other useful organotitanium(IV) reagents.[11]

(11) For a review, see: Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1.

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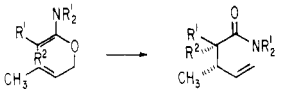
An Accelerated Diastereoselective Variant of the Amide Acetal Claisen Rearrangement

Summary: Salts derived from alkylation of propionamides or fluoroacetamides with methyl triflate or dimethyl sulfate reacted with the lithium alkoxide of (*E*)- or (*Z*)-2-buten-1-ol at room temperature to yield directly the product of 3,3-sigmatropic rearrangement of the corresponding N,O-ketene acetals.

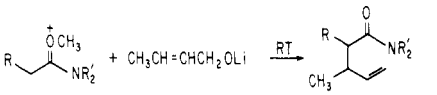
Sir: We have found that propionamides as well as fluoroacetamides may be utilized in a diastereoselective amide acetal Claisen rearrangement at room temperature. The Claisen rearrangement,[1] a powerful synthetic transformation, creates two new asymmetric centers diastereoselectively while concomittantly forming regio- and stereospecifically a new double bond. The sigmatropic rearrangement of N,O-ketene acetals, first developed by Eschenmoser,[2] preceded studies of the ynamine–Claisen rearrangement[3] where the reactive N,O-ketene acetal may be formed at much lower temperatures by treatment of the ynamine with an allylic alcohol.



In our development of new methods for the stereoselective synthesis of fluorinated molecules,[4] rearrangement of a fluorinated N,O-ketene acetal was an attractive approach. However, the necessary fluorinated ynamine was not synthetically accessible and the higher temperatures required for the amide acetal Claisen rearrangement appeared to prohibit the stereoselective formation of the fluoro N,O-ketene acetal by that route.

Three symmetric propionamides, *N*,*N*-dimethylpropionamide, *N*,*N*-diisopropylpropionamide, and *N*-propionylpyrrolidine, were examined in our initial studies. Following alkylation with dimethyl sulfate or methyl triflate, the amides were treated with the lithium salt of (*E*)- or (*Z*)-2-buten-1-ol. After as little as 14 h at room temperature, the rearranged amides were isolated in good yield[5] (See Table I). The observed diastereoselectivity

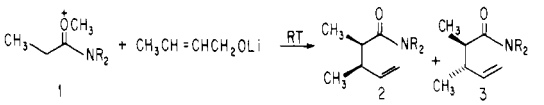
Table I. Amide Acetal Claisen Rearrangement of Propionamides and Fluoroacetamides



amide	alcohol	time,[a] h	diastereoselectivity[b]	yield,[c] %
			2:3	
1a	*E*	18	>10:1	51
1a	*Z*	16[d]	1:8[e]	79[f]
1b	*E*	14	17:1[e]	82
1b	*Z*	18	<1:10	30
1b	*E*	90	>10:1	70[g]
1b	*Z*	21[d]	<1:10	59[f]
1c	*E*	14	15:1[e]	45
1c	*E*	90	>10:1	44[g]
1c	*Z*	25[d]	<1:10	19[f]
			7:8	
5a	*E*	20	1:1.6	50
5a	*Z*	20	2.9:1	23
5b	*E*	14	1:2.7	87
5b	*Z*	18	5.1:1	77
5c	*E*	14	1:5.3	49
5c	*E*	14	1:4.8	40
5c	*E*	70	1:2.6	78
5c	*Z*	70	3.1:1	27
5c	*E*	18[h]	1:1.3	89

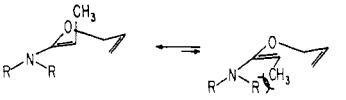
[a] Temperature 25 °C. [b] Determined by NMR spectroscopy at 7.04 T. [c] Determined by gas chromatographic analysis. [d] Temperature 67 °C. [e] Decoupled ^{13}C NMR spectra determined with NOE suppression and 50-s delay. [f] 0.0011 mol of alkoxide. [g] 0.0042 mol of alkoxide. [h] Temperature 42 °C.

was never worse than 8:1 and was as high at 17:1 in some cases as determined by ^1H and ^{13}C NMR spectroscopy.



a. R = CH_3
b. R = $(CH_2)_4$
c. R = $CH(CH_3)_2$

Stereospecificity in the amide acetal Claisen rearrangement has been suggested to result in part from unfavorable steric interactions between the alkyl substituents on nitrogen and the β-substituent of the enamine.[6] The *Z* ketene acetal was also reported to be the thermodynamic intermediate product in the boron trifluoride etherate promoted ynamine–Claisen rearrangement.[3a] With the



less sterically demanding fluorine, it was not clear if selectivity would be possible. *N*,*N*-Dimethylfluoroacetamide, *N*-(fluoroacetyl)pyrrolidine, and *N*,*N*-diisopropylfluoroacetamide were prepared as previously described.[7] Al-

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(2) Meerwein, H.; Florian, W.; Schon, N.; Stopp, G. *Justus Liebigs Ann. Chem.* **1961**, *641*, 1–39. (b) Wick, A. E.; Felix, D.; Steen, D.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425–2429. (c) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030–1042. (d) Sucrow, W.; Richter, W. *Chem. Ber.* **1971**, *104*, 3679–3688.

