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1,3-Cycloaddition of Nitrile Oxides to Cyclic and Open-Chain 4-Oxo-2-sulfinylbut-2-enoic Acid Derivatives

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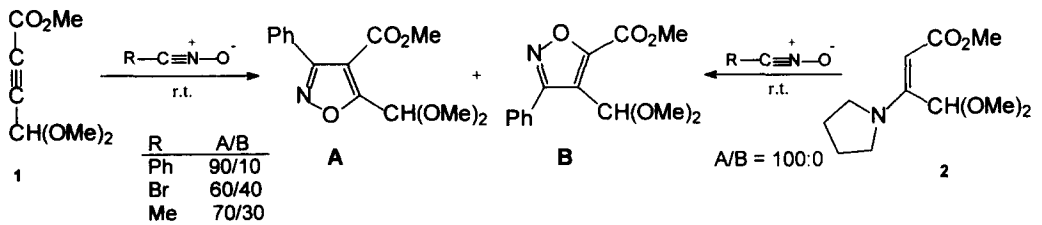
Abstract The reactions of *tert*-butyl (*E*)-4,4-diethoxy-2-*p*-tolylsulfinylbut-2-enoate with benzonitrile, acetonitrile, and bromoformonitrile oxides yield isoxazoles. However, (S_S,S_S)- and (R_S,S_S)-5-ethoxy-3-*p*-tolylsulfinylfuranones with benzonitrile oxide afford isoxazolines. The reactivity of the double bond as a dipolarophile is strongly increased by the sulfinyl group. This is also the case of the regioselectivity, which usually is opposite to that exhibited by dipolarophiles lacking the sulfinyl group. Electrostatic interactions seemingly explain this behaviour. The π-facial selectivity of the reactions with the cyclic dipolarophiles is dependent on steric effects, but some role seems to be exerted by electrostatic attraction.

Keywords: Cycloadditions, Sulfinyl compounds, Isoxazoles, Isoxazolines

1. Introduction

Isoxazoles exhibit interesting biological activities[1-3] and their further transformations offer a way of access to key intermediates in the synthesis of natural products and other pharmacologically active compounds.[4-5] One of the most general methods used to prepare isoxazole derivatives involves the 1,3-dipolar cycloaddition of nitrile oxides to alkynes or to alkenes bearing an easily removable substituent at the double bond, which makes them act as synthetic equivalents of alkynes.[6] In this context, we had previously reported the cycloadditions of nitrile oxides to methyl 4,4-dimethoxybut-2-ynoate (**1**) and (E)-4,4-dimethoxy-3-(pyrrolidin-1-yl)but-2-enoate (**2**).[7] Regioselectivity was usually very high (regioisomer **A** being favoured, (Scheme 1), thus providing a convenient entry to methyl 5-(dimethoxymethyl)isoxazole-4-carboxylates, in just one synthetic step.



Scheme 1

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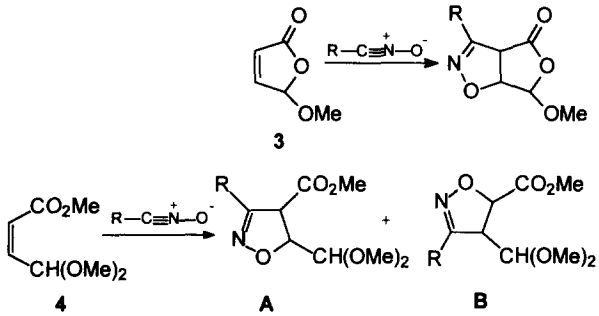
The reactions of nitrile oxides with alkenes lacking easily removable substituents yield isoxazolines. In this sense a complete regioselectivity was observed in reactions of 5-methoxyfuranone (**3**), whereas starting from methyl 4,4-dimethoxybut-2-enoate (**4**) the regioselectivity was lower and highly dependent on the nature of the substituent R at the dipole[8] (Scheme 2).



