ASYMMETRIC DIELS-ALDER REACTIONS OF CHIRAL ALKOXY IMINIUM SALTS

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Abstract: The optically active vinyl trimethylsilyloxy iminium salts, prepared from 8 and 14ab, were reacted with cyclopentadiene to give the optically active amides 15 and 16ab in high yield and with good diastereoselectivity.

A major goal in synthetic organic chemistry today is the easy and efficient production of optically active materials from prochiral precursors by asymmetric induction. Several recent publications have prompted us to report our preliminary results regarding the Diels-Alder reaction of dienophiles activated by an adjacent positive center.

In 1976, Baum and Viehe reported the first cycloadditions of acetylenic iminium salts such as 1 to afford the cycloadducts 2 in good to excellent yields. Hydrolysis of the cycloadducts under mild conditions gave the ester 3.

These alkoxy iminium salts exhibit substantially increased reactivity in Diels-Alder reactions. In fact, the alkoxy iminium group was found to be more activating than the corresponding acid chloride, nitrile, aldehyde, amide, or ester group. It occurred to us that a chiral amide such as 4 might allow for asymmetric induction in Diels-Alder reactions. Hydrolysis of the resulting cycloadduct should provide stereoselectively the bicyclic ester 6 and allow recovery of the chiral auxiliary in a single operation. To our knowledge there are no published reports concerning the Diels-Alder reaction of simple vinyl alkoxy iminium salts, such as 5. Furthermore there are no reports concerning the use of chiral amines in the preparation of acetylenic or vinylic alkoxy iminium salts. Examination of Dreiding models of 5 suggest that bulky cyclic amines would offer the best opportunity for asymmetric induction.

The chiral pyrrolidine 7 was prepared by known methods and acylated with acryloyl chloride and Hünig's base at -78 °C in ether. Removal of the cooling bath and stirring for 1h gave the required acrylamide 8 in 95% yield. Exposure of acrylamide 8 to triethyloxonium tetrafluoroborate at room temperature for 2 h provided 9. The solution was cooled to 0 °C and treated with cyclopentadiene. After 12h the reaction mixture was quenched with water. Chromatographic separation furnished 11 and 12 in a ratio of 2.3:1 in 84% yield. Hydride reduction of 12 afforded the known alcohol 13, the optical rotation of which corresponded to an enantiomeric excess of 85%. The high degree of diastereoselectivity coupled with the high chemical yields achieved in this cycloaddition process were very encouraging. It was disappointing however to find that the hydrolysis of cycloadduct 10 gave mixtures of amide and
ester products. Generally the hydrolysis of alkoxy iminium salts gives ester and amine products, but as the steric hindrance of the alkoxy iminium salt increases, various mixtures of amide, alcohol, amine and ester products are observed. All attempts to convert the cycloadduct 10 to a single product via hydrolysis (neutral, acidic, or basic), assisted hydrolysis [H2O, B(OMe)3/MeOH, AcCl/H2O, MeI/H2O], reduction [NaBH4, DIBAL, LiEt3BH, Et3SiH, K/18-Crown-6, Na(Hg), Na(nap)], or nucleophilic attack (ROH, ROH/H+, ROH/ROH, RSH, KO2, H2S/pyridine, pyridine, Na2O2, H2O2) were unsuccessful. François and Gittos reported that alkoxy iminium salts derived from morpholine afforded exclusively ester and amine products upon hydrolysis, whereas the iminium salts of other secondary amines gave mixtures of products. We prepared a series of chiral morpholinyl acrylamides 14 and examined their Diels-Alder chemistry. Unfortunately all attempts to convert the cycloadducts to a single product failed, again presumably due to the steric hindrance associated with the cycloadduct.

It is known that the hydrolysis of trimethylsilyloxy iminium triflates cleanly regenerates the amide functionality. The possibility of using the the trimethylsilyl triflate salts of acrylamides 8 and 14 was explored and was found to give the desired amides such as 15 and 16 in high yields and as the sole reaction products. The optimum reaction conditions were concentrations of 2.0 M or greater in methylene chloride and temperatures between -30 and -40 °C. The high diastereoselectivity, good endo/exo ratios, and excellent chemical yields associated with this cycloaddition process are very promising. However the removal of the chiral auxiliary remained. The C-N cleavage of hindered tertiary amides is often not a trivial task. Of all the procedures available for amide cleavage, only the method of Roush proved successful. Treatment of 15 with NBS in a mixture of 50% aqueous AcOH/THF at
room temperature provided the bromolactone 17 in 88% yield. The chiral auxiliary 7 was recovered in 65% yield. Zinc and acetic acid reduction of 17 gave the desired acid 18 in 92% yield. The optical rotation of 18 corresponds to an enantiomeric excess of 86% with the S configuration predominating. Compound 19 obtained from 16a by the same two steps was found to be predominately the R isomer in 88% optical purity.

