Michael Reactions of β-Keto Sulfoxides and β-Keto Sulfones

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The unprecedented Michael additions of racemic or enantiomerically pure β-keto sulfoxides (**1**, **6**, **10**−**12**) and β-keto sulfones (**23**, **25**, **27**, **29**, **30**) to the highly stabilized Michael acceptors **2**, **4**, **8**, and **21**, **31**, and **32** are described. The process proceeds efficiently, under very mild reaction conditions: ethanol, piperidine (catalytic), room temperature. The reaction of the β-keto sulfoxides having the 2-pyridyl ketone moiety, with arylidenemalononitriles (**2**, **4**) and α-cyanocinnamates (**8**) has given the polyfunctionalized 2-amino-4*H*-pyran adducts (**3**, **5**, **7**, **9**), in high yield, with total diastereo- and enantioselectivity. The reaction of 2-pyridyl ketone containing β-keto sulfone **23** with arylidenemalononitrile (**2**) gave the polyfunctionalized 2-amino-4*H*-pyran **24**, in high yield. Similar β-keto sulfoxides (**10**−**12**) or β-keto sulfones (**25**, **27**), lacking the 2-pyridyl ketone moiety, underwent the same reaction, but with lower yields and poor diastereoselection. In some cases, noncyclized intermediates have been detected. The β-keto sulfones **29** and **30** did not react under the same experimental conditions. Simple Michael acceptors such as ethyl acrylate, cinnamonitrile, or methyl vinyl ketone proved also to be reluctant to react with β-keto sulfoxides **1**. In summary, the powerful, strong, and particularly efficient stereodirecting properties of the 2-pyridyl ketone moiety embodied in the β-keto sulfoxides **1** and **6** or β-keto sulfone **23** have been observed for the first time. This fact coupled to the apparently critical and necessary influence of the π−π stacking interaction in the approach of reactants is discussed in depth here and used with obvious advantages in important synthetic transformations.

Introduction

The Michael reaction is one of the most useful processes in organic synthesis.[1] The 1,4-conjugate additions of stabilized carbanions to unsaturated acceptors is one of the fundamental and efficient methods for the formation of carbon−carbon bonds.[2] Asymmetric versions of these protocols have been exhaustively analyzed.[3]

In our laboratory, in the last years we have addressed for the first time the chiral Michael reaction of enantiomerically pure β-keto esters with arylidenemalononitriles, α-benzoylcinnamonitriles, and α-cyanocinnamates or the 1,4-conjugate addtions of stabilized carbanions derived from 1,3-dicarbonyl compounds with chiral α-cyanocinamates or α-cyanopropenoates.[4] As a result, we have reported the first synthesis of enantiomerically pure, polyfunctionalized 2-amino-4*H*-pyrans.[4,5] As an extension of our work on this topic, we have designed a new approach based on the 1,4-conjugate additions of sulfinyl carbanions derived from β-keto sulfoxides[6] and β-keto sulfones with highly stabilized Michael acceptors.

Although the Michael additions of α-thioesters,[7] α-thioacetonitriles,[8] sulfinyl, or sulfonyl carbanions[9,10] to unsaturated acceptors is well documented, a careful examination of the current literature has shown that 1,4-conjugate additions of β-keto sulfones[11] are unprecedented and that similar reactions of β-keto sulfoxides[6] with Michael acceptors are scarce and of limited scope. In some cases the sulfur moiety has been eliminated in the course of the reaction[12] or the intermediate adduct, without further analysis, has been submitted to reductive cleavage.[13] Chiral sulfoxides have been used frequently as chiral auxiliaries in highly asymmetric carbon−carbon bond formation.[14] *Surprisingly, in no case has the*

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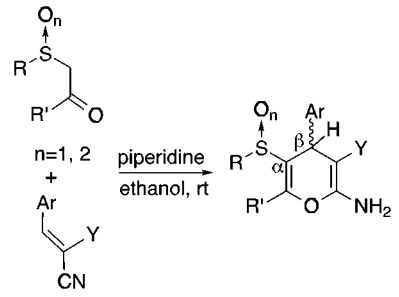
Scheme 1



stereochemical outcome of the 1,4-conjugate additions of chiral or racemic β-keto sulfoxides been defined and documented. Here we report the scope of these reactions.

Results and Discussion

In view of the potential in organic synthesis of these processes, in this paper we report the first analysis of the 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 arylidenemalononitriles, α-benzoylcinnamonitriles, and α-cyanocinnamates[15] (Scheme 1). The use of these substrates should in principle lead to exclusive 1,4-conjugate addition products,[1] followed by the expected final *O*-ring closure. If this is the case, this chemical transformation, giving 2-amino-4*H*-pyrans,[5] simplifies the stereochemical analysis and should allow us to define the extent of the asymmetric induction obtained at the distant C*β*-position with respect to the sulfur atom during the Michael addition (Scheme 1). An extremely efficient and highly stereocontrolled process has resulted, with significant synthetic and mechanistic interest.

