261. Methyl-triisopropoxy-titanium, a Highly Selective Nucleophilic Methylating Reagent[1])

Preliminary Communication

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Summary

Replacement of lithium or magnesium by titanium can furnish nucleophilic organometallic reagents of high selectivity as exemplified by the title compound **1** (see *Tables 1-3*).

After a period of vivid development of new synthetic methods in the past two decades, organic chemists will have to turn increased attention to the question of how to achieve *selectivities* of a degree which are usually observed in biochemical processes. The use of transition metals [1] for this purpose is just beginning to emerge. As a contribution, we describe a first example of application of a simple and probably general method of adjusting the reactivity of carbanionic reagents by the use of titanium derivatives.

The carbon nucleophiles now used most widely for C,C-bond formations are lithium and magnesium compounds. Their most serious drawbacks are pronounced basicity and too high reactivity[4]). They do not for instance, cleanly distinguish between the different types of carbonyl groups (aldehyde, ketone, ester, amide) and their analogues (cyano, nitro groups). As a rule, other electrophilic functional groups in the same molecule must be protected or should not be present when an RLi- or RMgX-addition to a carbonyl group is to be carried out[5]). A demonstration of this situation is given in *Table 1*, entry 1 and 2. From this and other

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[1]) Presented by *D.S.* at the meeting of the Organic Division of the German Chemical Society, Bad Nauheim, October 16, 1980.

[2]) Part of the projected PhD thesis of *B. W.*, ETH Zürich.

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[4]) We have measured the *heat of reaction* of the addition of butyllithium to propanal (in tetrahydrofuran/hexane at −95°) of *ca.* 45 kcal/mol (hitherto unpublished results by *A. Hidber* of these laboratories). To the best of our knowledge, the *activation energy* of this process has not been measured.

[5]) Cadmium- and zinc-derivatives have occasionally been used for increasing selectivity in reactions of carbonyl compounds [2].

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Table 1. *Result of the addition of methyllithium, methylmagnesium bromide, and* **1** (1 mol-equiv. of CH_3M) *to a 1:1 mixture of benzaldehyde and acetophenone* (1 mol-equiv. each) *in diethyl ether at room temperature.* The numbers given are approximate product distributions determined by gas-chromatographic FID-integrations. With CH_3Li and CH_3MgBr further, non-identified products are formed besides the three alcohols, which were characterized by comparison with authentic samples.

Entry		Relative peak areas of				
		$C_6H_5\overset{\overset{O}{\|}}{C}H$	$C_6H_5\overset{\overset{O}{\|}}{C}CH_3$	$C_6H_5-\overset{\overset{OH}{\vert}}{C}(CH_3)_2$	$C_6H_5\overset{\overset{OH}{\vert}}{C}HCH_3$	$C_6H_5-CH_2OH$
1	Li	3	0.5	32	23	8
2	MgBr	2	52	8	30	5
3	$Ti[OCH(CH_3)_2]_3$	0	48	$\leqslant 1$	44	0

experiments[4]), we can make a rough estimate that the activation energy[4]) of the addition of alkyllithium compounds to carbonyl groups is well below 10 kcal/mol and that $\Delta\Delta G^{\neq}$ (*i.e.* the selectivity) between the addition to benzaldehyde and to acetophenone is less than 1 kcal/mol. In sharp contrast to methyllithium and methylmagnesium bromide, the methyltitanium reagent **1**[6]), readily available [3] from commercial[7]) titanium tetra(2-propanolate) according to equation (1), adds

$$[(CH_3)_2CHO]_4Ti \xrightarrow{CH_3COCl} [(CH_3)_2CHO]_3TiCl \xrightarrow{CH_3Li} \underset{\mathbf{1}}{[(CH_3)_2CHO]_3TiCH_3} \quad (1)$$

with high selectivity to the carbonyl group of the aldehyde and does not generate side products (see entry 3 of *Table 1*). From this and the results assembled in *Table 2*, we conclude that the $\Delta\Delta G^{\neq}$-value for the two intermolecularly competing processes is approximately one order of magnitude larger with **1** than it is with methyllithium[8]). *Table 2* contains the reactions of **1** with various carbonyl compounds and the corresponding reaction conditions, *Table 3* shows the solvent dependence of the addition to 4-*t*-butyl-cyclohexanone.

The following remarks seem appropriate: The neat compound **1** is a distillable, yellow liquid which can be stored at least for several months under inert atmosphere in a refrigerator; it is miscible with most common aprotic organic solvents and can be employed with a rather small solvent effect in solvents ranging from pentane to acetonitrile. Compound **1** reacts at reasonable rates with aldehydes at temperatures between -70 and $-20°$ and with ketones between $+25$ and $+80°$. Additions to esters, *S*-thiolates, nitriles, and epoxides do not compete. At lower temperatures the carbonyl addition can be carried out in the presence of nitro groups. The preferred process is 1,2-addition to α,β-unsaturated aldehydes and

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[6]) Compound **1** and other alkyl- and aryl-titanium compounds with a variety of RO- and R_2N-groups have been known for some time (see [3] and ref. cited therein). As far as we know, bis(dimethylamino)-benzophenone, the *Gilman*-test reagent, was the only carbonyl compound to which the addition of these organometallic compounds was carried out.

