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Tris(trimethylsilylmethyl)alane: an aldehyde selective peterson methylenation reagent

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Abstract

Tris(trimethylsilylmethyl)alane (TTMA) is a rapid, efficient, and highly aldehyde-selective trimethylsilylmethylating reagent. A solid lithium halide complex of the reagent, TTMA · 3LiBr (TTMAs), is particularly effective in this transformation to the Peterson alcohol intermediate.

Keywords: Tris(trimethylsilylmethyl)alane; Aldehyde vs. ketone selectivity; Peterson methylenation

1. Introduction

The list of organometallic reagents applicable to organic synthesis continues to expand; however, the stated goal of reaction specificity for an indicated functional group, i.e. carbonyl, nitrile, epoxide, etc., remains elusive with rare exceptions [1]. For example, there is only one reported [2] example of a synthetically useful aldehyde selective Peterson methylenation reagent ($Me_3MCH_2TiCl_3$; M = Si, Ge). We now report that under proper conditions tris(trimethylsilylmethyl)alane (TTMA) functions as a rapid and effective trimethylsilylmethylating agent for aldehydes even in the presence of the ketone moiety.

Trialkylalanes are chemoselective in their reactions with carbonyl compounds [3]. In an effort to expand the synthetic potential of triorganoalanes, we discovered that the trimethylsilylmethyl ($TMSCH_2$) group competes poorly, if at all, with simple alkyls (methyl, ethyl) for transfer from aluminium to a ketone carbonyl [4]. These results formed the basis for an investigation of the known [5] TTMA as a chemoselective aldehyde reagent.

2. Results and discussion

There are three reported preparations of TTMA [5,6]. For our purposes, we found the reaction of $TMSCH_2Li$ with $AlBr_3$ in hexane the most convenient (Eq. 1) [6a]; however, the separation of TTMA from the lithium salts by distillation

$$3TMSCH_2Li + AlBr_3 \xrightarrow[\text{Reflux, 12h}]{\text{Hexanes}} (TMSCH_2)_3 + 3LiBr \quad (1)$$

from the reaction flask proved time consuming and low yielding. Furthermore, isolation of TTMA by cannula filtration of the liquid phase was also unsuccessful, leaving the alane apparently complexed with the LiBr salt. Evaporation of the remaining volatiles from this solid mixture led to the recovery of a white powder [TTMAs = $(TMSCH_2)_3Al \cdot 3LiBr$], which proved to be an unusually selective $TMSCH_2$ transfer agent with aldehydes (Scheme 1).

The reactions of both the neat TTMA and its halide bound salt (TTMAs) with selected aldehydes and ketones were investigated and the results compiled in Tables 1 and 2, respectively. The results in Table 1 indicate that in all instances the reactions of TTMAs are much cleaner (fewer products) and higher yielding than in TTMA alone. Still the carbonyl addition yields for both reagents decreased when reacted with readily enolizable carbonyls such as phenylacetaldehyde [7]. The lower

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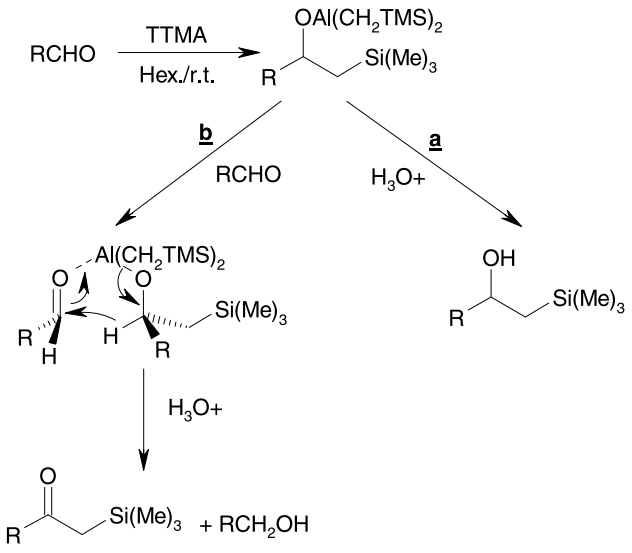


Scheme 1.

