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SYNTHESIS OF α-AMINO-β-HYDROXY ACIDS USING {N,N-BIS(TRIMETHYLSILYL)AMINO}KETENE BIS(TRIMETHYLSILYL) ACETAL OR ITS N-METHYL-N-TRIMETHYLSILYL ANALOG

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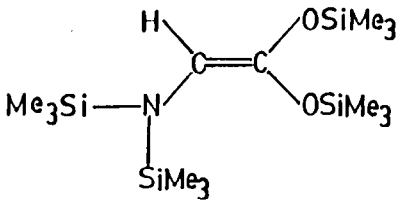
Abstract: Condensation of the title compounds with aldehydes and ketones in the presence of trimethylsilyl triflate provided the corresponding α-amino-β-hydroxy acids in fair to good yields as a mixture of diastereomers.

In the course of our work with carbohydrates containing an α-amino acid grouping, we required a new method of chain extension which would avoid the use of a strong base. Shanzer et al.[3] have described a stereospecific synthesis of α-amino-β-hydroxy acids; however, the method involves the use of lithium diisopropylamide. Several examples of condensations of aldehydes or ketones with silylated ketene acetals as protected ester enolates, using titanium(IV) chloride[4], fluoride ion[5], or trimethylsilyl triflate[6] as catalysts, have been reported. Here we describe reagents of this type derived from an amino acid, namely N,N-{bis(trimethylsilyl)amino}ketene bis(trimethylsilyl) acetal (1), and its N-methyl-N-trimethylsilyl analog (2),



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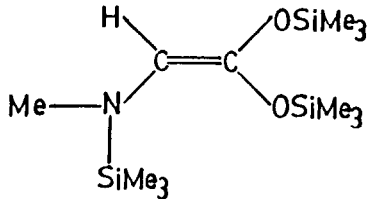

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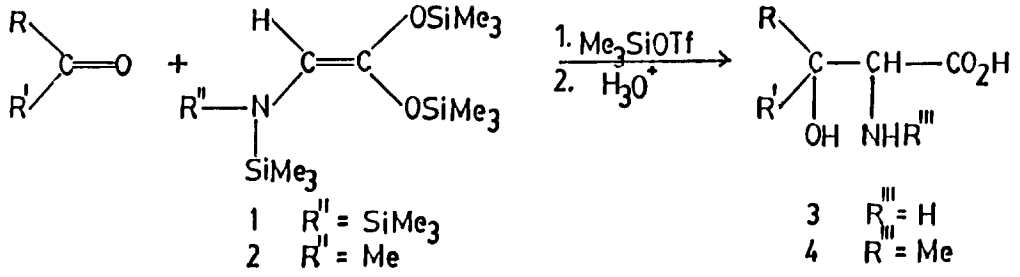
and their utility for the synthesis of α-amino-β-hydroxy acids from carbonyl compounds. The catalyst employed is trimethylsilyl triflate (Me_3SiOTf) and the reaction is shown below. After the present work had been completed, two related syntheses of α-amino-β-hydroxy acids were reported[7,8].

Reagent 1 [9,10] was readily prepared in two steps by silylation of glycine with trimethylsilyldiethylamine, to give N,N-bis(trimethylsilyl)-glycine trimethylsilyl ester, followed by generation of the corresponding enolate using lithium diisopropylamide and silylation of the enolate using

trimethylsilyl chloride at low temperature (-78°C). Reagent 2 [11] was prepared analogously starting from N-methylglycine (sarcosine).



Condensations were performed at -78°C or 0°C by adding 1 or 2 to a solution of the carbonyl compound (2—4 mmol) in dichloromethane (4 mL) at -78°C followed by the addition of 1.1 equiv of Me_3SiOTf after 10 min. ; if a catalytic amount (0.1 equiv) of Me_3SiOTf were used, a lower yield of product resulted. Intially, an attempt had been made to generate 1 from N,N-bis(trimethylsilyl)glycine trimethylsilyl ester using Me_3SiOTf and triethylamine, and to effect a reaction *in situ* with a carbonyl compound, as described by Yokozawa *et al.*[6] in the case of a nonaminated silylated ketene acetal; however, this attempt was unsuccessful.

