Switching stereocontrol in the high pressure-induced hetero-Diels–Alder reaction

Hashim Al-Badri,[a] Noël Collignon,[b] Jacques Maddaluno*[a] and Serge Masson[c]

[a] *Laboratoire des Fonctions Azotées et Oxygénées Complexes de l'IRCOF, UPRES-A 6014 CNRS, Université de Rouen, 76821 Mont-Saint-Aignan Cedex, France. E-mail: jmaddalu@crihan.fr*

[b] *Laboratoire d'Hétérochimie Organique de l'IRCOF, UPRES-A 6014 CNRS, INSA de Rouen, Place E. Blondel, BP 08, 76131 Mont-Saint-Aignan Cedex, France*

[c] *Laboratoire de Chimie Moléculaire et Thioorganique, UMR 6507 CNRS, Université de Caen et ISMRA, 6 Boulevard du Maréchal Juin, 14050 Caen Cedex, France*

Received (in Cambridge, UK) 17th April 2000, Accepted 19th May 2000

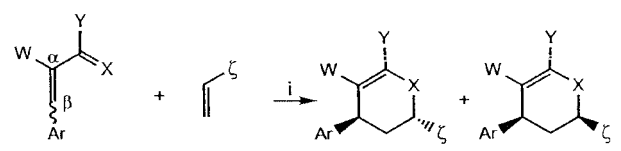
The formation of a transient Michael adduct, triggering an *in-situ* isomerization of the heterodiene, is postulated to explain the reversal of the diastereoselectivity of high pressure-promoted hetero-Diels–Alder reactions carried out in the presence of pyridine.

Application of high pressure in organic synthesis is a rapidly developing research area.[1] In particular, the use of these extreme conditions in [4+2] cycloadditions not only causes a marked acceleration of the reactions due to negative volumes of activation, but also often imposes efficient stereocontrol by favouring the more compact transition state, namely the *endo* state.[2]

Pursuing our work on the hetero-Diels–Alder reaction of α-phosphono-substituted heterodienes **1** [W = $(RO)_2P(O)$] with electron-rich dienophiles **2** (Scheme 1),[3] we recently observed an unexpected reversal of the diastereoselectivity of the resulting cycloadduct **3**, at high pressure, when the β-phenyl group of the diene was replaced by a pyridyl group.[4] Having postulated a possible *in situ* (*E*)- to (*Z*)-isomerization of the pyridyl-substituted diene, we decided to study, more generally, the possibility of modifying the selectivity of such high pressure-promoted cycloadditions by adding pyridine to the reaction mixture. We report here our first significant results (Table 1).

The synthesis of the phosphono-heterodienes (*E*)-**1a**–**c** were previously described.[3,4] The non-phosphonic diene **1d** was prepared according to a modification of the literature procedure,[5] giving a *ca.* 40:60 mixture of (*E*)/(*Z*)-isomers, which could be separated by HPLC. [6] Dienophiles **2a**,**b** are commercially available. The reactions of **1** with a ten-fold excess of **2** (acting also as solvent), at 20 °C and 11 kbar, led to the cycloadduct **3** as a mixture of two diastereomers, whose relative configuration was deduced from ^{1}H–^{1}H NOESY, ^{1}H and ^{13}C NMR spectra.[3,4] In the first set of experiments, we studied the reaction of the pair (*E*)-**1a**/**2a**. As we reported,[4] in the absence of pyridine the expected cycloadduct **3a** was obtained in very good yield after 72 h, with a predominent *trans*-diastereoselectivity (Table 1, entry 1), in agreement with the expectation of a preferred *endo*-transition state. In the presence of 1 equiv. of pyridine (entry 3), the reaction was complete after 24 h, giving **3a** in excellent yield, and with a high *cis*-selectivity (de = 82%), which was not altered by using an excess of pyridine (4 equiv., entry 4). However, with 0.5 equiv. of pyridine, the *cis*-selectivity of the cycloaddition dropped significantly (entry 2). At this stage, we checked that the 68/32 *t*-**3a**/*c*-**3a** mixture obtained in the first experiment was unchanged in the presence of 1 equiv. of pyridine for 48 h at 20 °C and 11 kbar. In addition, we verified that pure (*E*)-**1a** was configurationally stable at high pressure in the absence of pyridine, whereas we noticed that, in the presence of 1 equiv. of pyridine at 20 °C and 11 kbar for 48 h, it was partially isomerized into a 98:2 (*E*)-**1a**/(*Z*)-**1a** mixture. These accumulated results led us to think that the predominent *cis*-diastereoselectivity of the cycloaddition observed in the presence of pyridine was due to an equilibrated *in situ* isomerization of the (*E*)-heterodiene into its (*Z*)-isomer,[7] whose rate constant k_2 (reaction path b) should be higher, for steric reasons, than that (k_1) of its (*E*)-partner (reaction path a), *via* an *endo*-transition state assumed to be predominent in both cases (Scheme 2). We propose that such an unusual pyridine-promoted (*E*) ↔ (*Z*) isomerization[8] could take place through the formation, in hyperbaric conditions, of a transient adduct **4** resulting from a Michael-type addition of pyridine to (*E*)-**1a**.[9] The progressive decrease of the *trans*-selectivity from entry 1 to entries 3 and 4 seems to be in agreement with stoichiometric consumption of the (*E*)-heterodiene by the pyridine, to give the stabilized ionic adduct **4**, which likely decomposes into the (*Z*)-isomer by a retro-Michael release of pyridine, the overall process being equilibrated. Moreover, in order to account for the global selectivity of the cycloaddition, a minor contribution of the *exo*-approach mechanism (reaction paths c and d, in Scheme 2) could also be considered.