Table 2
Reaction of $(TMSCH_2)_3Al$ (TTMA) with selected ketones at room temperature

Ketone	TTMA[a]	Conversion (%)		
		Addition product	MPV Red.	S.M.
Cyclohexanone	A	26[b]	27	56
	B	39[b]	3	38
Acetophenone	A	7[b]	4	71
	B	8[b](5)	2	59
1-Indanone	–	–		93
	B	9[b](6)	2	36
9-Fluorenone	A	17[b]	–	55
	B	43[b]	–	51

[a] A: Neat $(TMSCH_2)_3Al$, B: $(TMSCH_2)_3Al \cdot LiBr$ salt.
[b] Total percentage of addition products (including the elimination products); S.M.: Starting material. Yields based on GC analysis, tridecane used as internal standard. Hexane or hexane/CH_2Cl_2 used as solvent; reactions quenched after 4 h.

yield observed with 4-methoxybenzaldehyde is apparently the result of facile elimination of trimethylsilanol from the addition product to form readily polymerizable 4-methoxystyrene. The major side products from these reactions, which are most pronounced in reactions of the neat TTMA, are the alcohols produced from the Meerwein–Pondorff–Verely (MPV) reduction of the starting aldehyde coupled with Oppenauer oxidation of the trimethylsilylmethyl alcohol (Scheme 1). These newly formed ketones have been observed to condense readily with the starting aldehyde in some instances, leading to a more complex product mixture. In reactions involving the TTMAs these reduction–oxidation processes are of minor significance [8].

The carbonyl selectivity of TTMA and TTMAs becomes evident upon examination of their reactivity with ketones (Table 2) in contrast with aldehydes. In all cases, the recovered starting ketone was the major constituent in the product mixture. The sluggish reactivity of TTMA (or TTMAs) with ketones is attributed to: (a) the bulk of the reagent, which may hinder complexation with the more sterically demanding ketones;

Table 1
Reaction of $(TMSCH_2)_3Al$ (TTMA) with selected aldehydes at room temperature

Aldehyde	TTMA[a]	Conversion (%)			
		Addition product	MPV Red.	Cond.[c]	S.M.[c]
Benzaldehyde	A	53[b](21)	27	–	–
	B	100[b]	–	–	–
4-Toluldehyde	A	63[b](21)	35		
	B	79[b]			19
4-Trifluoromethyl-benzaldehyde	–	–	–	–	–
	B	61[b]	–	–	–
4-Chlorobenzaldheyde	A	38[b](20)	10	–	31
	B	100[b]	–	–	–
Anisaldehyde	A	46[b](26)	33	4	10
	B	35[b](31)	2	6	–
Phenylacetaldehyde	A	41[b]	–	2	5
	B	38[b]	–	15	27
Heptanal	A	57[b](17)	24	–	–
	B	83[b](3)	4	–	2

[a] A: Neat $(TMSCH_2)_3Al$, B: $(TMSCH_2)_3Al \cdot LiBr$ salt.
[b] Total percentage of addition products (including the elimination products).
[c] Cond.: Total of condensation products. S.M.: Starting material. Yields based on GC analysis, tridecane used as internal standard. Hexane or hexane/CH_2Cl_2 used as solvent; reactions quenched after 4 h.

(b) steric crowding in the transition state for transfer of the bulky $TMSCH_2$ group from Al to carbon. One should note again, that the LiBr complex appears to be the more reactive reagent with ketones as well as aldehydes.

Although the data in Tables 1 and 2 provide adequate, if indirect evidence for the carbonyl selectivity of TTMA, a more direct and convincing measure of this selectivity is available when both aldehyde and ketone carbonyl functionalities are contained within the same substrate. Hence, the selectivity of TTMA was put to the more challenging test of reaction with keto-aldehydes 9-oxofluorenyl-4-carboxaldehyde (**1**) and 3-acetyl-2,2-dimethylcyclobutane-carboxaldehyde (**2**) [9] (Scheme 2). The reaction of TTMAs with **1** in hexane/methylene chloride solution (ca. 20 min) at room temperature yielded 94% of the aldehyde addition product **3**. Under similar conditions **2** yielded 76% of the aldehyde addition product **4** (ca. 15 min).

The high selectivity of TTMAs with **1** might have been expected, for steric reasons; however, in **2** the ketone and aldehyde moieties are sterically more comparable, and yet a 19 to 1 aldehyde selectivity is observed.

