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CONCERNING THE OPENING OF 1,3-DIENE-MONOEPOXIDES BY ORGANOMETALLIC REAGENTS: A GENERAL SYNTHESIS OF 9β-SUBSTITUTED 19-NORSTEROIDS

Georges Teutsch

Centre de Recherches Roussel-Uclaf
93230 Romainville (France)

Summary: Reactions of organogold, organo-aluminum and organocopper reagents with α,β-unsaturated steroidal epoxides are reported. One of them provided a convenient access to 9β-substituted 19-norsteroids.

We recently reported the regio and stereospecific synthesis of 11β-substituted 19-norsteroids, using the reaction of an allylic steroidal epoxide with organocopper reagents (1). Further results obtained by varying either the organometallic reagent or the epoxide are also relevant to the mechanism of copper mediated substitutions.

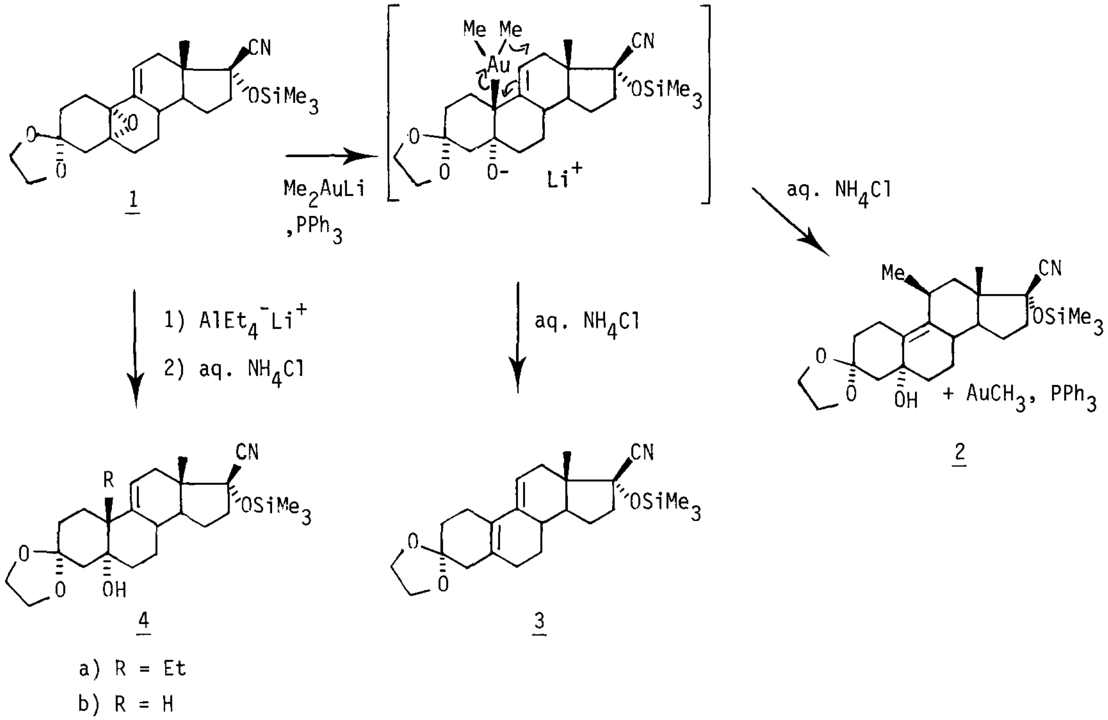
1. Organogold reagent

When epoxide 1 (4) was reacted with a solution of Me_2AuLi, PPh_3 (2) in Et_2O at 0°C for 2 hrs, the 11β-methyl-steroid 2 was isolated in 25 % yield [MP 165°C; $(\alpha)_D = -54°$ in $CHCl_3$; ^1H-NMR, δppm: 0.22 (9H, s, $SiMe_3$) 1.08 (3H, s, 18-Me) 1.17 (3H, d, 11-Me) 3.19 (1H, t, J = 7Hz, H-11) and 3.95 (4H, s, ketal)] along with the known diene 3 (4). Although this experiment does not represent a synthetically useful access to 11β-substituted steroids (5), it suggests a mechanistic similarity between the organocopper and the organogold mediated reactions. As trialkylgold derivatives are readily obtained by alkylation of dialkylaurates, decomposing thermally to a hydrocarbon and alkylgold (6), the existence of a relatively stable Au(III) intermediate in the epoxide opening reaction (scheme I) appears reasonable. Despite the fact that we were unable to isolate such a species, the formation of diene 3 upon hydrolysis (β-elimination) would be in favour of the proposed mechanism. This result tends to lend some support to the hypothesis of an analogous Cu(III) intermediate in the opening of epoxides by cuprates (1a) (7).

