262. Alkylative Amination of Non-enolizable Aldehydes with Alkyl(dialkylamino)titanium Derivatives[1])

Preliminary Communication

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Summary

The readily available tris(diethylamino)methyltitanium and related compounds (see **1** in *Scheme 2*) react with non-enolizable aldehydes to give tertiary amines **2**; these amines result from direct replacement of the carbonyl O-atom by an alkyl and an amino group *(Scheme 3)*. A tentative mechanism is proposed, according to which the amino group is transferred to the carbonyl C-atom prior to the alkyl group *(Scheme 4)*.

Conversions in which the O-atom of a carbonyl compound is directly replaced by other atoms are especially valuable for organic synthesis. In *Scheme 1* six such transformations are shown. The subject of the present communication is the alkylative amination, in which the carbonyl O-atom is replaced by an amino and by an alkyl group. Direct replacement of this type occurs in two classical transformations, the *Mannich* reaction (for reviews s. [5]) and the *Strecker* synthesis [6]. In the course of our investigation of organotitanium derivatives as selective carbonylophilic reagents [1] [2], we have now discovered that tris(dialkylamino)alkyltitanium compounds of type **1** transfer under certain conditions an alkyl *and* a dialkylamino group to the carbonyl C-atom, with removal of the O-atom. The dialkylamino-substituted organotitanium derivatives **1** are known[3]) to be the most stable ones in the $RTiX_3$ series. As shown in *Scheme 2* they are readily available from the corresponding halo-tris(dialkylamino)titanium compounds[4]) and organolithium or -magnesium

[1]) For our previous papers on organotitanium and organozirconium reagents and on titanate-catalyzed transesterifications see [1], [2] and [3], respectively. A review article about this topic is in print [4].

[2]) Part of the projected Ph.D. thesis of *M. Schiess*, ETH-Zürich.

[3]) See the excellent review entitled "Dialkylamido-Verbindungen des Titans" by *Bürger & Neese* [7], and references cited therein.

[4]) Most published procedures [7] use the bromo-tris(dialkylamino)titanium, however, the more readily available and less expensive chloro-analogs can be employed as well. **1a** and **1d** were obtained from the chloro-derivative; *cf.* [8].

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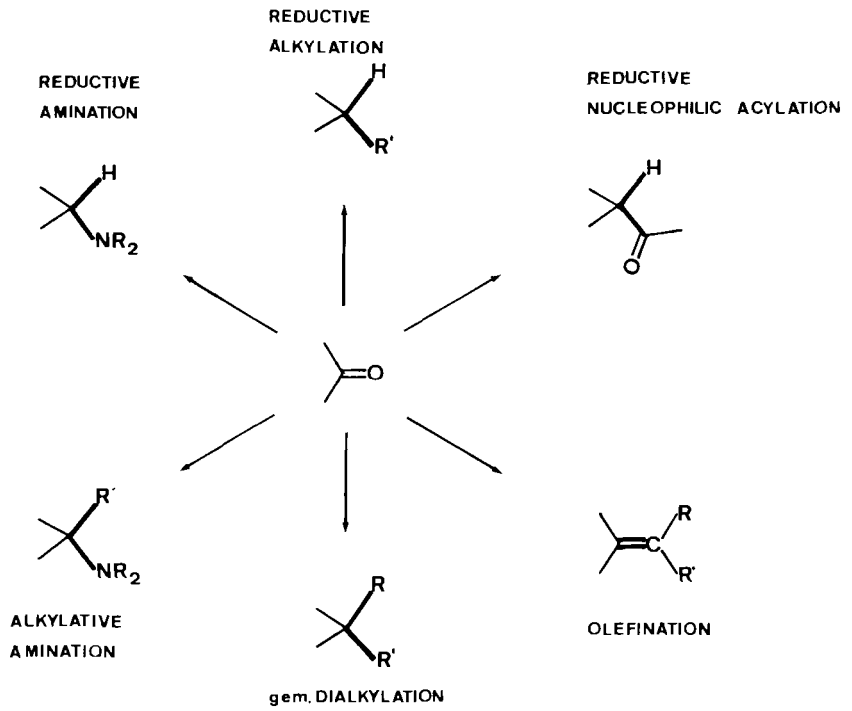
Scheme 1



