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Diels–Alder cycloadditions of functionalized (*Z*)-1-benzylidene-2-methylene cyclohexanes: the beneficial effect of high pressure

Thierry Lomberget,[a,†] Isabelle Chataigner,[b] Didier Bouyssi,[a] Jacques Maddaluno[b] and Geneviève Balme[a,*]

[a]*Laboratoire de Chimie Organique 1, associé au CNRS, Université Claude Bernard Lyon 1, CPE, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne, France*

[b]*Laboratoire des Fonctions Azotées et Oxygénées Complexes de l'IRCOF, UMR 6014 CNRS, Université de Rouen, 76821 Mont St. Aignan, France*

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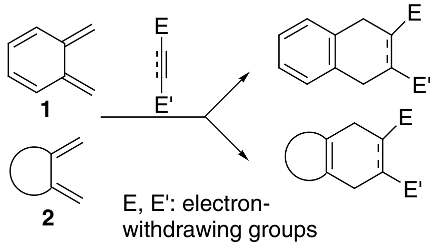
Abstract—Diels–Alder cycloaddition reactions have been studied on substituted (*Z*)-1-benzylidene-2-methylene cyclohexanes **3**. The use of very reactive dienophiles allowed the formation of the expected polycyclic structures whereas hyperbaric conditions (16 kbar) were necessary to form the adducts with less reactive dienophiles. An *exo* stereoselectivity was observed during the reaction with acrylates.

Among all the strategies described in the literature for the construction of carbo- and heterocycles in the cyclohexanic series, the [4 + 2] cycloaddition reaction between a diene and a dienophile is one of the most elegant and efficient approaches, since it allows the creation of two bonds and a cycle in one step, with a high level of regio-, stereo- and even enantioselectivity.[1] Since its discovery 75 years ago,[2] this reaction still remains a powerful tool and numerous syntheses of bioactive or natural products involving this method as the key step are described.[3]

A multitude of dienes can be used[4] such as *o*-quinodimethanes **1**, which are valuable substrates for the synthesis of aromatic bicyclic structures.[5] Indeed, these intermediates show a very high reactivity (the in situ preparation is always required) since: (i) they possess a *S-cis* blocked configuration; (ii) the aromaticity is recovered after the cycloaddition reaction (Scheme 1). Obviously, these very reactive dienes cannot be used for the synthesis of nonaromatic bicyclic derivatives. In this case, bis-exocyclic-1,3-dienes **2**, which display a similar blocked conformation, are required[6] (Scheme 1). Recently, we have described a palladium-catalyzed cyclization of conjugated enynes, which allowed an easy access to functionalized 1,3-bis-exocyclic dienes **3** having stereodefined (*Z*)-arylidene substituents with respect to the methylene group.[7]



Scheme 1.

Numerous Diels–Alder reactions involving (*E*)-1-benzylidene or alkylidene 2-methylene cycloalkanes or (*E*)-α-phenyl-*o*-quinodimethanes have been reported.[8] More seldom are the cases dealing with their corresponding sterically hindered (*Z*)-isomers.[9] Indeed, the (*Z*)-alkyl or -aryl substituent in the 1-position of the diene reduces its reactivity and [4 + 2] cycloadditions with these substrates usually require very harsh conditions and the use of activated dienophiles. However, since the cycloaddition

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Keywords: Exocyclic dienes; Diels–Alder reactions; High pressure; Stereoselectivity; Polycycles.

* Corresponding author. Tel.: +33-472431416; fax: +33-472431214; e-mail: balme@univ-lyon1.fr

† New address: University of Geneva, Department of Organic Chemistry, 30, quai E. Ansermet, CH-1211 Geneva 4, Switzerland.

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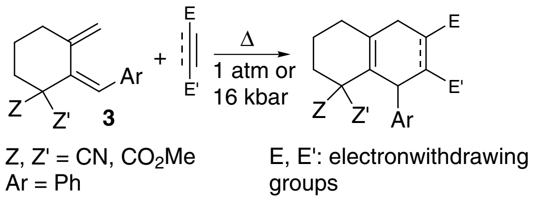


Scheme 2.

reaction conserves the stereochemistry of the alkene in the starting compound, it would be of interest to study the regio- and diastereoselectivity of the dienic derivatives **3** with various dienophiles (Scheme 2). In this article, the behaviour of dienes **3** in Diels–Alder reaction is therefore reported.