2. Organo-aluminum reagent

Aluminum is different in nature from copper or gold as it cannot extend its coordination number, thus excluding nucleophilic displacements by the metal. It is therefore not surprising to find that treatment of epoxide 1 with lithium tetra-ethyl-aluminate (Et_3Al + EtLi) in Et_2O at 20°C for 3 hrs, afforded only the 10β-ethyl derivative 4a in 70 % yield, [MP 154°C; $(\alpha)_D = 0°$ in $CHCl_3$; δppm: 0.225 (9H, s, $SiMe_3$) 0.65 (3H, t, Me of 10β-Et) 0.85 (3H, s, 18-Me) 3.95 (4H, s, ketal) 5.30 (1H, m, H-11)] along with some reduced material 4b (10 %) [H-11 centered at 5.33 ppm]. A similar result has already been reported with Grignard reagents (8).

Scheme I

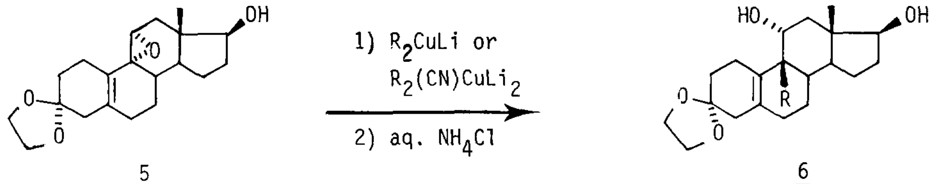


3. Organocopper-mediated opening of the 9α, 11α-epoxy-steroid 5

Opening of vinyl oxiranes by dialkyl cuprates has been reported to yield mainly (7) (9), if not exclusively (1) (10), the SN_2'-type products. However, when epoxide 5 (11) was treated for 3 hrs at 0° to 20°C, with dimethyl or diphenyl copper lithium in tetrahydrofuran (THF), the corresponding 9β-substituted compounds 6a and 6b were obtained in quantitative yields (12).

[6a: MP 176°C, $(\alpha)_D$ -81.5° in $CHCl_3$, δppm: 0.85 (3H, s, 18-Me) 1.26 (3H, s, 9-Me) 3.95 (4H, s, ketal) 3.58 to 3.83 (2H, m, H-11 and H-17) 6b: (amorphous), $(\alpha)_D$ -53° in $CHCl_3$, δppm: 1.04 (3H, s, 18-Me) 4.00 (4H, s, ketal) 4.62 (1H, dd, 12Hz and 4Hz, H-11) 7.37 (5H, m, phenyl)]. Vinylic substituents could be introduced in the same way, in albeit lower yields, as shown by the preparation of 6c (33 % yield) via the corresponding symmetrical cuprate (from 2,2-dimethyl-vinyl lithium and CuBr, Me_2S complex) [6c: (amorphous), $(\alpha)_D$ -55° in $CHCl_3$, δppm: 0.89 (3H, s, 18-Me), 1.70 and 1.77 (6H, d, J≃1.3Hz, Me's on C=C) 3.67 and 3.92 (2H, m, H-11 and H-17) 3.93 (4H, s, ketal) 4.97 (1H, w1/2=5Hz, vinylic H)]. Alkyl groups other than methyl could not be introduced by this method, probably due to the lower thermal stability of the corresponding cuprates (the reaction does not proceed below 0°C). A recent communication on higher order mixed organocuprates (13) prompted us to react epoxide 5 with dibutyl cyano copper dilithium$[Bu_2(CN)CuLi_2]$ in THF at -20°C. The expected 9β-butyl steroid 6d was isolated in 89.5% yield, thus extending the generality of our method of 9β-substitution. [Amorphous; $(\alpha)_D$ -53° in $CHCl_3$; δppm 0.86 (3H, s, 18-Me) 0.92 (3H, t, Me of n-Bu) 3.81 (2H, m, H-11 and H-17) 3.94 (4H, s, ketal)].

