On the Diels–Alder Reaction of Allenes Bearing a Diphenylphosphoryl or (Trichloromethyl)sulfonyl Substituent

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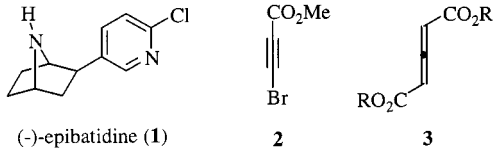
Diels–Alder reactions of two allenes, diphenyl(1,2-propadienyl)phosphane oxide (**4**) and 1,2-propadienyltrichloromethyl sulfone (**7**), with cyclic dienes were studied. While **4** only reacted with cyclopentadiene, to provide the *endo* adduct **5**, the allene **7** proved to be much more reactive. Thus, the cycloaddition between **7** and *N*-Boc-pyrrole gave a mixture of the *endo* and *exo* adducts **9**. The observed reactivities could be rationalized by semiempirical MO calculations.

Introduction

The bicyclo[2.2.1]heptane structure is a part of many natural products and often an entry point for the stereoselective synthesis of five-membered rings, by cleavage of a two-carbon bridge. This has to do with the fact that a Diels–Alder reaction of a cyclopentadiene or a heterocyclic analog is an effective way to construct bicyclo[2.2.1]heptane derivatives. A classic example is the synthesis of the Corey lactone by this strategy, from the Diels–Alder adduct of 5-methoxymethyl-1,3-cyclopentadiene and 2-chloroacrylonitrile, the latter functioning as a ketene equivalent.[1] If one uses furan as a diene, oxacycles and carbocycles can be obtained by cleavage of the bicyclic ring system.[2] With pyrrole derivatives, Diels–Alder reactions are possible only if an electron-withdrawing group is attached to the nitrogen, enhancing the diene character of the heterocyclic ring.[3,4] While such reactions have been known for some time, a resurgence of interest in pyrrole Diels–Alder reactions took place after the discovery of epibatidine (**1**) (Figure 1). This alkaloid was isolated from the poisonous frog *Epipedobates tricolor* by Daly and co-workers.[5]



(-)-epibatidine (**1**) **2** **3**

Figure 1. Structure of epibatidine (**1**) and dienophiles used for its synthesis

Thanks to its novel structure, featuring a 7-azabicyclo[2.2.1]heptane with a 2-chloro-5-pyridyl substituent, and its strong analgesic properties, epibatidine and its analogues have become popular synthetic targets.[6,7] The challenge in a Diels–Alder approach is to find a suitable reactive dienophile that already contains the pyridyl substituent, or that can be converted into a double bond (acetylene equivalent) or a ketone (ketene equivalent). Two ketene equivalents that have been used in the synthesis of epibatidine are methyl 3-bromopropiolate[8] (**2**) and allene-1,3-dicarboxylates[9] (**3**). With a view to the synthesis of epibatidine analogues,[10] we set out to examine the potential of activated allenes for the synthesis of bicyclo[2.2.1]heptane derivatives. In this paper we describe Diels–Alder reactions of diphenyl(1,2-propadienyl)phosphane oxide (**4**) with cyclopentadiene, and of 1,2-propadienyltrichloromethyl sulfone (**7**) with *N*-Boc-pyrrole (**8**).

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Results and Discussion

A number of activated allenes, such as dialkyl 2,3-pentadienedioates, alkyl 2,3-butadienoates and various 1,2-propadienyl sulfones[11] have been successfully employed in thermal [4 + 2] cycloadditions with various 1,3-dienes. Surprisingly, however, cycloaddition reactions of allenes carrying an electron-withdrawing, phosphorus-containing substituent seem to be unknown. As described in the literature, diphenyl(1,2-propadienyl)phosphane oxide can be obtained by treatment of propargylic alcohol with chlorodiphenylphosphane, through a [2,3] sigmatropic rearrangement of the intermediate phosphinites (Scheme 1). This rearrangement takes place even at room temperature.[12] As it turned out, stirring a solution of cyclopentadiene (10 equiv.) and the allene **4** in dichloromethane for several hours provided the cycloadduct in only about 5% yield. However, heating the two components in toluene brought about the Diels–Alder reaction. After chromatographic purification, the cycloadduct **5** could be isolated in reasonable yield as a single diastereomer.