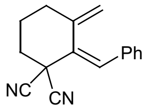
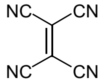
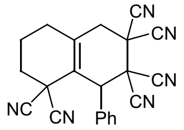
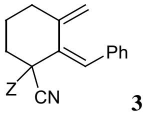
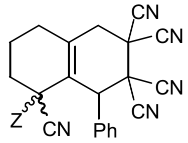
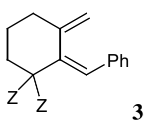
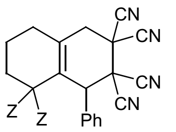
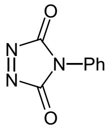
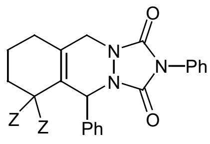
The Diels–Alder cycloadditions of **3a–c** were first investigated with highly reactive dienophiles such as tetracyanoethylene (TCNE) and *N*-phenyl-1,3,5-triazoline-2,4-dione (Table 1). The first attempts were realized with the dicyano derivative **3a** and after 6 h of reflux in the presence of a slight excess of TCNE, the expected adduct **4a** was obtained in 88% yield (Table 1, entry 1). The same procedure[10] was successfully applied to the other exocyclic dienes **3b** and **3c** to give the bicyclic products **4b** (as a 1/1 mixture of two diastereomers) and **4c** in high to quantitative yields (Table 1, entries 2 and 3). To further extend the scope of this method, the reaction between the diene **3c** and an heterodienophile, *N*-phenyl-1,3,5-triazoline-2,4-dione, was performed and the tricyclic heterocycle **4d** was obtained in 82% yield (Table 1, entry 4). The relatively hard conditions (toluene, reflux, 6 h), with respect to the very reactive TCNE, underline that despite the blocked *S-cis* configuration of the dienes **3a–c**, these compounds are poor partners in cycloadditions.

These preliminary observations were confirmed during the reaction of the diene **3c** with *N*-phenyl maleimide (NPM) or dimethyl acetylenedicarboxylate (DMAD). Even after prolonged reaction time (toluene, reflux, 2 days), we did not detect any traces of the expected adducts and only the starting material was recovered. This lack of reactivity is probably due to the steric hindrance imposed by both the phenyl group, and the *gem*-substituents. At this point, alternative activation methods had to be considered.

When using Lewis acids[11] such as $AlCl_3$, $BF_3{\cdot}Et_2O$, $SnCl_4$ or $Sc(OTf)_3$, an unexpected Friedel–Crafts reaction was observed leading exclusively to the 4*a*-methyl-tetrahydrofluorene skeleton in very high yields.[12] Aqueous conditions[13] (2/1 acetone/water mixture, 50 °C) were also tested for the reaction between diene **3c** and NPM but even after a long time (3 days), no reaction was observed. The use of an ionic medium[14a] (5 M $LiClO_4$ solution in diethylether, 40 °C, 2 days) led to the same results, even after addition of camphorsulfonic acid.[14b]

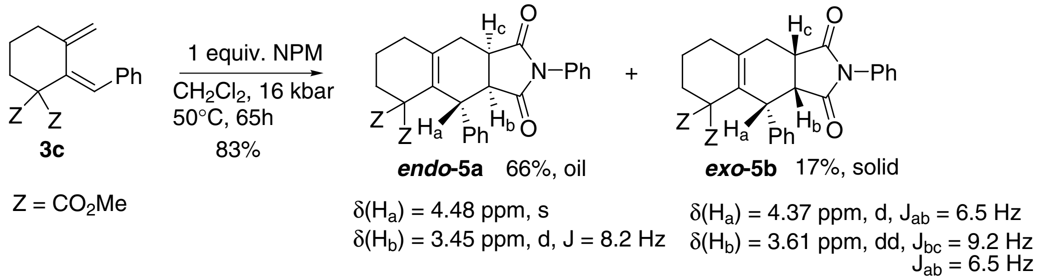
We then turned our attention to hyperbaric conditions, known to greatly facilitate Diels–Alder reactions.[15]

Table 1. Diels–Alder cycloadditions with highly reactive dienophiles

Entry	Starting diene	Dienophile	Reaction conditions (h)	Adduct	Yield[a] (%)
1	 **3a**	 TCNE (1.2 equiv)	Toluene, reflux, 6 h	 **4a**	88[b]
2	 **3b** Z = CO_2Me	TCNE (1.2 equiv)	Toluene, reflux, 6 h	 **4b** 1/1 diastereomeric ratio	89
3	 **3c** Z = CO_2Me	TCNE (1.2 equiv)	Toluene, reflux, 6 h	 **4c**	100
4	**3c**	 (1 equiv)	CH_2Cl_2, rt, 10 h	 **4d**	82

[a] Isolated products.

[b] Compound **4a** was isolated as a white solid after a simple filtration of the reaction mixture on a sintered glass and washing with cold toluene.