Reaction of *β*-Keto Sulfoxides with Michael Acceptors. A. Reaction of *β*-Keto Sulfoxides 1 and 6 with Arylidenemalononitriles 2 and 4. Racemic or enantiomerically pure β-keto sulfoxides **1** and **6** have been selected as Michael donors in these reactions (Table 1). In the initial experiments we tried the arylidenemalononitrile type of Michael acceptors (**2** and **4**). Thus, the coupling of racemic β-keto sulfoxide **1**[16] 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 (2−3 h) which afforded compound **3** in 78% yield as the exclusive isomer. The presumed intermediate δ-oxo nitrile addition product, as expected,[17] led smoothly to the polyfunctionalized 2-amino-4*H*-pyran nucleus, after *O*-ring closure. 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 same reaction, using ethanol as solvent at −78 °C and warming the reaction at −10 °C during 8 h, gave compound **3** in only 38% yield. When toluene was used as solvent the yield was only 30%. We also tested acetonitrile with limited success (46% yield). *In all these experiments, always only one stereoisomer was detected and isolated.*

In summary, ethanol at room temperature was the selected condition and has been used throughout these studies. Piperidine is a convenient and very mild base, routinely used in our precedent work,[4] and other bases tested (triethylamine, pyridine, potassium *tert*-butoxide) did not afford better results. After completion of the reaction, the precipitated adduct was isolated or the solvent was removed and the crude submitted to flash chromatography to purify the final reaction product.

The reaction of the same racemic Michael donor **1** with the acceptor **4**, under identical experimental conditions, afforded pyran **5** [^{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 racemic β-keto sulfoxide **6**[18] gave also the expected pyran **7** in 86% yield; only one isomer could be detected. X-ray analysis[19] 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 reaction of enantiomerically pure precursor (R_S)-**6** with compound **4** gave optically pure **7** (R_S, C_4R) {$[\alpha]^{25}_D$ −153 (*c* 0.88, $CHCl_3$)} in similar chemical yield. From this result it is clear that the type of functional residue attached to the sulfur moiety (methyl or *p*-tolyl) does not affect the stereochemical course of the Michael addition.

A 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) allowed us to tentatively assign the same relative *syn* stereochemistry at the sulfur atom and at C_4.

B. Reaction of *β*-Keto Sulfoxide 1 with α-Cyanocinnamate 8. In view of the success with some selected arylidenemalononitriles, we tried the α-cyanocinnamate **8** as the Michael acceptor. Reaction with racemic β-keto sulfoxide **1**, under the usual conditions, gave the expected pyran **9** [^{1}H NMR ($CDCl_3$) δ 5.38 (H_4); ^{13}C NMR ($CDCl_3$) δ 41.5 (C_4); 81.3 (C_3)]. Note that simultaneous transesterification in our standard experimental conditions (ethanol as solvent) resulted in the final ethyl ester **9**. *This compound was again obtained as the exclusive isomer*, but in lower yield [33% (50%, taking into account the recovered starting material)]. The structure of the product was confirmed after X-ray analysis.[19] In this instance, changing the Michael acceptor does not affect the qualitative and quantitative degree of the asymmetric induction, although the chemical yield is slightly lower; this is coherent with our observations of higher efficiency of arylidenemalononitriles compared with α-cyanocinnamates in Michael reactions.[4]

C. A Model for Acyclic Diastereoselection. At this point of our studies, a simple model for the transition state could be advanced to justify the high degree of

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(15) To our knowledge only the Michael addition of (phenylsulfinyl)acetone to dimethyl ethylideneacetoacetate or benzylideneacetoacetate has been reported and described with poor results: Jaxa-Chamiec, A. A.; Sammes, P. G.; Kennewell, P. D. *J. Chem. Soc, Perkin Trans. 1* **1980**, 170−175.

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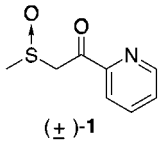
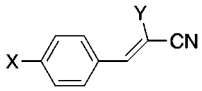
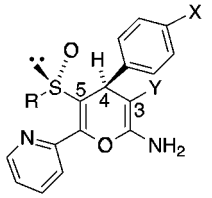
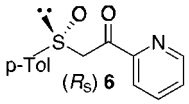
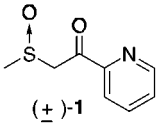
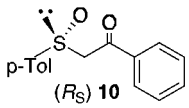
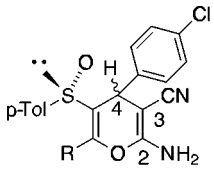
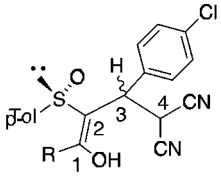
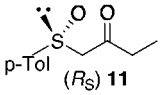
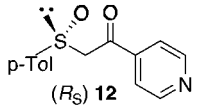
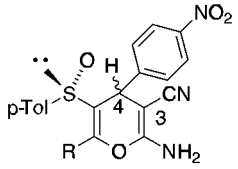
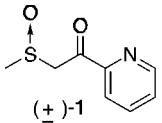
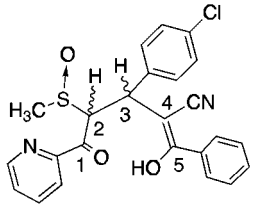
Table 1. Reaction of β-Keto Sulfoxides with Michael Acceptors

Michael Donors	Michael Acceptors	Products	Yield (%)
 (±)-**1**	 **2** X = NO_2, Y = CN **4** X = Cl, Y = CN	 **3** R = CH_3, X = NO_2, Y = CN **5** R = CH_3, X = Cl, Y = CN	78 92
 (R_S) **6**	**4**	**7** R = p-Tol, X = Cl, Y = CN	86
 (±)-**1**	**8** X = H, Y = CO_2Me	**9** R = CH_3, X =H, Y = CO_2Et	33 (50[a])
 (R_S) **10**	**4**	 **13** (C4 *S*)R= C_6H_5 **15** (C4 *R*)R= C_6H_5	 **14** R= C_6H_5	59[b]
 (R_S) **11**	**4**	**16** (C4 *S*) R= CH_2CH_3 **18** (C4 *R*) R= CH_2CH_3	**17** R= CH_2CH_3	86[b]
 (R_S) **12**	**2**	 **19** (C4 *S*)R= C_5H_4N **20** (C4 *R*)R= C_5H_4N	57[b]
 (±)-**1**	**21** X= Cl, Y= COC_6H_5	 **22**	17

[a] Taking into account the recoverd β-ketosulfoxide; [b] Total yield for the mixture of the isomers.

asymmetric induction obtained in the reaction of β-keto sulfoxides **1** and **6** with arylidenemalononitriles **2** and **4** or α-cyanocinnamate **8**. 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[20] 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[21] effect, and the stability of the piperidinium chelate in the 2-ketopyridyl moiety probably 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.

