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Aza Diels–Alder reactions of sulfinimines with the Rawal diene

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Abstract—The aza Diels–Alder reaction of optically active sulfinimines with the Rawal diene leads to enantiomerically enriched dihydropyridones with ees up to 90%. The reaction was catalyzed by TMSOTf. The best results were obtained using 10-isobornylsulfinimines. Removal of the sulfinyl auxiliary occurred during workup of the reaction mixture. The reaction most likely proceeds via a stepwise mechanism. The addition of lithium 4-*N*,*N*′-dimethylamino-1,3-buten-2-olate to sulfinimines, followed by hydrolysis, gave dihydropyridones in lower yields and with opposite stereochemistry.

1. Introduction

The aza Diels–Alder reaction is a well established method for the synthesis of derivatives of tetrahydropyridine.[1] The main methodology involves the cycloaddition of imines with dienes. This type of reaction can usually only be performed with reactive dienes such as Danishefsky's diene or using imines substituted with an electron withdrawing group. The presence of Lewis acid is often necessary. The development of an asymmetric version of the hetero-Diels–Alder reaction is the biggest challenge.[2] Several chiral imines prepared from optically active amines,[3] 1,2-amino alcohols,[4] α-aminoacids,[5] aminosugars[6] have been used in such reactions as dienophiles. However, the removal of a chiral auxiliary from the nitrogen atom is often difficult. Such a drawback does not occur in the case of the sulfinyl group, which can also serve as a powerful chiral auxiliary.[7] Especially useful are *N*-sulfinyl imines (sulfinimines), which appeared to be excellent substrates for the stereoselective synthesis of amines, β-aminoacids, aziridines, aminoketones, etc.[8] To the best of our knowledge only α,β-unsaturated sulfinimines have been used as dienes in aza Diels–Alder reaction under high pressure.[9]

2. Results and discussion

Our earlier experience in the reaction of sulfinimines with silyl nucleophiles prompted us to investigate cycloaddition of silyloxy dienes. Since the Danishefsky diene was not reactive, we tried to use 1-dimethylamino-3-*t*-butyldimethylsiloxy-1,3-butadiene **2**. This diene was developed by Rawal et al. in 1997.[10] It was shown that several classes of dienophiles including imines, react easily with the Rawal diene.[11] Herein, we report the use of optically active sulfinimines in this type of reaction. Diene **2** was prepared from 4-(dimethylamino)-3-buten-2-one according to an original procedure.[10] The reaction of 10-isobornylsulfinimines[12] **1a–e** with diene **2** in CH_2Cl_2 at −70 °C gave the expected dihydropyridones **3** in good yields (Scheme 1 and Table 1).

The reaction only takes place in the presence of Lewis acids, preferably TMSOTf. The use of BF_3 etherate gave low yields. Two methods were developed. 10-Isobornyl and 8-menthylsulfinimines[13] **1a–f** gave product **3** immediately after quenching the reaction mixture with water (Method A). In the case of *t*-butyl and *p*-tolylsulfinimines, **1g–h** open chain products **4** and **5** were obtained and an additional cyclization step using acid was needed (Method B). We suspect that products **3a–d** are formed via a stepwise mechanism, that is, (1) Mannich addition to sulfinimine, (2) loss of a sulfinyl group and (3) cyclization to a dihydropyridone. We could not find any spectral evidence for the presence of an *N*-sulfinyl tetrahydropyridine derivative, which would indicate a cycloaddition pathway. Actually, several pieces of evidence were shown for the stepwise mechanism in the case of the Danishefsky diene.[14] For dienophiles **1a–f**, we only observed cyclized product **3** because 10-isobornylsulfinyl group is a good leaving group. The driving force for this reaction is the formation of cyclic