R	T °C	Time	A/B
Ph	20	6 d.	74:26
Br	20	4 d.	38:62
Me	40	1 d.	35:65

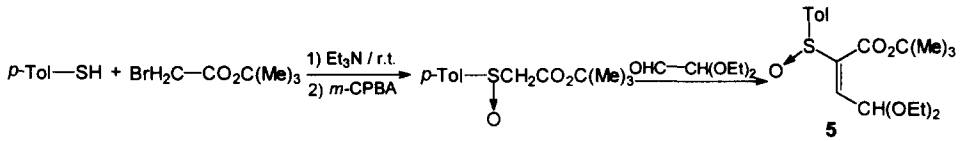
Scheme 2

Racemic vinyl sulfoxides have been widely used as synthetic equivalents of alkynes in Diels-Alder reactions[9-10] due to the easy elimination of the sulfinyl group, while its ability to control the π-facial selectivity of these cycloadditions has also found many applications in asymmetric synthesis.[11] By contrast, the behaviour of α,β-unsaturated sulfoxides as dipolarophiles has been much less investigated. Concerning asymmetric 1,3-dipolar reactions[12] with nitrile oxides, only studies on the use of sodium salts of β-ketosulfoxides[13] and their corresponding enolethers[14-15] have so far been reported. The low number of contributions in this field could be due to the seemingly weak influence of the sulfinyl group on the stereoselectivity control of these reactions deduced from the poor results observed in reactions of mesitonitrile oxide with racemic benzothiophene S-oxides,[16] yielding 1:1 mixtures of the two possible adducts resulting from the approach of dipole to either diastereotopic face of the sulfinylated double bond.

We are developing a wide research project to investigate the scope and stereoselectivity of the 1,3-dipolar cycloaddition of vinylsulfoxides. Our first reported contribution to this field consisted in asymmetric additions of diazomethane to enantiomerically pure 5-ethoxy-3-(*p*-tolylsulfinyl)furan-2(5*H*)-ones,[17] which revealed the highly positive effect of the sulfinyl group on both the reactivity and the π-facial selectivity of these cycloadditions. In this second paper we describe the reactions of some acyclic and cyclic vinylsulfoxides with nitrile oxides. As dipolarophiles we have studied the behaviour of *tert*-butyl (*E*)-4,4-diethoxy-2-(*p*-tolylsulfinyl)but-2-enoate (**5**), (S_5,S_S)- and (R_5,S_S)-5-ethoxy-3-(*p*-tolylsulfinyl)furan-2(5*H*)-ones (**6a** and **6b**). These compounds are the result of incorporating the sulfinyl group on the double bond of **4** and **3**, respectively.

2. RESULTS AND DISCUSSION

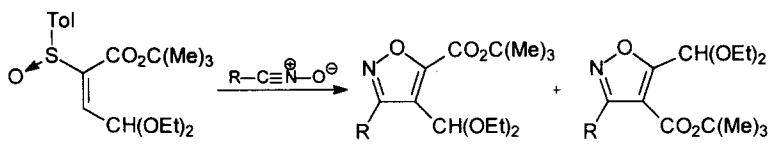
The synthesis of enantiomerically pure dipolarophiles **5** and **6** had been previously reported.[18] Racemic vinylsulfoxide (±)-**5** was synthesised from the commercially available *tert*-butyl bromoacetate and *p*-methylthiophenol (72% yield) following the procedure depicted in Scheme 3.



Scheme 3

Benzonitrile oxide and bromoformonitrile oxide were prepared by dehydrohalogenation of the corresponding hydroximic acid halides.[19-20] Acetonitrile oxide was generated *in situ* from nitroethane following Mukaiyama's method.[21]

Cycloaddition of benzonitrile oxide to vinylsulfoxide **5** was complete in 1 hour at 0 °C, affording a 16:1 mixture of regioisomeric isoxazoles **7B** and **7A** in high yield. Similar regioselectivity was observed in reactions using acetonitrile oxide (**8B** : **8A** = 14:1) and bromoformonitrile oxide (**9B** : **9A** = 14:1), but the reactivity of these last dipoles was lower (Scheme 4). The isoxazoline intermediate was not detected in any case, which prevented us obtaining any information about the influence of the sulfinyl group on the π-facial selectivity. These results also determined that these reactions were performed starting from racemic sulfoxide (±)-**5**. Isoxazoles **7B** and **8B** were isolated from the corresponding crude mixtures by column chromatography in 71% yield.