[7]) We thank Dr. *G. Bier* of the *Dynamit-Nobel AG*, Troisdorf, Germany, for generous gifts of titanium tetraalcoholates.

[8]) At room temperature, $\Delta\Delta G^{\neq}$-values of 1 and 10 kcal/mol lead to product ratios of 85:15 and 10^7:1, respectively.

Table 2. *Reactions of the methyltitanium derivative* **1** (conc. *ca.* 0.4M) *with carbonyl compounds* (conc. *ca.* 0.3M) *to give products of type* $R^1R^2C(OH)CH_3$. The products were identified by comparison of spectroscopic data with those of authentic samples; in most cases, the product purity was also determined by analytical gas-chromatography.

Carbonyl derivative	Mol-equiv. of **1**	Temp. [°C]	React. time [h]	Solvent	Product ($>C(OH)CH_3$) [%]
2,2-Dimethyl-propanal	1.2	−25	15	EtOEt	60
Heptanal	1.2	−50	4	THF	97
Cinnamaldehyde	1.2	−50	4	EtOEt	91[a])
Benzaldehyde	1.2	−50	4	THF	92
2-Nitro-benzaldehyde	1.2	−50	4	THF	92
4-Nitro-benzaldehyde	1.2	−50	4	THF	95
2-Naphtaldehyde	1.2	−50	4	THF	99.5
Cyclopentanone	2.0	RT.	48	EtOEt	70
Cyclohexanone	2.0	RT.	48	THF	79
(+)-Fenchone	10.0	+80°	10	Isooctane	84[b])
Acetophenone	2.0	RT.	48	EtOEt	96
Isopropyl benzoate	2.0	RT.	24	EtOEt	1.5[c])
S-t-Butylthiobenzoate	1.2	RT.	48	THF	-[d])
(Benzonitrile)	1.2	RT.	48	EtOEt	no reaction
(Styrene epoxide)	1.2	RT.	48	EtOEt	no reaction

[a]) No 1,4-adduct could be detected.

[b]) One diastereomer only.

[c]) 88.5% of unreacted ester was recovered; other esters are transesterified to give isopropyl esters.

[d]) *Ca.* 10% isopropyl benzoate was formed; >80% unreacted thioate was recovered.

Table 3. *Reaction times, yields and ratios of the diastereomeric alcohols from the addition of* **1** *to 4-*t*-butyl-cyclohexanone at room temperature in different solvents.* Concentration of **1**: 3 mmol/ml, concentration of the ketone: 1.5 mmol/ml, *i.e.* ratio 2:1. The *cis/trans*-ratios refer to 4-*t*-butyl-1-methyl-1-cyclohexanol, *cis* being the product of equatorial, *trans* the product of axial methyl attack [4].

Solvent	% Alcohol formation after					*cis/trans*
	½ h	1 h	2 h	3 h	4 h	Ratio
Pentane	98	99.8				89:11
Diethyl ether	96	99.3				86:14
Tetrahydrofuran		73		89		87:13
Pyridine	95	98	100			83:17
Methylene chloride	65	75	88		96	82:18
Acetonitrile 2-phase system, 14 h at 25°	-	-	-	-	-	86:14

ketones. Compound **1** transfers the methyl group diastereoselectively to 4-*t*-butyl-cyclohexanone *(Table 3)* and exhibits a pattern of basicity, nucleophilicity, *Lewis*-acid character, redox potential, hydride transfer ability, and sensitivity to steric hindrance, which are entirely different from those of methyl-lithium and *Grignard*-reagent.

From the results described, the following projects evolve and are being pursued in our laboratory: (i) *in situ* applications of other organometallic reagents of type **1** including those derived from less stable carbanionoid components; (ii) other RO- and R_2N-substituents[6]) at titanium and related metals for taylor-made reactivities; (iii) the use of chiral RO-groups leading to asymmetric alkylating reagents.

Experimental Part

*Typical Procedure [1-(*p*-nitrophenyl)-1-ethanol from* p*-nitro-benzaldehyde and* **1***].* To a solution of 820 mg (5.43 mmol) of *p*-nitro-benzaldehyde in 15 ml of THF, stirred at −50°, is added 1.6 ml (6.4 mmol) of neat **1**. After stirring for 4 h at −50°, the reaction mixture is poured on toluene/2N HCl. The organic layer is washed with $NaHCO_3$-solution, dried ($MgSO_4$) and concentrated evaporatively to give 867 mg (95.6%) of spectroscopically and chromatographically pure product as yellow oil. - ^{1}H-NMR. ($CDCl_3$): 1.55 (*d*, $J=7$, 3 H); 2.5 (br. *s*, 1 H); 5.45 (*qa*, $J=7$, 1 H); 7.2-8.0 (*AA'BB'*-system, 4 H).

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