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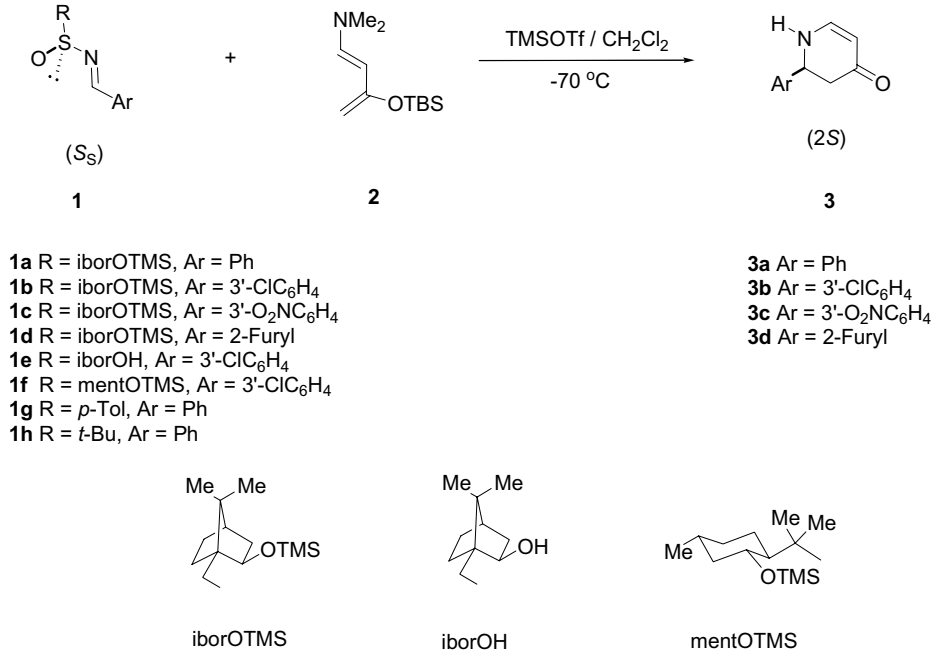


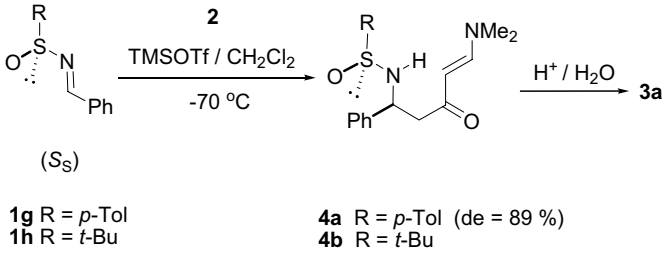
Scheme 1.

Table 1. Synthesis of dihydropyridinones

Entry	Substrate	R	Ar	Method[a]	Product	Yield (%)	ee (%)
1	**1a**	iborOTMS	Ph	A	**3a**	82	60
2	**1b**	iborOTMS	3′-ClC_6H_4	A	**3b**	82	68
3	**1c**	iborOTMS	3′-$O_2NC_6H_4$	A	**3c**	80	90
4	**1d**	iborOTMS	2-Furyl	A	**3d**	61	69
5	**1e**	iborOH	3′-ClC_6H_4	A	**3b**	75	14
6	**1f**	mentOTMS	3′-ClC_6H_4	A	**3b**	98	12
7	**1g**	*p*-Tol	Ph	B	**3a**	51	(89)[b]
8	**1h**	*t*-Bu	Ph	B	**3a**	40	49

[a] Method A: quench with water. Method B: quench with water, then aqueous acidic hydrolysis. Details in Section 4.
[b] de of **4** (see Scheme 2). Epimerization was not observed at either C-2 or the sulfur atom.

sulfinate (sultin)[12] in the presence of the acid. This is also the case for 8-menthyl derivative **1f**. Complete splitting of the sulfinyl group was even observed when the reaction mixture was quenched with satd aq $NaHCO_3$. Removal of the *t*-butyl and *p*-tolylsulfinyl groups proved more difficult. In this case, we observed the formation of enaminones of type **4**.[15] They can be cyclized to dihydropyridone **3** in the presence of acid, which is strong enough to cleave the sulfinyl group (Scheme 2).



Scheme 2.

For the *p*-tolyl derivative we used acetic acid while for *t*-butyl we used 4 M HCl. However, the overall yield was lower than using sulfinimines **1a**–**f**. The diastereoselectivity of the addition to 10-isobornylsulfinimines **1a**–**d** (R = iborOTMS) was good (60–90% ee). The steric effect of the TMS group seems to be important as the sulfinimine **1e** (R = iborOH) gave a low ee value. Surprisingly, the addition to 8-menthylsulfinimine **1f** was not stereoselective (12% ee). The use of a *t*-butylsulfinyl group also resulted in low ee of the product.

The stereochemistry of the addition of silyl nucleophiles to the C=N bond in sulfinimines has been well described by the Davis–Cram model.[16] The preferred conformation of the sulfinimine is that it has a synperiplanar arrangement around the S–N bond.[9,17] Nucleophile likely attacks this molecule from the *si* side (Fig. 1).