D. Reaction of β-Keto Sulfoxides 10−12 with Arylidenemalononitriles 2 and 4. With these results in mind and in order to verify this attractive hypothesis, we used once more the arylidenemalononitrile compound **4** as Michael acceptor but changed the type of β-keto sulfoxide. Note that the selected β-keto sulfoxides **1** and **6** had in common a *o*-pyridine ring attached at the ketone. We wondered also if this particular structural motif had a critical influence in the high stereochemical control observed and decided to study indepth this aspect. Thus,

(20) Davis, R.; Kern, J. R.; Kurz, L. J.; Pfister, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 7873−7874 and references cited therein.

(21) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475−497.

(22) El Ouzzani, H.; Khiar, N.; Fernández, I.; Alcudia, F. *J. Org. Chem.* **1997**, *62*, 287−291.

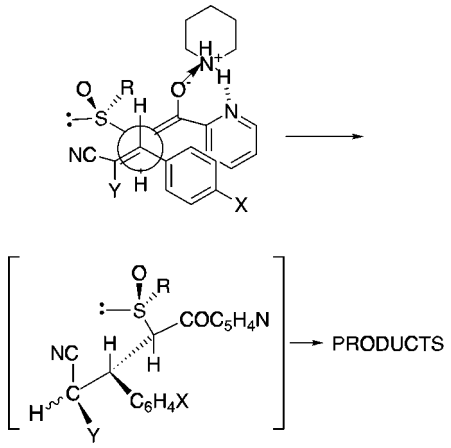
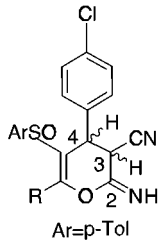


Figure 1. Transition state for the reaction of the β-keto sulfoxides with α-arylidenemalononitriles and benzylidenecyanoacetates.



14A
17A

Figure 2. Tautomeric forms of products **14** and **17**.

compounds **10**−**12** were selected.[22] In compounds **10** and **11**, a phenyl or ethyl group is attached, respectively, to the ketone; in compound **12**, the group attached at the ketone is a p-pyridine nucleus.

The reaction of the chiral compound **10** with the Michael acceptor **4** gave a mixture of isomers **13**, **14**, and **15** (ratio in crude determined by ^{1}H NMR: 1:2:1.6) in a 59% total yield. Compound **14** appears to be an "open" molecule, in the tautomeric form shown, that has not evolved into the cyclic form *via O*-ring closure or it is in equilibrium with the "cyclic forms" **13** and **15**. The high observed vicinal coupling constant (14.0 Hz) between H_3 (4.55 ppm) and H_4 (4.22 ppm) (these values can be interchanged) suggests an antiperiplanar arrangement of these hydrogens that also minimize the steric and stereoelectronic interactions of the substituents attached at these carbons. We were unable to establish the absolute configuration at C_3, but only one isomer was evident by ^{1}H NMR inspection. However, we cannot rule out out that product **14** is a cyclic compound in the C_2-imine-tautomeric form of compounds **13** and **15** (see structure **14A**; Figure 2). Adducts **13** [^{1}H NMR ($CDCl_3$) δ 3.89 (H_4); ^{13}C NMR ($CDCl_3$) δ 36.4 (C_4); 63.2 (C_3)] and **15** [^{1}H NMR ($CDCl_3$) δ 4.63 (H_4); ^{13}C NMR ($CDCl_3$) δ 33.9 (C_4); 63.3 (C_3)] are 2-amino-4*H*-pyrans and showed the expected typical NMR signals. We have assigned C4*R* to the major isomer **15**, by simple spectroscopic correlation with compounds **7** or **9**, whose stereochemistry at C_4 has been conclusively established by X-ray analysis.[19] In fact, C_4R isomers showed H_4 more shifted (>4.00 ppm, in $CDCl_3$ or in DMSO) than in C_4S isomers in the ^{1}H NMR spectrum. Note that for the first time in this work the asymmetric induction in the formation of new stereocenters has been scarcely stereoselective and the formation of simple 1,4-conjugate addition products (**14**) is also observed. Apparently, modification of the structure of the β-keto sulfoxide, as shown in compound **10**, has a dramatic effect in the reactive and stereochemical aspects of the Michael addition.

These important observations moved us to test the reactivity of chiral β-keto sulfoxide **11** with arylidenemalononitrile **4**. This reaction under the usual experimental conditions gave major compounds **16** (C_4S: H4 at 3.66 ppm) and **18** (C_4R: H4 at 4.46 ppm) (in a ratio 3/7, as determined in the crude by ^{1}H NMR; 86% total chemical yield). Compound **18** was isolated with inseparable traces of molecule **17** (H_3, 3.86 ppm, d, J = 13.5 Hz; H_4, 3.73 ppm, d, J = 13.5 Hz; this asignment can be interchanged). In summary, although in this case the presence of "open" molecules (**17**) is low (compare with the reaction of β-keto sulfoxide **10** with arylidenemalononitrile **4**), the stereoselection is still poor; however the same trend is observed as in the other cases and pyrans with C_4R results. As in the case of compound **14** (see above), we cannot rule out that product **17** is a cyclic compound in the C_2-imine-tautomeric form of compounds **16** and **18** (see structure **17A**; Figure 2).