(3) (a) Bartlett, P. A.; Hahne, W. F. *J. Org. Chem.* **1979**, *44*, 882–883. (b) Ficini, J.; Barbara, D. *Tetrahedron Lett.* **1966**, 6425–6429.

(4) (a) Welch, J. T.; Seper, K.; Eswarakrishnan, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720–4721. (b) Welch, J. T.; Eswarakrishnan, S. *J. Chem. Soc., Chem. Commun.* **1985**, 186–188. (c) Welch, J. T.; Seper, K. *Tetrahedron Lett.* **1984**, *25*, 5247–5250. (d) Welch, J. T.; Samartino, J. S. *J. Org. Chem.* **1985**, *50*, 3663–3665.

(5) **Typical Procedure**: To a magnetically stirred three-necked round-bottom flask under an inert atmosphere, containing 5 mL of anhydrous THF or ether, was added 0.003 mol of (*E*)- or (*Z*)-2-buten-1-ol followed by 0.003 mol of methyl lithium (1.55 M solution in diethyl ether) at room temperature. After the mixture was stirred for 5 min, 0.003 mol of the O-alkylated amide salt, prepared by treatment of the neat amide with a stoichiometric amount of methyl trifluoromethanesulfonate, was added in 4 mL of THF or CH_2Cl_2. The mixture was allowed to stir at room temperature for the specified time, was diluted with 20 mL of CH_2Cl_2, was washed with three 20-mL portions of saturated sodium bicarbonate and one 20-mL portion of saturated sodium chloride solution, was dried over anhydrous magnesium sulfate, and was concentrated in vacuo.

(6) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227–232.

(7) Welch, J. T.; Eswarakrishnan, S. *J. Org. Chem.*, in press.

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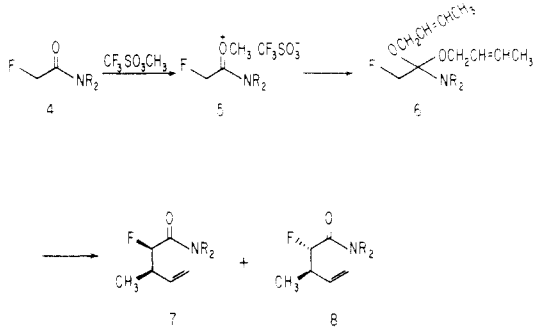
kylation of the fluoroacetamides with dimethyl sulfate[8] failed; presumably, fluorination diminishes the nucleophilicity of the carbonyl oxygen. Alkylation of **4a** with more reactive methyl triflate proceeded smoothly. In

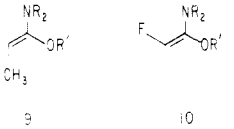


contrast to the ease with which **1a** formed the reactive N,O-ketene acetal, treatment of the O-methylated *N,N*-dimethylfluoroacetamide salt **5a** with 2 equiv of the lithium salt of (*E*)- or (*Z*)-2-buten-1-ol resulted in a 76% yield of the acetal **6a**. Heating this acetal at 80 °C for 7 h resulted in a nearly quantitative formation of the rearranged amides **7a** and **8a** but with poor diastereoselectivity. Reaction of **5a** with 3 equiv of the lithium salt of (*E*)- or (*Z*)-2-buten-1-ol (prepared by treatment of the alcohol with a slight excess of methyl lithium) resulted in the direct formation of **7a** and **8a** after 20 h at room temperature. The relative diastereoselectivity was determined by ^{19}F NMR in these cases.

In order to increase the steric demand of the *N*-alkyl substituents and therefore to increase the stereoselectivity of the N,O-ketene acetal formation, both pyrrolidinyl (**4b**) and diisopropyl fluoroacetamides (**4c**) were methylated with methyl triflate and were treated with the lithium alkoxides. In both cases the alkylated amides were converted into N,O-ketene acetals and rearranged in 12–70 h at room temperature directly to the amides **7** and **8** in good to fair yields with modest improvements in the diastereoselectivity. The acetals **6b** or **6c** were not isolated from the product mixture.

