Acetoxymaleic Anhydride as Ketene Equivalent in the Diels-Alder Reaction

Ernest Wenkert*, Christian Vial®, and Ferdinand Naf®

Abstract. Acetoxymaleic anhydride (AMA) has been shown to be a versatile ketene equivalent in the Diels-Alder reaction for the conversion of 1,3-dienes into cyclohexanes. The new transformation has been applied to an alternative synthesis of methyl cis-dihydrojasmonate, an important jasmine fragrance, and to several model systems.

Six-membered ring compounds cannot be obtained from simple ketenes and 1,3-dienes via a [4+2] cycloaddition reaction, since ketenes undergo exclusively [2+2] cycloaddition leading to four-membered ring structures instead. Therefore, synthons which are equivalent to ketenes but react in a [4+2] mode with 1,3-dienes are most useful building blocks [1].

In this publication, we describe the use of acetoxymaleic anhydride (AMA, 1) [2] as ketene equivalent in the Diels-Alder reaction (Scheme 1).

The known reaction of AMA (1) with cyclopentadiene 2 gave the adduct 3 (82%) [3]. It was assumed that acetoxyglutaric anhydride 4 or its dihydro derivative 5 would undergo hydrolytic decarbonylation in analogy to the behavior of α-oxo-acids, which lose CO upon acid treatment forming carbonyl compounds [4] (Scheme 2). When the saturated acetoxyglutaric anhydride 4 [5] was treated with 96% H₂SO₄ between 5 and 20°C, a 42:58 mixture of 5a and 5b, was obtained (Scheme 1). Acid-catalysed decarboxylation of the

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Scheme 1

![Scheme 1 Diagram](attachment:Scheme_1.png)

Reagents: a) 24 h/25°C, benzene; b) H₂/Pd-C; c) 96% H₂SO₄/25°C; d) AcOH, 2 h reflux.
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Abstract. Acetoxymaleic anhydride (AMA) has been shown to be a versatile ketene equivalent in the Diels-Alder reaction for the conversion of 1,3-dienes into cyclohexanones. The new transformation has been applied to an alternate synthesis of methyl cis-dihydrojasmonate, an important jasmine fragrance, and to several model systems.

Six-membered ring compounds cannot be obtained from simple ketenes and 1,3-dienes via either a [4+2] cycloaddition reaction, since ketenes undergo exclusively [2+2] cycloaddition leading to four-membered ring structures instead. Therefore, synths which are equivalent to ketenes but react in a [4+2] mode with 1,3-dienes are most useful building blocks [1].

In this publication, we describe the use of acetoxymaleic anhydride (AMA, 1) [2] as ketene equivalent in the Diels-Alder reaction (Scheme 1).

The known reaction of AMA (1) with cyclopentadiene 2 gave the adduct 3 (52%) [3]. It was assumed that acetoxymaleic anhydride 3 or its dihydro derivative 4 would undergo hydrolytic decarboxylation in analogy to the behavior of α-oxoacids, which lose CO upon acid treatment forming carbonyl compounds [4] (Scheme 2). When the saturated acetoxymaleic anhydride 4 [5] was treated with 96% H2SO4 between 5 and 20°, a 42:58 mixture (57%) of 5a and 5b, was obtained (Scheme 1). Acid-catalysed decarboxylation of the

Scheme 1
To further test the scope and limitation of the reaction sequence of Scheme 1, it was applied to various 1,3-dienes. The results are summarised in the Table. The following general experimental procedures were used.

A) Diels-Alder Step. AMA (1: 0.1 mol) was added at room temperature to a solution of the diene (0.2 mol) in 250 ml of solvent (benzene or toluene) under Ar. The mixture was stirred either at room temperature, at reflux temperature, or in a sealed tube for a given time (for specific conditions see Table). The reaction mixture was concentrated under vacuum and chromatographed over silica gel (hexane/EtO).

B) Hydrogenation Step. A mixture of the Diels-Alder adduct (0.2 mol) and ca. 5
dr°~
ii
eOOH
~ o 8b

Scheme 2

5a/b mixture produced norbornan-2-one 6 (72%).

