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C_2-Symmetric Bis-Sulfoxide: Highly Diastereoselective 1,4-Addition to Stabilised Michael Acceptors

Inmaculada Fernández,[a] Cristina S. Araújo,[a] M. José Romero,[a] Felipe Alcudia[a] and Noureddine Khiar[b,*]

[a]*Dpto. de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, c/Prof. García González, s/n, 41012 Seville, Spain*

[b]*Instituto de Investigaciones Químicas, C.S.I.C., c/Américo Vespucio, s/n, Isla de la Cartuja, 41092 Seville, Spain*

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Abstract—The reaction of (*S*,*S*)-bis-*p*-tolylsulfinylmethane with highly stabilised Michael acceptors was studied in detail. The stereochemical outcome of the reaction was shown to be under thermodynamic control. While an equimolar mixture of Michael adducts was obtained at −78°C, warming the reaction to room temperature allows the formation of a single isomer in quantitative yield.

Introduction

Michael addition is one of the most important C–C bond forming reactions.[1] It is not surprising that the development of highly stereoselective 1,4-addition is still an area of interest, in spite of the great advances achieved in recent decades.[2] Chiral non-racemic sulfoxides were among the first chiral controllers used in asymmetric Michael additions.[3,4] It was demonstrated early on that *tert*-butyl sulfoxide, and not the widely used *p*-tolyl sulfoxide, was necessary to achieve high stereocontrol in the reaction with acyclic α,β-unsaturated esters.[5] As a consequence, this has limited the use of chiral sulfoxides in Michael addition, as until recently there was no general and easy approach to optically pure *tert*-butyl sulfoxides.[6–8]

As a part of our interest in developing new asymmetric processes involving chiral non-racemic sulfoxides,[9] we report in this communication that C_2-symmetric bis-sulfoxide **1** (Fig. 1) is indeed highly diastereoselective in reactions with stabilised Michael acceptors.

We have recently reported the first use of chiral β-ketosulfoxides as Michael donors with highly stabilised Michael acceptors *en route* to the 2-amino-4*H*-pyran ring (Scheme 1).[10,11]

In the reported process, highly efficient stereocontrol by the sulfinyl sulfur has been observed. Coupling, for example, the optically pure oxisuran analogue β-ketosulfoxide **2** and (*p*-chlorobenzylidene)malononitrile **3** in ethanol, using piperidine as a mild base, gave a single isomer **8** with the *R* absolute configuration at the newly created stereogenic center. While a transition state model was advanced to explain the selectivity observed, no kinetic evidence could be proposed in order to corroborate it. The formation of the 2-amino-4*H*-pyran ring is a result of two successive reactions: the 1,4 conjugate addition, followed by the O-ring closure, which makes the determination of the origin of the stereochemical outcome of the first 1,4 addition step very difficult.

In order to determine the factors controlling the observed selectivity and to gain greater insight into the first step of the process, we report in this communication the use of optically pure C_2-symmetric (*S*,*S*)-bis-*p*-tolylsulfinylmethane **1** as Michael donor instead of the previously used β-ketosulfoxide.

Results and Discussion

The enantiopure bis-sulfoxide **1**, which can be easily

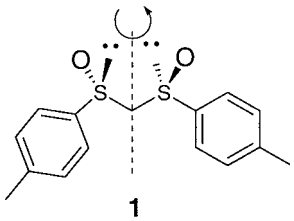

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Figure 1.

Keywords: diastereoselective synthesis; Michael addition; thermodynamic control; C_2-symmetric bis-sulfoxides.

* Corresponding author. Tel.: +349-544-89-559; fax: +349-544-60-565; e-mail: khiar@cica.es

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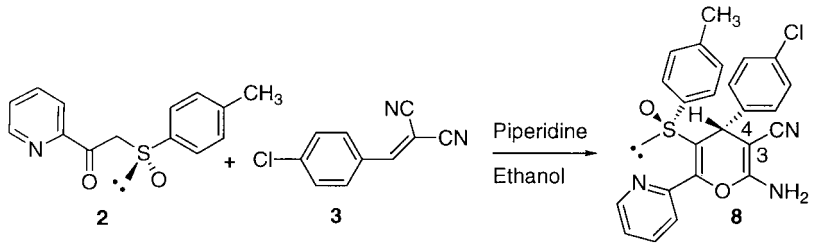


Scheme 1.

