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γ-SILYLATED α,β-UNSATURATED AMIDES. FORMATION BY [1,5] SILICON MIGRATION FROM O-SILYLATED VINYL KETENE AMINALS AND FLUORIDE- AND LEWIS ACID-MEDIATED ALDOL CONDENSATIONS

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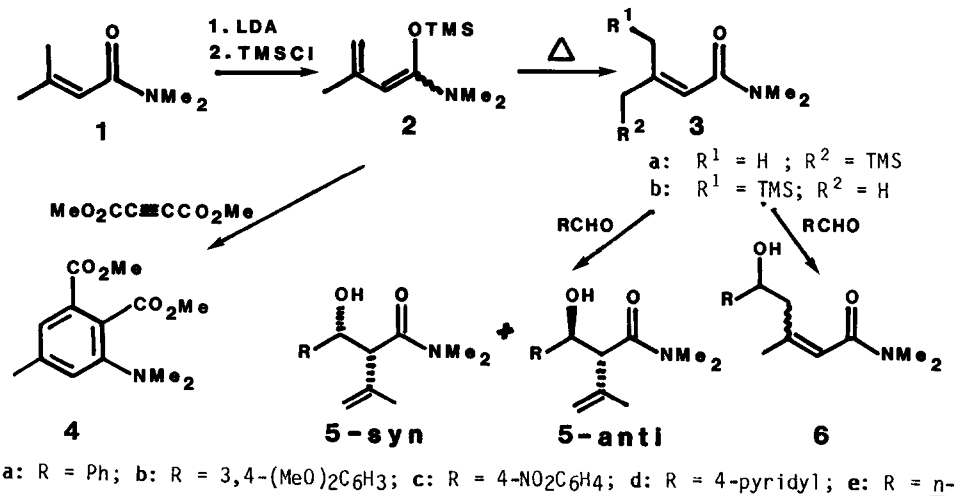
Abstract: O-Silylated vinyl ketene aminal **2**, obtained from lithiated unsaturated amide **1**, undergoes a thermal [1,5] silicon migration to give γ-silylated product **3b** which participates in fluoride- and titanium tetrachloride-mediated aldol condensations to give adducts **5** in poor and excellent **syn** diastereoselectivity respectively.

Among allylic organometallic reagents,[1] allyl silanes have emerged as versatile intermediates for C-C bond forming reactions featuring high reactivity and regio- and stereo-selectivity with a variety of carbon electrophiles.[2] To date, the reactivity of allyl silanes which incorporate interacting functional groups has received scant attention.[3] As a continuation of our methodological studies in metalated α,β-unsaturated amides,[4] we report on a) the preparation of O-silylated vinyl ketene aminal **2** [5] and its stereoselective [1,5] sigmatropic silicon rearrangement into the γ(Z)-silylated amide **3b** [6] and b) the Lewis acid[7]- and fluoride[8]-mediated condensation of **3b** with carbonyl compounds to give α- and γ-substituted products, **5** and **6**. These results further augment the position of unsaturated amides as attractive synthetic intermediates.



a: R = Ph; b: R = 3,4-$(MeO)_2C_6H_3$; c: R = 4-$NO_2C_6H_4$; d: R = 4-pyridyl; e: R = n-Pr; f: R = Et; g: R = Me_2CH

Standard metalation[4] of the senecioamide **1** followed by treatment with TMSCl and non-aqueous workup gave the O-silylated product **2**. Reaction with dimethyl acetylene dicaboxylate afforded the phthalate ester **4**. Refluxing a THF solution of **2** resulted in a [1,5] sigmatropic silicon migration to give **3b** and **3a** in a ratio of 91:9 in 74% yield.[9]