Scheme 2

$R^1\text{-}Ti(NR^2_2)_3$
1

a $R^1 = R^2 = CH_3$[5])
b $R^1 = CH_3$, $R^2 = C_2H_5$
c $R^1 = C_4H_9$, $R^2 = C_2H_5$
d $R^1 = CH_3$, $R^2\text{-}R^2 = (CH_2)_5$

$$X\text{-}Ti(NR_2)_3 + RLi\ (\text{or } RMgX) \rightarrow \mathbf{1} + LiX(MgX_2) \quad (1)$$

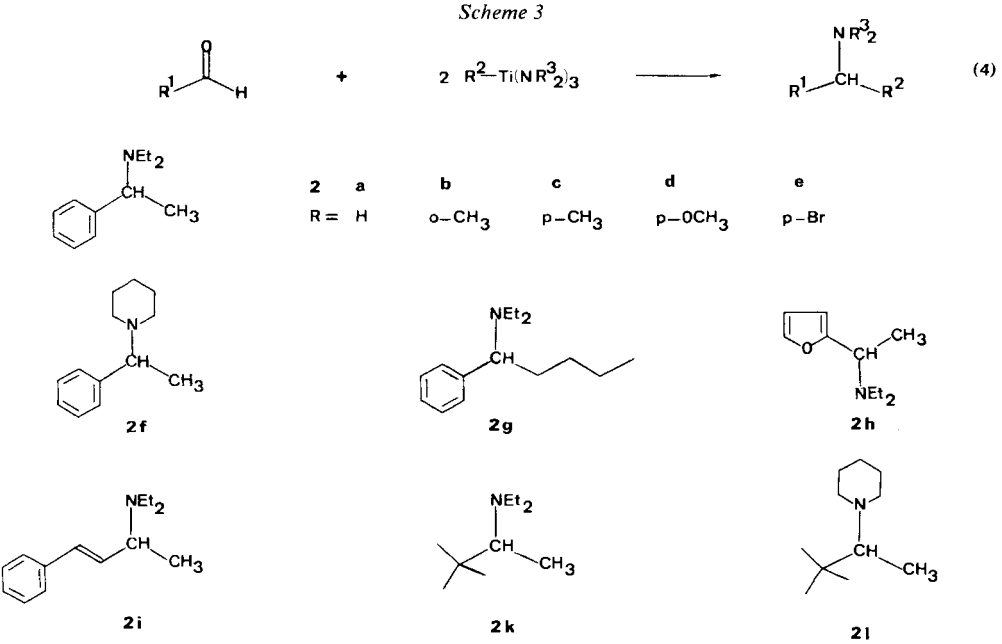
$$TiBr_4 + 3\ Ti(NR_2)_4 \rightarrow 4\ BrTi(NR_2)_3 \quad (2)$$

$$TiCl_4 + 3\ LiNR_2 \rightarrow ClTi(NR_2)_3 + 3\ LiCl \quad (3)$$

derivatives (*Eqn. 1*, [7–9]). Bromo- and chloro-tris(dialkylamino)titanium, in turn, are prepared following literature procedures (see the *Eqn. 2* and *3* [7] [10] [11] in *Scheme 2*). Ethereal solutions of the reagents **1** are prepared *in situ* and combined with aldehydes to give variable amounts of the tertiary amines **2** (*eqn. 4* in *Scheme 3*). The highest conversions are observed with a 2:1-stoichiometry, *i.e.* a twofold

[5]) This reagent added to benzaldehyde to give only traces (< 1%) of the desired product of type **2**.

Scheme 3



excess of the organotitanium reagents **1**. The products **2** are easily separated from the crude reaction mixtures through an extraction with aqueous acid solution. The yields of the amines **2** shown in *Scheme 3* may be high (73% of **2h**), are mostly moderate (40–50%), but can be as low as 7% (**2f**) (see the *Table*). On the other hand, after aqueous workup, the recoveries of aldehydes are essentially quantitative. Only non-enolizable aliphatic, α,β-unsaturated, and aromatic or heteroaromatic aldehydes undergo this reaction – at least under the conditions tested so far. The yield of addition to benzaldehyde drops when changing R^1 in the reagent **1** from CH_3 to C_4H_9 to C_6H_5[6]) (see the *Table*).

