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A FACILE ACCESS TO MASKED ISOBENZOFURANS ; HIGH EXO-STEREOSELECTIVITY IN THE DIELS-ALDER REACTIONS OF 4,7-DIHYDRO-4,7-ETHANOISOBENZOFURAN[1].

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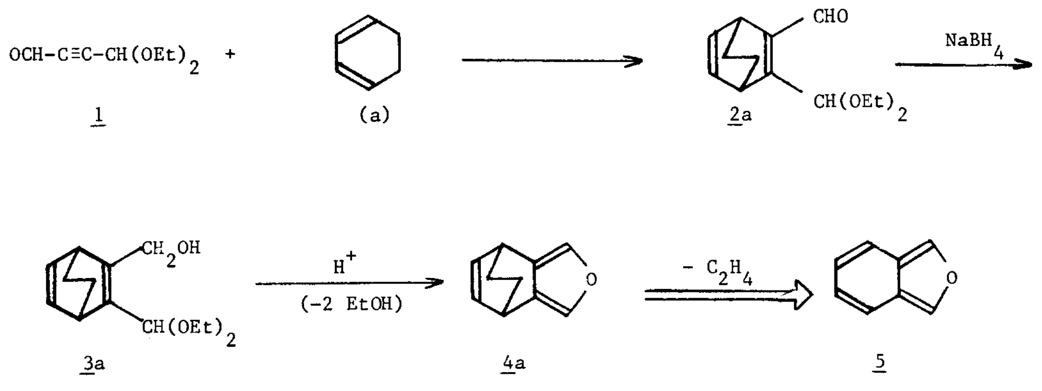
Summary- The isobenzofuran derivatives precursors 4a-c are readily prepared from 1 ; their Diels-Alder adducts with cis-dienophiles present a stereochemistry endo>exo from 4b,c and, interestingly, only exo (towards the furan moiety) from 4a.

Owing to their great reactivity, isobenzofuran (IBF) and its derivatives[2,3] have been used, of late, as intermediates in the synthesis of polycyclic compounds including biomolecules such as anthracyclines and lignans. Besides reverse Diels-Alder processes, their generation has been achieved by elimination of HOR from 1-alkoxyphtalans[4,5] and, more recently, by cyclisation of γ-hydroxyacetals.[6-8] We have defined, on these grounds, a new simple route[9] to 4,7-dihydroisobenzofuran derivatives 4 from the readily available monoacetal of acetylenedicarbaldehyde 1.[10,11] We have also studied the Diels-Alder rèactivity of the compounds with usual cis-dienophiles in order to compare the stereochemistry of the adducts produced to those of IBF itself, given that the latter generally affords a mixture of diastereoisomers with endo > exo.

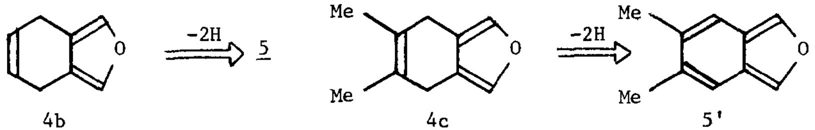
Thus 2a[12] (90 % improved yield from 1 and 1,3-cyclohexadiene (a), 3 days at 75°C under inert atmosphere) is cleanly reduced ($NaBH_4$, MeOH, 95% yield) to the corresponding γ-hydroxyacetal 3a. (scheme 1). When small amounts of acid (HCO_2H or HCl) are added to a



SCHEME 1

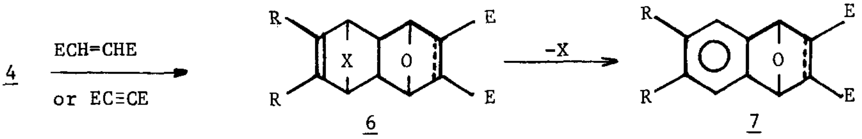
CH_2Cl_2 solution of the latter,a loss of ethanol occurs very readily giving rise to 4a, isolated (75% yield), after aqueous work-up and SiO_2 column chromatography (pentane-ether 95:5), as a colourless solid, m.p. 25°C, ^1H n.m.r. ($CDCl_3$ with Me_4Si) δ 1.60 (m, 4H, bridge), 3.80 (m, 2H, bridgehead), 6.52 (m, 2H, CH=) and 7.15 (s, 2H, =CH-O).

Similarly reaction of 1 with 1,3-butadiene (b) and 2,3-dimethyl-1,3-butadiene (c) afford compounds 4b[13] and 4c[11] respectively (overall yields 60 % and 68% from 2b and 2c).



