Highly Selective High-Pressure Cycloadditions

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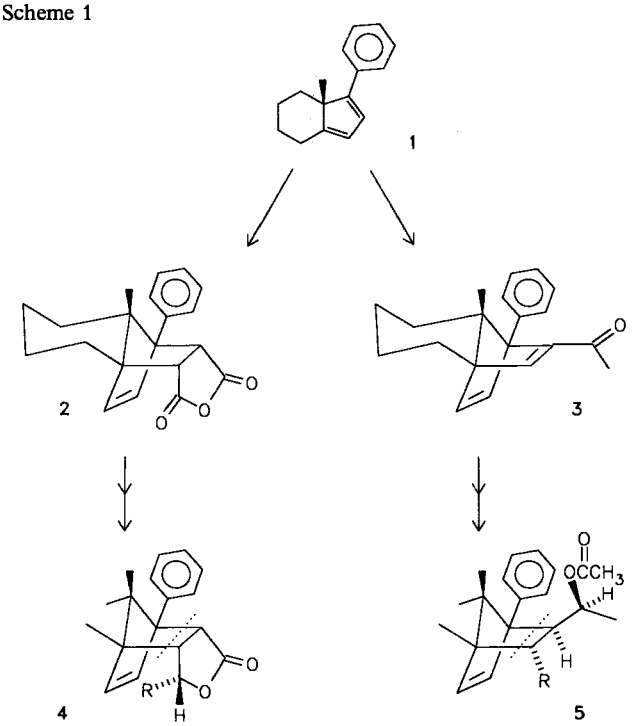
High-pressure cycloadditions of the nonsymmetric dienophiles itaconic anhydride (**6**) and citraconic anhydride (**7**) to the homochiral cyclopentadiene **1** can be exercised with excellent regioselectivity (100%) and face selectivity

We have recently reported on the preparation and some cycloaddition reactions of the homochiral cyclopentadiene **1**[1,2]. This diene was prepared with the intention to use it as a chiral template, since cycloadducts like **2** or **3**, owing to their conformational rigidity, should undergo highly chemoselective, regioselective, and also stereoselective transformations. Finally, a retro Diels-Alder process is expected to give rise to enantiomerically pure retro products and should simultaneously regenerate the diene (Scheme 1; see dotted lines).

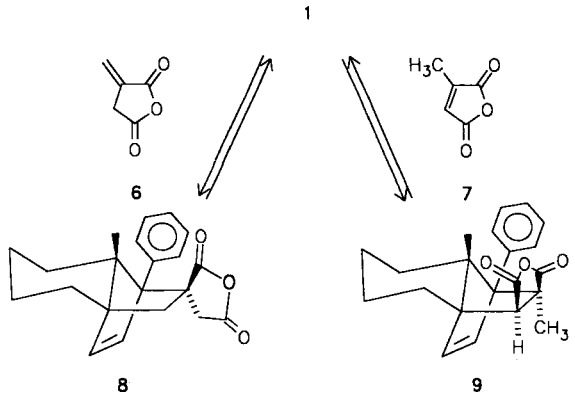
Scheme 1



With very simple cases like **4** (prepared from **2**) and **5** (prepared from **3**) this concept has been shown to work very well[2], and we were also able to convert quinones into optically pure 4-hydroxycyclohexenones[3]. While the cycloadditions with butynone and other acetylenic carbonyl compounds had indicated high β-face selectivity and remarkable regioselectivity, the symmeric dienophiles quinone and maleic anhydride had demonstrated that *endo* adducts are formed exclusively with compounds of this type. This has recently been shown to be the case with cyclic imides, too.

Since chemoselective and regioselective transformations should be particularly easy with adducts to cyclic nonsymmetric dienophiles like itaconic anhydride (**6**) and its isomer citraconic anhydride (**7**) we embarked on their room-temperature, high-pressure cycloaddition to diene **1**.

Scheme 2



Both reactions proved to be slow as the creation of a quaternary carbon atom was required. They took 8 to 10 days at 6.5 kbar, but although only one single cycloadduct was formed we were quite confused at the beginning as, according to the first impression, the reactions never ran to completion. It was proven later, however, that solutions of **8** and **9** are prone to a slow retroprocess at room temperature at normal pressure, which led to the regeneration of the starting materials already during workup and chromatography. Only after crystallization could the solid material be stored in the refrigerator without decomposition.

As quite a number of stereoisomers and regioisomers are in principle available we decided on extensive NMR experiments for structure elucidation.