The processing procedure employed is as follows. The reaction mixture was quenched with water, the organic solvent evaporated, the mixture made homogeneous by addition of ethanol, the pH adjusted to 2 by the addition of aqueous HCl, and the solution passed through a column of Amberlite CG-120(H^+) (100—200 mesh) ion-exchange resin; the column was washed with 1:1 (v/v) water—ethanol, then with water, and the final product was eluted with 0.5 N aqueous ammonia. Further purification was effected using column chromatography on silica gel (*t*-butanol—water—acetic acid 5:1:1 (v/v) or dichloromethane—methanol—water 3:1:0.1 (v/v)) and/or recrystallization (ethanol—water). The yields and the diastereomeric ratios are given in the Table.

Although the reaction does not proceed with a high degree of diastereoselectivity, nevertheless, the procedure is a viable one for the synthesis of α-amino-β-hydroxy acids, in particular in the case of base-sensitive carbonyl substrates. The work provides examples of the synthesis of α-amino-β-hydroxy acids using an acid-catalyzed version of the aldol condensation. Another noteworthy feature is the fact that, in one step, the condensation product having the three functional groups unprotected is obtained directly. In the case of the carbohydrates employed, the reaction was found not to be suitable.

Table. Yields and Ratios of Diastereomers of Products[a] from the Condensation of 1 or 2 with Aldehydes and Ketones

substrate	equiv substrate/1	equiv substrate/2	time	temp	% yield[b]	threo/erythro[c]
benzaldehyde	2/1		3 h	-78°C	95	2/1
		2/1	6 h	-78°C	69	3/2
3,4-dimethoxy-benzaldehyde	2/1		4 h	-78°C	48	4/5
		2/1	4 h	-78°C	71	1/1
n-butanal	2/1		2.5 h	0°C	46	1/1
		2/1	16 h	0°C	27	1/1
2-propanone	2/1		17 h	0°C	50	—
		2/1	12 h	0°C	7[d]	—
2,3,4,5-tetra-O-acetyl-aldehydo-D-arabinose	2/3		17 h	0°C	e	
2,3,4,5-tetra-O-methyl-aldehydo-D-arabinose	1/2		17 h	0°C	e	
2,3:4,5-di-O-isopropylidene-aldehydo-β-D-arabino-hexosulo-2,6-pyranose	2/3		16 h	0°C	e	
1,2:3,4-di-O-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose	1/2		20 h	0°C	e	

[a] The ^{1}H NMR spectral data of the products were consistent with the assigned structures. [b] Isolated yields. [c] Ratios were determined by ^{1}H NMR spectroscopy (see ref. 12); the definitions of "threo" and "erythro" are also given in ref. 12. [d] The isolated yield was substantially lower than the actual yield because of difficulty of resolution of the reaction mixture. [e] No reaction.

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References and Notes

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(9) Reagent 1 was purified by distillation at 115°C (bath temperature)/ 2 torr ; 40% overall yield; ^{1}H NMR data (400 MHz, $CDCl_3$, $SiMe_4$ internal standard): δ 4.28 (1H, s, CH), 0.22 and 0.18 (18H, s's, $2OSiMe_3$), 0.06 (18H, s, $2NSiMe_3$).

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(11) Reagent 2 was purified by distillation , bp 59—61°C/0.3 torr ; 85% overall yield ; ^{1}H NMR data: δ 4.50 (1H, s, CH), 2.53 (3H, s, NMe), 0.21 and 0.20 (18H, s's, $2OSiMe_3$), 0.05 (9H, s, $NSiMe_3$); ^{13}C NMR data (100.6 MHz, $CDCl_3$; chemical shifts are reported in ppm (δ) downfield from the signal of $SiMe_4$): δ 148.4 (C-1), 97.8 (C-2), 36.4 (NMe), 0.61, -0.01, -0.77 ($2OSiMe_3$, $NSiMe_3$).

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