# [4 + 2], [2 + 2], and Carbene Addition Reactions Involving Cyclohexa-3,5-diene-*cis*-1,2-diol Derivatives

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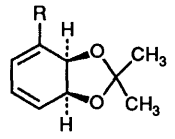
The reactions of *cis*-1,2-isopropylidenedioxycyclohexa-3,5-diene (**1**) with two *N*-substituted maleimides, diphenylketene, dichlorocarbene and ethoxycarbonylcarbene are described. Selected reactions of the 3-trifluoromethyl- (**2**) and 3-fluoro-(**3**) analogues with these reagents are also reported.

The microbiological method for the preparation of (3-substituted) cyclohexa-3,5-diene-1,2-diol(s) has attracted considerable attention.[1] Various aspects of the chemistry of the parent compound have been investigated[2] and some reactions of 3-chlorocyclohexa-3,5-diene-1*S*,2*S*-diol[3] and 3-methylcyclohexa-3,5-diene-1*S*,2*R*-diol[4] have been described.

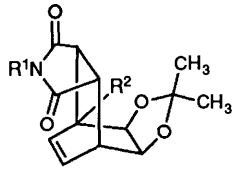
We have previously reported[5] that the isopropylidene derivative of cyclohexa-3,5-diene-1,2-diol (**1**) undergoes Diels–Alder reactions with various acyclic dienophiles to give products resulting from addition to the less hindered face. Interestingly, Gillard and Burnell reported recently[6] that *N*-phenylmaleimide reacts with the same diene in chloroform to give a 60:40 mixture of the *endo*/*syn* (**4**) and *endo*/*anti* (**7**) products. We can add that the same effect is seen with *N*-ethylmaleimide [furnishing the adducts (**5**) and (**8**)] and the effect is solvent dependent (Table). The isopropylidene

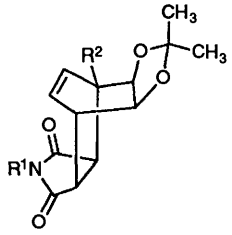
**Table.** Cycloaddition of dienes (**1**) and (**2**) with *N*-ethylmaleimide (NEM) and/or *N*-phenylmaleimide (NPM).

| Diene | Dienophile | Solvent | Products; (Ratio) | Yield (%) |
|---|---|---|---|---|
| (1) | NPM | $CHCl_3$ | (4), (7); (60:40)[6] | — |
| (1) | NPM | $C_6H_6$ | (4), (7); (52:48) | 86 |
| (1) | NPM | $H_2O$ | (4), (7); (33:67) | 85 |
| (1) | NPM | $(CH_2OH)_2$ | (4), (7); (27:73) | 95 |
| (1) | NEM | $CHCl_3$ | (5), (8); (50:50) | 98 |
| (1) | NEM | $C_6H_6$ | (5), (8); (39:61) | 96 |
| (1) | NEM | $H_2O$ | (5), (8); (18:82) | 79 |
| (1) | NEM | $(CH_2OH)_2$ | (5), (8); (12:88) | 73 |
| (2) | NEM | $C_6H_6$ | (6), (9); (43:57) | 79[7] |

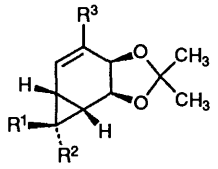


(**1**) R = H
(**2**) R = $CF_3$
(**3**) R = F

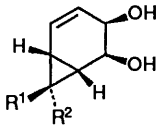




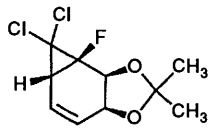
(**4**).....$R^1$ = Ph; $R^2$ = H.....(**7**)
(**5**).....$R^1$ = Et; $R^2$ = H.....(**8**)
(**6**).....$R^1$ = Et; $R^2$ = $CF_3$.....(**9**)