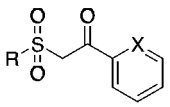
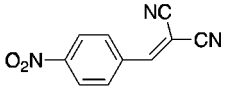
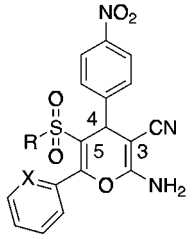
At this point it was clear that the 2-pyridyl ketone in the β-keto sulfoxides **1** and **6** has an important and critical effect on chemical yields, asymmetric induction, and regiochemistry (Michael additions *vs* Michael additions followed by *O*-ring closure to give the 2-amino-4*H*-pyrans). In addition, the $\pi-\pi$ staking effect turns out to be significant. When this stabilizing interaction is absent due to the nature of reagents, the yields, regioselectivity, and diastereoselectivity is negatively affected.

The effect of the 2-pyridyl ketone was definitively clear when we undertook the coupling of β-keto sulfoxides **12** with compound **2**. In fact, in our standard experimental conditions we obtained the expected 2-amino-4*H*-pyrans **19** and **20** in 57% chemical yield, as a mixture of diastereomers at C_4 in ≈1:10 ratio. After careful chromatography we isolated a mixture of **19** and **20** (1:2.3) and the more polar isomer **20** pure, which showed typical spectroscopic values for the major isomer C_4R, as in the other cases studied here [**19**: ^{1}H NMR (DMSO + $CDCl_3$) δ 3.96 (H_4); ^{13}C NMR ($CDCl_3$) δ 36.3 (C_4); 57.9 (C_3). **20**: ^{1}H NMR (DMSO + $CDCl_3$) δ 4.43 (H_4); ^{13}C NMR ($CDCl_3$) δ 33.1 (C_4); 59.0 (C_3)]. This asignment is in agreement with the spectroscopic data recorded for compound **7** (see above). Note that in isomers **7** and **20** (R_S, C_4R) H_4 appears at lower chemical field (δ > 4.00 ppm) than in compound **19** (R_S, C_4S). Not surprisingly, products **3** and **5** show values for H_4, in their ^{1}H NMR spectra, similar to those observed for compounds **7** and **20**, giving additional support to our initial assignments.

The favorable influence of 2-pyridyl ketone in these β-keto sulfoxides during the Michael reaction has not been previously documented. This effect is reminiscent of the well-known and exploited role played by nitrogen in heteroatom ring-substituted 2-pyridyl sulfones for their effective reduction by samarium diiodide, whereas phenyl sulfones were practically inert under identical conditions.[23]

(23) (a) Mazéas, D.; Skrydstrup, T.; Doumieux, O.; Beau J.-M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1383−1386. (b) Kende, A.; Mendoza, J. S. *Tetrahedron Lett.* **1990**, *31*, 7105−7108. (c) de Puilly, P.; Chénedé, A.; Mallet, J.-M.; Sinaÿ, P. *Bull. Soc. Chim. Fr.* **1993**, *130*, 256−265.

Table 2. Reaction of β-Keto Sulfones with Michael Acceptors

Michael Donors	Michael Acceptors	Products	Yield (%)
			
23 R = CH_3, X= N	**2**	**24** R = CH_3, X = N	81
25 R = p-Tol, X= CH	**2**	**26** R = p-Tol, X = CH	28 (48[a])
27 R = C_6H_5, X= CH	**2**	**28** R = C_6H_5, X= CH	27 (36[a])

[a] Taking into account the recoverd β-ketosulfone.

E. Reaction of β-Keto Sulfoxides 1 with α-Benzoylcinnamonitrile (21). Continuing with our systematic analysis of the structure−reactivity relationship, we next studied the reaction of racemic donor **1** with α-benzoylcinnamonitrile (**21**). A complex reaction mixture resulted, and after chromatography and recrystallization we only could isolate product **22** (~90% purity) in poor yield (17%). The structure of this compound has been established by detailed analysis of the spectroscopic and analytical data. The ^{1}H NMR spectrum of this sample showed, in addition to aromatic signals between 8.50 and 6.75 ppm (m, 18 H) and a methyl at 2.29 ppm (s), two doublets at 6.00 and 5.00 ppm (J = 12.8 Hz). No singlet for H4, characteristic for 2-amino-4*H*-pyran-like compounds, was observed. These data point to an "open" 1,5-dicarbonylic molecule, the major tautomer form as shown in structure **22**, that has not evolved into the cyclic form after *O*-ring closure. The large vicinal coupling constant between H2 and H3 suggests an antiperiplanar arrangement of these hydrogens that also minimizes the steric and stereolectronic interactions of the substituents attached at these carbons. This structural hypothesis was nicely confirmed upon ^{13}C NMR spectrum examination. In fact, we observed signals at 191.5 and 167.9 ppm for C1 (unsaturated ketone) and C5 (enol form of an unsaturated ketone), the expected four quaternary carbons in the aromatic rings (152.2, 137.9, 133.8, 131.9 ppm), the cyano signal at 119.4, 87.1 (quaternary, C4) and 61.9, 37.03 (CH, C2, and C3) and 30.0 (CH_3SO) ppm.