Table 1. Fluoride-Induced Reaction of 3b with Aromatic Aldehydes

E^+	Conditions[a]	Product[b]	Yield,%[c]	Ratio (5)syn:anti	Ratio (6)Z:E
PhCHO	A	**5a/6a**	69	44:48	8:0
PhCHO	B	**6a**	72	-	80:20
$3,4\text{-}(OMe)_2CH_6C_3HO$	A	**5b/6b**	58	43:46	11:0
$3,4\text{-}(OMe)_2C_6H_3CHO$	B	**5b**	75	-	65:35
$4\text{-}NO_2\text{-}C_6H_4CHO$	A	**5c/6c**	85	29:36	35:0
$4\text{-}NO_2\text{-}C_6H_4CHO$	B	**5c/6c**	80	27:33	40:0
Pyridine-4-CHO	A	**5d/6d**	74	37:46	17:0
Pyridine-3-CHO	B	**6d**	70	-	81:19

[a] A: 1.2 equiv. ArCHO/100 mol % TBAF/-45°C/2 min; B: 1.2 equiv. ArCHO/5 mol % TBAF/-78°C→RT/15-20 h followed by saturated aq NH_4Cl work up. [b] All products were characterized by direct comparison with authentic materials (ref. 4). [c] Of chromatographically (silica gel, EtOAc-hexane) pure materials.

Table 2. $TiCl_4$-Mediated Condensation of 3b with Carbonyl Electrophiles[a]

Electrophile	Product[b]	Yield,%[c]	Ratio[d] syn:anti
PhCHO	**5a**	62	97:3
$3,4\text{-}(OMe)_2C_6H_3CHO$	**5b**	47	70:30
$4\text{-}NO_2\text{-}C_6H_4CHO$	**5c**	74	99:1
n-PrCHO	**5e**	65	96:4
EtCHO	**5f**	25	97:3
Me_2CHCHO	**5g**	68	59:41

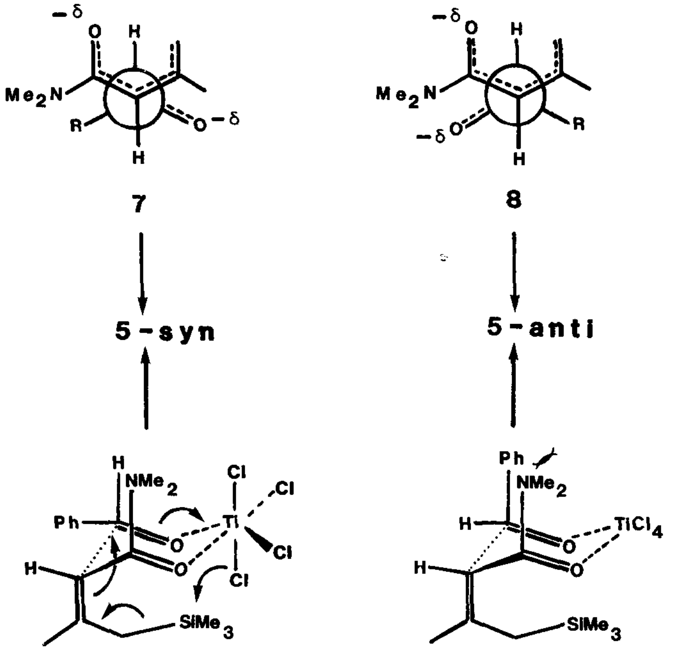
[a] Typical procedure: To a solution of carbonyl compound (1 equiv) and $TiCL_4$ (1 equiv) in anhydrous CH_2Cl_2 at -78° was added **3b** in CH_2Cl_2. After stirring for 2 h at -78°, the solution was warmed to room temperature over 8-12 h and worked up conventionally. [b] See footnote b, **Table 1.** [c] See footnote c, **Table 1.** [d] Established by glc analysis.