Scheme II



5 → 6

a) R = CH_3

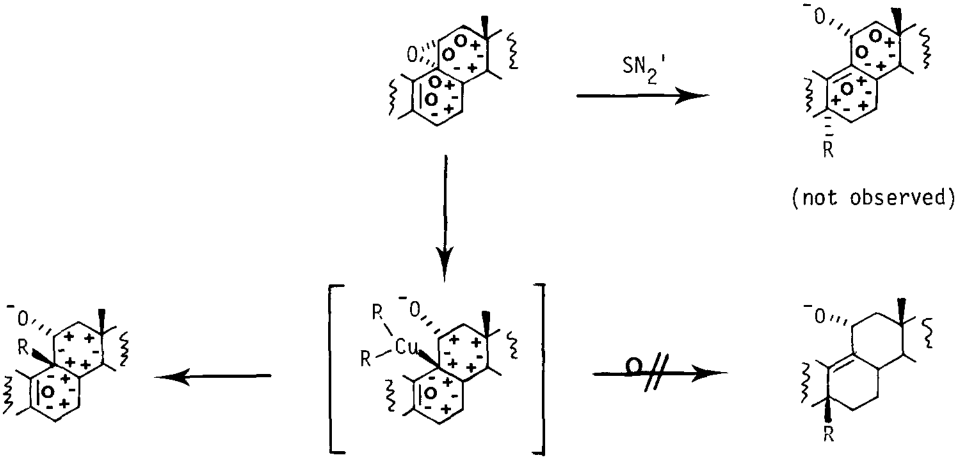
b) R = C_6H_5

c) R = $CH{=}C(CH_3)_2$

d) R = $n\text{-}C_4H_9$

From a mechanistic point of view, the opening of epoxide 5 is quite informative. Indeed, it has been shown that for substitution of conformationally constrained allylic systems, such as cyclohexenyl or cyclopentenyl derivatives, the stereoelectronic requirements (axial attack and axial leaving group) impose a conformational control on the reaction pathway (14). As can be seen on Scheme III, the 9α, 11α-epoxide is perfectly suited for a SN' displacement, which should lead to a 5α-substituted steroid if we consider a one step mechanism. Curiously the observed reaction product seems to arise via a SN_2 transition state, necessarily of higher energy in this system (15). If, however, we consider the previously proposed two step mechanism (1a), that is SN_2 displacement on C-9 by the metal, it is possible to rationalize the observed result. The primary final conformation of the hypothetical Cu(III) intermediate is such that the intramolecular allylic rearrangement is energetically disfavoured. Indeed, the rearranging R-group should approach C-5 axially from the α-face while being attached equatorially via the copper atom to C-9 on the β-face. The only possibility remaining is the internal rearrangement on C-9 with retention of configuration, if we postulate that the half-life of the Cu(III) species is short compared to the conformational reorganization.

Scheme III



This synthetically useful result opens up the way to the synthesis of a variety of hitherto unknown 9β-substituted 19-norsteroids and should stimulate further work on the mechanism of 1,3-diene-monoepoxide opening by organocopper reagents.

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3. ^{1}H-NMR spectra were recorded on Brucker WH-90 and WP-60 spectrometers as solutions in $CDCl_3$. Chemical shifts are in ppm downfield from internal TMS. All compounds gave satisfactory elemental analyses.

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12. The structures were determined on the basis of the NMR spectra which were compared with those of related compounds [A.C. Campbell, C.L. Hewett, M.S. Maidment and G.F. Woods; J. Chem. Soc. Perk. I, 1799 (1974); J.R. Bull, J. Floor and A. Tuinman; Tetrahedron 31 2157 (1975)]. Furthermore, deketalization with oxalic acid in aqueous acetone afforded the corresponding ketones, which exhibited the expected signals for the 4-H protons in the NMR spectra.

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