F. Other Michael Acceptors. Finally, it was of great interest to see if not so highly stabilized acceptors could react with our Michael donors. To our surprise methyl vinyl ketone, ethyl acrylate, or cinnamonitrile did not react with our sulfoxides in our standard experimental conditions. It is obvious that these β-keto sulfoxides, using our experimental conditions, only react with triply, electron-withdrawing substituted Michael acceptors. However, special care has to be paid to the selection of these substrates, because we observed that, for instance, ethyl α-acetylcinnamate on reaction with compound **6** gave a complex reaction mixture and no defined reaction product could be isolated and characterized. Probably the 1,4-conjugate addition occurs, but subsequent *O*-ring closure followed by partial aromatization as above is now prevented, and aldol reactions or polymerization giving telomers is the only result.

Reaction of β-Keto Sulfones with Michael Acceptors: Reaction of β-Keto Sulfones 23, 25, and 27 with Arylidenemalononitrile 2. The selected β-keto sulfones were compounds **23**, **25**,[22] and the commercially available **27**.

In view of the previous results we were not surprised to find that the reaction of β-keto sulfone **23** with compound **2**, under the same mild experimental conditions, afforded in good yield (81%) the derivative **24** [^{1}H 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 **25** and the acceptor **2** gave the expected pyrano−sulfone derivative **26** [^{1}H NMR (DMSO) δ 4.88 (H_4); ^{13}C NMR (DMSO) δ 40.8 (C_4); 60.4 (C_3)] in a low 28% yield. The reaction of β-keto sulfones **27** with the same Micahel acceptor **2** gave the 2-amino-4*H*-pyran **28** [^{1}H NMR ($CDCl_3$) δ 4.95 (H_4); ^{13}C NMR ($CDCl_3$) δ 39.5 (C_4); 52.6 (C_3)] in very poor yield (27%) and 90% purity (we were unable to obtain it chemically pure).

Finally, we analyzed some reactions: (a) β-keto sulfones **29** and **30** with compound **31**; (b) β-keto sulfone **30** with arylidenemalononitrile **2**, and (c) β-keto sulfone **27** with Michael acceptor **32**, with deceiving results; no reaction was observed, even under forcing conditions (Figure 3).

These are again good examples of the efficiency of Michael donors having the particular *o*-pyridine ring nucleus attached to the ketone, compared with the donors where this particular structural feature is absent, and the coupled effect of the π−π aromatic stacking interactions. Note also that in this case no "open-type-molecule", resulting from simple 1,4-conjugate addition, was detected; this is possibly a consequence of the stonger electron-withdrawing ability of the sulfone group com-

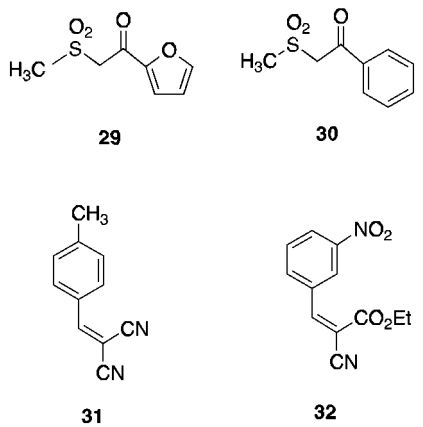


Figure 3. β-Keto sulfones **29**−**32**.

pared with that of the sulfoxide. As a result, the equilibrium ketone/enol ether is more shifted to the enol tautomer, and more *O*-ring closures are effected.

Conclusions

In summary, with these simple cases we have described the first successful examples of the Michael addition of β-keto sulfoxides and β-keto sulfones to Michael acceptors. Simple partners such as acrylates or cinnamates are unreactive. The reaction is only successul with triply, highly deactivated Michael acceptors. The reaction proceeds under mild reaction conditions, using piperidine as catalyst and ethanol as solvent, in moderate to good yields. In the case of the β-keto sulfoxides, depending on the type of Michael acceptor, we have isolated simple 1,4-conjugate addition products, in the case of benzoylcinnamonitriles, or, after *O*-ring closure, 2-amino-4*H*-pyrans, in the case of arylidenemalonitriles. We have observed for the first time the critical effect of the 2-pyridyl ketone moiety in these Michael reactions. Substrates having this structural motif give excellent diastereoselectivities in the 1,4-conjugate additions.

Experimental Section

Reactions were monitored by TLC using precoated silica gel aluminum plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric−acetic acid spray, 1% aqueous potassium permanganate solution, or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na_2SO_4 was used to dry organic solutions during workups, and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using Kieselgel 60 (230−400 mesh, Merck) and hexane−ethyl acetate mixtures as eluent. ^{1}H and ^{13}C NMR spectra were recorded with a Varian VXR-300S spectrometer, using tetramethylsilane as internal standard. All the Michael acceptors have been prepared according to the standard methodologies.[24]

General Procedure for the Coupling of β-Keto Sulfoxides and β-Keto Sulfones (Donors) with Michael Acceptors. An ethanol solution of equimolecular quantities of the donor with the appropriate Michael acceptor (0.5 M) was treated with piperidine (some drops, catalytic), at room temperature. 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.