Treatment of **3b** with benzaldehyde (THF/RT/15 h) in the presence of TBAF (5 mole %) followed by aq NH_4Cl quench (thermodynamic control) led to the formation of γ-alkylated products **6a** favoring the γ(Z)-isomer **(Table 1)**. Under kinetic conditions (THF/-45°C/2 min/-100 mole % TBAF), this reaction led predominantly to α-alkylated products **5** in fair yield but with essentially no diastereoselectivity. The observed behaviour in α:γ regioselectivity but not in α-diastereoselectivity is reminiscent of that observed for the reaction of lithiated **1** with PhCHO.[4] Reaction of **3b** with other aromatic aldehydes provided similar results. Yields of products using veratraldehyde and p-NO_2-benzaldehyde reflect the expected substituent electronic effects on the position of the mobile equilibrium.[10] Aliphatic aldehydes failed to provide condensation products.

Thus the fluoride-induced nucleophilic reactivity of **3b** is low relative to simple allyl silanes **2c**. In the proposed mechanism **(Scheme)**, the tetra-n-butylammonium dienolate resulting from **3b** undergoes reaction with the aldehyde via acyclic, extended transition states **7** and **8** of similar energy requirements in contrast to the analogous quaternary ammonium fluoride- or tris(dialkylamino)sulfonium fluoride-catalyzed aldol condensation of silyl enolates with carbonyl compounds.[10] In contrast to these kinetic control conditions, thermodynamic control (→ RT/15-20 h) resulted in the predominant formation of γ-substituted products **6** favouring the γ(Z)-isomers. These results strongly suggest that isomer distribution is dependent upon retroaldol processes analogous to those reported for quaternary ammonium enolates.[10,11]

On the other hand, when **3b** was subjected to $TiCl_4$-mediated condensation with PhCHO, **5a** was obtained as a **syn:anti** mixture showing high **syn** diastereoselectivity **(Table 2).** This ratio contrasts sharply with that **(syn:anti** = 29:71) obtained for the reaction of lithiated **1** with PhCHO under kinetic control conditions.[4] Similar predominantly **syn** stereoselectivity was observed for reactions of **3b** with other carbonyl compounds **(Table 2).**

The generally high **syn** diastereoselectivity for the formation of **5** agrees with that obtained for the reaction of simple allyl silanes with aldehydes.[2e] Several indirected paths to **5** can be ruled out or are unlikely: a) reaction of the silylated vinyl ketene aminal **2** with PhCHO under the same conditions leads to poor diastereoselectivity **(5a, syn:anti** = 60:40, 45% yield) making it unlikely that **5a** is formed by C to O silicon migration under the influence of $TiCl_4$; b) the order of mixing of reagents **5a,** $TiCl_4$, and PhCHO is immaterial thus raising the possibility of a titanium dienolate.[12] However, the reaction of PhCHO with the titanium dienolate, prepared from **2** according to Kuwajima,[12] resulted in the formation of oligomeric materials and only trace amounts of condensation products; c) 1,3 silicon migration to an α-silylated β,γ-unsaturated amide should yield only γ-substituted product **6** by analogy with the reaction of corresponding α-silylated β,γ-unsaturated ester with carbonyl electrophiles.[3a]



Scheme

While a precise mechanism for the $TiCl_4$-catalyzed aldol coupling of **3b** with carbonyl compounds cannot be formulated,[13] a working hypothesis based on the strong affinity of titanium for oxygen[13] and the intramolecular transfer of chloride to silicon[8a,14] may account for the observed stereoselectivity. Examination of the cyclic transition states **9** and **10** shows that the latter suffers from steric repulsion between R = Ph and NMe_2 groups (1,3-diaxial interaction). **9** is therefore favoured and leads to the **5-syn** isomer. Consonant with this hypothesis, the E-silylated amide **3a** under identical conditions undergoes a sluggish, incomplete reaction with PhCHO to give **5a-syn** in 12% yield (no **5a-anti**, 51% recovered starting material). The diminished diastereoselectivity when R = i-Pr **(Table 2)** stems from unknown origin, but has been observed in similar condensations.[8a]

Stereoselective C-C bond formation and regiospecific γ-functionalization using silylated vinyl ketene aminals **2** constitute complementary methodologies to that derived from metalated unsaturated amides[4] *and underscores the increasing utility of silicon functionality in* synthesis.[15,16]

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