The results obtained in the following seem to agree with the mechanism proposed in Scheme 2 and illustrate the advantage and easiness of the method. In particular, the phosphono-heterodienes **1a**–**c**, for which only the (*E*)-isomers are available,[3,4] were efficiently transformed, as depicted in Scheme 1, into very interesting dihydro-pyrans or -thiopyrans **3**, usually obtained as their predominent *trans*-diastereoisomers, but often with a modest selectivity (Table 1, entries 1, 5, 7, 9 and 11).[10] The addition of 1 equiv. of pyridine to the reaction mixture, under the same conditions, allowed us to accelerate the reaction, as well as to reverse its selectivity, giving access to the less common *cis*-isomer (entries, 3, 6, 8, 10 and 12), occasionally with a diastereomeric excess up to 97% (entry 6).



1a X = S, Y = SEt, W = $(EtO)_2P(O)$, Ar = Ph
b X = S, Y = SEt, W = $(EtO)_2P(O)$, Ar = 4-NO_2-C_6H_4
c X = O, Y = Me, W = $(MeO)_2P(O)$, Ar = 4-NO_2-C_6H_4
d X = O, Y = Me, W = EtOC(O), Ar = Ph

2a ζ = OEt
b ζ = SEt

3a X = S, Y = SEt, W = $(EtO)_2P(O)$, Ar = Ph, ζ = OEt
b X = S, Y = SEt, W = $(EtO)_2P(O)$, Ar = Ph, ζ = SEt
c X = S, Y = SEt, W = $(EtO)_2P(O)$, Ar = 4-NO_2-C_6H_4, ζ = SEt
d X = O, Y = Me, W = $(MeO)_2P(O)$, Ar = 4-NO_2-C_6H_4, ζ = OEt
e X = O, Y = Me, W = $(MeO)_2P(O)$, Ar = 4-NO_2-C_6H_4, ζ = SEt
f X = O, Y = Me, W = EtOC(O), Ar = Ph, ζ = OEt

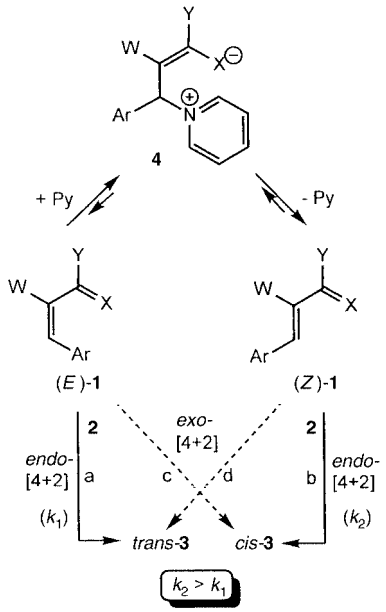
Scheme 1 *Reagents and conditions*: i, without solvent, **2** in ten-fold excess, *n* equiv. of pyridine, 11 kbar, 20 °C.

DOI: 10.1039/b003060k

Table 1 Selectivity and yield of the high pressure-promoted synthesis of cycloadducts **3a–f**, in the presence or absence of pyridine

Entry	Diene	Dienophile	Equiv. Py (*n*)	Products[a]	Selectivity[b] *trans/cis*	Yield[c] (%)
1[d]	(*E*)-**1a**	**2a**	0	*t*-**3a**/*c*-**3a**	68:32	88
2			0.5		16:84	87
3			1		8:92	90
4			4		9:91	88
5	(*E*)-**1a**	**2b**	0	*t*-**3b**/*c*-**3b**	66:34	84
6			1		1.5:98.5	88
7[d]	(*E*)-**1b**	**2b**	0	*t*-**3c**/*c*-**3c**	86:14	83
8			1		6.5:93.5	86
9[e]	(*E*)-**1c**	**2a**	0	*t*-**3d**/*c*-**3d**	75:25	95
10			1		30:70	93
11	(*E*)-**1c**	**2b**	0	*t*-**3e**/*c*-**3e**	93:7	89
12			1		18:82	91
13	(*E*)-**1d**	**2a**	0	*t*-**3f**/*c*-**3f**	64:36	92
14			1		14:86	93
15	(*Z*)-**1d**	**2a**	0		13:87	92
16			1		15:85	92

[a] The experimental procedure was described in ref. 3. [b] Determined after pressure release, on the crude mixture, by ^{31}P and/or ^{1}H NMR integration measurements. [c] Yields of purified oily products. Purification by flash chromatography over silica gel [eluent: ether/MeOH (95:5) for **3a** and **3e**; ether/CH_2Cl_2 (70:30) for **3b** and **3c**; ether for **3d**; heptane/AcOEt (80:20) for **3f**]. Purity checked and structures established by ^{1}H and ^{13}C NMR spectroscopy. Satisfactory microanalyses or HRMS were obtained. [d] Results taken from ref. 4. [e] Results taken from ref. 3.



