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A few new methods for asymmetric synthesis

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Aza-Claisen rearrangement of N-2(E)-butenyl-N-butylpropanamide was found to proceed smoothly at∿135°C in the presence of LDA to furnish syn-N-butyl-2,3-dimethyl-4-pentenamide in∿94% yield and >99% de. The reaction with the corresponding N-(1S)-1-phenethyl derivative yielded (2R,3S)-N-[(1S)-1-phenethyl]-2,3-dimethyl-4-pentenamide in 83% de. An efficient and generally-applicable two-step procedure for the hydrolysis of N-mono-substituted amides was also developed and the corresponding carboxylic acids were obtained in good yields without any epimerization at the α-position of the acyl group. The amines used for the chiral induction can be recovered in 71% yield.

INTRODUCTION

Stereoselectivity is one of the major concerns of chemists interested in modern organic synthesis. In this talk, we will discuss a few developments achieved by our group in this area.

AZA-CLAISEN REARRANGEMENT OF AMIDE ENOLATES

Claisen rearrangement of ester enolates initiated by Ireland (ref. 1) has widespread application in the homologation of acids and alcohols (ref. 2). From the present standard, however, the diastereoselectivity observed (syn:anti=8:92 (ref.1)) is not entirely satisfactory. This is mainly due to the insufficient stereocontrol in the enolate formation (E:Z=95:5 in kinetic enolate (ref. 3)). On the other hand, aza-Claisen rearrangement of the enolates of N-2-alkenyl-N-alkylcarboxamides has not fully been investigated for the synthetic utility, probably because the resulted N-alkylamides have little synthetic value. However, since bulkier dialkylamino groups tend to produce more Z-enolates (often > 99:1 (ref. 3)) than alkoxyl groups and a trivalent nitrogen atom could have an auxiliary for the chiral induction unlike a divalent oxygen atom, we have investigated the rearrangement in order to establish its stereochemical outcome and to develop a methodology in asymmetric synthesis.

Diastereoselectivity

N-2(E or Z)-butenyl-N-butylpropanamide (**1E** or **1Z**)(ref. 4) was treated in THF at -78°C with LDA to form the corresponding amide enolate **2**. The solvent was removed at 0°C in vacuo and the residue was heated in a high-boiling nonpolar solvent to give N-butyl-2,3-dimethyl-4-pentenamide (**4**: a mixture of the syn and anti isomers, **4s** and **4a**) (Method A). The results are listed in TABLE 1 (ref. 5).

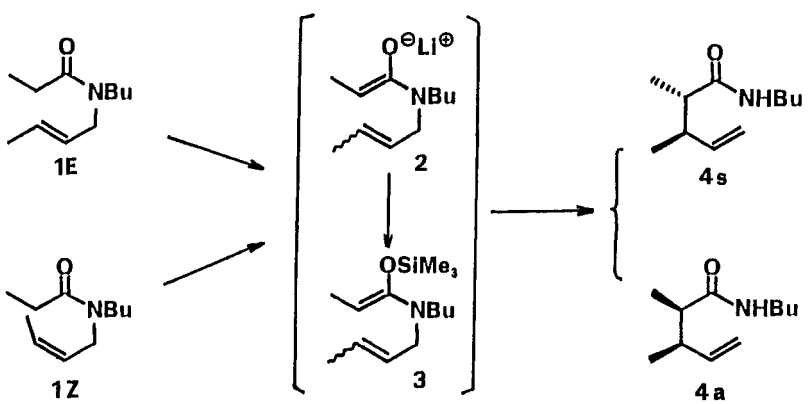
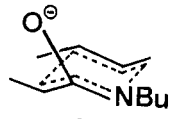


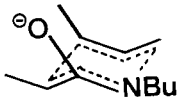
TABLE 1. Aza-Claisen rearrangement of N-butenyl-N-butylpropanamides (**1**)

Entry	Compd	Method	Conditions			Isolated yield of **4** (%)	Ratio **4s**:**4a**
			Solvent	Temp. (°C)	Period (h)		
1	**1E**	A	xylene	135	4	92	99.5:0.5
2	**1E**	A	decane	135	4	94	99.4:0.6
3	**1E**	A	decane	148	14	90	37:63
4	**1Z**	A	decalin	180	1	46	22:78
5	**1Z**	A	decalin	180	5	39	31:69

The reaction of **1E** proceeded smoothly at ~135°C, though it was too slow in boiling THF (14% yield after 14 h). Satisfactory yield (92%) and syn-anti ratio (99.5:0.5) was obtained after 4h (entry 1). The excellent diastereoselectivity revealed both the exclusive formation of the Z-enolate **2E** from **1E** and the unique intervention of a chair-like conformation (**A**) in the transition state of the rearrangement. Choice of nonpolar solvent has little effect (entries 1,3), but prolonged heating caused extensive epimerization at the α-position of the carbonyl group (entry 3) (ref. 6).