The task was comparatively simple with **8** as the downfield shift of the signal of the angular methyl group to $\delta = 1.29$ compared to $\delta = 0.8-0.9$ in *endo* adducts must be due to the close vicinity of a carbonyl group which is only possible in a β-*exo* adduct like **8**. The regioselectivity displayed by **8** is first of all in line with all nonsymmetric acceptor-substituted dienophiles investigated so far. Additionally, the resonance signal of the geminal protons in the

  0009–2940/92/0909–2159 $ 3.50+.25/0

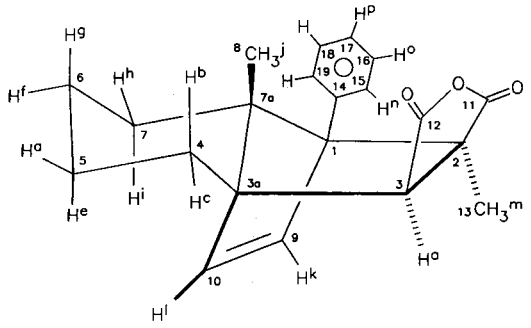
cyclopentane ring (centered at δ = 2.0) is typical of the CH_2 group opposite to the phenyl ring. The alternate situation would call for the well-established downfield shift for the signal of these protons to values between δ = 3.3 and 4.0 caused by the aromatic ring. Last but not least there is a typical downfield shift of the signal of the two aromatic *ortho* protons from δ = 7.3 to 7.4 on opening of the anhydride with an amine to generate the corresponding ester amide. This is probably due to additional degrees of freedom for rotation leading to a slight deshielding of these protons by the neighboring carbonyl groups.

Structure **8**, which is supported by all of these data, represents the first *exo* adduct to diene **1**, thus indicating that a dienophile with an sp^2 as well as an sp^3 center located at the 2π system will preferentially place the sp^3 center on the side of the less space-demanding double bond. This approach minimizes steric interactions with the angular methyl group.

If this explanation is accepted one would predict stereoselective *exo* addition for citraconic anhydride as well to form adduct **9**. First-hand NMR data left no doubt that this is the case, since again the signal of the angular methyl group shows this typical downfield shift to δ = 1.42 bringing it very close to the signal of the methyl group at the anhydride moiety (δ = 1.45). An even more pronounced shift is already noticed for the signal of the two *ortho* protons (δ = 7.66) in the anhydride. This is certainly due to the different angle of the carbonyl plane with respect to the aromatic ring in **9** compared to the spiro system **8**.

While arguments in favor of *exo* selectivity were easy to find, regioselectivity initially remained obscure, and since there was no precedence available we solved the problem with a 2D-COSY spectrum by using a 2D ^{13}C-^1H corelation of ^{13}C assignment; ^1H-detected long-range ^{13}C-^1H correlations allowed positional assignments of substituents. As these data additionally confirm the *exo* assignment they should be discussed in detail, and Table 1 with a list of correlations (long range only!) holds all the relevant information.

Table 1. ^{13}C-^1H NMR correlations and NOE difference spectra

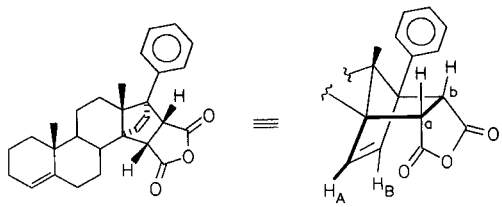


9'

Carbon atom	Hydrogen atom	Irradiation of	NOE at
1	n, k, l, m, j	n	o, k
2	l, m	k	n, l, i
3	k, b, m	l	k, e, m
3a	k, l, a, i, b, j, h	a	l, m
7a	k, l, c, i, j, h		
8	h, i		
9	l		
10	k, a, b, c		
13	a		

The most remarkable finding in this connection are the four-bond long-range couplings between H_l and C-2 (see bold line in formula **9'**) and between H_k and C-3, which was thought to be possible by analogy with the well-known allylic proton coupling and which was checked with the also very rigid, stable anhydride adduct **10** prepared in connection with another project[2].

Scheme 3



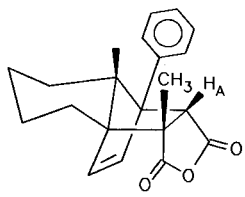
10

After an unambiguous assignment of protons H_A and H_B as well as the corresponding protons at C-a and C-b two four-bond couplings were also detected in compound **10**.

With these data available there is ample evidence for the regioselective formation of the *exo* adduct **9**. Although the *exo* selectivity is well understood and in line with the explanation given in connection with *exo* adduct **8** there is no simple explanation for the high degree of regioselectivity in this particular addition. It should, however, be mentioned that after combining mother liquors from various cycloadditions we detected a small amount of a slightly more polar second isomer.