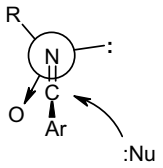
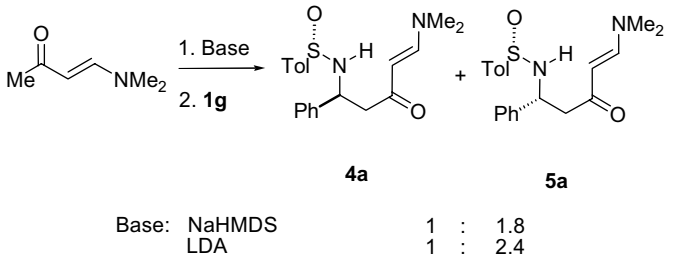


Figure 1.

This results in the formation of a product with a *like* configuration. In the case of (S_S)-sulfinimines **1**, the dihydropyridone also has an (*S*)-configuration at C-2. Opposite effect is observed when the nucleophilic reagent contains metal as counterion. The addition is controlled by a chelated transition state. This is usually the case when organolithium or Grignard reagents are used. To check this hypothesis, an enolate was generated from 4-(dimethylamino)-3-buten-2-one using LDA or NaHMDS as a base. The reaction with sulfinimine **1g** gave two diastereoisomeric sulfinamides **4a** and **5a**. The conversion of the substrate as well as the diastereoisomeric excess was low. However, the direction of diastereoselectivity of this process was opposite to that observed when the Rawal diene was used. The major diastereoisomer had an *unlike* configuration (Scheme 3).



Scheme 3.

3. Conclusion

We have demonstrated that optically active sulfinimines may act as formal dienophiles. The use of highly reactive dienes as well as Lewis acid is necessary. The reaction of the Rawal diene with 10-isobornylsulfinimines in the presence of TMSOTf leads to enantiomerically enriched, N-unsubstituted dihydropyridones in good yields. Removal of the sulfinyl group occurs during aqueous workup. The stereoselectivity of the reaction is modest; the method is limited to 2-aryl substituted derivatives.

4. Experimental

4.1. General

NMR spectra were recorded at 200 and 500 MHz (^{1}H). All spectra were referenced to a residual solvent peak (chloroform 7.26 and 77.0 ppm for ^{1}H and ^{13}C, respectively). Dichloromethane was distilled from CaH_2. All experiments, except for acidic hydrolysis, were conducted under an atmosphere of argon. The Rawal diene was synthesized from 4-(dimethylamino)-3-buten-2-one.[10] Sulfinimines **1a–e**,[12,18] **1g**[19] and **1h**[20] were obtained as described in original procedures.

4.1.1. (1*R*,2*R*,4*R*,S_S)-*N*-[(1*E*)-3-Chlorophenylmethylene]-2-(2-trimethylsilyloxy-4-methylcyclohexyl)propane-2-sulfinamide, 1f. This compound was obtained according to the procedure described earlier.[18] To a solution of sulfinamide (651 mg, 2.2 mmol) and 3-chlorobenzaldehyde (369 mg, 2.6 mmol) in THF (10 mL) was added tetraethoxytitanium (1.10 g, 4.8 mmol) and the mixture stirred at rt for 16 h. A saturated solution of KCl (1.5 mL) was added and the suspension filtered through Celite. The precipitate was washed with ethyl acetate. The filtrate was dried ($MgSO_4$) and evaporated. Chromatography on silica gel (AcOEt–hexane 1:1) gave a colourless oil (0.82 g, 90%). Spectral data for **1f**: $[\alpha]_D^{21} = +92.9$ (*c* 1.03, acetone). IR (neat) 1074; 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.16 (s, 9H), 0.86–1.21 (m, 3H), 0.92 (d, $J = 6.3$ Hz, 3H), 1.00 (s, 3H), 1.25 (s, 3H), 1.31–1.54 (m, 1H), 1.61–1.75 (m, 1H), 1.82–2.10 (m, 3H), 3.76 (ddd, $J = 4.2$, 10.2, 10.2 Hz, 1H), 7.34–7.49 (m, 2H), 7.69 (dt, $J = 7.0$, 1.6 Hz, 1H), 7.87 (t, $J = 1.6$ Hz, 1H), 8.49 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 1.1; 16.6; 17.5; 22.0; 26.2; 31.3; 34.4; 45.4; 49.1; 65.2; 73.1; 127.8; 128.6; 130.0; 131.9; 134.9; 135.9; 161.1. Anal. Calcd for $C_{20}H_{32}ClNO_2SSi$: C, 58.01; H, 7.79; N, 3.38. Found: C, 58.08; H, 7.81; N, 3.23.