Other conditions, that included carrying out the reaction in the presence of boron trifluoride–diethyl ether (10 equiv.) or aluminium trichloride (1.2 equiv.) in dichloromethane (−78 °C to 23 °C), did not yield any product. This result points to a relatively low reactivity towards Diels–Alder reaction. In line with this was the observation that isoprene also failed to produce a cycloadduct with **4** (80 °C, 24 h). Moreover, neither *N*-Boc-pyrrole nor *N*-tosylpyrrole underwent a Diels–Alder reaction. The structure of the cycloadduct was assigned on the basis of NMR spec-

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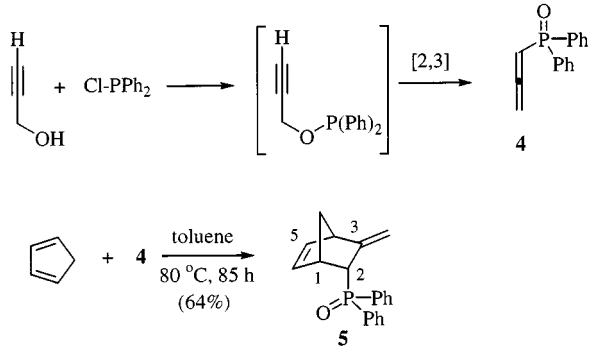
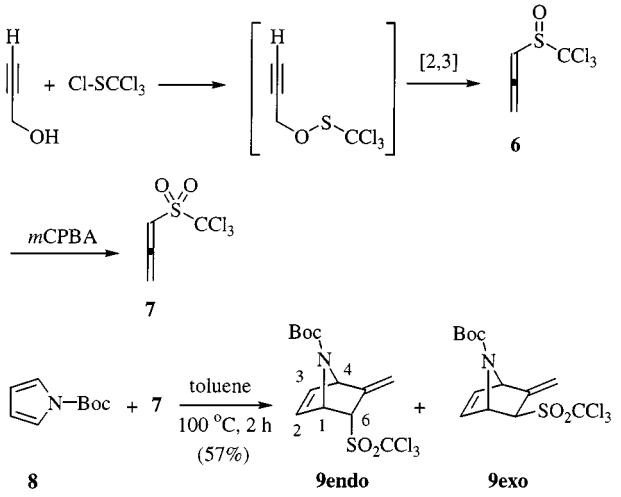


Scheme 1. *Endo*-selective Diels–Alder reaction of diphenyl(1,2-propadienyl)phosphane oxide (**4**) with cyclopentadiene

troscopic data. Particularly intriguing was the fact that one of the *exo* methylene protons appears at a relatively high field of δ = 4.04. In contrast, the other proton resonates at δ = 4.96. This indicates that one of the protons is subject to the influence of the diamagnetic ring current of one of the phenyl rings. This can be best explained by invoking an *endo* orientation of the (diphenyl)phosphane oxide group.

With regard to Diels–Alder reaction of *N*-Boc-pyrrole, we turned to a more reactive monosubstituted allene, investigating in this context the reaction of 1,2-propadienyltrichloromethyl sulfone. This highly electron-deficient allene is known to undergo Diels–Alder reactions with cyclopentadiene as well as with furan.[13] Gratifyingly, the reaction of allene **7** with the pyrrole[14] **8** took place successfully (Scheme 2). Thus, heating of a mixture of *N*-Boc-pyrrole **8** and the allenylsulfone **7** for 2 h provided a mixture of the *exo* and *endo* isomers ***9exo*** and ***9endo*** in a ratio of 2:1. Because of the presence of the urethane group, some of the signals in the ^{1}H NMR spectra were broadened. The stereochemistry was assigned on the basis of the known phenomenon that the proton next to the activating group – in this case H-6 – of an *exo* isomer is shifted upfield by at least 0.5 ppm relative to the *endo* isomer.[15] In the case to hand, the following shifts were observed: H-6 *exo*: δ = 4.87, H-6 *endo*: δ = 5.43 (Δδ = 0.56).