With enolizable aldehydes and ketones[7]), the reaction produces the corresponding enamines after non-aqueous workup. This result and exploratory experiments aiming at the elucidation of the mechanism of the present reaction may be interpreted in the following way, using the methyl-titanium compound **1** as an example (see *Scheme 4*): with all carbonyl substrates, the first step is the transfer of an amino group to give a tetrahedral intermediate **3**; depending upon the structure of the carbonyl compound and of the NR_2-group in the reagent **1** employed, this intermediate is converted – possibly through an iminium salt **4** – to either the product **2** of *C*-methylation, or an aminal **5**, or an enamine **6** (*cf.* the *Weingarten* reaction [12]); the latter two compounds are hydrolyzed back to the starting carbonyl compound during acidic aqueous workup. Further mechanistic investigations

[6]) No arylative amination of benzaldehyde or pivalaldehyde occurred with **1** ($R^1 = C_6H_5$, $R^2 = C_2H_5$) in ether or toluene.

[7]) Also, the reaction of the non-enolizable ketoester C_6H_5–CO–$COOH_3$ with **1b** gave a complex mixture of products.

Table. *Starting materials, yields and NMR. data of the products* **2** *of alkylative amination*

The yields are calculated from the amounts of aldehydes employed in the reaction. Characteristic chemical shifts δ in ppm with internal standard tetramethylsilane (TMS) in CCl_4; 90 MHz for ^{1}H-, 20 MHz for ^{13}C-spectra; multiplicities *s, d, t, qa, qi, m* for singlet, doublet, triplet, quadruplet, quintuplet and multiplet, respectively.

2a (= *Diethyl(1-phenylethyl)amine*), 48% from benzaldehyde and **1b**; b.p. as in [16]. – ^{1}H-NMR.: 1.25 (*d*, J = 6, 3 H, CH_3CH); 2.5 (*qa*, J = 6, 4 H, 2 CH_2CH_3); 3.75 (*qa*, J = 6, 1 H, $CHCH_3$)

2b (= *Diethyl(1-o-tolyl-ethyl)amine*), 28% from 2-methylbenzaldehyde and **1b**. – ^{1}H-NMR.: 1.25 (*d*, J = 6, 3 H, CH_3CH); 2.4 (*s*, 3 H, aryl-CH_3); 2.4–2.7 (*m*, 4 H, 2 CH_2CH_3); 3.95 (*qa*, J = 6, 1 H, $CHCH_3$)

2c (= *Diethyl(1-p-tolyl-ethyl)amine*), 47% from 4-methylbenzaldehyde and **1b**. – ^{1}H-NMR.: 1.25 (*d*, J = 6, 3 H, CH_3CH); 2.3 (*s*, 3 H, aryl-CH_3); 2.5 (*qa*, J = 6, 4 H, 2 CH_2CH_3); 3.7 (*qa*, J = 6, 1 H, $CHCH_3$)

2d (= *Diethyl(1-anisylethyl)amine*), 45% from *p*-methoxy-benzaldehyde and **1b**. – ^{1}H-NMR.: 1.25 (*d*, J = 6, 3 H, CH_3CH); 2.45 (*qa*, J = 6, 4 H, 2 CH_2CH_3); 3.70 (*s*, 3 H, OCH_3); 3.70 (*qa*, J = 6, 1 H, $CHCH_3$)

2e (= *Diethyl(1-p-bromophenyl-ethyl)amine*), 46% from 4-bromobenzaldehyde and **1b**. – ^{1}H-NMR. ($CDCl_3$): 1.3 (*d*, J = 6, 3 H, CH_3CH); 2.50 (*qa*, J = 6, 4 H, 2 CH_2CH_3, 3.75 (*qa*, J = 6, 1 H, $CHCH_3$)

2g (= *Diethyl(1-phenylpentyl)amine*), 15% from benzaldehyde and **1c**. – ^{1}H-NMR.: 3.50 (*d*×*d*, J_1 = 9, J_2 = 6, 1 H, $CHCH_2$)