Scheme 2 Proposed mechanism for the pyridine-induced *cis*-diastereoselectivity of the [4+2] cycloaddition of **1** to **2**, at high pressure.

Finally, we report the cycloaddition of the cetoester **1d** with the dienophile **2a**, leading to the dihydropyran **3e** (entries 13–16). As observed above, in the absence of pyridine the diene (*E*)-**1d** gave **3e** with modest *trans*-diastereoselectivity (entry 13),[10] whereas in the presence of 1 equiv. (or an excess) of pyridine the *cis*-isomer became greatly predominant (entry 14). Interestingly, the same selectivity was obtained by using the diene (*Z*)-**1d** in the absence (entry 15) as well as in the presence of pyridine (entry 16). The remarkable similarity of these last three results suggests that in these three cases, and in particular for the first of them, the main reaction path was path b (Scheme 2). Moreover, we found that when pure diene (*E*)-**1d** was treated with 1 equiv. of pyridine in an inert solvent at 20 °C and 11 kbar for 48 h, it was isomerized into a 43:57 (*E*)-**1d**/(*Z*)-**1d** mixture. The same ratio was obtained when starting from pure (*Z*)-**1d**, indicative of a thermodynamic (*E*)/(*Z*) equilibration of **1d** at high pressure in the presence of pyridine.

In conclusion, this communication describes a straightforward method allowing, by addition of pyridine, the reversal of the diastereoselectivity of some high pressure-promoted hetero-Diels–Alder reactions, giving access, at room temperature, to unusual cycloadduct isomers. This method is especially useful when only the (*E*)-isomer of the heterodiene is available. In order to explain the observed results, a mechanism involving a transient Michael addition of pyridine to the starting (*E*)-diene,[11] and allowing the *in situ* formation of the more reactive (*Z*)-isomer, is proposed.

Notes and references

1 Review: G. Jenner, *Tetrahedron*, 1997, **53**, 2669: for recent important results, see: (*a*) S. Hillers and O. Reiser, *Chem. Commun.*, 1996, 2197; (*b*) F.-G. Klärner and V. Breitkopf, *Eur. J. Org. Chem.*, 1999, 2757; (*c*) G. J. Kuster and H. W. Scheeren, *Tetrahedron Lett.*, 2000, **41**, 515.

2 L. F. Tietze, M. Henrich, A. Niklaus and M. Buback, *Chem. Eur. J.*, 1999, **5**, 297 and references therein.

3 H. Al-Badri, J. Maddaluno, S. Masson and N. Collignon, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2225.

4 H. Al-Badri, N. Collignon, J. Maddaluno and S. Masson, *Tetrahedron*, 2000, **56**, 3909.

5 We prepared **1d** by condensing methyl acetoacetate with benzaldehyde bis(morpholino)aminal (following the procedure described in ref. 3), instead of benzaldehyde used by: C. A. Kingsbury, D. Draney, A. Sopchik, W. Rissler and D. Durham, *J. Org. Chem.*, 1976, **41**, 3863.

6 The separation of the isomers was achieved by using a Waters HPLC chromatograph, a Nova Pack (L = 10 cm, Φ = 0.8 cm) silica gel column and heptane/AcOEt (97:3) as eluent.

7 An example of light-promoted (*E*)/(*Z*)-heterodiene isomerization preceding the cycloaddition has been reported by: L. F. Tietze, T. Brumby, M. Pretor and G. Remberg, *J. Org. Chem.*, 1988, **53**, 810.

8 (*E*)-**1a** was configurationally stable in the presence of pyridine, at 20 °C and atmospheric pressure for several days.

9 High pressure-induced hetero-Michael additions of primary amines have been described in the literature [see for example: (*a*) J. d'Angelo and J. Maddaluno, *J. Am. Chem. Soc.*, 1986, **108**, 8112; (*b*) F. Dumas, B. Mezrhab, J. d'Angelo, C. Riche and A. Chiaroni, *J. Org. Chem.*, 1996, **61**, 2293], and are currently under study in our laboratories (A. Y. Rulev, J. Maddaluno, G. Plé, J. C. Plaquevent and L. Duhamel, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1397, and work in preparation).

10 In each case, we verified, first, that the starting diene was configurationally stable at 11 kbar in the absence of pyridine, and secondly that the obtained cycloadduct mixture did not isomerize, at 11 kbar, in the presence of pyridine.

11 The postulated addition of the nucleophilic pyridine to the heterodiene is to be considered in relation to the first step of the Baylis–Hillman reaction, which is known to be very sensitive to pressure; see for instance: A. Gilbert, T. W. Heritage and N. S. Isaacs, *Tetrahedron: Asymmetry*, 1991, **2**, 969; I. E. Markó, P. R. Giles and N. J. Hindley, *Tetrahedron*, 1997, **53**, 1015.