prepared from optically pure (−)-(*S*)-menthyl *p*-toluenesulfinate and (+)-(*R*)-methyl *p*-tolyl sulfoxide, as described by Kuneida,[12] has been used with success by Solladié in condensations with carbonyl compounds[13] and later on by us as chiral ligand in Fe(III) catalysed Diels–Alder reaction.[14] The utilisation of **1** as Michael donor serves the important task of simplifying the stereochemical analysis of the final product. In the Michael adduct the α position is not a stereogenic centre due to the C_2 symmetric nature of the bis-sulfoxide, which will allow us to determine the diastereoselectivity at the distant β position. No reaction took place using piperidine as base in ethanol, probably because of the lower acidity of the protons at the α position to the sulfinyl sulfur in **1** compared to those in **2**. Deprotonation using LDA (Scheme 2) and addition of (*p*-chlorobenzylidene)malononitrile at −78°C led to the formation of adducts **9A** and **9B** in a 1:1 ratio and the reaction was found to be under kinetic control.

The diastereomeric ratio was easily determined by either the α (H-1), the β (H-2) or the γ (H-3) proton to the sulfinyl groups in the Michael adduct (Table 1). We were delighted to find that when the reaction was allowed to warm to room temperature overnight, equilibration occurs and a single isomer was obtained.

Various benzylidene malononitriles were tried under the above conditions and the results are summarised in Table 2. In all the studied cases an equimolar mixture of adducts is produced at −78°C which evolve to a single isomer after warming to room temperature, which was generally isolated in quantitative yield.

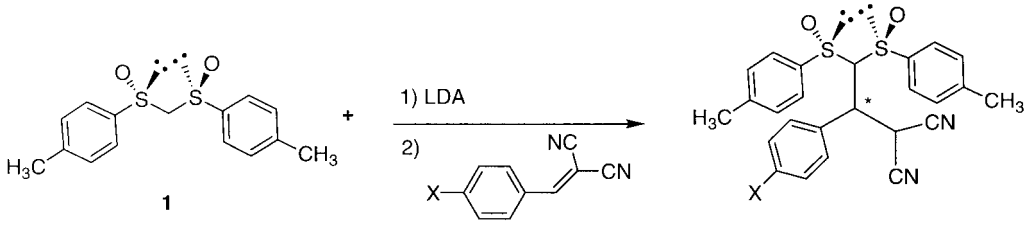
Assuming that the stereochemistry of the major diastereomer obtained under thermodynamic control is the same in all cases, from a comparison of the ^{1}H NMR data in $CDCl_3$ for all the adducts, a correlation between stereochemistry and chemical shift differences was observed. For all the adducts, the H(1), H(2) and H(3) protons are more deshielded in the product of thermodynamic control (**9A**–**13A**), Table 1, which additionally showed significantly lower *J*(2,3) coupling constant values.

It is worth noting that the stereochemical behaviour of bis-sulfoxide **1** in the Michael additions is equivalent to that recently described by Aggarwal et al. for the addition of *trans*-1,3-dithiane 1,3-dioxide to aromatic aldehydes (vide infra).[15]

In order to ascertain the stereochemical role of the bis-sulfoxide in the course of the reaction, the condensation was performed using (*R*)-methyl *p*-tolyl sulfoxide as the Michael donor. In this case no epimerisation took place and the reaction was under kinetic control, the same equimolar mixture was obtained both at −78°C and at room temperature. It is worth noting that no reaction took place when reacting the bis-sulfoxide **1** with non-stabilised Michael acceptors such as cyclopentanone or cyclohexanone.

Possible Origin of the Diastereoselection

In spite of many efforts, the diastereoselection at the distant β-carbon, in the addition of sulfoxide stabilized carbanions to electrophiles is in general very poor.[16] While the utilisation of chiral sulfoxides in Michael addition has been scarce, the addition of sulfoxide stabilised anions to aldehydes has been studied in more detail.[17] Apart from the first successful addition of the magnesium enolate of α-sulfinyl esters to aldehydes reported by Solladié,[18,19] there have been substantial advances in the last decade. In this respect, it is worth noting the good selectivities achieved using the lithiated naphthyl methyl sulfoxide **14**,[20] binaphthyl-based dithiepine **15**,[21] C_2-symmetric bis-sulfoxide **1**,[13] and racemic *trans*-1,3-dithiane 1,3-dioxide **16** (Fig. 2).[15] A common feature of all these studies is that the best diastereoselectivities were obtained with aromatic aldehydes under kinetic control, except for **16**, where high diastereoselectivities were obtained under equilibrium control. However, the best results were recently reported by Aggarwal's group



Scheme 2.