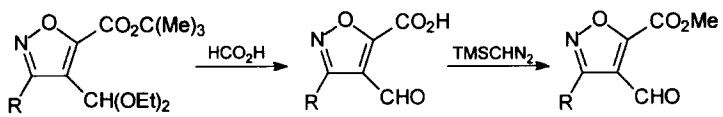


5 **7B-9B** **7A-9A**

R	°C	Time	B/A	Isoxazoles
Ph	0	60 min	16:1	7B + 7A
Me	20	23 h	14:1	8B + 8A
Br	20	60 min	14:1	9B + 9A

Scheme 4

Tentative structural assignments of the regioisomers **A** and **B** were made, according to our previous results,[7] from the relative δ value of their acetal CH. This structure was unequivocally ascertained by transformation of **7B** and **8B** into their corresponding methyl formylisoxazolecarboxylates **12** and **13** (Scheme 5) by reaction with formic acid and subsequent treatment with trimethylsilyldiazomethane. Compounds **12** and **13** had been previously reported as the minor regioisomers obtained from acetylenic dipolarophile **1**.[7]



7B: R = Ph
9B: R = Me

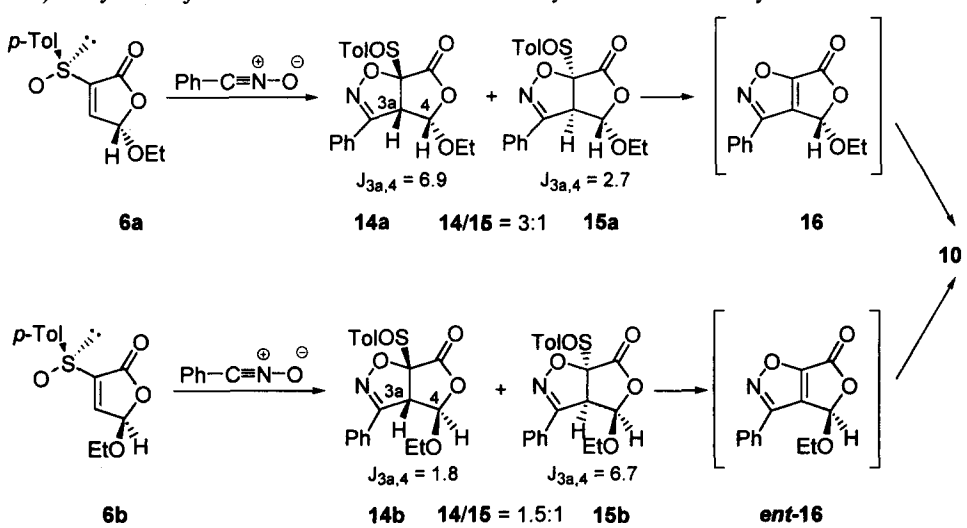
10: R = Ph
11: R = Me

12: R = Ph
13: R = Me

Scheme 5

The comparison of the results obtained from compounds **4** (Scheme 2) and **5** (Scheme 4) suggests that the sulfinyl group has a significant influence on both reactivity and regioselectivity. The milder reaction conditions required by the sulfinyl derivatives evidence their higher reactivity. The regioselectivity is very high, regardless of the substituent at the dipole, the regioisomer **B** being the major one in all cases. In this sense, the reactions of dipolarophile **5** are complementary to those of the alkyne **1** and enaminoester **2** (Scheme 1), since they afford a different isoxazole regioisomer as the major product. This change in the regioselectivity induced by the sulfinyl group cannot be explained by invoking its influence on the frontier orbital coefficients of the reacting atoms, because this factor would reinforce the orientating character of the alkoxycarbonyl group. Steric interactions, favouring the attack of the carbon atom at nitrile oxide (the most crowded extreme of the dipole) to the less substituted carbon of the dipolarophilic double bond, could be invoked to explain the observed regioselectivity. Nevertheless, the fact that the size of the R group at the dipole has little influence on the regioselectivity suggests that other more important contributing factors must also be considered. The assumption of a significant role of the electrostatic attraction between the negatively charged oxygen at the dipole and the positively charged sulfur at the dipolarophile, which remains almost constant for all these reactions, could reasonably explain the observed regioselectivity.

The presumably higher stability of the bicyclic adduct toward desulfinylation prompted us to study the reactions of benzonitrile oxide with the cyclic dipolarophiles **6a** and **6b**, in order to obtain information about the influence of the sulfinyl group on the π-facial selectivity. Compounds **6a** and **6b** reacted with benzonitrile oxide under mild conditions (5 minutes at 0 °C), affording mixtures of stereoisomeric furoisoxazolines (Scheme 6). Only the major adduct **14a** could be isolated as a yellow solid in 55% yield.



Scheme 6