When the isolated amides were resubjected to the reaction conditions there was no change in the ratio of the diastereomers formed. The product amides were not further epimerized under the reaction conditions.[9]

The rearrangement products of both the (*E*)- and (*Z*)-2-buten-1-ol with **1b** were halolactonized with iodine in dimethoxyethane.[10] Characterization of the resultant iodolactones by ^{13}C NMR spectroscopy[11] confirmed the assignment of structures of the respective major products as **2b** and **3b**, the predicted products of the rearrangement of the thermodynamically favored *Z* N,O-ketene acetal **9**.



The amides formed on rearrangement of **5b** with (*E*)- and (*Z*)-2-buten-1-ol were iodolactonized under the same conditions. Comparison of the ^1H and ^{13}C NMR spectra of these products with previously determined spectra[4d,12] indicated the *E* N,O-ketene acetal **10** was being formed preferentially. The diminished steric demand of fluorine is apparently offset by stereoelectronic factors in the formation of the ketene acetal.

A comprehensive investigation of the effect of solvent and stoichiometry on the yield and diastereoselectivity of the rearrangement is in progress. The results of a study of the rearrangement of dissymmetric fluoroacetamides will be reported shortly.

Acknowledgment. Financial support of this work by the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Supplementary Material Available: Analytical and complete spectral data for all new compounds (8 pages). Ordering information is given on any current masthead page.

(8) (a) Bredereck, H.; Effenberger, F.; Bergerlin, H. P. *Chem. Ber.* **1964**, *97*, 3081–3087. (b) Bredereck, H.; Effenberger, F.; Simchen, G. *Chem. Ber.* **1963**, *96*, 1350–1355. (c) Salomon, R. G.; Raychaudhuri, S. R. *J. Org. Chem.* **1984**, *49*, 3659–3660.

(9) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327–4331.

(10) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079–1085.

(11) For the iodolactone from **2b**: ^{13}C NMR ($CDCl_3$) δ 178.36, 83.25, 38.00, 37.53, 13.51, 10.13, 5.45. For **3b**: ^{13}C NMR ($CDCl_3$) δ 178.18, 79.80, 40.83, 40.38, 13.74, 12.60, 1.81.

(12) For the iodolactone from **7b**: ^{13}C NMR ($CDCl_3$) δ 170.5 ($J_{C,F}$ = 22.2 Hz), 88.21 ($J_{C,F}$ = 201.5 Hz), 77.63 ($J_{C,F}$ = 7.0 Hz), 37.28 ($J_{C,F}$ = 18.1 Hz), 14.01, 5.17. For **8b**, ^{13}C NMR ($CDCl_3$) δ 169.63 ($J_{C,F}$ = 21.2 Hz), 91.29 ($J_{C,F}$ = 197.4 Hz), 79.85 ($J_{C,F}$ = 9.1 Hz), 43.07 ($J_{C,F}$ = 18.2 Hz), 13.99, 4.04.

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Z Stereoselective Wittig Olefination of 2-Oxygenated Cyclohexanones

Summary: Protected 2-hydroxy- and 2,3-epoxycyclohexanones provided (*Z*)-ethylidenecyclohexanes in a highly stereoselective manner upon their reactions with ethylidenetriphenylphosphorane in both the lithium base and the lithium-free conditions of the Wittig reaction.

Sir: Allylic alcohols, allylic epoxides and their equivalents are highly versatile intermediates to which numerous regio- and stereocontrolled methods can be applied for further synthetic manipulations.[1] Presumably the most obvious general synthetic route to these compounds would involve a direct Wittig reaction of the 2-oxygenated ketones. While Still[2] reported the synthesis of *Z* trisubstituted allylic alcohol systems using the Wittig reaction, this aspect of the Wittig reaction has not been well documented in the literature, especially for 2-oxygenated cyclic ketones. We wish to report that the lithium-free Wittig reaction of various 2-oxygenated cyclohexanones with ethylidenetriphenylphosphorane yields almost exclusively the trisubstituted allylic oxygenated olefins with *Z* stereochemistry.

The Wittig reaction of protected 2-hydroxycyclohexanones with ethylidenetriphenylphosphorane was examined with particular emphasis on the stereoselectivity of the reaction under both the lithium-base[3] and lithium-

(1) Reviews: (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (c) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (d) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589. See also: (e) Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4257. (f) Marino, J. P.; Abe, H. *Synthesis* **1980**, 872. (g) Ziegler, F. E.; Cady, M. A. *J. Org. Chem.* **1981**, *46*, 122. (h) Marino, J. P.; Abe, H. *J. Am. Chem. Soc.* **1981**, *103*, 2907. (i) Visnick, M.; Strekowski, L.; Battiste, M. *Synthesis* **1983**, 284.

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