A



B

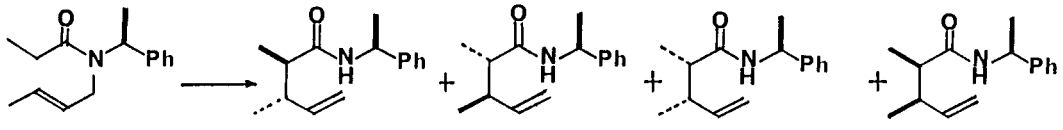
The rearrangement of **1Z** (ref. 4) required much higher temperature than for **1E**, and yet the yield and the ratio were poor after 1 h (entry 4), the reason presumably being steric in nature (cf. **B**). Prolonged heating not only changed the ratio but also decomposed the product **4**.

Although somewhat higher temperatures are required, the aza-Claisen rearrangement of amide enolates is superior to the Claisen rearrangement of ester enolates because of better yield and higher stereoselection.

Chiral induction

A trivalent nitrogen atom can have an extra alkyl group which can be used as a chiral auxiliary, in addition to the two groups participating in the rearrangement. Thus the aza-Claisen rearrangement of amide enolates can be utilized for the enantioselective synthesis of chiral acid derivatives unlike that of ester enolates.

In principle, the rearrangement of N-2(E)-butenyl-N-[(1S)-1-phenethyl]-propanamide (**6**) would give a diastereomeric mixture (**7**) of N-[(1S)-1-phenethyl]-2,3-dimethyl-4-pentenamides (designated as **7sS**, **7sR**, **7aS**, **and 7aR** as shown). While the diastereoselectivity (syn:anti) is determined by the factors described above, the diastereofacial selectivity, which results in the enantiomeric ratio (S:R) of the acids, the ultimate products, would be controlled by the chirality of the auxiliary. We have investigated the reaction of **6**.



6 **7sS** **7sR** **7aS** **7aR**

In addition to the Method A described above, Method B was introduced, in which amide enolate was prepared in toluene (or hexane) at -78°C in the presence of lithium hexamethyldisilazide (or LDA) (1.2-1.5 equiv.), and then heated in a sealed tube. The results are listed in TABLE 2 (ref. 7).

TABLE 2. Aza-Claisen rearrangement of N-2(E)-butenyl-N-[(1S)-1-phenetyl]-propanamide (**6**)

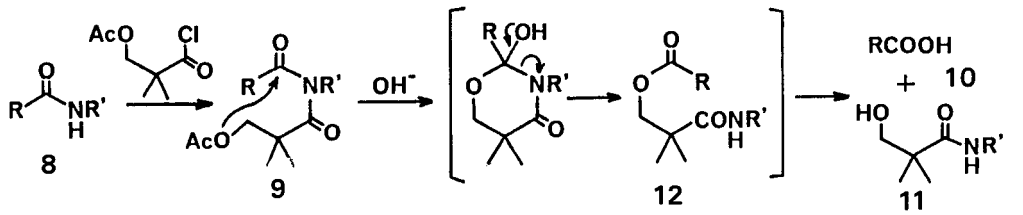
Entry	Method	Conditions		Isolated yield of **7**(%)	Diastereomeric ratio			
		Temp.(°C)	Period(h)		**7sS**	**7sR**	**7aS**	**7aR**
1	A	150	6	48	42.0	5.9	47.1	4.9
2	B (LDA)	120	6	68	91.8	8.2	—	—
3	B	120	6	85	91.5	8.5	—	—
4	B (hex)	120	71	71	91.6	8.4	—	—

As is seen in TABLE 2, no anti isomer was detected in Method B. The diastereoselectivity (S:R), however, remained at 11:1 (83% de).

