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A STEREOCHEMICAL STUDY ON ORGANOCOPPER(I) INDUCED 1,3-SUBSTITUTION IN EPI-MESTRANOL METHANESULFINATE.

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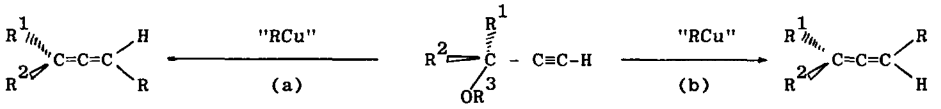
Summary : Organocopper(I) reagents induce a syn 1,3-substitution reaction in the methanesulfinate of epi-mestranol with formation of the corresponding (R)-allenes.

Since the work of Rona and Crabbé on the stereochemistry of lithium dimethylcuprate induced 1,3-substitution in acetate esters derived from 17α-ethynyl-17β-hydroxysteroids[1] a number of interesting papers have appeared concerning the stereochemical course of allene formation from propargylic esters and organocopper(I) species[2-6].From the referred papers the following conclusion can be drawn: Organocopper(I) induced 1,3-substitution in esters derived from 17α-ethynyl-17β-hydroxysteroids preferentially[1,2] or exclusively[3] proceed in a syn manner (reaction path a in eq. 1).Anti 1,3-substitution predominates in propargylic esters in which the chiral carbon atom is not part of a steroid system (reaction path b in eq. 2).It is noteworthy that in the latter cases the studies were restricted to esters of secondary propargylic alcohols [4-6].



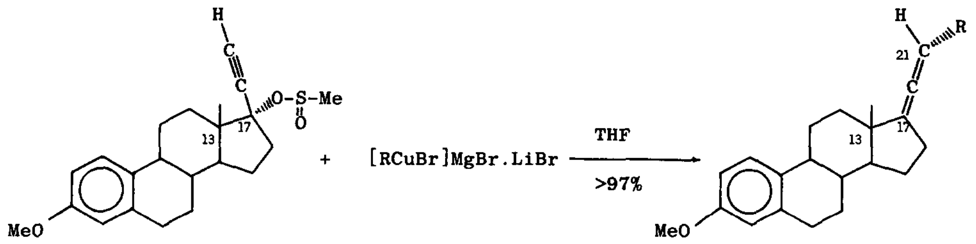
(1)

$R^3 = -C(O)CH_3$ [1,2,5] , $-S(O)CH_3$ [3,4] , $-C(O)-NH-R$[6].

At the moment we initiated this work no data were available concerning the stereochemical course of allene formation from esters of 17β-ethynyl-17α-hydroxysteroids.In our opinion such a study would be valuable in order to see if the stereochemical course of organocopper(I) induced 1,3-substitution in esters derived from 17-ethynyl-17-hydroxysteroids is dependent on the stereochemistry at C-17.Although 17β-ethynyl-17α-hydroxysteroids are not well known in the literature, a recent report on the synthesis of 3-methoxy-17β-ethynyl-17α-hydroxyestra-1,3,5(10)-triene (epi - mestranol) [7] enabled us to carry out this investigation.

For our purpose we first converted epi - mestranol into the methanesulfinate 1 following the procedure given in reference 3 for its epimer mestranol.We have chosen the methanesulfinate group because of its excellent leaving group character in organocopper(I) reactions and because of the fact that in mestranol methanesulfinate this group was substituted completely in a syn manner(cf[3]) Treatment of 1 (0.010 mol) in dry tetrahydrofuran (THF, 60 ml) with equimolar amounts of the heterocuprate 2 [3] for 1 hr at 0°C (2a and 2c , R = Me and Ph respectively) or at -50°C

(2b , R = t-Bu) furnished in all cases allenes 3 in nearly quantitative yield (eq. 2). To these allenes we have assigned the (R)-configuration (*vide infra*).



(2)

1 2a-c 3a-c

a : R = Me ; b : R = t-Bu ; c : R = Ph .

For the allenes 3 the following characteristic physical data were found : Compound 3a :m.p. 131.0-131.5°C, $[\alpha]_D^{20}$ in CH_2Cl_2: +80.7°, ^1H-NMR(CCl_4,TMS) signals at 0.88 ppm(δ 13-CH_3),1.63 ppm(δ21 α-CH_3) and 5.03 ppm(δ 21 β-H); compound 3b : m.p. 136.5-137.0°C, $[\alpha]_D^{20}$ in CH_2Cl_2: + 92.7°, ^1H-NMR(CCl_4,TMS) signals at 0.91 ppm (δ13-CH_3),1.02 ppm(δ 21α-t-Bu) and 5.13 ppm (δ 21 β-H); compound 3c : m.p. 115.0-115.5°C, $[\alpha]_D^{20}$ in CH_2Cl_2 : +296.4°, ^1H-NMR(CCl_4,TMS) signals at 1.07 ppm(δ 13-CH_3) and 6.10 ppm (δ 21 β-H).The physical data of our compound 3a are in good agreement with those reported in reference 2. The epimer of 3a with the 21 β-methyl group is also known[2,3].This compound has a negative specific rotation ($[\alpha]_D^{20}$ in CH_2Cl_2 : -15.5°) and a ^1H-NMR signal for the 13-CH_3 group at higher field (δ13-CH_3 : 0.86 ppm).Neither compounds 3b and 3c nor their epimers have yet been described in the literature but based on their high positive specific rotation and the rules of Brewster and Lowe 3b and 3c will equally possess the (R)-configuration (cf[2]).

From this and other work (cf[3]) it can be concluded that for the reaction of the methanesulfinate derived from both epimers of 3-methoxy-17-ethynyl-17-hydroxyestra-1,3,5(10)-triene with organocopper(I) compounds a *syn* 1,3-substitution pattern is observed, i.e. the stereochemical course of the reaction does not depend on the stereochemistry at C-17.Most likely this phenomenon will also be observed with other 17-ethynyl-17-hydroxysteroids.Further work in this field is in progress.

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