The configurational assignment of the primary adducts (**14a,b** and **15a,b**) was based on the relative values of the vicinal coupling constants shown in Scheme 6. We have assumed that both the *cis* relationship between the sulfinyl group and H-3a as well as the configuration at C-5 existing in the starting dipolarophile remains unaltered for the adducts.

When the crude reaction mixture **14a** + **15a** (or pure **14a**) was allowed to stand in $CHCl_3$ solution at room temperature, it was completely transformed into 4-formylisoxazole-5 carboxylic acid **10**, indicating that both adducts are stereoisomers. This confirms that regioselectivity of the cycloaddition has been complete. Compound **10** was also formed when the crude reaction mixture **14b** + **15b** was allowed to stand in $CHCl_3$ solution. By monitoring the evolution of these reactions by ^{1}H-nmr, we could detect the formation of an intermediate compound, the structure of which was tentatively assigned as **16** (Scheme 6), based on the detection of a singlet signal at 5.70 ppm assigned to the acetal-type proton.

The presence of the sulfinyl group at the dipolarophile induces very significant changes in these 1,3-dipolar reactions. First of all, a substantial increase of the dipolarophilic reactivity of the double bond was observed (compound **3** requires 36 hours for complete reaction with benzonitrile oxide at room temperature[8] whereas the reactions of **6a** and **6b** are almost instantaneous at 0 °C). This fact, which had also been observed in reactions of **6a** or **6b** with diazomethane,[17] contrasts with the rather low influence of the sulfinyl group on the dienophilic reactivity of the double bond, deduced from the results obtained in reactions of **6a** and **6b** with cyclopentadiene.[18] Electrostatic interactions between the charged atoms at the dipole and the highly polarised sulfinyl group could be invoked to explain the observed differences in reactivity of vinyl sulfoxides in Diels-Alder and 1,3-dipolar reactions.

Additionally, the regioselectivity observed in the reactions of **6a** and **6b** is complete, but it is just the opposite to that observed from **3** (Scheme 2) and other furan-2(5*H*)-ones bearing alkoxy,[8,22-24] alkylthio or alkylsulfonyl groups[25] at C-5. This complete inversion of the regioselectivity can be explained taking into account that steric effects favour the approach of the less crowded extreme of the dipole to the more crowded one of the dipolarophile. However, the possible contribution of attractive interactions of the negatively charged oxygen at nitrile oxide with the sulfinyl sulfur and the carbonyl carbon, both positively charged, cannot be ignored. In this connection we must indicate that other sulfinylethylenes exhibit a lower[26,27] and even opposite[15] regioselectivity. This suggests that electrostatic attraction of the oxygen at the dipole with the sulfinyl sulfur, by itself, is not enough to explain the regioselective behaviour of compounds **6**, which therefore must be the result of a much more complex situation.