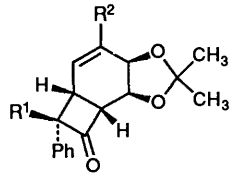
(**15**) $R^1$ and $R^2$ = Cl; $R^3$ = H
(**16**) $R^1$, $R^2$ = H, $CO_2Et$; $R^3$ = H
(**17**) $R^1$ = $R^3$ = H; $R^2$ = $CH_2OH$
(**18**) $R^1$ and $R^2$ = Cl; $R^3$ = $CF_3$
(**19**) $R^1$ and $R^2$ = Cl; $R^3$ = F



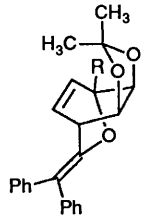
(**20**) $R^1$ = H; $R^2$ = $CO_2Et$
(**21**) $R^1$ = $CO_2Et$; $R^2$ = H



(**24**)



(**10**) $R^1$ = Ph; $R^2$ = H
(**11**) $R^1$ = $CH_3$; $R^2$ = H
(**12**) $R^1$ = Ph; $R^2$ = F



(**13**) R = H
(**14**) R = F

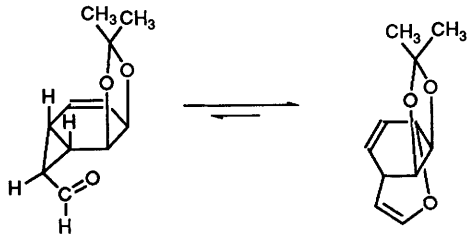
derivative of 3-trifluoromethylcyclohexa-3,5-diene-1,2-diol (**2**) also undergoes a facile Diels–Alder [4 + 2] reaction with *N*-ethylmaleimide to produce the *endo*/*syn*-(**6**) and *endo*/*anti*-(**9**) adducts in the ratio 4:5.[7] We now report that other addition reactions involving the dienes (**1**), (**2**) and the isopropylidene derivative (**3**) of 3-fluorocyclohexa-3,5-diene-1,2-diol lead to interesting results.

## Results and Discussion

Diphenylketene[8] and the diene (**1**) were heated under reflux in tetrahydrofuran (THF) for 20 h to furnish a mixture of the [2 + 2]-adduct (**10**) and the [4 + 2]-adduct (**13**) in the ratio 5:4 (59% yield). (The compounds (**10**) and (**13**) are not interconverted in hot THF). The identity of the oxabicyclo-[2.2.2]octane was established by NMR spectroscopy (*vide infra*): nuclear Overhauser effects clearly showed that the cycloaddition had taken place from the more exposed *exo*-face of the molecule. The regio- and stereo-chemistry of the reaction leading to the cyclobutanone derivative (**10**) is as expected for a concerted [2 + 2] addition reaction.[9] The formation of the enol ether (**13**) was not anticipated (cyclohexa-1,3-diene and diphenylketene give only the [2 + 2]-adduct[10]) although isolated reports of similar reactions involving dienes and ketenes can be found in the literature.[11] The [4 + 2] reaction that produces the adduct (**13**) appears to proceed through a non-polar transition state since the ratio of (**10**) and (**13**) is found to change little (5 : 3) when the reaction is conducted in the less polar medium of hexane (84% yield). In contrast, reaction of the diene (**1**) with methylphenylketene (prepared *in situ* from the acyl chloride in hexane) gave the [2 + 2]-cycloaddition product (**11**) as the only isolated product, in 41.5% yield.

The reaction of diphenylketene with the fluorodiene (**3**) in THF gave mainly the bicyclic compound (**14**) (77%) and only a small amount of the isomer (**12**) (9%). Again, the stereochemistry of the enol ether (**14**) was evident from the NMR spectrum.