2-Amino-4*H*-pyran (3). Starting from β-keto sulfoxide **1** (112 mg, 0.61 mmol) and compound **2** (134 mg, 0.67 mmol, 1.1 equiv), following the general procedure, pyran **3** was obtained (192 mg, 78% yield): mp 224−227 °C; IR (KBr) ν 3500−3300, 3200−3000, 2190, 1665 cm^{-1}; ^{1}H NMR (200 MHz, DMSO) δ 8.68 (d, J = 4.8 Hz, 1H), 8.25 (d, J = 8.7 Hz, 2 H), 8.07−8.03 (m, 2 H), 7.59 (d, J = 8.7 Hz, 2 H), 7.56−7.52 (m, 1 H), 7.40 (br s, 2 H), 4.95 (s, 1 H), 2.35 (s, 3 H); ^{13}C NMR (50 MHz, DMSO) δ 160.3, 151.9, 148.9, 148.6, 147.3, 145.4, 137.9, 129.5, 124.6, 125.1, 123.2, 122.2, 119.6, 57.6, 41.6, 33.3; MS (70 eV) *m*/*z* 319 (M^+ − 63), 78 (100). Anal. Calcd for $C_{18}H_{14}N_4O_4S$: C, 56.54; H, 3.69; N, 14.66; S, 8.37. Found: C, 56.35; H, 3.63; N, 14.72; S, 8.19.

2-Amino-4*H*-pyran (5). Starting from β-keto sulfoxide **1** (252 mg, 1.3 mmol) and compound **4** (264 mg, 1.4 mmol, 1.1 equiv), following the general procedure, pyran **5** was obtained (475 mg, 92% yield): mp 215−217 °C dec; IR (KBr) ν 3320, 3160, 2200, 1665 cm^{-1}; ^{1}H NMR (200 MHz, DMSO) δ 8.65 (d, J = 4.7 Hz, 1H), 8.03−7.99 (m, 2 H), 7.52−7.50 (m, 1 H), 7.43 (d, J = 8.5 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H), 7.26 (br s, 2 H), 4.80 (s, 1 H), 2.34 (s, 3 H); ^{13}C NMR (50 MHz, DMSO) δ 159.7, 148.4, 148.3, 144.6, 143.2, 137.4, 132.1, 129.6, 128.8, 124.6, 123.3, 121.7, 119.4, 57.9, 40.9, 32.4; MS (70 eV) *m*/*z* 354 (M^+ − 17), 308 (100). Anal. Calcd for $C_{18}H_{14}ClN_3O_2S$: C, 58.14; H, 3.79; N, 11.29; S, 8.62. Found: C, 58.21; H, 3.72; N, 11.23; S, 8.35.

2-Amino-4*H*-pyran (7). Starting from β-keto sulfoxide **6** (119 mg, 0.45 mmol) and compound **4** (94 mg, 0.5 mmol, 1.1 equiv), following the general procedure, pyran **7** was obtained (173 mg, 86% yield): mp 228−230 °C; IR (KBr) ν 3400, 3300, 2200, 1655 cm^{-1}; ^{1}H NMR (200 MHz, DMSO) δ 8.69 (d, J = 4.3 Hz, 1 H), 8.08−7.80 (m, 2 H), 7.58 (m, 1 H), 7.44 (d, J = 7.9 Hz, 2 H), 7.24 (m, 2 H), 6.95−6.88 (m, 4 H), 6.74 (d, J= 7.9 Hz, 2H), 4.67 (s, 1 H), 2.18 (s, 3 H); ^{13}C NMR (50 MHz, DMSO) δ 159.9, 149.2, 148.6, 148.0, 141.9, 139.5, 128.7, 128.5, 127.8, 125.1, 137.5, 131.0, 125.5, 123.0, 122.6, 119.2, 58.4, 31.7, 20.5; MS (70 eV) *m*/*z* 364 (4), 139 (100). Anal. Calcd for $C_{23}H_{18}ClN_3O_2S$: C, 63.37; H, 4.16; N, 9.63; S, 7.35. Found: C, 63.60; H, 4.03; N, 9.38; S, 7.10.

2-Amino-4*H*-pyran (9). Starting from β-keto sulfoxide **1** (303 mg, 1.6 mmol) and compound **8** (336 mg, 1.8 mmol, 1.1 equiv), following the general procedure, pyran **9** was obtained [191 mg, 33% yield (50% taking into account the recovered **1**): mp 184−187 °C; IR (KBr) ν 3400, 3300, 1745, 1655 cm^{-1}; ^{1}H NMR (200 MHz, DMSO) δ 8.59 (d, J = 4.8 Hz, 1 H), 7.90−7.75 (m, 2 H), 7.50−7.20 (m, 6 H), 6.30 (br s, 2H), 5.38 (s, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 2.35 (s, 3 H), 1.22 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz, DMSO) δ 169.5, 159.3, 149.2, 149.8, 148.6, 144.7, 146.2, 137.1, 129.5, 128.7, 127.4, 124.2, 121.9, 81.3, 60.2, 41.5, 32.1, 14.7; MS (70 eV) *m*/*z* 384 (M^+, 3), 367 (34), 78 (100). Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.49; H, 5.24; N, 7.29; S, 8.32. Found: C, 62.47; H, 5.32; N, 7.53; S, 8.12.

Reaction of Donor 10 with the Arylidenemalononitrile 4. Starting from enantiomerically pure β-keto sulfoxide **10** (173 mg, 0.67 mmol) and compound **4** (140 mg, 0.74 mmol, 1.1 equiv), following the general procedure, after evaporation of the solvent, the residue was submitted to flash chromatography (hexane/ethyl acetate 30%) to give fractions A (58 mg), B (23 mg), and C (101 mg); 59% overall yield.