4.2. General method for the aza Diels–Alder reactions of sulfinimines. Method A

To a solution of sulfinimine **1** (0.26 mmol) and Rawal diene **2** (117 mg, 0.52 mmol) in dry dichloromethane (3 mL), TMSOTf (145 mg, 0.65 mmol) was added dropwise at −70 °C. The resulting mixture was stirred for 3.5 h at −70 °C. Water (2 mL) was then added and the mixture warmed to rt. The mixture was alkalized with satd aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and evaporated. The solid residue was purified by chromatography on silica gel (AcOEt–hexane 25:10). Yields and enantiomeric enrichment are shown in Table 1. Ee was determined by HPLC (Nucleodex β-PM, MeOH–0.1% TEAA in H_2O pH = 4.0 45:55).

The configuration at C-2 of dihydropyridone **3a** was established by comparison of the specific rotation sign of the known derivative.[21] Spectral data of dihydropyridones were identical to that published elsewhere.

4.3. General method for the aza Diels–Alder reactions of sulfinimines. Method B

The conditions of diene addition were the same as above. The crude product was dissolved in MeOH (4 mL) and concentrated aq HCl (2 mL) was added. The mixture was kept at rt for 5 h. MeOH was removed by evaporation and the residue neutralized with satd aq $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. The product was purified by chromatography on silica gel (AcOEt–hexane 25:10).

4.3.1. 2,3-Dihydro-2-phenyl-4(1*H*)-pyridinone, 3a. $[\alpha]_D^{20} = +195.3$ (*c* 2.51, EtOH). Spectral data are identical to those reported.[21]

4.3.2. 2-(3-Chlorophenyl)-2,3-dihydro-4(1*H*)-pyridinone, 3b. $[\alpha]_D^{20} = +104.9$ (*c* 2.14, $CHCl_3$). Spectral data are identical to those reported.[22]

4.3.3. 2,3-Dihydro-2-(3-nitrophenyl)-4(1*H*)-pyridinone, 3c. Mp = 172–178 °C. IR (KBr) 3313; 1610; 1588; 1554; 1533 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.66 (1/2ABX, $J = 16.0$, 5.3 Hz, 1H); 2.74 (1/2ABX, $J = 16.0$, 13.3 Hz, 1H), 4.91 (dd, $J = 13.3$, 5.3 Hz, 1H); 5.12 (br, 1H); 5.19 (d, $J = 7.6$ Hz, 1H); 7.31 (dd, $J = 7.6$, 6.8 Hz, 1H); 7.60 (t, 8.0, 1H); 7.73 (d, $J = 8.0$ Hz, 1H); 8.21 (ddd, $J = 8.0$, 2.0, 1.0 Hz, 1H); 8.30 (d, $J = 2.0$ Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 44.4; 57.8; 101.0; 121.5; 123.5; 130.2; 132.6; 142.2; 148.7; 150.6; 191.0. HRMS (EI) calcd for $C_{11}H_{10}O_3N_2$ 218.0691 (M^+). Found 218.0684.

4.3.4. 2,3-Dihydro-2-(2-furyl)-4-(1*H*)-pyridinone, 3d. $[\alpha]_D^{20} = +430.1$ (*c* 0.565, $CHCl_3$). Enantiomeric excess of this derivative was established by ^1H NMR using *t*-butylphenylphosphinothioic acid[23] as the chiral solvating agent. Spectral data are identical to those reported.[22]

4.4. Addition of enolate to sulfinimine 1g

A solution of enaminone **2** (70 mg, 0.62 mmol) in THF (1 mL) was slowly added to a solution of NaHMDS (1 mL, 0.6 M, toluene) in THF (1 mL) at −50 °C. The reaction mixture was stirred for 1 h at − 65 °C and a solution of sulfinimine **1g** (150 mg, 0.62 mmol) in THF (1 mL) was added. The reaction mixture was kept at −65 °C for 1 h and quenched with satd aq NH_4Cl solution. The diastereoisomer ratio was established from ^1H NMR spectra. Enaminones **4** and **5** were hydrolyzed in aq AcOH/MeOH for 16 h at rt. The solution was alkalized with $NaHCO_3$ and extracted with CH_2Cl_2 to give dihydropyridone **3a**. Purification as above.

The structure of **4a** was established using NMR data only (because of purification problems). ^1H NMR ($CDCl_3$, 200 MHz): δ 2.27 (s, 3H); 2.70 (br, 3H); 2.92 (m, 2H); 2.94 (br, 3H); 4.74 (ddd, $J = 6.1$ Hz, 1H); 4.88 (d, $J = 12.6$ Hz, 1H); 5.93 (d, $J = 6.1$ Hz, 1H); 7.03–7.19 (m, 7H); 7.37–7.46 (m, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.1; 36.8 br; 44.6 br; 47.9 br; 53.6; 96.1 br, 125.8; 126.7; 126.8; 127.9; 128.9; 140.5, 141.3; 142.0; 152.8; 194.7.

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