The stereochemistry of the products obtained from the cycloaddition reaction can be rationalized by considering transition states 20 and 21. In transition state 20 the diene approaches in an endo fashion from the more sterically hindered side of the dienophile, while in transition state 21 the diene again approaches in an endo fashion but from the less sterically hindered side of the dienophile. Transition state 21 is clearly lower in energy than transition state 20, and leads to the observed Diels-Alder product 15 with the S configuration α to the carbonyl group. The same rationale can be applied to the dienophiles 14ab where the alkyl groups of the chiral morpholines are on the opposite face of the dienophile resulting in Diels-Alder products with an R configuration. Both the R and S acids 18 and 19 are readily prepared in optically active form by using either the morpholine or pyrrolidine chiral auxiliaries. We are now exploring the scope and generality of this cycloaddition process. However our preliminary results show that other dienes, e.g., isoprene and 1,3-cyclohexadiene, work less well with these dienophiles and thus this process may be limited to very reactive dienes, such as cyclopentadiene. We will report on these studies in full in due course.

Acknowledgement: We thank the National Institutes of Health (GM-31349) for their generous financial support.

References and Notes
1. Presented at the 196th ACS meeting in Los Angeles, CA, September, 1988, ORGN 230.


11. Typical Diels-Alder reaction: (3S)-3-Benzylmorpholinyl bicyclo[2.2.1]hept-5-en-2-carboxamide 16a: TMS triflate (0.137 mL, 0.709 mmol) was added to a 0 °C solution of (3S)-3-benzylmorpholinyl 2-propenamide 14a (0.149 g, 0.644 mmol) in 0.25 mL CH$_2$Cl$_2$. The cooling bath was removed and the clear solution was stirred at room temperature for 30 min, cooled to -40 °C (CO$_2$/CH$_3$CN) and treated with cyclopentadiene (0.106 mL, 1.29 mmol, precooled to -78 °C). The clear reaction mixture was held at -30 °C overnight (~15h). The purplish reaction mixture was quenched with saturated NaHCO$_3$, extracted with CH$_2$Cl$_2$ and concentrated via rotary evaporator onto SiO$_2$ (230-400 mesh, ca. 1 g SiO$_2$/mmol dienophile). The free-flowing powder was loaded onto a chromatography column packed with SiO$_2$ (230-400 mesh) and pet. ether. The column was eluted with 3 column volumes of pet. ether to remove the dimer of cyclopentadiene, followed by elution with 50% EtOAc/pet. ether to provide 0.1863 g (97%) of the title compound as a clear viscous oil, which solidified to a white waxy solid. mp 90-2°C. $^1$H NMR (CDCl$_3$, 200 MHz): δ 7.389-7.031 (5H, m, aromatics), 6.250-5.5 14 (2H, m, CH=CH), 4.703-4.281 (1H, m), 4.109-3.281 (5H, m), 3.218-2.469 (5H, m), 1.930-1.875 (1H, m), 1.609-1.109 (4H, m). IR (neat): 3060, 2970, 2860, 1735, 1635, 1498, 1450, 1415, 1370, 1335, 1280, 1255, 1220, 1080, 1060, 1055, 1030, 1010, 985, 900, 840, 748, 710, 703 cm$^{-1}$. MS (EI, m/e (relative intensity)): 297 (M$^+$, 30), 206 (62), 140 (20), 121 (19), 93 (22), 86 (100), 55 (34). Exact mass calculated for C$_{19}$H$_{23}$N$_2$O$_2$: 297.1730; found: 297.1729. VPC (12.5 m x 0.22 mm SE-30 column, 1.5 mL/min., 15 psi, 50/1 split ratio, 200 °C): exo cycloadducts elute as a single peak $R_f$ = 11.42 min, minor endo cycloadduct $R_f$ = 11.92 min; major endo cycloadduct $R_f$ = 12.42 min, endo/exo = 13, dec of endo products 92%. TLC: $R_f$ (50% EtOAc/Pet. Ether) 0.40, visualized with I$_2$. W. R. Roush, J. Am. Chem. Soc. 1980, 102, 1390.

13. MM2 calculations on the analogue of 9 with C in place of N indicated that the geometry about the double bond shown, namely ethoxy trans to the substituted carbon, was by far the more stable one and further that the transoid conformation of the diene unit was more stable than the cisoid one. Therefore we believe that the transition states 20 and 21 are reasonably accurate representations of the transition state of the reaction.

(Received in USA 13 January 1989)