CHIRAL BUTENOLIDES IN DIELS-ALDER CYCLOADDITIONS WITH ISOPRENE AND CYCLOPENTADIENE

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Summary.- Chiral α,β -butenolides react with isoprene at 125-220° giving a 1:1 mixture of Diels-Alder regioisomers, selectivity being dramatically increased by the use of AlCl₃ as catalyst. While these butenolides give no reaction with furan even in the presence of catalysts, they react smoothly with cyclopentadiene, endo/exo selectivity being temperature dependent.

Chiral α , β -butenolides have proved to be useful synthons to prepare natural products¹. There is an increasing interest on their use as dienophiles in stereo- and regiocontrolled Diels-Alder cycloadditions, in order to have an easy access to more complicated skeletons containing several asymmetric centers. Thus, it has been recently reported that many chiral buteno-lides react with butadiene to afford good yields of enantiomerically pure adducts with excellent diastereofacial selectivity.^{2,3}

Diels-Alder reactions of lactones 1-3 with isoprene, furan and cyclopentadiene are now described in this paper, focussing the attention towards the regio- and the <u>endo/exo</u> selectivities. Compounds 1, 4 2 and 3⁵ were prepared from <u>D</u>-ribonolactone and chosen as representative chiral butenolides having substituents at the C-4 position that differ in size and polarity.

Reactions of 1 and 2 with excess isoprene at $185-220^{\circ}$ for 20 hours afforded 4a/b and 5a/b,⁶ respectively, as a 1:1 mixture of para/meta regioisomers, in good yields (55-80%). The equimolecular mixture 4a/b was also produced when lactone 1 reacted with isoprene at 125° , but in this case the yield in adducts was only 22%. Thus, the reaction temperature seems to have no influence on the regioselectivity.⁷.

The presence of a/b regioisomers of 4 and 5 was detected by analytical HPLC and capillary GC, and confirmed by 400 MHz pmr (all absorption peaks appeared duplicated), but no separation was possible.

Complete anti stereofacial selectivity in these cycloadditions was evidenced by the trans relationship found between the Z group and the cyclohexene moiety in all adducts 4 and 5, as deduced from the fairly constant value (4 Hz) of the coupling constants $J_{6,7}$, that requires a

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trans arrangement for these protons, by analogy with the cycloadducts obtained from similar butenolides and butadiene.^{2,8}

The use of AlCl₃ as catalyst resulted in a remarkable regioselectivity in the cycloaddition, the major products being assumed to be the 4a/5a adducts, as deduced from the calculated frontier orbital coefficients of these reactants in a normal Diels-Alder cycloaddition,⁹ and also considering the experimental results on catalyzed cycloadditions of acrylic acid derivatives and isoprene.¹⁰ The role of temperature, amount of catalyst and diene, and reaction time was investigated in order to maximize regioselectivity, while keeping good yields. The optimal conditions found consisted in treatment of lactone 1, chosen as a model, with 23 moles of isoprene and 0.33 moles of AlCl₃ in dichloromethane as solvent at 50° for six days, affording 4a/b, as a 85:15 mixture, in 84% yield.¹¹

In the reactions with cyclic dienes, butenolides 1 and 3 were inert towards furan under a variety of conditions: temperature (r.t. to 60°), reaction time (2-21 days) and catalysts, $(SnCl_4, {}^{12} ZnI_2, {}^{13} and AlCl_3{}^{14})$. In all cases the unaltered lactones were recovered, along with some polymeric material when conditions were forced.

However, butenolides 1, 2 and 3 reacted with cyclopentadiene, at temperatures ranging from 70 to 110°, giving tricyclic endo (6, 8, 10) and exo (7, 9, 11) adducts in 55-85% overall yields. All these compounds, 6-11, could be isolated and fully characterized.⁶ Endo and exo as well as facial diastereoisomerism were assigned from the 400 MHz 2-D COSY NMR spectrum of 8, that allowed the assignment of all signals and couplings, and from differential n.0.e. experiments performed on all these products. Thus, a 4.5% n.0.e. was observed on H_5 from H_8 and on H_{10a} from H_6 in endo adducts, while this effect would not exist in exo stereoisomers.

Optical purity of these substances was established using the chiral shift reagent tris-|3-heptafluorobutiryl-<u>d</u>-camphorato|europium(III): only one set of pmr signals was visible for each adduct in the presence of 0.6 eq. of lanthanide, while the spectra of racemic mixtures, obtained from racemic butenolides,^{15,16} exhibited duplication of some signals, in the same conditions.

While dienophiles 2 and 3 gave only two kinds of adducts in their reactions with cyclopentadiene, lactone 1 afforded two more products, 12 and 13, when reactions were performed at temperatures higher than 120°. These compounds were identified on the basis of their spectral data (pmr, ms) as the <u>endo/exo</u> isomers that could result from attack of cyclopentadiene on the same side of the methyl group, revealing that in this case diastereofacial selectivity falls off at high temperature.

On the other hand, <u>endo/exo</u> selectivity was shown to be temperature dependent. Thus, <u>endo</u> adducts were almost exclusively produced at room temperature, although in low yield, and mixtures of about 75:25 <u>endo-exo</u> isomers were formed at 80-120°. When <u>endo</u> 8 was heated at 155° for 21 hours, neither butenolide 2 nor <u>exo</u> 9 were detected. Furthermore, we have found that similar adducts, bearing an alkyl substituent at the α -carbonyl position C_2 , need temperatures higher than 225° to undergo retro Diels-Alder reaction. Therefore, the obtention of thermodinamically more stable <u>exo</u> isomers seems not to be the result of an equilibration process and kinetic control of the reaction in the studied range of temperatures could govern the attack of the diene either to an endo or to an <u>exo</u> orientation.

Kinetic studies of these latter reactions are being carried out in our laboratory in



endo

exo





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order to understand the influence of the factors affecting the formation of endo/exo isomers. Use of cycloadducts 6-11 for synthetic purposes is also under active investigation.

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NOTES AND REFERENCES

- See for instance: (a) K. Tomioka, F. Sato and K. Koga, <u>Heterocycles</u>, 17, 311 (1982); (b) R.
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- Diels-Alder reaction of furan with acrolein and methyl vinyl ketone, catalyzed by AlCl₃: P. Laszlo and J. Lucchetti, <u>Tetrahedron Lett.</u>, 25, 4387 (1984).
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