Michael Additions of α-Sulfinyl and α-Sulfonyl Carbanions: The Unprecedented Reaction of β-Keto Sulfoxides and β-Keto Sulfones with Highly Stabilized Michael Acceptors

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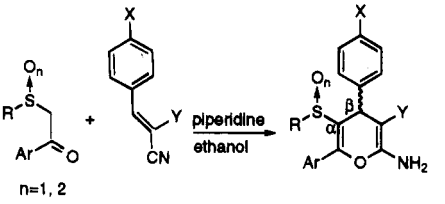
A careful examination of the current literature has shown that 1,4-conjugate additions[1] of β-keto sulfones[2] are unprecedented and that similar reactions of β-keto sulfoxides[3] with Michael acceptors are scarce and of limited scope. In some cases, the sulfur moiety has been eliminated in the course of the reaction[4] or the intermediate adduct, without further analysis, has been submitted to reductive cleavage.[5] Chiral sulfoxides have been used frequently as chiral controllers in highly asymmetric C–C bond formations.[6] *Surprisingly, in no case has the stereochemical outcome of the 1,4-conjugate additions of chiral or racemic β-keto sulfoxides been defined and documented.*

In view of the potential for asymmetric synthesis of these processes, we have approached this problem, and in this paper we report the initial analysis of 1,4-conjugate addition of some selected, readily available chiral or racemic β-keto sulfoxides and β-keto sulfones to highly stabilized Michael acceptors, such as arylidenemalonitriles and benzylidenecyanoacetates.[7] The use of these substrates should lead to exclusive 1,4-conjugate addition,[1] followed by the expected final *O*-ring closure. Fortunately, this chemical transformation, leading to the 2-amino-4*H*-pyran ring,[8] simplifies the stereochemical analysis and should allow us to define the extent of the asymmetric induction obtained at the distant Cβ-position in respect to the sulfur atom during the Michael addition (Scheme 1). An extremely efficient and highly stereocontrolled process has resulted.

Scheme 1



In the initial experiments, the coupling of β-keto sulfoxide **1**[9] and (*p*-nitrobenzylidene)malononitrile (**2**) was investigated. Mixing equimolar quantities of these reagents in ethanol with catalytic piperidine as mild base, at room temperature, led to a rapid reaction which afforded compound **3**[9,10] in 78% yield as the exclusive isomer. The presumed intermediate δ-oxonitrile addition product, as expected,[11] led smoothly to the polyfunctionalized 2-amino-4*H*-pyran ring. The relative *syn* stereochemistry between the oxygen and the proton in the structural moiety $CH_3SO(C_5)C_4HAr$ has been established by comparison of the spectroscopic data of compound **3** [^{1}H NMR (DMSO) (δ) 4.95 (H_4); ^{13}C NMR (DMSO) (δ) 41.6 (C_4); 57.6 (C_3)] with those of compound **7** (see below). The reaction of the same racemic Michael donor **1** with the acceptor **4**, under identical experimental conditions, afforded pyran **5**[9,10] [^{1}H NMR (DMSO) (δ) 4.80 (H_4); ^{13}C NMR (DMSO) (δ) 40.9 (C_4); 57.9 (C_3)] in 92% yield as the only observed and isolated isomer.

Coupling compound **4** with the β-keto sulfoxide **6**[9,12] gave also the expected pyran **7**[9,10] in 86% yield; only one isomer could be detected. X-ray analysis[13] allowed us to assign the relative stereochemistry at the different stereocenters in compound **7**. The configuration at C4 and S5 is *RR* (or *SS*). The conformation of the pyran ring is a distorted boat as can be deduced from the selected torsion angles (see the supporting information).