Table 1. ^{1}H NMR Data of diastereomeric Michael adducts **9**–**13**, obtained at −78°C (Scheme 2)

Entry	X	Michael adduct[a]	δ(ppm)			Coupling constants (Hz)	
			H(1)	H(2)	H(3)	*J*(1,2)	*J*(2,3)
1	Cl	**9A**	5.10	4.36	3.92	4.8	9.6
2	Cl	**9B**	4.99	4.21	3.90	4.4	12.2
3	H	**10A**	5.09	4.30	3.98	4.7	8.5
4	H	**10B**	5.00	4.20	3.96	4.4	12.3
5	CH_3	**11A**	5.09	4.25	3.96	4.7	8.2
6	CH_3	**11B**	4.97	4.19	3.94	4.3	12.3
7	NO_2	**12A**	5.57	4.84	4.01	4.9	10.9
8	NO_2	**12B**	–	–	–	–	–
9	OMe	**13A**	5.14	4.32	3.96	4.8	8.8
10	OMe	**13B**	–	–	–	–	–

[a] **A**: Diastereomer from thermodynamic control. **B**: Epimer of diastereomer **A** at C3 position.

Table 2. Reaction of (*S*,*S*)-bis-*p*-tolylsulfinylmethane **1** with various benzylidene malononitriles (Scheme 2) (all the reactions were conducted in THF at −78°C and warmed to room temperature before work up)

Entry	X	Michael acceptor	Michael adduct[a]	$[\alpha]_D$[b]	Mp (°C)
1	Cl	**3**	**9**	+44.7	144–146
2	H	**4**	**10**	+8.17	152–154
3	CH_3	**5**	**11**	+18.5	137–139
4	NO_2	**6**	**12**[c]	+70.8	90–92
5	OMe	**7**	**13**	+25.6	138–140

[a] All the reactions gave the desired compound in quantitative yield.
[b] In CH_2Cl_2.
[c] Compound decomposes slowly at room temperature.

using the lithiated anion of racemic *trans*-1,3-dithiolane 1,3-dioxide[22] **17** where good yields and selectivities were obtained not only with aromatic but also with aliphatic aldehydes under kinetic control.

In order to explain the diastereoselectivity observed in the Michael addition, only two lithium carbanions **18** and **19** should be considered, as the reaction is under thermodynamic control. From the two diastereomeric carbanions, isomer **19** would be preferred on the assumption that there is a π−π charge transfer interaction[20,23] between the two aromatic rings. This assumption is reinforced by the result obtained with (*R*)-methyl *p*-tolyl sulfoxide as Michael donor where, the π−π stacking depending upon the orientation of the flat π-electron faces of two aromatic rings is not operative.

At the present time, all the attempts to obtain suitable crystals of one of the Michael adducts, **9A**–**13A**, to determine the configuration of the newly created stereogenic centre by X-ray crystallography were unsuccessful. However, the model depicted in Scheme 3 is supported by our previous

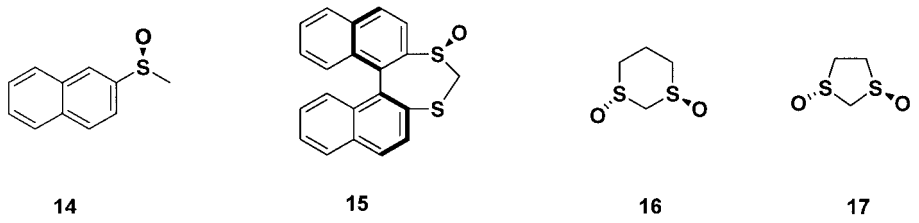
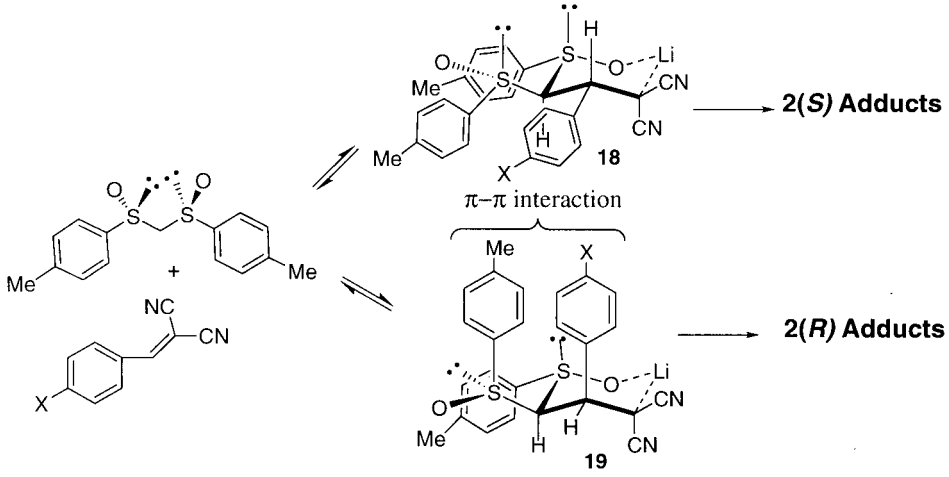


Figure 2.