Scheme 2. Diels–Alder reaction between *N*-Boc-pyrrole (**8**) and 1,2-propadienyl trichloromethyl sulfone (**7**)

MO Calculations

In order to rationalize the different reactivities of the two allenes, the HOMO/LUMO energy levels of various allenes were calculated, using AM1 as implemented in HyperChem 5.1. Calculations of this type have already been performed on other allenes.[16,17] In the calculation, the allene **4** was substituted with dimethyl(1,2-propadienyl)phosphane ox-

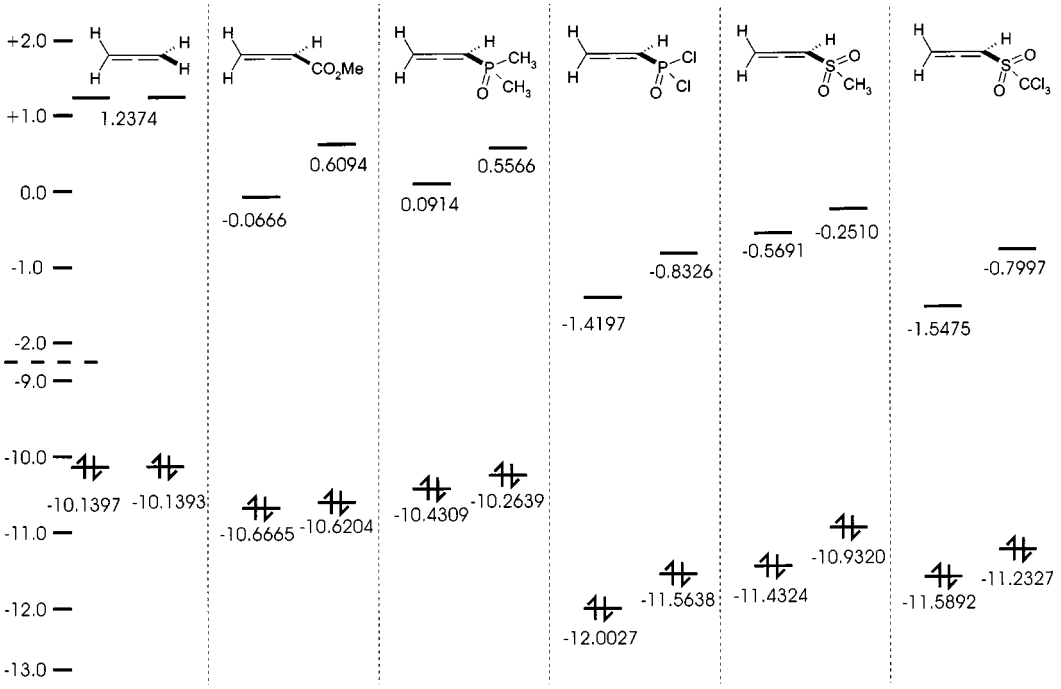


Figure 2. Calculated HOMO/LUMO energy levels (AM1) for various substituted allenes

ide. Allene itself is characterized by two degenerate HOMO and LUMO orbitals, which are essentially orthogonal. For substituted allenes, these orbitals have different energy levels. As can be seen from Figure 2, the dimethylphosphane oxide substituent does lower the energy levels; the effect, however, is less distinct than with an ester group. Thus, allene **4** can be considered as a rather unreactive dienophile. On the other hand, the electron-withdrawing effect is drastically enhanced in the related dienophile 1,2-propadienylphosphonic dichloride.[18,19] This activating effect might become manifested to some extent by using aryl residues bearing electronegative substituents.

It is clear that a methylsulfonyl group, with one more oxygen atom, causes a more pronounced lowering of the frontier orbital levels. In fact, even Diels−Alder reactions with (1,2-propadienylsulfonyl)benzene have been described in the literature.[15] Replacement of the methyl group with a trichloromethyl residue lowers the LUMO levels considerably, which explains the high reactivity of this dienophile in Diels−Alder reactions with normal electron demand.[13,20,21]

To summarize, we were able to demonstrate the first Diels−Alder reaction of diphenyl(1,2-propadienyl)phosphane oxide (**4**) with cyclopentadiene, and the first Diels−Alder reaction of 1,2-propadienyltrichloromethyl sulfone (**7**) with *N*-Boc-pyrrole. The observed reactivities can be understood on the basis of semiempirical calculations.

