ISOXAZOLIDINE BASED NEW CHIRAL AUXILIARY FOR ASYMMETRIC SYNTHESIS

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Abstract

The diastereomerically single chiral sulfonyl substituated isoxazolidine derivative (+)-**1** (1) was prepared from L-phenylalanine via practical procedures. The acrylamide (-)-**2** underwent dipolar cycloaddition reaction with nitrones and an azide with a high level of diastereoselectivity. The facial selectivity observed was consistent with the geometry optimized steric energies of the cycloadducts disclosed by MM2 calculations.

Introduction

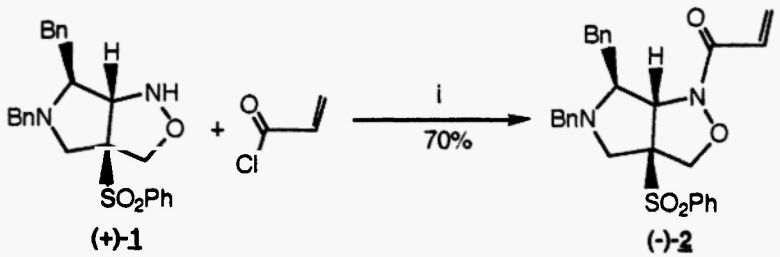
The importance of chiral auxiliaries to control the stereoselectivity of the carbon-carbon or carbon-heteroatom bond forming reactions is an indispensable strategy in asymmetric synthesis and in the rapid expansion of this area, the development of efficient chiral auxiliaries and reagents has been a matter of the most importance (2-4). Until now, most chiral auxiliaries and reagents have been derived from naturally occuring chiral compounds, but limitations in their structural modification are sometimes an obstracle in improvement of the selectivity of asymmetric reactions (5-6). Therefore, the development of artificial chiral compounds, which could be suitably designed for each asymmtric process, has recently been drawing considerable attentions, and in fact some successful examples have been reported (7-11).

Herein we wish to report the application of (+)-**1** (1) as an efficient chiral auxiliary in the asymmetric dipolar addition of nitrones and an azide to its N-acryloyl derivative (-)-**2**. In addition the geometry optimized steric energies calculated by MM2 are discussed.

Results and Discussion

The acrylamide (-)-**2** was synthesized by the deprotonation of the amine function of (+)-**1** followed by addition of acryloyl chloride. The yield was rather low due to the propensity of the acid chloride towards polymerization under the applied reaction conditions (12). To improve the yield, several conditions were surveyed. The best to result, a 70% isolated yield, was obtained using exactly

the two equivalent of triethylamine and acryloyl chloride and running the reaction in methylene chloride at -40°C for 30 min (Scheme 1).

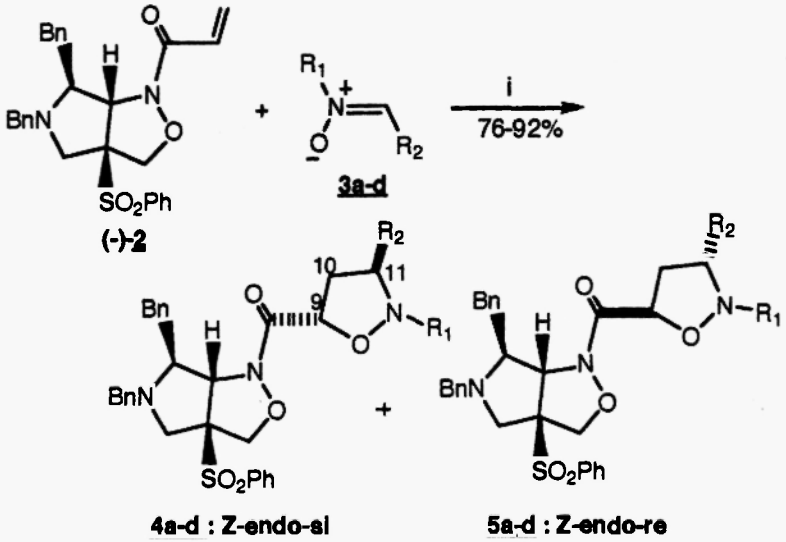


Reagents and Conditions : i) Et_3N/CH_2Cl_2, -40°C

Scheme 1

Nitrone Additions

The preparation of optically active isoxazolidines via the asymmetric 1,3-dipolar cycloaddition of nitrones has been extensively utilized in the total synthesis of diverse natural products (13) e.g., alkaloids (14), amino sugars (15), β-lactams (16) and antibiotics (17). In fact, the asymmetric nitrone-alkene cycloadditions involve either chiral nitrones (18), chiral alkenes (19) or chiral catalysts (20). In the context of our ongoing interest in the use of chiral α,β-unsaturated dipolarophiles, we wish to describe the facial selectivity observed during the cycloadditions of a series of nitrones **3a-d** onto (-)-**2**. The nitrones **3a-d** were prepared according to the reported procedures (21,22). The reaction between (-)-**2** and the nitrones were performed in toluene at reflux temperature (23). The cycloaddition afforded in all cases two diastereomeric isoxazolidines **4a-d** and **5a-d** (Scheme 2) in good yields. The ultimate outcome is summerized in the Table 1. The spectroscopic properties of the cycloadducts disclosed their structural features as illustrated in Scheme 2.