Scheme 3.

report on the diastereoselective synthesis of 2-amino-4*H*-pyran where the newly created stereogenic centre had an *R* absolute configuration as demonstrated by X-ray analysis of compound **8**.[10]

Conclusion

We have shown that the reaction of (*S*,*S*)-bis-*p*-tolylsulfinylmethane with stabilised Michael acceptors is completely diastereoselective. From this study we have demonstrated that the stereochemical outcome of the reaction is under thermodynamic control. While an equimolar mixture of Michael adduct was obtained at −78°C, warming the reaction to room temperature allowed the formation of a single isomer in quantitative yield. A Zimmermann–Traxler like model for aldol reactions has been proposed in order to explain the high diastereoselectivity observed, and to account for the relative stereochemistry of the major isomer. The key feature of this model is the juxtaposition of two aromatic rings, one belonging to the Michael donor and the other to the Michael acceptor, favouring a stabilizing π–π charge transfer. Additionally, we beleive that the π–π interaction invoked here is a general behaviour in the reaction of stabilized sulfoxide anions with electrophiles. Thus, the high diastereoselectivities observed in the reactions of lithiated anions of **1**, **14** and **15** with aromatic aldehydes can be accounted for by a favorable π–π charge transfer in the transition state.

Additionally, these results indicate that the high diastereoselectivity observed in the formation of the 2-amino-4*H*-pyran ring by Michael addition of β-ketosulfoxides to the Michael acceptor **3** has its origin in thermodynamic control of the first step of the process.

Experimental

Melting points were determined in open capillary tubes on a Gallenkamp apparatus and are not corrected. Routine monitoring of reactions was performed using Merck 60 F254 silica gel, glass supported TLC plates. ^{1}H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra at 50 MHz, on Bruker instruments using tetramethylsilane as internal standard. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. High resolution mass spectra were recorded on a Kratos MS-80-RFA spectrometer. Optical rotations were taken on a Perkin–Elmer 241-MC apparatus. All reactions were run under an atmosphere of dry argon using flame-dried glassware and freshly distilled and dried solvents. The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. All the Michael acceptors (**3**–**7**) have been prepared according to the standard methodologies.[11]

General procedure for the Michael additions

To a solution of (*S*,*S*)-bis-*p*-tolylsulfinylmethane **1** (100 mg, 0.34 mmol, 1 equiv.) in THF (15 mL) was added a solution of LDA (0.56 mmol, 1.6 equiv.) at −78°C. After 30 min, a solution of the corresponding Michael acceptor **3**–**7** (0.376 mmol, 1.1 equiv.) in THF (5 mL) was added. The mixture was stirred at room temperature over night, then quenched with saturated NH_4Cl solution (15 mL), and extracted with AcOEt (3×20 mL). The organic layer was treated with saturated aqueous $NaHCO_3$ solution (20 mL), dried over sodium sulfate and evaporated under vacuum to yield quantitatively the corresponding adduct **9A**–**13A** as a single isomer.

2-[1-(4-Chloro-phenyl)-2,2-bis-[(*R*)-*p*-tolylsulfinyl]-ethyl]-malononitrile, 9A. White solid; mp 144–146°C; $[\alpha]_D^{25}$=+44.7 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 2.25 (s, 3H), 2.30 (s, 3H), 2.49 (s, 3H), 3.92 (d, 1H, *J*=9.5 Hz), 4.36 (dd, 1H, *J*=4.8, 9.5 Hz), 5.10 (d, 1H, *J*=4.8 Hz), 6.16 (m, 2H), 7.11 (m, 2H), 7.19 (m, 2H), 7.47 (m, 2H), 7.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.1, 21.6, 28.7, 39.5, 86.7, 110.7, 112.2, 122.5, 125.0, 129.0, 129.6, 130.5, 130.7, 131.6, 135.6, 136.1, 138.6, 141.0, 143.4. HRMS Calcd for $C_{25}H_{21}N_2O_2NaS_2^{35}Cl(M+Na)^+$: 503.0630, Found: 503.0661 (−6.1 ppm), HRMS Calcd for $C_{25}H_{21}N_2O_2NaS_2^{37}Cl(M+Na)^+$: 505.0601, Found: 505.0605 (−0.8 ppm).