Reaction of the diene (**1**) with dichlorocarbene (generated using 50% aqueous sodium hydroxide and chloroform containing triethylbenzylammonium chloride, at room temperature) gave the adduct (**15**), while reaction of compound (**1**) with ethyl diazoacetate in solvent containing rhodium(II) acetate gave a mixture of the bicycloheptanes (**16**). Treatment of this mixture with 80% aqueous acetic acid at 70 °C gave the diols (**20**) (39%) and (**21**) (47%). Reprotection of the diol (**20**) using dimethoxypropane and toluene-*p*-sulphonic acid, followed by



(22) (23)

**Figure.**

treatment with di(isobutyl)aluminium hydride at −100 °C gave as the major product (*ca.* 43%) the enol ether (**23**), formed through an *oxa*-Cope rearrangement of the aldehyde (**22**) (Figure). The NMR spectrum of the major product showed that the aldehyde (**22**) contributed *ca.* 10% to the equilibrium mixture in $CDCl_3$ solution, while slow and complete crystallization of the mixture from light petroleum gave uncontaminated enol ether (**23**). The relative stability and ease of isolation of the enol ether (**23**) sharply contrast with similar systems[12] wherein the enol ether is much more labile. A small amount (15%) of the alcohol (**17**) was also obtained from the reduction reaction.

It is noteworthy that the diene (**2**) reacts with dichlorocarbene in a regioselective manner to give the adduct (**18**) while reaction of the same carbene with the isopropylidene derivative (**3**) afforded a mixture of the isomers (**19**) (42%) and (**24**) (20%).

## Experimental

*Reaction of Diphenylketene and* cis-1,2-*Isopropylidenedioxycyclohexa*-3,5-*diene* (**1**).—The diene (**1**) (0.15 g) and diphenylketene (0.29 g) were heated under reflux in dry tetrahydrofuran for 20 h. Water (20 ml) was added and saturated aqueous sodium hydrogen carbonate was added to give pH 5. The solution was extracted with diethyl ether (3 × 20 ml) and the combined organic phases were washed with brine (60 ml) and water (60 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed over silica gel using ethyl acetate in light petroleum (b.p. 60–80 °C; ratio 1:15) to give the *enol ether* (**13**) (0.092 g); δ($CDCl_3$) 7.60–7.20 (10 H, m, ArH), 6.39 (2 H, m, 5-H and 6-H), 5.11 (1 H, ddd, *J* 4.5, 4.0, and 2.0 Hz, 1-H), 4.61 (1 H, dd, *J* 7.0 and 4.0 Hz, 7-H or 8-H), 4.45 (1 H, dd, *J* 7.0 and 4.0 Hz, 8-H or 7-H, 3.92 (1 H, ddd, *J* 6.0, 4.0, and 2.0 Hz, 4-H), and 1.34 and 1.33 (2 × 3 H, 2 × s, 2 × $CH_3$); $\nu_{max}$ 1 275 $cm^{-1}$ (Found: $M^+$, 346.1569. $C_{23}H_{22}O_3$ requires *M*, 346.1569). Later fractions contained the ketone (**10**) (0.112 g); δ($CDCl_3$) 7.60–7.20 (10 H, m, ArH), 5.65 (1 H, d, *J* 10.7 Hz, 2-H or 3-H), 5.51 (1 H, dd, *J* 10.7 and 3.5 Hz, 3-H or 2-H), 4.68 (1 H, dd, *J* 6.0 and 2.3 Hz, 5-H), 4.53 (1 H, dm, *J* 6.0 Hz, 4-H), 4.12 (1 H, dd, *J* 8.9 and 2.3 Hz, 6-H), 3.95 (1 H, dm, *J* 8.9 and 3.5 Hz, 1-H), and 1.40 and 1.36 (2 × 3 H, 2 × s, 2 × $CH_3$); $\nu_{max}$ 1 770 $cm^{-1}$ (Found: $M^+$, 346.1569. C, 79.6; H, 6.5%. $C_{23}H_{22}O_3$ requires *M*, 346.1569; C, 79.7; H, 6.4%).

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