Fraction A is an inseparable mixture formed by traces of compound **14** and pyran **13**: mp 148−152 °C; $[\alpha]^{25}_D$ +169 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3600−3240, 3190, 2200, 1670 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) (signals for pyran **13**) δ 7.71−7.11 (m, 13 H), 4.69 (br s, 2 H), 3.89 (s, 1 H), 2.39 (s, 3 H); ^{13}C NMR (50 MHz, DMSO) (signals for pyran **13**) δ 158.2, 154.7, 141.7, 141.6, 138.5, 133.3, 131.3, 130.3−129.4, 124.5, 121.4, 118.0, 63.2, 36.4, 21.4; MS (70 eV) *m*/*z* 429 (M^+ − 18, 2), 105 (100). Anal. Calcd for $C_{25}H_{19}ClN_2O_2S$: C, 67.18; H, 4.28; N, 6.26; S, 7.17. Found: C, 66.90; H, 4.03; N, 6.38; S, 7.30.

Fraction B is an inseparable mixture of compound **14** and pyran **13**, in a 2:1 ratio, respectively.

Fraction C is an inseparable mixture of compound **14** and pyran **15**, in a 5:3 ratio, respectively: IR (KBr) ν 3600−3240, 3190, 2200, 1665 cm^{-1}; ^{1}H NMR (see text); MS (70 eV) *m*/*z* 139 (100). Anal. Calcd for $C_{25}H_{19}ClN_2O_2S$: C, 67.18; H, 4.28; N, 6.26; S, 7.17. Found: C, 67.20; H, 4.31; N, 5.98; S, 7.01.

Reaction of β-Keto Sulfoxide 11 with the Arylidenemalononitrile 4. Starting from enantiomerically pure β-keto sulfoxide **11** (134 mg, 0.63 mmol) and compound **4** (132 mg, 0.70 mmol, 1.1 equiv), following the general procedure, after evaporation of the solvent, the residue was submitted to flash chromatography (hexane/ethyl acetate 30%) to give fractions A (87 mg) and B (133 mg); 86% overall yield.

Fraction A is formed by pyran **16**: mp 174−177 °C; $[\alpha]^{25}_D$ +277 (*c* 0.49, $CHCl_3$); IR (KBr) ν 3600−3240, 3190, 2200, 1670 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (s, 4 H), 7.00 (d, J = 8.1 Hz, 2 H), 6.96 (d, J = 8.1 Hz, 2 H), 4.55 (br s, 2 H), 3.66 (s, 1 H), 2.80 (q, J = 5.1 Hz, 2 H), 2.39 (s, 3 H), 1.29 (t, J = 5.1 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.5, 158.3, 142.3, 142.1, 138.5, 133.5, 130.6, 129.2, 129.0, 125.0, 119.4, 118.8, 63.2, 36.6, 24.5, 21.9, 12.8; MS (70 eV) *m*/*z* 381 (M^+ − 17, 22), 139 (60), 57 (100). Anal. Calcd for $C_{21}H_{19}ClN_2O_2S$: C, 63.20; H, 4.79; N, 7.00; S, 8.03. Found: C, 63.29; H, 4.68; N, 6.86; S, 8.04.

(24) (a) Pratt, E. F.; Werble, E. *J. Am. Chem. Soc.* **1950**, *72*, 4638−4645. (b) Soto, J. L.; Seoane, C.; Martín, N.; Quinteiro, M. *Heterocycles* **1984**, *22*, 1−6. (c) Quinteiro, M.; Seoane, C.; Soto, J. L. *J. Heterocycl. Chem.* **1978**, *15*, 57−61.

Fraction B is an inseparable mixture of compound **17** (traces) and pyran **18**: mp 206−209 °C; $[\alpha]^{25}_D$ +65 (*c* 0.99, $CHCl_3$); IR (KBr) *ν* 3600−3240, 3190, 2220, 2200, 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ* 6.96 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 6.64 (d, *J* = 8.4 Hz, 2 H), 4.71 (br s, 2 H), 4.50 (s, 1 H), 2.83 (q, *J* = 7.3 Hz, 2 H), 2.25 (s, 3 H), 1.32 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 158.7, 157.6, 141.4, 141.0, 138.0, 132.9, 129.6, 129.4, 128.6, 124.2, 119.4, 118.7, 63.3, 33.4, 24.6, 21.5, 12.2; MS (70 eV) *m*/*z* 139 (100). Anal. Calcd for $C_{21}H_{19}ClN_2O_2S$: C, 63.20; H, 4.79; N, 7.00; S, 8.03. Found: C, 63.57; H, 5.04; N, 7.24; S, 8.40.

Reaction of β-Keto Sulfoxide 12 with the Arylidenemalononitrile 2. Starting from enantiomerically pure β-keto sulfoxide **12** (82 mg, 0.31 mmol) and compound **2** (105 mg, 0.52 mmol, 1.6 equiv), following the general procedure, after evaporation of the solvent, the residue was submitted to flash chromatography (methylene chloride/methanol 2.5%) to give fractions A (26 mg) and B (59 mg); 57% overall yield.

Fraction A is a mixture of pyrans **19** and **20** in a 1:2.3 ratio; ^1H NMR and ^{13}C NMR (see text).

Fraction B is major pyran **20** pure: mp 137−140 °C; IR (KBr) *ν* 3600−3100, 2200, 1670, 1600, 1350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + DMSO) *δ* 8.53 (d, *J* = 6.1 Hz, 2 H), 7.48 (d, *J* = 8.7 Hz, 2 H), 7.37 (d, *J* = 6.1 Hz, 2 H), 6.77 (d, *J* = 8.3 Hz, 2 H), 6.65 (d, *J* = 8.7 Hz, 2 H), 6.58 (d, *J* = 6.1 Hz, 2 H), 6.26 (br s, 2 H), 4.43 (s, 1 H), 1.89 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO) *δ* 159.0, 152.1, 149.3, 149.1, 145.2, 140.6, 136.8, 135.8, 135.7, 128.4, 127.3, 123.6, 122.8, 122.3, 122.0, 117.6, 59.0, 33.1, 20.0. Anal. Calcd for $C_{24}H_{18}N_4O_4S$: C, 62.88; H, 3.96; N, 12.22; S, 6.98. Found: C, 63.01; H, 4.11; N, 12.24; S, 6.88.

