Titanium-mediated Synthesis of Vicinal Glycols from Carboxylic Acids and Organolithium Compounds

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Summary Carboxylic acids, alkyl-lithium compounds, and titanium trichloride interact with the formation of 1,2-diols.

SHARPLESS, HANZLIK, AND VAN TAMELEN[1] have described a titanium-based procedure for the deoxygenative coupling of allylic and benzylic alcohols. In a typical example, the action of titanium trichloride and alkyl-lithium on geraniol (molar proportions 1 : 3 : 2) produces bigeranyl as a mixtue of five *cis, trans*, primary–primary, and primary–tertiary coupled isomers. Saturated alcohols are recovered unchanged under these conditions. Mechanistic studies[2] support the intermediacy of geranyl radicals and suggest that the key reaction step is the homolysis of C–O bonds in a dialkoxytitanium(II) intermediate.

$$(\mathrm{RO})_2\mathrm{TiCl} + \mathrm{MeLi} \rightarrow (\mathrm{RO})_2\mathrm{TiMe} \rightarrow (\mathrm{RO})_2\mathrm{Ti} \rightarrow \mathrm{TiO}_2 + 2\mathrm{R}^{\bullet} \rightarrow \mathrm{R{-}R}$$

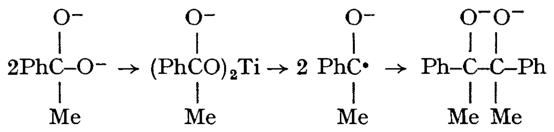
Although this method of constructing 1,5-dienes (*e.g.*, bigeranyl) has been largely superseded by superior procedures,[3,4] the generation of suitably reactive radicals by the $\mathrm{TiCl_3}$–alkyl-lithium system offers a number of other synthetic possibilities. It is known,[5] for example, that under the influence of $\mathrm{TiCl_3}$–MeLi, benzyl mercaptan affords bibenzyl (53% yield), and *cis*-9,10-dimethyl-9,10-dihydroanthracene-9,10-diol[6] forms 9,10-dimethylanthracene (51%; 88% after correcting for recovered diol).

It is now found that 1,2-diols are formed when carboxylic acids and alkyl-lithium compounds interact with $\mathrm{TiCl_3}$ in 1,2-dimethoxyethane, at −78° initially, followed by 30 min. under reflux and aqueous work-up. Thus, benzoic acid (0·02 moles), $\mathrm{TiCl_3}$ (0·01 mole), and MeLi (0·05 moles) afford[‡] acetophenone (27%), 2,3-diphenylbutane-2,3-diol[7] (33%), and 1,2-diphenylpropan-1-one[8] (11%).

$$2\mathrm{PhCO_2H} + \mathrm{TiCl_3} + 5\mathrm{MeLi} \rightarrow \mathrm{PhCOMe} + [\mathrm{PhCMe(OH)}]_2 + \mathrm{PhCH(Me){\cdot}COPh}$$

The diol is obtained as a mixture of the (±)- and *meso*-isomers in the ratio 2·4 : 1, as assessed by comparison of the mixture, using g.l.c., i.r.,[7] and n.m.r., with a mixture of known isomeric composition, resulting from the addition of methyl-lithium to benzil. Although formed in only moderate yield, the diol is easily separated by chromatography on silica gel from the less polar by-products.

In the presence of $\mathrm{TiCl_3}$–MeLi, the doubly-charged addition product of methyl-lithium and benzoic acid is presumably deoxygenated to a radical anion which undergoes dimerization, and thence protonation upon work-up. In agreement with this mechanism, acetophenone is virtually the only non-acidic product formed when only 0·03 moles of methyl-lithium are employed.



$$2\mathrm{Ph}\underset{\mathrm{Me}}{\overset{\mathrm{O^-}}{\mathrm{C}}}\mathrm{{-}O^-} \rightarrow (\mathrm{Ph}\underset{\mathrm{Me}}{\overset{\mathrm{O^-}}{\mathrm{C}}}\mathrm{O})_2\mathrm{Ti} \rightarrow 2\,\mathrm{Ph}\underset{\mathrm{Me}}{\overset{\mathrm{O^-}}{\mathrm{C}}}{}^{\bullet} \rightarrow \mathrm{Ph{-}}\underset{\mathrm{Me}}{\overset{\mathrm{O^-}}{\mathrm{C}}}\mathrm{{-}}\underset{\mathrm{Me}}{\overset{\mathrm{O^-}}{\mathrm{C}}}\mathrm{{-}Ph}$$

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Treatment of valeric acid with n-butyl-lithium and $TiCl_3$ gives an analogous, though slightly more complex, array of products. In addition to 5,6-dibutyldecane-5,6-diol[9] (22%) there is isolated‡ nonan-5-one (15%), tributylmethanol[10] (16%), and 6-butyldecan-5-one[11] (8%).§

$$2\,BuCO_2H + 5BuLi + TiCl_3 \rightarrow (Bu_2COH)_2 + Bu_2CO + Bu_3COH + Bu_2CH{\cdot}COBu$$

The yield of glycol compares favourably with that reported (10%) for the pinacol reduction of nonan-5-one.[9]

Precedent[2] indicates the likelihood that acceptable yields of unsymmetrical diols will be obtained on starting from a mixture of two carboxylic acids, one in a large excess.

(*Received, January 5th,* 1970; *Com.* 023.)

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‡ Pure samples were isolated by preparative g.l.c. Yields were determined by co-injection of authentic materials with the non-acidic fraction of the reaction product.

§ Identified by spectral properties only: i.r. ($CHCl_3$) 1703 cm^{-1}; n.m.r. (100 MHz, $CDCl_3$) δ 2·4 (m, 3H), 1·4 (m, 16H), and 0·85 (m, 9H) p.p.m.

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