Experimental Section

^{1}H and ^{13}C NMR: Bruker AC 250; all spectra were recorded in $CDCl_3$. The signal multiplicities were determined by DEPT 135; + for CH or CH_3, − for CH_2, × for C. − IR: Jasco FT/IR 430 spectrometer. EI/MS: Finnigan MAT, TSQ 70. − HRMS: AMD Intectra GmbH, AMD 402. − Flash chromatography: Merck (Darmstadt) silica gel 60, 0.04−0.063 mm. − Thin layer chromatography: Machery−Nagel (Düren): Polygram Sil G UV_{254}. − Solvents were distilled prior to use; petroleum ether with a boiling range of 35−65 °C was used.

The following compounds were prepared according to the literature: allene **4**,[12] *N*-Boc-pyrrole (**8**).[14]

3-Methylenebicyclo[2.2.1]hept-5-en-2-yl(diphenyl)phosphane Oxide (5): A solution of freshly cracked cyclopentadiene (1.38 g, 1.72 mL, 20.8 mmol) and the allene **4** (0.50 g, 2.08 mmol) in toluene (2 mL) was stirred for 85 h at 80 °C. After 20 h of stirring, additional cyclopentadiene (1.38 g, 1.72 mL, 20.8 mmol) was added. Cooling and evaporation of the solvent left a residue that was purified by flash chromatography. Initially, petroleum ether was used as eluent to separate the dicyclopentadiene. Subsequent elution with ethyl acetate provided the cycloadduct **5** (0.40 g, 64%) as a colorless solid, m.p. 151−152 °C. − TLC (ethyl acetate): R_f = 0.68. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (d, J = 8.7 Hz, 1 H, H-7a), 2.18 (d, J = 8.7 Hz, 1 H, H-7b), 2.88, 3.03, 3.22 (3 s, br., 1H each, H-2, H-1, H-4), 3.99, 4.93 (2 s, br., 1H each, H-1a, H-1b), 6.17 (s, br., 2 H, H-5, H-6), 7.35−7.43 (m, 6 H, aromatic H), 7.74−7.83 (m, 4 H, aromatic H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 42.6 (+, C-2), 45.3 (+, C-1 or C-4), 47.4 (−, C-7), 52.0 (−, C-1 or C-4), 108.1 (−, C=CH_2), 128.8, 131.5 (+, aromatic C), 132.0−134.7 (×, 4 lines, aromatic C), 137.9 (+, C-5, C-6), 146.2 (×, C-3). − MS(EI), *m/z* (%): 307 (20) [M^+ + H], 306 (80) [M^+], 201 (100) [M^+ + H − P(O)Ph_2]. − IR (KBr): $\tilde{\nu}$ = 3052 cm^{-1}, 2976, 1485, 1436. − HRMS ($C_{20}H_{19}OP$): calcd. 306.11758, found 306.11759.

1,2-Propadienyl Trichloromethyl Sulfoxide (6): A solution of trichloromethanesulfenyl chloride (7.44 g, 4.37 mL, 40.00 mmol) in dichloromethane (40 mL) was added dropwise to a stirred solution of propargylic alcohol (2.24 g, 5.56 mL, 40.0 mmol) and triethylamine (4.04 g, 5.56 mL, 40.00 mmol) in dichloromethane (160 mL). The addition was carried out under an argon atmosphere over a period of 1 h at 0 °C. Stirring was continued for 5 h, during which the reaction mixture reached room temperature. Water was added to dissolve the triethylamine hydrochloride and the mixture was extracted with dichloromethane (2 × 80 mL). The combined organic layers were washed twice with dilute hydrochloric acid and 10% aqueous potassium carbonate, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was separated by flash chromatography (petroleum ether/ethyl acetate, 5:1) to give the sulfoxide **6** (7.21 g, 88%) as a slightly yellow oil. − TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.50. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.48 (dd, ^4J = 6.3 Hz, ^2J = 0.8 Hz, 2 H, H-3), 6.14 (dd, ^4J = 6.3, ^4J = 6.3, 1 H, H-1). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 83.6 (C-1), 97.2 (C-3), 108.1 (CCl_3), 211.1 (C-2). − MS (EI), *m/z* (%): 205 (48) [M^+], 134 (3) [M^+ − Cl_2], 118 (100) [M^+ − C_3H_3OS], 106 (10) [M^+ − C_4H_3OS], 87 (4) [M^+ − CCl_3], 39 (27) [M^+ − CCl_3OS]. − IR (film): $\tilde{\nu}$ = 2990 cm^{-1}, 1959, 1109.