The detailed comparison of the relevant spectroscopic data for compound **7** [^{1}H NMR (DMSO) (δ) 4.67 (H_4); ^{13}C NMR (DMSO) (δ) 31.7 (C_4); 58.4 (C_3)], with those from compounds **3** and **5** (see above), permits assignment of the same relative *syn* stereochemistry at the sulfur atom and at C_4. The reaction of enantiomerically pure precursor (R_S)-**6** with compound **4** gave optically pure **7** (R_S, C_4R) in similar chemical yield. From this result, it is clear that the type of functional residue attached to the sulfur moiety does not affect the stereochemical course of the Michael addition.

Using benzylidene cyanoacetate **8** as the Michael acceptor and sulfoxide **1**, the expected pyran **9**[9,10] [^{1}H

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(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series No. 9; Pergamon Press: Oxford, 1992.
(2) Simpkins, N. S. *Sulfones in Organic Synthesis*; Tetrahedron Organic Chemistry Series No. 10; Pergamon Press: Oxford, 1993.
(3) (a) Posner, G. H. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; New York, 1988; pp 823. (b) Solladié, G. *Synthesis* **1981**, 185.
(4) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1980**, *45*, 5002.
(5) (a) Nozaki, H.; Mori, T.; Kawanisi, M. *Can. J. Chem.* **1968**, *46*, 3767. (b) Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1969**, *34*, 3624. (c) Vig, O. P.; Matta, K. L.; Sehgal, J. M.; Sharma, S. D. *J. Indian Chem. Soc.* **1970**, *47*, 894.
(6) (a) See ref 3. (b) Khiar, N.; Fernández, I.; Alcudia, F. *Tetrahedron Lett.* **1993**, *34*, 123. (c) Khiar, N.; Fernández, I.; Alcudia, F.; Hua, D. H. *Tetrahedron Lett.* **1993**, *34*, 699.
(7) To our knowledge, only the Michael addition of (phenylsulfinyl)-acetone to dimethyl ethylideneacetoacetate or benzylideneacetoacetate has been reported and described as having poor results: Jaxa-Chamiec, A. A.; Sammes, P. G.; Kennewell, P. D. *J. Chem. Soc, Perkin Trans. 1* **1980**, 170.
(8) Kuthan, J. *Adv. Heterocycl. Chem.* **1983**, *34*, 146.
(9) (a) Kazmer, J. S.; Daddona, P. E.; Dalke, A. P.; Kelley, W. N. *Biochem. Pharmacol.* **1983**, *32*, 805. (b) Alcudia, F.; Fernández, I.; Trujillo, M.; Zorrilla, F. *Tetrahedron* **1989**, *45*, 1491 and references cited therein. When not specifically stated, the β-sulfoxides used and the 2-amino-4*H*-pyrans obtained here are racemic samples.
(10) All new compounds showed good spectroscopic and analytical data. The final products were isolated after a short reaction time (2–3 h) as solids by simple filtration and washing with cold ethanol. Simple recrystallization from the appropriate solvent gave pure analytical samples. Yields refer to pure, recrystallized materials. In the case of compound **9** total transesterification gave the ethyl ester derivative.
(11) Soto, J. L.; Seoane, C.; Martín, N.; Blanco, L. A. *Heterocycles* **1983**, *20*, 803.
(12) Garcia-Ruano, J. L.; Pedregal, C.; Rodríguez, J. H. *Tetrahedron* **1987**, *43*, 4407
(13) The authors have deposited atomic coordinates of this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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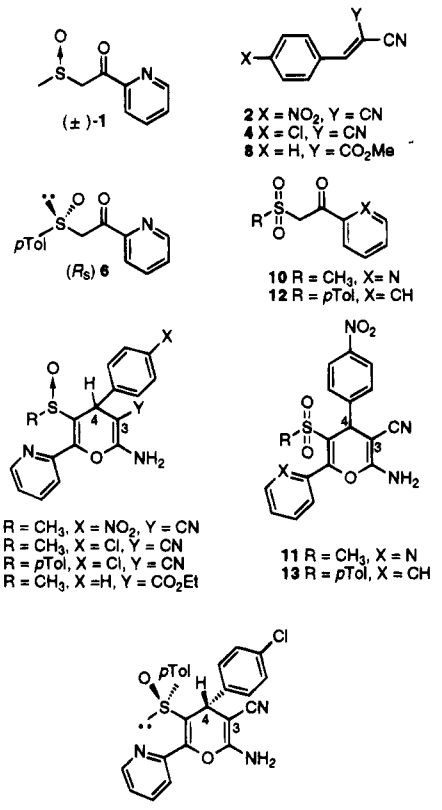

