A Simplified Method for the Titanium(II)-Induced Coupling of Allylic and Benzylic Alcohols

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Some years ago, van Tamelen and Schwartz introduced a conceptually elegant method, based on the thermal fragmentation of a titanium(II) dialkoxide, to effect the reductive coupling of allylic and benzylic alcohols.[1] Operationally, titanium tetrachloride was added to 2 equiv of alkoxide ion, and the resulting dichlorotitanium(IV) dialkoxide was reduced with molten potassium in refluxing benzene. After solvent removal, the resulting black residue of titanium(II) dialkoxide was heated to effect fragmentation and coupling. Benzyl alcohol, for example, coupled to bibenzyl in 51% yield based on recovered starting material.

$$\begin{tikzcd}
2RO^- + TiCl_4 \arrow[r] & TiCl_2(OR)_2 \arrow[r, "K"] & Ti(OR)_2 \arrow[d] \\
& R{-}R & {[2R\cdot] + TiO_2} \arrow[l]
\end{tikzcd}$$

Subsequently, a modification based on the use of titanium trichloride and methyllithium was introduced, simplifying the procedure considerably.[2]

We have been exploring the chemistry of a reagent derived by reaction of titanium trichloride with lithium aluminum hydride,[3] and we suggested in a recent review that this reagent might prove effective and convenient in the alcohol reductive coupling reaction.[4] We have now demonstrated this to be the case, and we wish to report our results.

Cautious addition of 1 molar equiv of $LiAlH_4$ to a slurry of 3 molar equiv[5] of $TiCl_3$ in dry dimethoxyethane (glyme) results in instantaneous evolution of hydrogen and formation of a black suspension [presumably containing Ti(II)]. Alternatively, addition to glyme of a 3:1 ball-milled premix of $TiCl_3$–$LiAlH_4$ prepared for us by Alfa Inorganics[6] gives the same black suspension. The major advantage of this premix is that it serves as a convenient one-bottle source of reagent.

Addition of 1 molar equiv of alcohol, followed by overnight reflux, then gives the coupled product in high yield. A summary of our results is presented in Table I.

As can be seen, both allylic and benzylic alcohols couple well, and steric bulk of the alcohol seems to have no deleterious effect, since 2-phenyl-2-propanol couples in 95% yield. The most interesting results in Table I are those of farnesol. As expected for a radical mechanism,[7] coupling occurs at both ends of the allylic system in the farnesyl radical, leading to a mixture of primary–primary and primary–tertiary coupled products in a 2:1 ratio. We were unable to find any tertiary–tertiary product. In addition, farnesyl radical abstracted hydrogen from solvent in significant amounts, leading to a mixture of allylically rearranged and unrearranged uncoupled hydrocarbons. We were unable to suppress this side reaction by changing solvents and conditions. Use of tetrahydrofuran, dioxane, or benzene–THF mixtures gave much more hydrogenolysis product.

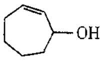
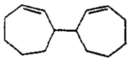
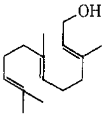
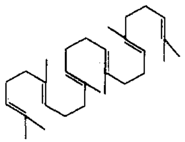
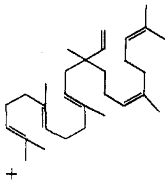
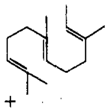
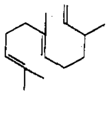
In summary, we feel that the efficiency and operational ease of the $TiCl_3$–$LiAlH_4$ mixture make it a desirable reagent choice for carrying out the reductive coupling of alcohols.

Experimental Section

General Reaction Procedure. A suspension of titanium(II) reagent was prepared in either of the following ways. **A.** Titanium

Table I
Reductive Coupling of Alcohols Using $TiCl_3$-$LiAlH_4$

$$ROH + TiCl_3\text{–}LiAlH_4 \longrightarrow R\text{–}R$$

ROH	+	Registry no.	R–R	Registry no.	Isolated yield, %
$PhCH_2OH$		100-51-6	$PhCH_2CH_2Ph$	103-29-7	78
$PhCH(OH)CH_3$		98-85-1	$PhCH(CH_3)CH(CH_3)Ph$	4613-11-0 (meso) 2726-2-8 (*dl*)	68
$PhC(OH)(CH_3)_2$		617-94-7	$PhC(CH_3)_2C(CH_3)_2Ph$	1889-67-4	95
		4096-38-2		55759-30-3	87
		4602-84-0	 +	7683-64-9	33
			 +	55759-31-4	15
			 +	7681-88-1	8
				55759-32-5	13

trichloride (2.3 g, 15.0 mmol) was weighed under dry nitrogen in a glove bag and placed under nitrogen in a 100-ml three-neck flask with 70 ml of dry glyme. $LiAlH_4$ (190 mg, 5.0 mmol) was quickly added to the stirred $TiCl_3$ slurry, and the resulting black suspension was stirred for 10 min before use. **B.** Alternatively, a 3:1 $TiCl_3$–$LiAlH_4$ premix (effective mol wt 167, 2.50 g, 15.0 mmol) was weighed under nitrogen in a glove bag and added to 70 ml of dry glyme under nitrogen. The resulting black suspension was stirred for 10 min before use.

The substrate alcohol (5.0 mmol) in several milliliters of glyme was then added, and the reaction mixture was refluxed for 16 hr. After cooling, the reaction mixture was quenched by addition of dilute aqueous hydrochloric acid, then diluted with water and extracted with ether. The ether extracts were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated at the rotary evaporator. Crude products were then purified either by crystallization or distillation. In this manner, the following reactions were run.

Benzyl alcohol gave **bibenzyl,** 78%, mp 51–51.5° (lit.[8] mp 52°).