After separation of **9** by further crystallization we obtained a mixture containing up to 16% of this more polar anhydride which was purified by flash chromatography to yield a few mg of this second adduct. As with the main product the mass spectrum did only exhibit the peak of the retro Diels-Ader product and so we were left with the NMR data for structure determination. These immediately suggested the *endo*-adduct structure **11** for this very low-yield (ca. 1–2%) byproduct.

Scheme 4



11

First of all, as there is no shift for any signals of aromatic protons, the signal of the angular methyl group is similar to that of many other *endo* adducts seen at δ = 0.92, and the signal of the tertiary proton shows up at δ = 4.10. As all this compares extremely well with signals of analogous protons in these positons we have no doubt that this byproduct is again the result of a highly regioselective *endo*-addition process.

Although the applications of these adducts in template-directed transformations are severly limited by their very strong tendency for retro processes, they represent convincing examples for highly stereoselective and regioselective cycloadditions of a nonsymmetric diene to also nonsymmetric acceptor-substituted dienophiles. In both cases not easily to be constructed quaternary carbon atoms[4] are formed, and the *exo-endo* selectivity is governed by preferential arrangement of an sp^3 center *trans* to the quaternary carbon atom

carrying the angular methyl group. With two examples only, one hesitates of course to call this a general trend. Further experiments are clearly warranted.

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Experimental

TLC: Merck plates with silica gel 60 F/254. – Flash chromatography: Baker silica gel 30–60 μ. – IR ($CHCl_3$ solutions between KCl discs): Perkin-Elmer 580. – ^{1}H-NMR: Bruker WP-200; AM-600. – Ms (70 eV): Finnigan MAT-312. – Elementar analyses: Heraeus CHN rapid analyzer.

General Procedure for Cycloadditions: 3.00 g (1.43 mmol) of diene **1** was dissolved in 20 ml of dry dichloromethane, and 1.50 g (1.40 mmol) of anhydride **6** or **7** was added to the solution which was pressurized in a teflon hose at 6.5 kbar for 10 d. Evaporation of the solvent at room temp. afforded an oily residue which was crystallized from ether/petroleum ether.

Anhydride Adduct **8**: Yield 4.00 g (88%), m.p. 89–93°C. – IR: $\tilde{\nu}$ = 2950 cm^{-1}, 1840, 1780, 1280, 970, 930. – ^{1}H NMR: δ = 1.29 (d, J = 1.3 Hz, 3H), 1.35–1.95 (m, 8H), 1.9 (d, J = 12 Hz, 1H), 2.1 (d, J = 12 Hz, 1H), 2.83 (d, J = 18 Hz, 1H), 3.08 (d, J = 18 Hz, 1H), 6.20 (s, 2H), 7.30 (m, 5H). – MS (70 eV, 20°C): m/z (%) = 210 (100), 195 (35), 181 (30), 167 (61).

$C_{21}H_{22}O_3$ (322.4) Calcd. C 78.23 H 6.88
Found C 78.22 H 6.90

Anhydride Adduct **9**: Yield 4.20 g (94%), m.p. 122°C. – IR: $\tilde{\nu}$ = 2940 cm^{-1}, 1840, 1770, 1250, 920, 940. – ^{1}H NMR: δ = 1.42 (d, J = 1 Hz, 3H), 1.45 (s, 3H), 1.3–2.3 (m, 8H), 3.18 (s, 1H), 6.07 (d, J = 6 Hz, 1H), 6.54 (d, J = 6 Hz, 1H), 7.38 (m, 3H), 7.66 (m, sH). – MS (70 eV, 20°C): m/z (%) = 210 (100), 195 (18), 181 (17), 167 (25).

$C_{21}H_{22}O_3$ (322.4) Calcd. C 78.23 H 6.88
Found C 78.59 H 6.86

Anhydride Adduct **11**: Yield ca. 44 mg (ca. 1%). – ^{1}H NMR: δ = 0.92 (s, 3H), 1.66 (s, 3H), 0.7–2.2 (m, 8H), 4.10 (s, 1H), 6.22 (d, J = 6 Hz, 1H), 6.38 (d, J = 6 Hz, 1H), 7.38 (m, 5H).

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[202/92]

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1: 126971-21-9 / **6**: 2170-03-8 / **7**: 616-02-4 / **8**: 142746-83-6 / **9**: 142746-84-7 / **11**: 142746-85-8