Reaction of Donor 1 with the α-Benzoylcinnamonitrile (21). Starting from β-keto sulfoxide **1** (362 mg, 2.0 mmol) and compound **10** (588 mg, 2.2 mmol, 1.1 equiv), following the general procedure, after evaporation of the solvent, the residue was submitted to flash chromatography (methylene chloride/methanol 1%) giving a material (842 mg), whose NMR analysis showed a very complex reaction mixture. Recrystallization from hexane/etyhyl acetate gave product **22** (145 mg, 17%): mp 142−144 °C; IR (KBr) *ν* 3600−3100, 2200, 1695 cm^{-1}; ^1H NMR and ^{13}C NMR (see text). Anal. Calcd for $C_{24}H_{19}ClN_2O_2S$: C, 66.28; H, 4.37; N, 6.44; S, 7.36. Found: C, 66.39; H, 4.26; N, 6.38; S, 7.22.

2-Amino-4*H*-pyran (24). Starting from enantiomerically pure β-keto sulfone **23** (315 mg, 1.60 mmol) and compound **2** (360 mg, 1.80 mmol, 1.1 equiv), following the general procedure, compound **24** (524 mg, 81% yield) was obtained: mp 175−178 °C; IR (KBr) *ν* 3485, 3320, 3200, 2200, 1680 cm^{-1}; ^1H NMR (200 MHz, DMSO) *δ* 8.68 (d, *J* = 4.8 Hz, 1 H), 8.32 (d, *J* = 8.1 Hz, 2 H), 8.02 (t, *J* = 7.7 Hz, 1 H), 7.84 (d, *J* = 7.7 Hz, 1 H), 7.63 (d, *J* = 8.1 Hz, 2 H), 7.58 (m, 1 H), 7.45 (br s, 2 H), 4.86 (s, 1 H), 2.96 (s, 3 H); ^{13}C NMR (50 MHz, DMSO) *δ* 159.1, 155.6, 150.6, 150.2, 149.1, 147.1, 137.4, 129.1, 125.8, 124.9, 124.6, 119.2, 119.0, 57.2, 45.9, 39.5; MS (70 ev) *m*/*z* 398 (M^+, 1), 79 (100). Anal. Calcd for $C_{18}H_{14}N_4OS$: C, 54.27; H, 3.54; N, 14.07; S, 8.12. Found: C, 54.41; H, 3.31; N, 14.25; S, 7.69.

2-Amino-4*H*-pyran (26). Starting from enantiomerically pure β-keto sulfone **25** (130 mg, 0.47 mmol) and compound **2** (104 mg, 0.52 mmol, 1.1 equiv), following the general procedure, after evaporation of the solvent and flash chromatography (hexane/ethyl acetate 30%) compound **26** [65 mg, 28% yield (45% taking into account the recovered starting material)] was obtained: mp 184−187 °C; IR (KBr) *ν* 3500−3200, 2200, 1670 cm^{-1}; ^1H NMR (200 MHz, CD_3COCD_3) *δ* 8.25 (d, *J* = 6.7 Hz, 2 H), 7.67 (d, *J* = 6.7 Hz, 2 H), 7.40 (m, 5H), 7.18 (d, *J* = 8.5 Hz, 2 H), 7.09 (d, *J* = 8.5 Hz, 2 H), 6.34 (br s, 2 H), 4.88 (s, 1 H), 2.77 (s, 3 H); ^{13}C NMR (50 MHz, CD_3COCD_3) *δ* 160.0, 158.0, 151.7, 148.2, 145.1, 138.9, 131.9, 131.5−124.7, 121.7, 118.4, 60.4, 40.8, 21.3; MS (70 eV) *m*/*z* 105 (100). Anal. Calcd for $C_{25}H_{19}N_3O_5S$: C, 63.42; H, 4.05; N, 8.88; S, 6.76. Found: C, 63.70; H, 4.35; N, 9.21; S, 6.48.

2-Amino-4*H*-pyran (28). Starting from enantiomerically pure β-keto sulfone **27** (94 mg, 0.36 mmol) and compound **2** (110 mg, 0.55 mmol, 1.5 equiv), following the general procedure, after evaporation of the solvent and flash chromatography (hexane/ethyl acetate 50%) compound **28** [48 mg, 27% yield (36% taking into account the recovered starting material)] was obtained: mp 60−65 °C; IR (KBr) *ν* 3500−3200, 2200, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ* 8.35 (d, *J* = 8.7 Hz, 2 H), 7.67−7.10 (m, 12 H), 4.95 (s, 1 H), 4.88 (br s, 2 H); ^{13}C NMR (50 MHz, CD_3COCD_3) *δ* 160.0, 158.0, 151.7, 148.2, 145.1, 138.9, 131.9, 131.5−124.7, 121.7, 118.4, 52.7, 39.5; MS (70 eV) *m*/*z* 105 (100). Anal. Calcd for $C_{24}H_{17}N_3O_5S$: C, 62.74; H, 3.73; N, 9.15; S, 6.96. Found: C, 62.90; H, 3.45; N, 9.21; S, 6.78.

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