3. Conclusions

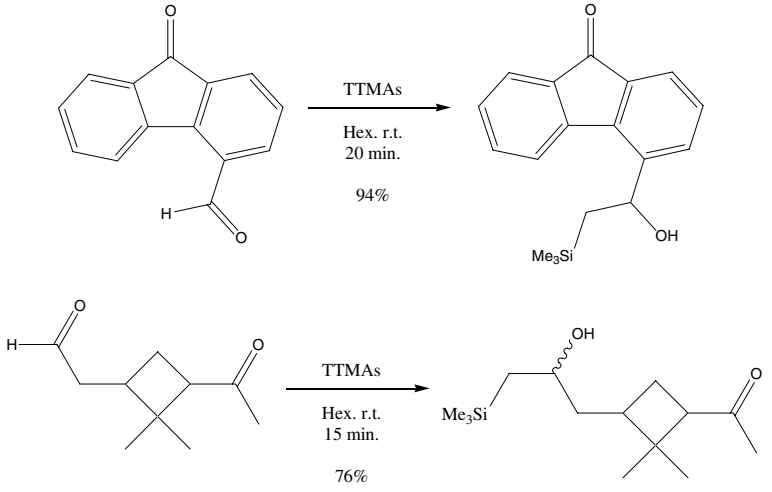
The superiority of the LiBr salt of the TTMA (TTMAs) compared to the neat liquid reagent is clear in that: (a) it affords much higher yields; (b) it is more stable when exposed to moisture and oxygen; (c) it is easier to handle (powder) and can be stored for months. When compared to other Peterson methylenation reagents [1,2,7], TTMAs is also advantageous since it requires moderate temperatures (0–25 °C), shorter reaction times, and a 1.3–1 ratio of reagent to aldehyde.

4. Experimental

Distilled TTMA was obtained by the previously described procedure [6a]. For TTMAs (LiBr salt) similar steps were followed as for neat TTMA up to the distillation step; at this point the solids were filtered using a cannula filter and washed with hexane. The solid powder was then dried under vacuum (0.01 mm Hg) and stored in the dry box. The IR (KBr) spectrum of the powder was essentially indentical to that reported for TTMA [6], while the ^1H NMR (THF-d_8) spectrum revealed a broadened complex multipet centered at 0.00 ppm. The mass spectrum (70 eV) of the powder showed a base peak at m/z 73 (Me_3Si) and a parent peak at 295 [$(Me_3SiCH_2)_3AlLi$]. As required, the reagent (TTMA or TTMAs) was weighed into the appropriate flask (in the dry box) before each reaction.

4.1. Typical procedure for reaction of TTMA or TTMAs with aldehydes

All glassware and syringes were dried in the oven over night and all reactions were carried out under an Ar atmosphere. In the dry box, 2.5 mmol of TTMA or TTMAs were weighed into a round bottom flask equipped with a septum and a magnetic stirring bar. Freshly distilled hexane (25 ml) was added and the suspension (or solution) stirred for 15 min. A solution of aldehyde (2.0 mmol) in 4 ml of hexane was added dropwise to the cooled (0 °C) suspension (or solution) of the reagent and then allowed to warm to room temperature. After 4 h the reaction mixture was quenched by addition of 1.0 M HCl (with cooling). The usual workup afforded a yellow clear oil which was analyzed by capillary GC. Note: appropriate amounts of CH_2Cl_2 were used to dissolve those carbonyl compounds which



Scheme 2.

were not completely soluble in hexane. All reactions with aldehydes were complete within 30 min.

1: [from reduction of corresponding acid chloride (Aldrich)]: m.p. 173–175 °C; ^{1}H NMR: ($CDCl_3$) δ 7.41 (td, $J_{Hz} = 7.2$, 1.0; 1H), 7.48 (t, $J_{Hz} = 7.3$: 1H), 7.56 (td, $J_{Hz} = 7.5$, 1.5; 1H), 7.73 (dm, $J_{Hz} = 7.27$; 1H), 7.89 (dd, $J_{Hz} = 7.2$, 1.5; 1H), 7.98 (dd, $J_{Hz} = 7.4$, 1.5; 1H), 8.33 (dt, $J_{Hz} = 7.4$, <0.5; 1H), 10.43 (s, 1H); ^{13}C NMR: δ 124.4, 126.7, 128.8, 129.1, 130.4, 132.5, 134.4, 135.4, 135.6, 137.5, 142.9, 144.8, 190.8, 192.3; HRMS: m/z (70 eV), 208 (100), 180 (88), 152 (40), 151 (46.0), 150 (32.5), 75 (21.0); calculated for $C_{14}H_8O_2$ 208.05243, found 208.05060; IR (KBr): (C=O) 1718, 1688 cm^{-1}.