Reagents and Conditions : i) Toluene, reflux

Scheme 2

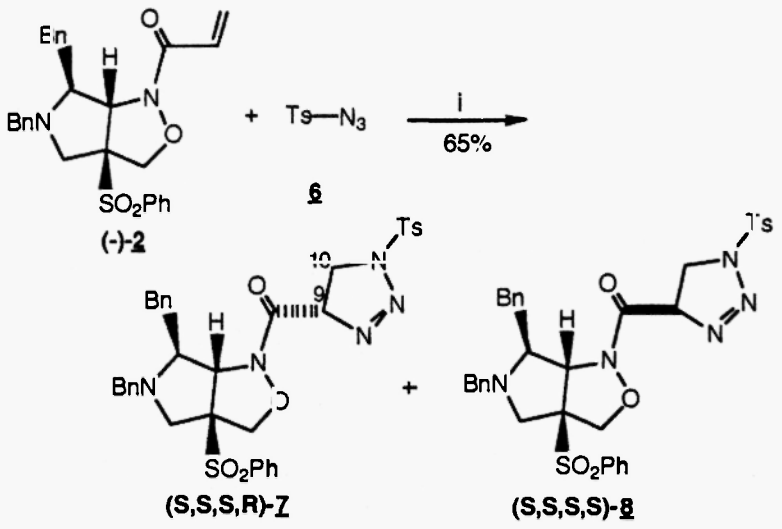
Table 1. Asymmetric 1,3-dipolar cycloaddition of nitrones **3a-d** with **(-)-2**

Nitrone	R_1	R_2	Adduct (major)	Adduct (minor)	%Yield (total)	%de (major)
3a	Ph	(p-Cl)Ph	**4a**	**5a**	76	>96 [a,b]
3b	Bn	Ph	**4b**	**5b**	88	30 [c]
3c	Ph	Naphthyl	**4c**	**5c**	82	>96 a,b
3d	Ph	Ph	**4d**	**5d**	92	>96 a,b

[a] The de values were determined by ^{1}H NMR spectroscopy (Bruker DRX 400 MHz spectrometer), in which no peaks corresponding to the other diastereomers were observed.
[b] After purification
[c] The de value was determined by HPLC analysis JASCO (Gulliver) LCSS 905

Accordingly the protons located at H10 on the new isoxazolidine ring appeared as multipletes at δ=4.16-4.25 ppm in compound **4a**, which outlined the regiochemical information of the cycloaddition process. The cycloaddition of the nitrone **3a** with (-)-**2** afforded a mixture of two diastereomeric isoxazolidines **4a** and **5a** in 76% total yield. The diastereomeric ratio obtained was 85:15 by HPLC and **4a** was purified by column chromatogrphy and whose structure was recognized by NMR, notably which displayed a doublet of doublets for proton H9 at δ=2.78 ppm with coupling constants *J*= 7.34 and 7.14Hz and H11 at δ=3.10 as a doublet of doublets with coupling constant *J*=6.55 and 6.95Hz. Similar results were obtained for cycloadditions of C-phenyl-N-benzylnitrone **3b**, C-naphthyl-N-phenylnitrone **3c** and C,N-diphenylnitrone **3d**. The stereochemical outcome, for example, in **4a** of the newly formed stereogenic centers, C9 and C11, were examined based on extensive 2D NMR (C-H COSY, H-H COSY and NOESY) inverstigations. The stereochemical courses could be rationalized by the inspection of the transition state models. Fundamentally, the C9 stereogenic center is governed by the facial selectivity and the C11 stereogenic center is related to the topographical selectivity. Among the four possible transition states, the major **4** products resulted from the **Z-endo** tansition state of the cycloadition process. This transition state is stabilized by the favorable secondary orbital interactions between the molecular orbitals of the nitrone nitrogen and the carbonyl carbon, which minimized the steric or electronic encumbrance between the incoming nitrone and one of the sulfonyl oxygens in the chiral dipolarophile. The obtained π-face (**si**-face) selectivity could be assigned by the shielding due to the repulsive interaction between the dipolar oxygen and the sulfonyl moiety. In addition, the steric energies calculated by MM2 are consistant with the observed experimental results. Accordingly, among the four possible conformations, the conformer having the lowest geometry optimized steric energies (9.1713 kcal/mole) resembled structure **4** (Scheme 2). In a similar experiment, Curran's group experienced the identical conformational preferences (24).

Azide Addition



Reagents and Conditions : i) $CHCl_3$/reflux (in dark).