1,2-Propadienyl Trichloromethyl Sulfone (7):[13] A solution of 70% *m*CPBA (0.45 g, 2.62 mmol) in petroleum ether (100 mL) was dried over anhydrous sodium sulfate, filtered and added dropwise to a solution of the sulfoxide **6** (0.54 g, 2.62 mmol) in dichloromethane (10 mL) at 0 °C. To complete the reaction, the mixture was stirred at 0 °C for 4 h and allowed to warm to room temperature. To remove the benzoic acid, the mixture was washed twice with saturated aqueous sodium bicarbonate solution and the organic layer dried with anhydrous sodium sulfate. Filtration and evaporation of the solvent left a residue that was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to give the sulfone **7** (0.40 g, 69%) as a slightly yellow solid, m.p. 29−30 °C. − TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.39. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.70 (d, J = 6.4 Hz 2 H, H-3), 6.40 (dd, ^4J = 6.3, ^4J = 6.3, 1 H, H-1). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 84.4 (C-1), 90.4 (C-3), 104.7 (CCl_3), 211.1 (C-2). − MS (EI), *m/z* (%): 182 (19) [M^+ − C_3H_3], 118 (100) [M^+ − $C_3H_3O_2S$], 103 (3) [M^+ − CCl_3], 83 (7) [M^+ − $C_3H_3ClO_2S$], 39 (23) [M^+ − CCl_3O_2S]. − IR (KBr): $\tilde{\nu}$ = 2997 cm^{-1}, 1963, 1733, 1356, 1154.

tert*-Butyl 5-Methylene-6-[(trichloromethyl)sulfonyl]-7-azabicyclo-[2.2.1]hept-2-ene-7-carboxylates (9):** A solution of *N*-Boc-pyrrole **8** (719 mg, 4.30 mmol) and the allenylsulfone **7** (190 mg, 0.86 mmol) in toluene (5 mL) was stirred for 2 h at 100 °C. After cooling and evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to provide the *exo*-adduct **9*exo (126 mg) and the *endo*-adduct **9*endo*** (64 mg) in a combined yield of 57%.

Isomer 9*exo*: Slightly yellow solid, m.p. 108−109 °C. − TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.64. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (s, 9 H, *t*Bu), 4.87 (s, br., 2 H, H-1, H-6), 5.12 (s, br., 1 H, H-4), 5.44, 5.49 (2 s, br., 1 H each, C=CH_2), 6.44−6.47, 6.53−6.56 (2 m, 1H each, H-2, H-3). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 28.1 (+, *t*Bu), 59.8 (+, C-1 or C-4), 63.5 (+, C-6), 66.8 (+, C-1 or C-4), 81.8 [×, $C(CH_3)_3$], 104.2 (×, CCl_3), 113.3

(−, C=*C*H$_2$), 133.8, 135.9 (+, C-2, C-3), 138.1 (×, C-5), 153.9 (×, C=O). − MS (EI), *m*/*z* (%): 390, 388 (20) [M$^+$ + 2, M$^+$], 333, 332 [M$^+$ − C$_4$H$_9$], 288 [M$^+$ − CO$_2$C$_4$H$_9$]. − IR (KBr): $\tilde{\nu}$ = 2974 cm^{-1}, 1701, 1351, 1158. − HRMS ($C_{13}H_{16}NO_4SCl_3$): calcd. 386.986529, found 386.980945.

Isomer 9*endo*: Slightly yellow solid, m.p. 109 °C TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.35. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, *t*Bu), 4.21 (s, br., 1 H, H-1 or H-4), 5.02 (s, br., 1 H, H-1 or H-4), 5.43 (s, br., 2 H, C=C*H*H, H-6), 5.49 (s, br., 1 H, C=CH*H*), 6.37, 6.60 (2 s, br., 1H each, H-2, H-3). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 28.0 (+, *t*Bu), 60.8, 62.1 (+, C-1 or C-4), 64.9 (+, C-6), 81.3 [×, *C*(CH$_3$)$_3$], 104.6 (×, *C*Cl$_3$), 114.4 (−, C=*C*H$_2$), 134.8, 141.5 (+, C-2, C-3), 139.4 (×, C-5), 153.4 (×, C=O). − MS (EI), *m*/*z* (%): 390 (4) [M$^+$ + 2], 328 (10). − IR (KBr): $\tilde{\nu}$ = 2976 cm^{-1}, 1713, 1357, 1155.

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