2-[1-(Phenyl)-2,2-bis-[(*R*)-*p*-tolylsulfinyl]-ethyl]-malononitrile, 10A. White solid; mp 152–154°C; $[\alpha]_D^{25}$=+8.2 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 2.21 (s, 3H), 2.49 (s, 3H), 3.98 (d, 1H, *J*=8.5 Hz), 4.30 (dd, 1H, *J*=4.7, 8.5 Hz), 5.09 (d, 1H, *J*=4.7 Hz), 6.19 (m, 2H), 6.83 (m, 2H), 7.15–7.40 (m, 5H), 7.46 (m, 2H), 7.65 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 21.2, 21.6, 28.6, 40.7, 86.1, 111.0, 112.0, 122.8, 125.0, 129.0, 129.1, 129.5, 129.7, 130.6, 133.1, 136.1, 138.7, 141.0, 143.3. HRMS Calcd for $C_{25}H_{22}N_2O_2NaS_2$ $(M+Na)^+$: 469.1022, Found: 469.1026 (−1.1 ppm). IR (KBr): 3070–3040, 2960–2840, 1490, 1080, 1060, 810 cm^{-1}.

2-[1-(*p*-Tolyl)-2,2-bis-[(*R*)-*p*-tolylsulfinyl]-ethyl]-malononitrile, 11A. White solid; mp 137–139°C; $[\alpha]_D^{25}$=+18.5 (*c* 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 2.23 (s, 3H), 2.30 (s, 3H), 2.48 (s, 3H), 3.96 (d, 1H, *J*=8.8 Hz), 4.25 (dd, 1H, *J*=4.7, 8.2 Hz), 5.09 (d, 1H, *J*=4.7 Hz), 6.26 (m, 2H), 6.85 (m, 2H), 6.99 (m, 2H), 7.18 (m, 2H), 7.44 (m, 2H), 7.63 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 21.0, 21.1, 21.5, 28.7, 40.0, 86.5, 111.2, 112.3, 122.7, 124.9, 128.8, 129.4, 129.5, 130.3, 130.5, 136.3, 138.7, 139.4, 140.8, 143.1. HRMS Calcd for $C_{26}H_{24}N_2O_2NaS_2$ $(M+Na)^+$: 483.1177, Found: 483.1191 (−3.0 ppm).

2-[1-(4-Nitro-phenyl)-2,2-bis-[(*R*)-*p*-tolylsulfinyl]-ethyl]-malononitrile, 12A. White solid; mp 90–92°C; $[\alpha]_D^{25}$= +70.8 (*c* 0.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 2.22 (s, 3H), 2.51 (s, 3H), 4.01 (d, 1H, *J*=10.1 Hz), 4.77 (dd, 1H, *J*=4.8, 10.1 Hz), 5.48 (d, 1H, *J*=4.8 Hz), 6.07 (m, 2H), 6.79 (m, 2H), 7.30 (m, 2H), 7.45 (m, 2H), 7.70 (m, 2H), 7.90 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 21.1, 21.7, 28.6, 38.9, 87.5, 110.6, 112.5, 122.2, 123.4, 124.9, 129.6, 130.5. 130.8, 136.1, 138.3, 1140.3, 141.1, 143.6, 148.0. HRMS Calcd for $C_{25}H_{21}N_3O_4NaS_2$ $(M+Na)^+$: 514.0871, Found: 514.0877 (−1.2 ppm). IR (KBr): 3120–3040, 2960–2820, 1514, 1352, 1081, 1053, 809, 725 cm^{-1}.

2-[1-(4-Methoxy-phenyl)-2,2-bis-[(*R*)-*p*-tolylsulfinyl]-ethyl]-malononitrile, 13A. White solid; mp 138–140°C; $[\alpha]_D^{25}$= +25.6 (*c* 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 2.22 (s, 3H), 2.48 (s, 3H), 3.76 (s, 3H), 3.96 (d, 1H, *J*=8.8 Hz), 4.32 (dd,

1H, J=4.8, 8.8 Hz), 5.14 (d, 1H, J=4.8 Hz), 6.23 (m, 2H), 6.68 (m, 2H), 6.85 (m, 2H), 7.21 (m, 2H), 7.45 (m, 2H), 7.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.2, 21.6, 28.8, 40.0, 55.3, 86.5, 111.1, 112.2, 114.3, 122.8, 124.9, 129.5, 130.2, 130.5, 136.2, 138.8, 140.8, 143.2, 160.4. HRMS Calcd for $C_{26}H_{24}N_2O_3NaS_2$ $(M+Na)^+$: 499.1126, Found: 499.1109 (3.3 ppm).

Acknowledgements

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