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Synthesis of allylsilane-containing amino acids via the Claisen rearrangement

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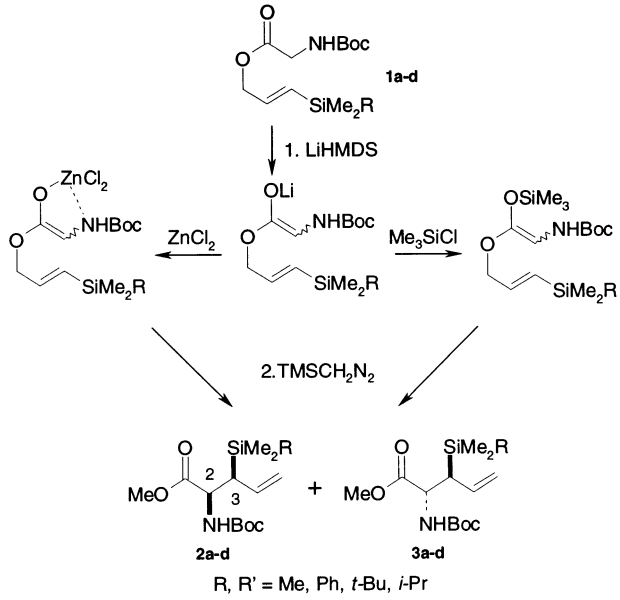
Abstract—The Claisen rearrangement of *N*-BOC-glycinate esters **1a**–**1d** led to the formation of α-allylsilane-functionalized amino acids **2**–**3** in good yield (up to 80%). The diastereoselectivity of the reaction varied from 2:1 to 29:1 (*syn*:*anti*) for **1a** depending on reaction conditions. In the case of the Ireland–Claisen variant, the relationship between size of the alkyl groups on the enolate trap ($Me_2R'SiCl$, R = Me, *t*-Bu, Ph) and diastereoselectivity was investigated, showing that chlorotrimethylsilane gave the best results. The size of the alkyl groups on the allylsilane do not exert a significant effect on the diastereoselectivity or yield (Me_2RSi, R = Me, *t*-Bu, Ph, *i*-Pr). © 2000 Published by Elsevier Science Ltd.

The ester enolate version of the Claisen rearrangement[1] has become an important method for C–C bond formation and vicinal stereochemical control.[2] For example, Barlett and co-workers described the Ireland–Claisen rearrangement of glycine allylic esters in depth and reported a strong dependence of the diastereoselectivity on both the solvent and *N*-protecting group used.[3] Kazmaier demonstrated that chelation control, with an allylic glycinate, led to enhanced selectivity in the ester enolate Claisen rearrangement.[4] More important for the current research, however, is the work of Panek and co-workers who utilized the Ireland–Claisen rearrangement for the synthesis of chiral crotylsilanes and attributed the observed high diastereoselectivity to a highly ordered transition state in the rearrangement.[5] We were attracted to this work because of the utility of allylsilanes in organic synthesis.[6]

γ,δ-Unsaturated amino acids have become the subject of intense investigation due to their biological activity.[7] We sought to synthesize allylsilane containing amino acids not only for the inherent bioactivity of such compounds, but also because of the potential for further functionalization at the allylic position taking advantage of well-documented allylsilane chemistry.[8] We surmised that the combination of the stereocontrol of the Claisen rearrangement to give allylsilanes, described by Panek and others for non-amino acids, might prove a new, generic entry to unnatural amino acids. To this end, we have investigated methods to facilitate the rearrangement of 3-silylpropen-1-ol-glycinate esters to α-allylsilane-amino acids (Scheme 1).

The starting silyl-aminoesters **1a**–**1d** were obtained by the condensation of glycine and *E*-3-silylpropen-1-ol.[9] A variety of synthetic protocols for the Claisen rearrangement, already described in the literature, were examined with these compounds. The ratios of starting materials and yields of a number of Claisen reactions,



Scheme 1.

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Table 1. Selectivity of Claisen rearrangements of silylallyl glycinates

Entry	Substrate	Enolate trap[b]	SiR_3	$^3J_{2,3}$ (Hz)[c]		δ (ppm)[d]		(Yield)[a] (**2**:**3**)
				syn **2**	*anti* **3**	*syn* **2**	*anti* **3**	*syn*/*anti* ratio
1	**1a**	$ZnCl_2$	Me_3Si	5.86	4.59	1.95	2.03	(50) 23:1
2		Me_3SiCl/Et_3N						(79) 19:1
3		Reverse add.						(82) 29:1
4		DMAP/TMSCl						9:1
5		$PhMe_2SiCl/Et_3N$						15:1
6		*t*-$BuMe_2SiCl/Et_3N$						(28) 2.6:1
7	**1b**	Me_3SiCl/Et_3N	$PhMe_2Si$	6.37	5.28	2.18	2.29	(62) 5.5:1[e]
8	**1c**	Me_3SiCl/Et_3N	*t*-$BuMe_2Si$	6.87	4.40	2.16	2.41	16:1
9	**1d**	Me_3SiCl/Et_3N	*i*-$PrMe_2Si$	5.99[f]		2.01		(60) 22:1

[a] Diastereomeric ratio determined by GC.
[b] LiHMDS was added in all cases, other bases were in addition.
[c] Three-bond coupling constant $^3J_{2,3}$ value of the ^1H of the methine C3, of the methyl esters of **2**,**3a**–**d**, see Scheme 1 for labels.
[d] ^1H NMR chemical shift of the methine C3 of the methyl esters of **2**,**3a**–**d**.
[e] Determined by ^1H NMR.
[f] Only one isomer detected by ^1H NMR.

using different variants and reaction conditions, and a series of related vinylsilanes are given in Table 1.[10] The assignment of the relative stereochemistry for the α-allylsilane–amino acid products is based upon the careful work of Sparks and Panek.[5] We, as they, used the three-bond coupling constant values ($^3J_{2,3}$) of the C3 methine proton of the corresponding methyl esters as key structural evidence, as shown in Table 1, Scheme 1.