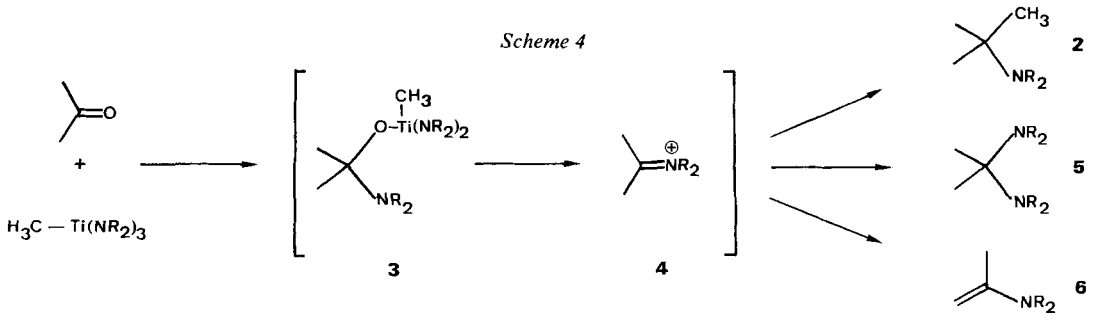
2h (= *Diethyl(1-(2'-furyl)ethyl)amine*), 73% from 2-furylaldehyde and **1b**. – ^{1}H-NMR.: 1.35 (*d*, J = 6, 3 H, CH_3CH); 2.40 (*m*, 4 H, 2 CH_2CH_3); 3.90 (*qa*, J = 6, 1 H, $CHCH_3$)

2i (= *Diethyl(4-phenyl-3-buten-2-yl)amine*), 44% from cinnamicaldehyde and **1b**. – ^{1}H-NMR.: 2.50 (*qa*, J = 6, 4 H, 2 CH_2CH_3); 3.4 (*qi*, J = 6, 1 H, $CHCH_3$); 6.2 (*d*×*d*, J_1 = 16, J_2 = 6, 1 H, C=CHCH); 6.35 (*d*, J_1 = 16, 1 H, aryl-CH)

2k (= *Diethyl(3,3-dimethyl-2-butyl)amine*), 55% from pivalaldehyde and **1b**. – ^{13}C-NMR.: 8.24 (*qa*); 14.24 (*qa*); 27.43 (*qa*); 35.57 (*s*); 45.44 (*t*); 63.56 (*d*)

2l (= *1-(3,3-Dimethyl-2-butyl)piperidine*), 21% from pivalaldehyde and **1d**. – ^{1}H-NMR.: 0.8–1.0 (*m*, 12 H, $C(CH_3)_3$ and CH_3CH); 1.25–1.75 (*m*, 6 H); 2.0–2.8 (*m*, 5 H)

Scheme 4



R-$TiCl_3$ R_2TiCl_2 R^1-$Ti(OR^2)_3$ R^1-$Zr(OR^2)_3$

7 **8** **9** **10**

will hopefully lead to the elaboration of conditions under which the conversion is higher. The reagents[8]) of type **1** increase the versatility of the series of organotitanium and -zirconium reagents **7**–**10** *(Scheme 4)* of the general types $RTiX_3$ and R_2TiX_2: the chloro-derivatives **7** are the most reactive ones, replacing tertiary OH and halogen by R(=CH_3) [13]. The dichlorodimethyltitanium (**8**, R=CH_3) is a reagent for geminal dialkylation (see *Scheme 1*) [14]. The organometallic compounds **9** and **10** are highly selective nucleophiles in additions to aldehydes and ketones [1] [2] [15]. Finally, the most stable and least reactive tris(dialkylamino)-alkyltitanium reagents **1** presented here bring about a novel type of synthetic transformation, the direct alkylative amination to products **2**. This multitude of reactivity is observed with the same metal and the same organic groups R, by just changing the ligands X attached to the metal besides the organic substituent!

Experimental Part

General procedure. Preparation of **2c** from **1b** and *p*-tolylaldehyde. Methyllithium (4 mmol, 1.6M in ether) is added slowly to a stirred solution of 1.40 g (4 mmol) of $BrTi(NEt_2)_3$ [10] in 30 ml of ether at −30°. After 30 min at −30° and 1 h at r.t., the yellow solution of **1b** is combined at −60° with 0.22 g (1.83 mmol) of *p*-tolyl-aldehyde and then stirred at r.t. for 18 h. The mixture containing a white precipitate is quenched with 30 ml H_2O, the aqueous phase is extracted with 3×20 ml portions of ether, and from the combined organic layers the amines are extracted with 2N aqueous HCl. After addition of Na_2CO_3 to a pH of *ca.* 9, the amine is extracted into ether (3×20 ml), the ether solution is washed (water), dried (Na_2SO_4) and concentrated to give 0.17 g (47%) of **2c** as a liquid (NMR. see the *Table*).

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[8]) So far, only allylic tris(diethylamino)organotitanium derivatives have been used as reagents [8]. They *behave normally, i.e.* they give alcohols as simple adducts to the carbonyl substrates.