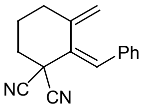
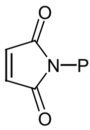
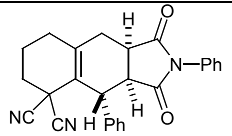
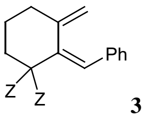
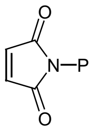
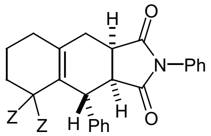
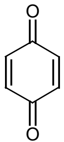
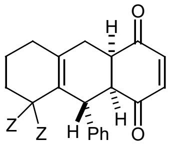
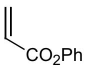
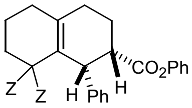


Scheme 3.

When an equimolar mixture of diene **3c** and NPM in CH_2Cl_2 was left at 16 kbar[16] for 65 h at 50 °C, the expected cycloadducts were isolated in a very good 83% yield.[17] Both diastereomers resulting from *endo* and *exo* approaches were easily separated by flash chromatography on silica gel (Scheme 3). The relative configuration of the minor *exo* adduct **5b** could be established by X-ray diffraction analysis.[18]

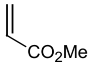
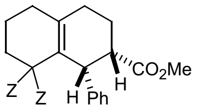
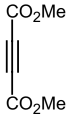
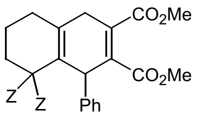
In order to correlate the X-ray structure of the *exo* adduct **5b** with the ^{1}H NMR spectra of both diastereomers, COSY 2D NMR experiments and selective irradiations of protons $H_{a\text{–}c}$ were carried out (see ^{1}H NMR data in Scheme 3).[19] These experiments showed that the deshielded H_a proton appears as a singlet in the *endo* adduct **5a** of the reaction whereas this proton was characterized by a doublet in the *exo* adduct **5b**. The same spectral characteristics were observed for the other cycloadducts (Table 2, entries 1–5) and were used for the determination of the *endo*/*exo* diastereomeric ratio.The same reaction was carried out on diene **3a** and both diastereomers *endo*-**6a** and *exo*-**6b** were isolated with a very good combined yield (Table 2, entry 1) and a similar *endo*/*exo* ratio (80/20). The scope of the Diels–Alder reaction on the 1,3-bis-exocyclic diene **3c** was then extended to other dienophiles (Table 2, entries 3–6). A total diastereoselectivity was observed in the reaction of diene **3c** with benzoquinone and the sole *endo* adduct **7** was isolated in 69% yield (Table 2, entry 3). Nonsymmetrical dienophiles such as phenyl or methyl acrylates have also been employed in this reaction. The *ortho* regioisomers[20] **8** and **9** were the exclusive products, obtained in good yields (Table 2, entries 4–5). It is interesting to note the considerable influence exerted by the phenyl group borne by the diene on the regioselectivity of this [4 + 2] cycloaddition. Interestingly, the

Table 2. Diels-alder cycloadditions under hyperbaric conditions (16 kBar, 50 °C)

Entry	Starting diene	Dienophile	Reaction time[a] (h)	Major adduct (diastereomeric ratio)[b]	Yield[c] (%)
1	 **3a**	 (1 equiv)	60	 **6a** (*endo*/*exo*: 80/20)	81
2	 **3c** Z = CO_2Me	 (1 equiv)	65	 **5a** (*endo*/*exo*: 80/20)	83
3	**3c**	 (1 equiv)	110	 **7** (*endo*/*exo*: 100/0)	69
4	**3c**	 (4 equiv)	90	 **8b** (*endo*/*exo*: 40/60)	70

(*continued on next page*)

Table 2 (*continued*)

Entry	Starting diene	Dienophile	Reaction time[a] (h)	Major adduct (diastereomeric ratio)[b]	Yield[c] (%)
5	**3c**	 (3.7 equiv)	110	 **9b** (*endo*/*exo*: 20/80)	82
6	**3c**	 (1.5 equiv)	70	 **10**	53

[a] All reactions were carried out at 50 °C, in CH_2Cl_2, at 16 kbar.

[b] The *endo*/*exo* ratio was determined on the base of the ^{1}H NMR spectrum of the crude product and/or the isolated products.

[c] Isolated products.

[d] *endo* Adduct **9a** was contaminated by 25% of *exo* adduct **9b** (due to a difficult chromatographic separation).

major products were the *exo*-adducts **8b** and **9b** in this case (40/60 and 20/80 *endo*/*exo* ratio, respectively). This result is to be related to previous observations on the impact of a phenyl substituent on *ortho*-quinodimethane cycloadditions.[8b] This unexpected *exo* selectivity under high pressure should probably be considered in relation with the works of Mellor and Webb[21] on the one hand and Tietze on the other who established that the *endo*/*exo* ratio is the result of a delicate balance between orbitalar and steric effects.[22] This cycloaddition reaction was finally extended to an acetylenic dienophile, DMAD, and the cyclohexadiene adduct **10** was obtained in 53% yield (Table 2, entry 6).