Unfortunately, the initial Diels-Alder adduct 3 gave no decarbonylation and furnished only lactone 7, m.p. 180–184° (dec.).

To illustrate the utility of the new method (Scheme 1), it was applied to the synthesis of methyl cis-dihydrojasmonate, a key constituent of the commercial jasmine fragrance Hedione® [6], the thermodynamic mixture of methyl cis- and trans-dihydrojasmonate (8a and 8b ~96:4) [7]. Odor evaluation has demonstrated clearly the cis-isomer to be much stronger, thus emphasizing the importance of direct access to 8a [8].

Diels-Alder reaction of fulvene 9 [9] [10] and AMA (1) in benzene furnished in 65% yield a mixture of the four isomeric cycloadducts 10a, 10b, 10c, and 10d (1:1:1:1; Scheme 3). Subsequent catalytic hydrogenation gave the two isomers 11a and 11b (1:1) which, upon treatment with 96% H₂SO₄ followed by decarboxylation, led to 98% pure syn-7-pentylnorbornan-2-one (13) [11] (the yields being 68% from pure 11a and 74% from pure 11b). Bayer-Villiger reaction (40% Ac₂O, H (10 equiv.), 96% H₂SO₄ (3.4 equiv.), 18 h at room temperature) of ketone 13 gave in 67% yield an inseparable mixture (7:3) of desired lactone 14 [11] and undesired lactone 15. Alternative methods (m-chloroperoxybenzoic acid/CHCl₃, reflux; 35% AcOOH/AcOH/CH₂Cl₂) left the starting material unchanged. A reaction sequence [11] of saponification, esterification, and oxidation finally led to an easily separable mixture (by flash chromatography on silica gel) of methyl cis-dihydrojasmonate 8a (containing 6% 8b, 57% yield of 8a/b based on 14) and 16.
### Table. Reaction of AMA (1) with Various Dienes, Followed by a Hydrogenation/Decarbonylation-Hydrolysis/Decarboxylation Reaction Sequence

| Entry | Diene Method | Diels-Alder Adduct [yield] | Method | Final Product [yield] |
|-------|--------------|---------------------------|--------|-----------------------|
| 1     | A: 26 h/110° benzene, sealed tube | ![Diels-Alder Adduct](image1) (49%) | B, C | (76%) |
| 2     | A: 24 h/110° benzene, sealed tube | ![Diels-Alder Adduct](image2) (31%) | B, C | (43%) |
| 3     | A: 24 h/110° benzene, sealed tube | ![Diels-Alder Adduct](image3) (4-7%) polymers | - | - |
| 4     | A: 5 h/110° toluene, reflux | ![Diels-Alder Adduct](image4) (76%) | B, C | (ca. 15%) |

* ) Z/E ratio 1:2.  
* ) Z/E ratio 3:7.

Reflex temperature for 2 h. The mixture was diluted with pentane and the layers were separated. The pentane phase was washed with sat. Na₂CO₃ and brine to neutrality. The pentane extract was dried (Na₂SO₄), concentrated and distilled.

It follows from the Table and from the preceding experiments that AMA (1) is only a moderately reactive dienophile not undergoing any preparatively useful reactions with unreactive dienes such as cyclohexa-1,3-diene, but reacting well with reactive dienes such as cyclopentadiene and 1-acetoxybuta-1,3-diene. Attempts to prepare the presumably more reactive dienophiles tosylxymaleic anhydride and trifluoroacetoxymaleic anhydride failed. The relatively vigorous conditions needed for the decarbonylation of the acetoxyglutaric anhydrides is not compatible with labile structures such as in Entry 4. In the latter case only double elimination of AcOH and hydrolysis of the anhydride, giving phthalic acid was observed. Reagents alternative to 96% H₂SO₄ (e.g., various Pd⁰, Rh¹, Ru¹ complexes) were also tried, but gave unfavourable results.

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