2: (from ozonization of α-pinene) [9]: ^{1}H NMR: ($CDCl_3$) δ 0.85 (s, 3H), 1,34 (s, 3H), 1.98 (q, $J_{Hz} = 7.64$; 2H), 2.06 (s, 3H), overlapping peaks 2.25–2.54 (m, 3H), 2.93 (dd, $J_{Hz} = 9.76$, 7.81; 1H), 9.75 (t, $J_{Hz} = 1.45$; 1H); ^{13}C NMR: δ 17.50, 17.55, 22.7, 30.0, 35,6 43.2, 44.9, 54.2, 201.4, 207.4; GC/MS m/z (CI, methane), 169 (14), 151 (72), 127 (14), 107 (39), 99 (58), 71 (100); IR (neat): (C=O) 1724, 1705 cm^{-1}.

3: m.p. 121–123 °C; ^{1}H NMR: ($CDCl_3$), δ 0.00 [(ref. Me_3Si–) (s, 9H)], overlapping peaks 1.18: [(d, $J_{Hz} = 8.35$; 1H), (d, $J_{Hz} = 6.29$; 1H)], 2.01 (d, $J_{Hz} = 3.61$; 1H), 5.34 (td, $J_{Hz} = 7.26$, 3.54; 1H), 7.16 (t, $J_{Hz} = 7.62$; 1H), 7.18 (t, $J_{Hz} = 7.84$; 1H), 7.38 (td, $J_{Hz} = 7.59$, 1.30; 1H), 7.44 (br d, $J_{Hz} = 7.18$; 1H), 7.56 (br d, $J_{Hz} = 7.87$; 1H), 7.61 (br d, $J_{Hz} = 7.76$; 1H); ^{13}C NMR: δ −0.76, 26.2, 69.1, 123.1, 124.3, 124.8, 128.5, 129.1, 132.1, 134.0, 134.5, 134.7, 134.7, 143.3, 144.2, 194.2; HRMS: m/z (GC/EI, 70 eV), 296 (36), 281 (100), 267 (18), 209 (65), 206 (36), 178 (82), 162 (40), 75 (99), 73 (48) calculated for $C_{18}H_{20}O_2Si$, 296.1233, measured 296.123; IR (KBr): (OH) 3509, (C=O) 1608 cm^{-1}.

4: ^{1}H NMR: ($CDCl_3$), δ 0.00 [(ref. Me_3Si–), (s, 9H)], overlapping peaks [0.78 (d, $J_{Hz} = 6.9$), 0.81 (s), 0.82 (d, $J_{Hz} = 6.2$); total 5H], 1.25 (s, 3H), overlapping peaks [1.30–1.56 (m), total 3H)], 1.75–1.98 (m, 2H), 2.00 (s, 3H), 2.02–2.14 (m, 1H), 2.79 (dd, $J_{Hz} = 8.88$, 8.62; 1H), 3.70 (m, 1H); ^{13}C NMR shows mixture of two isomers: δ 0.00, 18.09(18.05), 23.93, 24.74, 27.86(29.16), 30.78(31.16), 39.70(39.37), 41.91(41.48), 44.23(43.91), 55.34(55.08), 68.63(70.02), 208.70(208.65); HRMS: m/z (GC/CI), calculated for $C_{14}H_{28}O_2Si$ 256.1859, found 256.1885; GC/MS: m/z, (70 eV) 241 (0.3), 223(1), 199(2), 171(2), 117(21), 99(38), 75(48), 73(100): IR (neat): (OH) 3439, (C=O) 1710 cm^{-1}.

Acknowledgements

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[8] The enhanced reactivity of the TTMAs may be tentatively attributed to several factors: (a) the observed higher stability of the TTMAs towards exposure to oxygen and moisture which may contribute to a reduction in reactivity of the reagent and lead to undesired side products; (b) increased electrophiliciy of the carbonyl group due to complexation of Li^+ with the carbonyl oxygen; and (c) the presence of the Br^- in the reaction mixture appears to assist in breaking up alkylaluminum-oxide aggregates. The latter effect should increase the reactivity of the alane as well as counteract the reduction–oxidation processes which involve an alkoxyaluminum-aldehyde complex (Scheme 1; path b).
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