HYDROLYSIS OF N-MONOSUBSTITUTED AMIDES VIA ACETOXYPIVALIMIDES

The classical procedures for the hydrolysis of amide linkage require severe conditions (strong bases or acids, and elevated temperature) incompatible with substrates having acid- or base-sensitive groups. Although many excellent methods have been developed for nonsubstituted and N,N-disubstituted amides (ref. 9), the available methods for the hydrolysis of N-monosubstituted amides seem to suffer from serious limitations. Since they were quite unsatisfactory in our hand to hydrolyze the N-substituted amides obtained above (ref. 10), we have developed another mild and efficient method of our own.

The present method consists of two steps: N-alkylcarboxamides **8** were converted to N-acyl-N-alkylacetoxypivalamides **9**, and then, taking advantage of much faster hydrolysis of imides than that of amides, and utilizing the intramolecular nucleophilic attack (N-O acyl migration), the desired amides bonds were selectively cleaved under mild conditions to give the correspending carboxylic acids **10** and N-alkylhydroxypivalamides **11** via acyloxy-pivalamides **12**.



The results are listed in TABLE 3. As a typical example (entry 2), N-butylcyclohexane-carboxamide (**8a**) was converted to the correspending acetoxypivalimide **9a** in 89% yield with acetoxypivaloyl chloride (2 equiv.) in CH_2Cl_2 (room temp., 2.5 h) in the presence of Et_3N (2 equiv.) and 4-N,N-dimethylaminopyridine (0.1 equiv.). The imide **9a** was then hydrolyzed in THF (room temp., 19 h) with 1M LiOH (2.2 equiv.) to give cyclohexanecarboxylic acid **10a** in 87% yield along with **8a**, the product of the alternative cleavage, in 10% yield.

TABLE 3. Two-step hydrolysis of N-monosubstituted carboxamides **8**

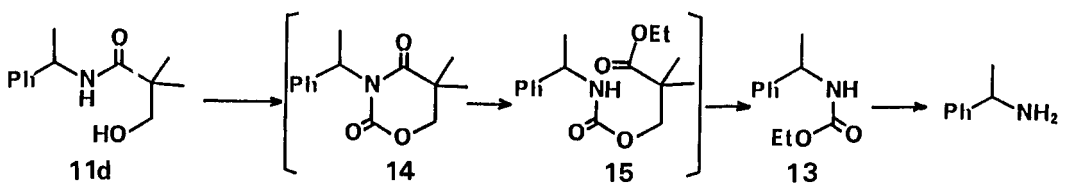
Entry	Amides **8**		Acylation		Hydrolysis	
	R	R'	Period (h)	Yield of **9** (%)	Period (h)	Yield of **10** (%)
1	c-Hex	$PhCH_2$	6	90	24	71
2	c-Hex	Bu	2.5	89	19	87
3	Pent	Bu	0.75	91	19	74
4	Ph	Bu	19[a]	99	19	84
5	c-Hex	1-Phenetyl	8[b]	92	24	89

[a]Three equiv. of acyl chloride and Et_3N were used.
[b]Five equiv. of acyl chloride and Et_3N were used.

The method can satisfactorily be applied to the straight chain (entry 3), branched chain (entries 1,2,5) and aromatic (entry 4) carboxamides. The sterically hindered amides such as N-1-phenethylcyclohexanecarboxamide, can also be hydrolyzed smoothly (entry 5)(ref. 11).

In order to test the mildness of the hydrolytic conditions, the amide **4** (syn:anti=99.5:0.5, entry 1, TABLE 1) was sujected to the reaction sequence. 2,3-Dimethyl-4-pentenoic acid **10c** obtained in 76% overall yield showed practically no indication of epimerization (syn:anti=99.2:0.8).

The recovery of amines is often desirable, especially when chiral amines are used in asymmetric synthesis. This can also be realized in two steps: For example, N-1-phene-thylhydroxypivalamide **11d**, the by-product of the hydrolysis (entry 5, TABLE 3), was converted to the carbamate **13** (diethyl carbamate (1.4 equiv.), NaH (2.8 eqiv.) in DMF, room temp., 21 h) in 89% yield, through the cyclic carbamate **14** (ref. 12). The carbamate was smoothly hydrolyzed by 48% NaOH (large excess) at 120° to give 1-phenethylamine in 80% yield.