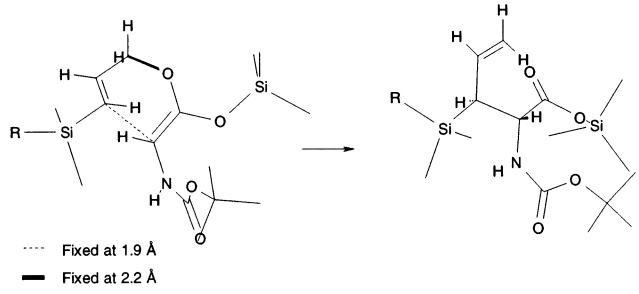
The attempt to use the zinc-chelated[4] enolate, to drive the Claisen rearrangement of the glycinate vinyl ester derivative **1a**, was successful from the perspective of diastereoselectivity: products **2a** and **3a** were identified by ^1H NMR in a *syn*:*anti* ratio of 23:1 (entry 1, Table 1).[11] Unfortunately, a substantial amount of starting ester hydrolysis was associated with this procedure and the combined chemical yield of the two isomeric amino acids was only 50%.[12]

Good diastereoselectivity (19:1) and high yield (80%, entry 2) was observed by using the standard Ireland–Claisen rearrangement conditions (sequential addition of the ester, to LHMDS and quenching with the chlorotrialkyl(aryl)silane and Et_3N).[13] Although the products were formed in moderate to excellent (5:1> 22:1) diastereoselectivity and a good yield (62–79%), both the stereoselectivity and the yield improved when the reverse addition of the base to the ester was employed (29:1, 82%), entry 3. The product carboxylic acids were converted to the corresponding methyl esters to facilitate characterization as noted above;[14] the major isomer in each case was purified by flash chromatography.

The effect of different silyl groups on the starting ester (R′ = Me, *i*-Pr, *t*-Bu, Ph) was studied to see if such groups could affect the diastereoinduction. It was expected that greater steric bulk on the silane would lead to an enhanced diastereoselectivity due to reduced degrees of freedom in the transition state of the Claisen rearrangement. In all the reaction conditions tested, **1a** and **1d** showed the best stereoselectivity and the best chemical yield. Use of the other groups led either to an erosion in yield or selectivity (Table 1).

In retrospect, the reduced or comparable selectivity might have been expected. Simple molecular modeling[15] of the transition state (lengthening of the C–O bond, shortening of the =C···C= distance, dotted line, 1.9 Å, bold line 2.2 Å) following the work of Houk,[16] showed that in the first instance the silyl group is somewhat remote from the reaction center and secondly, the large group can avoid the reaction center by simple rotation (Scheme 2). We are currently considering the use of more sophisticated silyl groups to improve stereoselective control in this and subsequent reactions of the allylsilanes **2a**–**d** with aldehydes and other electrophiles. These results will be reported in due course.

In summary, the Claisen rearrangement of *E*-3-silylpropene-glycinate esters shows high diastereoselectivity favoring the formation of the *syn* product isomer. This can be explained in terms of a traditional chair-like transition state, which is generally postulated for [3,3]-sigmatropic rearrangement of acyclic systems.[17]



Scheme 2.

Acknowledgements

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11. For the experimental procedure, see reference 4.
12. The allylic alcohol was observed in the ^{1}H NMR of the crude product.
13. Claisen rearrangements: To a solution of lithium hexamethyldisilazide (1.0 M in hexane, 2.5 mL, 2.5 mmol) in anhydrous THF (1 mL) at −78°C was added to the ester (0.287 g, 1 mmol). After 3 min, TMSCl (0.33 g, 0.38 mL) was added, followed by addition of Et_3N (0.40 mL) (addition of Et_3N was found to improve product yield). The solution was then stirred for 10 min, and the cooling bath was removed. After stirring (3 h), the solution was diluted with ethyl acetate and mixed with 4 mL of 1N HCl solution and stirred vigorously for 30 min. The aqueous layer was extracted with ethyl acetate (2×5 mL), the combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo.
14. Methyl esters: To a solution of the crude acid in methanol (5 mL) at rt was added trimethylsilyldiazomethane until yellow color persisted, and the solvent was removed in vacuo. **2a**: ^{1}H NMR δ 5.55 (m, 1H), 5.52 (s, 1H), 4.97 (dd, 2H, $J = 16.8$, 10.70 Hz), 4.37 (m, 1H), 3.65 (s, 3H), 1.91 (dd, 1H, $J = 10.75$, 5.86 Hz), 1.38 (s, 9H), 0.03 (s, 9H); ^{13}C NMR 172.68, 154.98, 134.05, 116.79, 79.86, 53.75, 51.77, 39.75, 28.30, −2.54; HRMS *m/e* (M+1) 302.1775 ($C_{14}H_{28}NO_4Si$ required: 302.1788).
15. MM2, using Hyperchem 5.01, Gainsville, Florida.
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