Scheme 3

The dipolar cycloaddition of azides with an olefin leads to the formation of triazoline skeletons which are fundamentals for synthesizing series of natural products (25), e.g., (-)-slaframine (26), (+)-crotanecine (27). In this study the tosyl azide **6** was prepared by displacement of the chloride function from tosyl chloride by the azide ion in acetone at -20°C (28). The dipolar cycloaddition of the azide **6** with the dipolarphile (-)-**2** proceeded smoothly in absence of light in boiling chloroform to afford a diastereomeric mixture of cycloadducts **7** and **8** in 65% total yield (Scheme 3) (29). The obtained diastereomeric ratio was 77:23 (%de 54) as determined by the HPLC analysis. It was impossible to purify the major diastereomer **7** as a single compound, but purification achieved up to a trace of **8** as a contaminant by column chromatography, whose (**7**) NMR chemical shifts and coupling patterns of H10 disclosed the regiochemistry of the cycloaddition reaction. This result agreed with the structure represented in Scheme 3, notably H10 displayed as multipletes at δ=4.09-4.12 ppm. The molecular model inspection disclosed that an *endo* attack could build both the **R** and **S** configurations of the C9 stereogenic center, but the **endo-si** face mode could produce only **R**. On the other hand the **endo-re** face attack is difficult due to the face shielding exerted by the *cis*-fused rigid bicyclic system of the auxiliary and the electronic repulsion between the sulfonyl oxygen and terminal nitrogen of the azide group. Therefore the obvious major diastereomer corresponded to the configuration of **7** as ellustrated in Scheme 3.

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(23) (a)H. Ina, M. Ito, C. J. Kibayashi, *J. Org. Chem.* **61**, 1023 (1996): (b)A solution of the nitrone **3a** (1.4 mmol) in anhyd. toluene (10 mL) was added to a solution of (-)-**2** (0.7 mmol) in anhyd. toluene (30 mL) at r.t. under N_2. The reaction mixture was refluxed for 16 h, the solvent was evaporated and the residue was then chromatographed on silica gel column (hexane/EtOAc, 3:1) to afford **4a** and **5a** as a diastereomeric mixture (colored syrup) (Scheme 2 and Table 1) in 76% total yield. The major isomer **4a** was purified by column chromatography and analyzed (>96% de after purification). MS : *m/z* (M^++1) 719. IR(neat): ν= 3060, 3020. 2980, 2850 1680, 1620, 1550, 1480, 1450, 1380, 1360, 1350, 1300, 1240, 1150, 1100, 1090, 1050, 950, 940, 750, 700, 680 cm-1.1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.10-1.45 (m,4H), 2.17 (d, 1H, *J*=1.28Hz), 2.18-2.27 (m,5H), 2.78 (dd,1H, *J*=7.34, 7.14Hz), 3.10(dd,1H, *J*=6.55,6.95 Hz), 3.78-3.91 (m, 4H), 4.16-4.25(m,2H) 6.79-7.23 (m,19H) 13C NMR (100.62 MHz, DEPT, $CDCl_3$): δ=29.35 (CH_2), 37.73 (CH_2), 54.29 (CH), 54.40(CH), 54.55(CH_2), 56.26(CH_2), 58.43(CH), 67.15 (CH_2), 70.47(CH), 78.43 (C), 126.35-137.50 (Ph), 135.5 (Ph-ipso), 134.3 (Ph-ipso), 135.1(Ph-ipso), 135.8 (Ph-ipso), 136.36(Ph-ipso),137.36 (SO_2Ph-ipso), 158.9 (C=O).

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(29)A solution of tosyl azide **6** (1.0 mmol) in anhyd. $CHCl_3$ (10 mL) was added to a solution of (-)-**2** (0.7 mmol) in anhyd. $CHCl_3$ (20 mL) at r.t. under N_2 then the resultant system was refluxed for 6 h in the absence of light. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel columns (hexane/EtOAc, 3:1) to afford **7** and **8** as a diastereomeric mixture (brown syrup) (Scheme 3) in 65% total yield. The diastereomeric ratio obtained was 77:23 (%de 54). The major diastereomer **7** was purified up to a trace of **8** as a contaminant by column chromatography, which (**7**) was then subjected to spectroscopic analysis. HRMS (FAB): *m/z* (M+1) calcd for $C_{35}H_{36}N_5O_6S_2$: 686.2013, found: 686.2014. IR(neat): ν= 3050, 3010 2990, 2860, 2110, 2100, 1650, 1680, 1590, 1460, 1450, 1360, 1320, 1310, 1300, 1250, 1140, 1100, 1050, 1040, 950, 940, 750, 700, 680 cm-1.1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.24 (s,3H), 2.02 (d,1H, *J*=10.2Hz), 2.25-2.65 (m, 3H), 2.85-2.96 (m, 2H), 3.05-3.15 (m,2H), 3.25-3.45 (m, 2H), 3.49-3.59 (m, 2H), 4.09-4.12 (m, 1H, *J*=9.2Hz), 6.89-7.32 (m,19H) 13C NMR (100.62 MHz, DEPT, $CDCl_3$): δ=14.19 (CH_3), 36.05 (CH_2), 55.81 (CH_2), 56.67 (CH_2), 60.38 (CH_2), 70.87 (CH), 75.46 (CH_2), 76.72(CH), 81.73(CH),125.65-130.50 (Ph), 135.5 (Ph-ipso), 134.3 (Ph-ipso), 135.1(Ph-ipso), 135.8 (Ph-ipso), 137.36 (SO_2Ph-ipso), 158.45 (C=O).

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