α-Phenethyl alcohol gave a liquid mixture of meso and *dl* forms of **2,3-diphenylbutane,** 68%. Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.59; H, 8.67.

2-Phenyl-2-propanol gave **2,3-dimethyl-2,3-diphenylbutane,** 95%, mp 117–118° (lit.[9] mp 118–119°).

2-Cycloheptenol gave **3-(2-cycloheptenyl)cycloheptene,** 87%. Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.14; H, 11.76.

Farnesol gave a mixture of products which was separated by high-pressure liquid chromatography on Porosil A[10] (16 ft × 0.25 in.). The results are shown in Table I. Identifications were made on spectroscopic grounds (100-MHz NMR and mass spectra) and were unequivocal.

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Registry No.—Titanium trichloride, 7705-07-9; $LiAlH_4$, 16853-85-3.

References and Notes

(1) E. E. van Tamelen and M. A. Schwartz, *J. Am. Chem. Soc.*, **87,** 3277 (1965).

(2) K. B. Sharpless, R. P. Hanzlik, and E. E. van Tamelen, *J. Am. Chem. Soc.*, **90,** 209 (1968).

(3) J. E. Mc Murry and M. P. Fleming, *J. Am. Chem. Soc.*, **96,** 4708 (1974).

(4) J. E. Mc Murry, *Acc. Chem. Res.*, **7,** 281 (1974).

(5) This stoichiometry is chosen so that excess hydride [over the theoretical amount necessary to effect the Ti(III) → Ti(II) reduction] is present to react with substrate alcohol, thereby forming the necessary alkoxide ion.

(6) We thank Mr. Robert Wade, Alfa Inorganics, Beverly, Mass., for preparing this premix.

(7) E. E. van Tamelen, B. Akermark, and K. B. Sharpless, *J. Am. Chem. Soc.*, **91,** 1552 (1969).

(8) "The Merck Index", 8th ed, Merck and Co., Rahway, N.J., 1968, p 147.

(9) P. E. Verkade, K. S. de Vries, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **82,** 637 (1963).

(10) Porosil A is a registered trademark of Waters Associates, Framingham, Mass.

Formation of a Stable Enol from a Michael Addition

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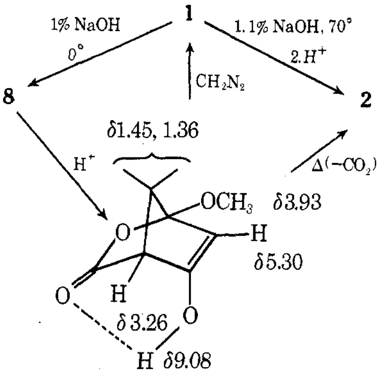
During the course of an earlier investigation,[1] difficulty was encountered in the hydrolysis of keto ester **1** (see Chart I). Base hydrolysis yielded only the enol ether **2** and not the corresponding acid **3**. This contrasted with the isomer **4**, which readily gave the acid **5** under similar conditions. Reinvestigation gave the γ-lactoenol **6**; evidence for the structure of this novel enol resulting from an internal Michael addition is presented here.

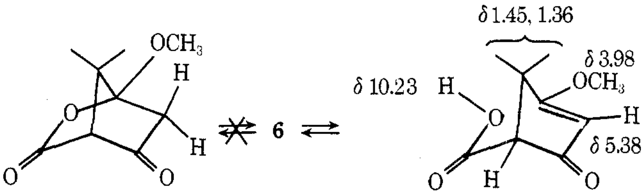
Chart I



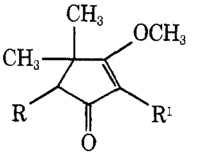
6 (1)

$$4 \xrightarrow[70°]{1.\ 1\%\ NaOH} 5 \qquad (2)$$

2. H+



7 **3** (3)



	R	R1
1	CO_2CH_3	H
2	H	H
4	H	CO_2CH_3
5	H	CO_2H
8	CO_2^-	H

Saponification of **1** is effected by 1% sodium hydroxide at 0° and crystalline solid **6** precipitates on acidification. Treatment of this saponified product with diazomethane regenerates **1**. Elemental analysis shows that **6** is isomeric with **5**. On melting, mp 102° dec, **6** decomposes, a gas evolves, and oil **2** results (previously identified[1]).

The infrared spectrum indicates, however, that **6** is *not* the carboxylic acid **3** but the γ-lactoenol **6**. A freshly prepared chloroform solution of **6** shows a strong absorption at ν 1780 cm^{-1}. This is characteristic of the five-membered lactone ring.[2,3] A solution of **6**, on standing at room temperature or on heating, undergoes changes in the infrared spectrum: the absorption at ν 1780 cm^{-1} decreases while an absorption at ν 1725 cm^{-1} increases; this would correspond to the formation of keto acid **3** by a retro-Michael; prolonged standing or heating finally yields the infrared spectrum of **2**. A methanol solution of **6** has only infrared absorptions which would be characteristic of **3** [ν 1725 (acid C=O), 1675 (α,β-unsaturated C=O), 1600 cm^{-1} (C=C)]. Thus, in solution **6** opens to give **3**, which eventually gives off CO_2 and leads to **2**. Attempts to isolate **3** only yield mixtures of **6** and **2**.

The nuclear magnetic resonance spectrum supports the above observations. In $CDCl_3$ **6** exhibits a chemical shift for the enolic proton at δ 9.08;[4] this is at higher magnetic field (δ 2.29 upfield) than the chemical shift of the carboxylic acid hydrogen of **5** (δ 11.37).[1] Heating the NMR solution (50°, 0.5 hr) brings about ring opening of **6** and the formation of **3**; a low-field absorption appears at δ 10.37[5] while the δ 9.08 signal decreases (and eventually disappears). No equilibrium with keto ester **7** is observed. NMR experi-