Finally, the stereoselectivity of the reactions of compounds **6** is striking, because it cannot be ju: ied according to the assumptions usually accepted to explain the behaviour of vinyl sulfoxides in Diels der reactions. The results obtained in reactions of **6a** and **6b** with cyclopentadiene[18] indicated that the π cial selectivity was very high, the approach of diene from the opposite face to that occupied by the alkoxy group at C-5 being the favoured one. This tendency was higher for **6b**, which reacts with complete π-facial selectivity. Taking into account the usually accepted conformational preferences of the sulfinyl group (the antiperiplanar arrangement of sulfinyl and carbonyl oxygens must be favoured from an electrostatic point of view), this behaviour was explained by assuming steric interactions as the main factor controlling of the stereoselectivity. The lone electron pair at sulfur is oriented towards the same face as the hydrogen at C-5 of **6b**, thus reinforcing the steric tendency imposed by the substituent at C-5. By contrast, the orientation of the tolyl group in **6a** impedes the approach of diene from the face supporting the OEt group, which would justify the observed decrease in the π-facial selectivity. As we can see, the influence of C-5 on the stereoselectivity of the Diels-Alder reactions is clearly higher than that of the sulfur atom.

The results obtained with benzonitrile oxide are quite different from those observed in reactions with cyclopentadiene. The stereoselectivity of **6a** (75:25) is now higher than that of **6b** (60:40), the attack from the opposite face to that supporting the tolyl group in the preferred rotamer being the favoured one in both cases. These changes suggest that the factors controlling the stereoselectivity of 1,3-dipolar reactions must be different from those of Diels-Alder reactions. In Fig.1 are depicted the two possible transition states for each diastereomeric sulfoxide. The major diastereoisomers (**14a** and **14b**) derive from transition states (**A-6a** and

