1H NMR: δ 0.96 (s, 9H) ; 2.86 (s, 3H) ; 3.42 (d, 1H, J = 16.9) ; 3.59 (d, 1H, J = 16.9) ; 4.29 (d, 1H, J = 0.9) ; 4.43 (d, 1H, J = 14.0) ; 4.60 (d, 1H, 14.0) ; 6.75 (s, 2H). ^{13}C NMR δ 25.6 ; 31.4 ; 38.9 ; 53.0 ; 59.5 ; 89.3 ; 134.4 ; 171.7 ; 173.1 (Found : C, 58.7 ; H, 7,2 ; N, 15,8 . Calc. for $C_{13}H_{19}N_3O_3$: C, 58.86 ; H, 7.17 ; N, 15.84).

Reaction of 8 with benzaldehyde and N-phenyl maleimide. Major adduct **15a**. m.p. = 222-224°C. Rf = 0.30 (ether/hexane : 80/20). ^1H NMR : δ 0.88 (s, 9H) ; 2.92 (s, 3H) ; 3.43 (dd, 1H, J = 4.1 and 8.4) ; 3.76 (t, 1H, J = 9.6) ; 3.79 (s, 1H) ; 4.42 (d, 1H, J = 4.0) ; 4.51 (d, 1H, J = 9.6) ; 7.26 - 7.49 (m, 5H). ^{13}C NMR : δ 26.1 ; 32.0 ; 38.2 ; 47.5 ; 55.6 ; 66.2 ; 72.9 ; 90.7 ; 126.2 ; 126.4 ; 127.0 ; 127.9 ; 128.6 , 128.9 ; 129.2 ; 129.3 ; 131.8 ; 141.1 ; 170.7 ; 172.5 ; 175.7 (Found : C, 71.3 ; H, 6.6 ; N, 10.5. Calc. for $C_{25}H_{27}N_3O_3$: C, 71.93 ; H, 6.52 ; N, 10.06).

Reaction of 8 with hexanal and N-phenyl maleimide. Major adduct **15b** m.p. 160-162°C. Rf = 0.40 (ether-hexane : 80/20). ^1H NMR : δ : 0.88 - 0.94 (t, 3H, J = 6.6) ; 0.98 (s, 9H) ; 1.23 - 1.83 (m, 8H) ; 2.89 (s, 3H) ; 3.13 - 3.25 (m, 2H) ; 3.66 (s, 1H) ; 3.73 (dd, 1H, J = 7.6 and 9.5) ; 4.28 (d, 1H, J = 9.5) ; 7.30 - 7.48 (m, 5H). ^{13}C NMR : δ 14.1 ; 22.6 ; 25.2 ; 26.4 ; 31.8 ; 32.2 ; 32.8 ; 38.0 ; 47.4 ; 50.6 ; 65.6 ; 69.8 ; 90.8 ; 126.4 ; 128.5 ; 129.1 ; 132.0 ; 171.3 ; 173.1 ; 176.5 (Found : C, 70,1 ; H, 8,1 ; N, 10,0. Calc. for $C_{24}H_{33}N_3O_3$ C, 70,07 ; H, 8.02 ; N, 10.21.

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11 All reactions were performed with racemic 2-(tert-butyl)-3-imidazolidin-4-one **8**.

12 Crystal data for **10a** : $C_{19}H_{23}N_3O_3$: Mr = 341.4, monoclinic, $P2_1/c$, a = 13.097(9), b = 12.945(5), c = 11.030(4) Å, β = 105.81(5)°, V = 1895(2) Å^{-3}, Z = 4, D_x = 1.26 Mg.m^{-3}, λ(MoKα) = 0.71069 Å, μ = 0.81 cm^{-1}, F(000) = 728, T = 294 K, final R = 0.045 for 1792 reflexions. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.

13 Examination of the ^{1}H and ^{13}C NMR spectra of the crude mixtures revealed the presence of two diasterereoisomers **15** and **15'** only. However, the formation of traces of other cycloadducts cannot

be totally excluded. The ratio of the two diastereoisomers was determined by the average of the integration of several signals in ^{13}C NMR.

14 Crystal data for **15a** : $C_{25}H_{27}N_3O_3$: Mr = 417.51, monoclinic, $P2_1/n$, a = 16.459(5), b = 10.558(6), c = 25.742(9) Å, b = 96.35(3)°, V = 4446(2) $Å^{-3}$; Z = 8, D_x = 1.248 $Mg.m^{-3}$, λ(MoKα) = 0.70926 Å, μ = 0.77 cm^{-1}, F(000) = 1776, T = 294 K, final R = 0.044 for 3654 reflexions. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.

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