Thus, the present reaction sequence was shown to have wide applicability to the hydrolysis of N-monosubstituted amides.

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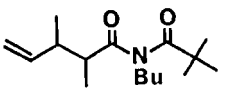
3. D.A. Evans in Asymmetric synthesis, J.D. Morrison ed., Academic Press, Orlando, 1984, Vol. 3, p. 1.
4. The compounds **1E** and **1Z** were prepared from N-butylpropanamide by the sequencial reactions with NaH in DMF and E-crotyl bromide (77% yield) or Z-crotyl tosylate (90% yield). The minor isomers present in the products were separated by SiO_2 impregnated with $AgNO_3$. The compound **6** was prepared from N- (1S)-1-phenethyl propanamide and E-crotyl bromide (60% yield). The purity was~100% in all cases.
5. While the syn:anti ratio of the product was determined by GLC after the conversion of **4** to the pivalimide **5** (pivaloyl chloride, Et_3N, 4-N,N-dimethylaminopyridine), their stereochemistry was established by the comparison of **5** with those obtained by the Claisen rearrangement of the corresponding ester enolates (ref.1).



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6. The reaction in polar solvents proceeded with poor selectivity (e.g. Compound **6** in THF at 120°C for 2 h gave the ratio **7sS**:**7sR** =79:21) and greater tendency of epimerization.
7. The diastereomeric ratio in **7** was determined by LC. The configuration of each diastereomers was established by 1) the conversion of **4s** to the mixture of **7sS** and **7sR**, and 2) the hydrolysis of **7sS** and subsequent ozonolysis of the product to (+)-2,3-dimethylsuccinic acid (ref. 8).
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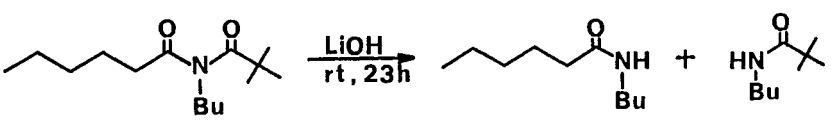
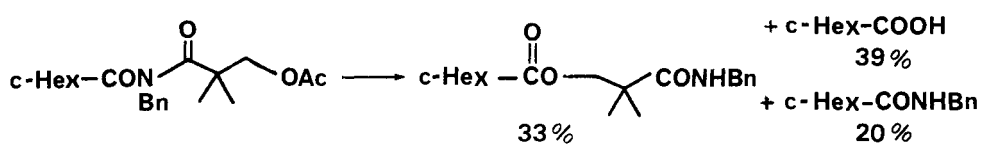
10. For examples, the sulfurane reagent (J.C. Martin and J.A. Franz, J. Am. Chem. Soc., **95**, 2017 (1973), **97**, 6137 (1975) is only applicable to benzamides. Grieco's two-step procedure (D.L. Flynn, R.E. Zelle, and P.A. Grieco, J. Org. Chem., **48**, 2424 (1983)) was very slow with α,β-unsaturated carboxamides and the formation of the t-Boc derivatives was unsuccessful with N-1-phenethylcarboxamides. In Sonnet's procedure (P.E. Sonnet and R.R. Heath, ibid., **45**, 3137 (1980); idem., J. Chem. Ecol., **8**, 41 (1982); P.E. Sonnet, J. Org. Chem., **47**, 3793 (1982)), the amine part can not be recovered. This is a substancial drawback when precious chiral amines are employed in asymmetric synthesis.
11. The participation of the neighboring hydroxyl group in the hydrolysis was verified by the following experiments: The hydrolysis of N-butyl-N-hexanoylpivalamide with no site of possible participation gave N-butylhexanamide in 79% yield under the same conditions as in entry 3, TABLE 3, revealing the preferencial nucleophilic attack on the "wrong" carbonyl group.



Furthermore, N-benzyl-N-cyclohexanecarbonyloxypivalamide was isolated (33% yield) along with hydrolysis products, when the reaction of N-benzyl-N-(cyclohexanecarbonyl)-acetoxypivalamide was quenched after 10 h.



12. When the reaction was quenched after 0.5 h, the carbamate **15** was isolated in 27% yield along with **13** (18% yield) and the starting **11d** (42% yield).