4b 4c 5'

These furans can act as convenient precursors of the corresponding IBF derivatives 5 and 5' since they react with ethylenic or acetylenic dienophiles (dimethyl maleate and fumarate, maleic anhydride, N-phenylmaleimide, methyl vinyl ketone, dimethyl acetylenedicarboxylate) to afford the expected cycloadducts 6 (or directly 7a depending on the thermal conditions), which could be aromatized either on heating (loss of C_2H_4) for 6a or by DDQ oxidation[14] for 6b,c into 7 (scheme 2).



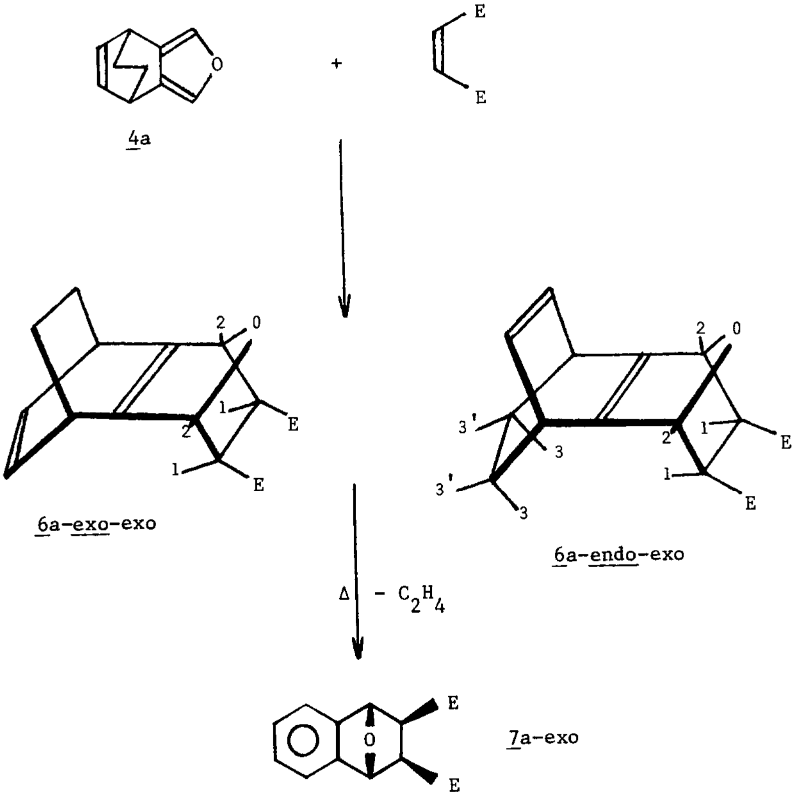
4a : X=CH_2-CH_2, R=H ; 4b : X=2H, R=H ; 4c : X=2H, R=Me.

SCHEME 2

Whereas the stereochemistry of the Diels-Alder reaction of 4b,c with cis-dienophiles resembles that of IBF itself[2], with formation of a mixture of endo and exo isomers of 6b,c or 7b,c (endo > exo, 2-3:1), interestingly, only exo additions take place with 4a.

For instance, after refluxing a $CHCl_3$ solution of 4a for 20 hrs inthe presence of an excess of dimethyl maleate (8 mol per mol), the exo adduct 7a only (scheme 3) is produced (70% isolated yield) as a white solid , m.p. 150°C, litt.[15] 146-7°C.

The cycloaddition can proceed at lower temperature with more potent dienophiles such as maleic anhydride and N-phenylmaleimide enabling the isolation of the non-aromatized cycloadducts 6a. For example, from N-phenylmaleimide (2 mol per mol of 4a, CH_2Cl_2 solution, 2.5 hrs, 20°C), 6a is obtained (70% yield) as a white solid, m.p. 138-156°C, consisting of unequal amounts of the two diastereoisomers exo-exo (75%) end endo-exo (25%), these assignements being established by ^1H n.m.r. : no coupling is observed between H_1 and H_2 in both isomers (exo configuration), and nuclear Overhauser experiments (at 300 MHz) give a Δ intensity (H_1) = + 16% by irradiation of the ethylene protons H_3 only in the minor isomer (endo configuration). On heating this mixture at 160°C for 5 mn it is converted quantitatively into the exo isomer of 7a, white solid, m.p. (benzene) 208°C. Since none of the other endo isomers of 6a could be detected by monotoring this cycloaddition at low temperature (^{1}H n.m.r., - 20°C, CDCl$_3$), we assume that the reaction proceeded under kinetic control through a sterically favoured exo approach of the dienophile onto 4a.[16]



SCHEME 3

In conclusion, the present methodology for the synthesis of 4 constitutes a good new entry into IBF chemistry with interesting stereochemical implications in the case of 4a. Its generalisation to the case of isoindole precursors will be later reported.

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