NMR ($CDCl_3$) (δ) 5.38 (H_4); ^{13}C NMR ($CDCl_3$) (δ) 41.5 (C_4); 81.3 (C_3)] was obtained as the exclusive isomer in lower yield [33% (50%, taking into account the recovered starting material)]. The structure of the product was confirmed after X-ray analysis.[14] In this instance, the change in the Michael acceptor does not affect the qualitative and quantitative degree of the asymmetric induction, although in this case the chemical yield is slightly lower.

A simple model for the transition state can be advanced to justify the high degree of asymmetric induction obtained in these cases. As shown in Figure 1, we have assumed that the donor–acceptor couple approach in an "open chain" model, in which the lone pair on sulfur and the pyridine ring are in an antiperiplanar[15] arrangement and the attack on the Michael acceptor occurs from the opposite side of the *p*-tolylsulfinyl or methylsulfinyl groups. The favored arrangement of the aromatic rings, due to the π-stacking[16] effect, and the stability of the piperidinium chelate in the ketopyridine moiety probably

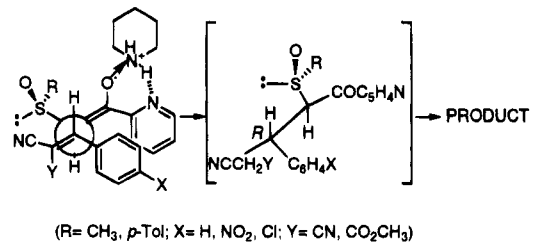

Figure 1. Transition state for the reaction of the β-keto sulfoxides with γ-arylidenemalonitriles and benzylidenecyanoacetates.

explain the formation of the only observed isomer. However, the possibility that the reaction is under thermodynamic, rather than kinetic, control cannot be ruled out. The C_4-H is acidic and epimerization at C_4 may explain the formation of only one (the thermodynamic) product.[17]

In view of the previous results, we were not surprised to find that the reaction of β-keto sulfone **10** with compound **2**, under the same mild experimental conditions, afforded in good yield (81%) the derivative **11**[10] [^1H NMR DMSO) (δ) 4.86 (H_4); ^{13}C NMR (DMSO) (δ) 45.9 (C_4); 57.2 (C_3)]. However, a similar coupling between compound **12** and the acceptor **2** gave the expected pyrano sulfone derivative **13**[10] [^1H NMR (DMSO) (δ) 4.88 (H_4); ^{13}C NMR (DMSO) (δ) 40.8 (C_4); 60.4 (C_3)] in lower 28% yield (45% yield, taking into account the recovered starting material).

In summary, with these simple cases we have shown the first successful examples of the Michael addition of β-keto sulfoxides and β-keto sulfones to highly stabilized Michael acceptors. Reasearch is now in progress to define the synthetic scope and general stereochemical aspects of these highly stereocontrolled Michael additions.

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Supporting Information Available: Experimental procedure, compound characterization data, ORTEP drawing, and X-ray data acquisition of compound (±)-**7** (7 pages).

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(14) The X-ray structure of compound **9** will be reported elsewhere.
(15) Davis, R.; Kern, J. R.; Kurz, L. J.; Pfister, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 7873 and references cited therein.
(16) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475.
(17) The authors thank the reviewer for useful suggestions concerning this point.