In conclusion, the present work makes an interesting and valuable complement to the Diels–Alder cycloaddition of the corresponding (*E*) isomers. With highly reactive dienophiles, the reaction of 1,3-bis-exocyclic dienes **3a–c** could be carried out under atmospheric pressure and thermal activation while 'standard' dienophiles require pressures (16 kbar) to provide the expected cycloadducts in good yields.

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10. *Typical experimental procedure for the Diels–Alder reactions with TCNE*: A mixture of the compound **3c** (50 mg, 0.166 mmol) and TCNE (26 mg, 0.2 mmol) in 2 mL toluene was heated at reflux (110 °C) during 4 h. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography with petroleum ether/AcOEt 50/50) to afford **4c** as a white solid (72 mg, quantitative yield). Mp 209–211 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): $\delta = 1.46$–1.56 (1H, m), 1.95 (1H, m), 2.16 (1H, m), 2.20–2.42 (3H, m), 2.85 (3H, s), 3.13 (1H, d, $J = 19.0$ Hz), 3.29 (1H, d, $J = 19.0$ Hz), 3.79 (3H, s), 4.87 (1H, s), 7.38 (5H, m). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): $\delta = 18.4$, 30.0, 31.1, 36.1, 37.2, 44.3, 47.9, 52.6, 53.3, 58.6, 110.6, 110.7, 110.9, 112.1, 124.0, 128.4, 130.1, 130.6 (2C), 131.9 (2C), 132.2, 169.0, 170.8. Anal. calcd for $C_{24}H_{20}N_4O_4$: C, 67.28, H 4.71, N 13.08. Found C 67.18, H 4.88, N 12.79.
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16. *Typical experimental procedure for the Diels–Alder reactions under high pressure*: To a solution of compound **3c** (60 mg, 0.2 mmol) in 0.5 mL of CH_2Cl_2, were added under stirring a spatula tip of hydroquinone then *N*-phenylmaleimide (35 mg, 0.2 mmol). This solution was then transferred into a 0.7 mL high pressure glass vessel. This vessel was then submitted to 16 kbar, 50 °C, during 65 h. After decompression, the solvent was removed under reduced pressure and the residue purified by flash chromatography with petroleum ether/AcOEt 60/40 to afford two fractions.
    The less polar fraction was product *endo*-**5a**, which was obtained as a viscous colorless oil (62 mg, 66%). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): $\delta = 1.52$–1.64 (1H, m), 1.91–2.08 (2H, m), 2.20 (1H, dt, $J = 18.5$, 10.4 Hz), 2.26–2.39 (3H, m), 2.68 (1H, dd, $J = 15.2$, 1.5 Hz), 2.84 (3H, s), 3.19 (1H, m), 3.44 (1H, m), 3.45 (3H, s), 4.48 (1H, s), 7.19 (3H, m), 7.29–7.47 (7H, m). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): $\delta = 19.3$, 30.0, 31.6, 31.8, 39.9, 44.6, 49.9, 51.7, 52.9, 58.7, 126.2, 126.6, 126.7, 127.7, 128.5, 128.8, 129.1, 132.5, 139.9, 141.2, 169.9, 172.0, 177.6, 179.0. HRMS (CI) calcd for $C_{28}H_{27}NO_6$: 474.19166 (MH^+). Found: 474.19164. The more polar fraction was product *exo*-**5b**, which was obtained as a colourless solid (16 mg, 17%). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): $\delta = 1.58$ (2H, m), 2.10–2.28 (2H, m), 2.30–2.46 (2H, m), 2.58 (1H, dd, $J = 18.2$, 11.3 Hz), 2.82 (3H, s), 2.98 (1H, dd, $J = 18.2$, 5.6 Hz), 3.35 (1H, m), 3.61 (1H, dd, $J = 9.2$, 6.5 Hz), 3.82 (3H, s), 4.35 (1H, d, $J = 6.5$ Hz), 6.46 (2H, m), 7.04 (2H, m), 7.19–7.25 (8H, m). HRMS (CI) calcd for $C_{28}H_{27}NO_6$: 474.19166 (MH^+). Found: 474.19164.
17. Under lower pressure conditions (12 kbar), the reaction was not complete, even after longer reaction time (96 h) and the adducts **6a** and **6b** were obtained 29% and 10% yield, respectively.
18. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No 225497. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk).
19. The stereochemistry of the minor compounds isolated in the present work is that of the major adducts obtained with the corresponding (*E*)-1-alkylidene or benzylidene-2-methylene cyclohexanes, see Ref. 8.
20. The structure of the *ortho* adducts **9** was deduced after 2D NMR COSY experiments and selective irradiations.
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