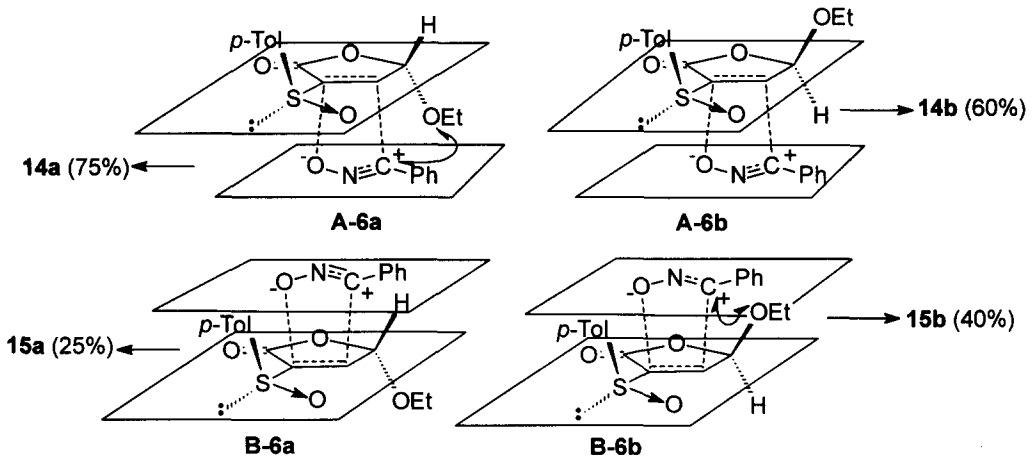


Figure 1

A-6b in Fig. 1), which show small hindrance by the tolyl group with the nitrile oxide, indicating the influence of the sulfur configuration is now clearly higher than that at C-5. This behaviour had also been found in 1,3-dipolar reactions with diazomethane,[17] and suggests that the linear structure of both dipoles decreases the steric interaction with substituents at C-5, thus increasing the relative contribution of the interactions with sulfur substituents. However, the fact that the π-facial selectivity of the reactions with diazomethane was complete for **6a** and **6b**, whereas it is rather low with benzonitrile oxide, suggests that additional factors must be considered to explain these differences. On the other hand, the lower selectivity observed for **6b** in reactions with benzonitrile oxide cannot be explained on steric grounds, because **A-6b** and **B-6b** (Fig. 1) would be respectively the least and the most hindered transition states, thus predicting the highest stereoselectivity for **6b**. The spatial arrangement of the substituents, shown in Fig. 1 for the different transition states, suggests that the contribution of electrostatic factors could be, once more, responsible for the observed behaviour.

The experimental results could be easily explained by assuming that electrostatic attraction between the positively charged carbon atom at dipole (according to theoretical calculations[28] the carbon atom at nitrile oxides has a significant positive charge) and the oxygen at OEt group is able to compensate and even overcome the steric repulsion between Ph (dipole) and OEt (dipolarophile) groups. It would determine a slightly stabilising character for the overall interaction between the extremes of the reactants increasing the stability of the transition states **A-6a** and **B-6b**.

In summary, we have reported the results obtained in 1,3-dipolar reactions of nitrile oxides with *tert*-butyl 4-diethoxy-3-*p*-tolylsulfinylbut-2-enoate and 5-ethoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-ones. The sulfinyl group significantly increases the reactivity of the dipolarophiles and plays an important role in the regioselectivity of

these reactions, allowing a new entry to furoisoxazolines and isoxazoles, regiochemically complementary to that of the butenolides lacking the sulfinyl group. Electrostatic interactions seem to play an important role in the course of these 1,3-dipolar reactions and they might be partially responsible of their reactivity, regioselectivity, and π-facial selectivity. We are now studying the 1,3-dipolar reactions of nitrile oxides with 3-tolylsulfinylfuran-2(5*H*)-ones (without an alkoxy group at C-5) in order to clarify the role here assigned to the electrostatic interactions in the control of the π-facial selectivity of **6a** and **6b**.

3. EXPERIMENTAL

Mp are uncorrected. Microanalyses were performed with a Perkin Elmer 2400 CHN analyzer. Ir spectra were recorded on Perkin Elmer model 681 and FT 1600 grating spectrophotometers, ν values are in cm^{-1}. ^1H and ^{13}C nmr spectra are determined with Bruker AC-200, in $CDCl_3$ solution, unless otherwise stated. Chemical shifts (δ) were reported in ppm downfield from Me_4Si. Silica gel Merck 60 (230-400 mesh) was used for flash column chromatography. Optical rotation was measured with a Perkin-Elmer model 241 polarimeter, at room temperature in $CHCl_3$ solution [1 g/100 mL].

3.1. Cycloaddition of benzonitrile oxide

3.1.1 To a stirred ice-cooled solution of *tert*-butyl (*E*)-4,4-diethoxy-2-*p*-tolylsulfinylbut-2-enoate (**5**) (200 mg, 0.5 mmol) and benzaldehyde chloroxime (420 mg, 2.7 mmol) in dichloromethane (6 mL) was added triethylamine (376 μl, 2.7 mmol) in small portions. After 30 min at 0 °C further portions of benzaldehyde chloroxime and triethylamine were added and the mixture was allowed to stand for 30 min. The solvent was removed under reduced pressure. Hexane was added and the resulting precipitate was filtered off and the solution washed several times with water. The organic layer was dried, and the solvent was removed yielding an oil containing the regioisomeric isoxazoles **7B** and **7A** in a 16:1 ratio (determined by ^1H nmr). The crude mixture was chromatographed on silica gel (hexane-ethyl acetate, 30:1) to afford pure **7B**.

***tert*-Butyl 4,4-diethoxymetyl-3-phenylisoxazole-5-carboxylate (7B)**. Colourless oil. Yield 71%. Anal. Calcd. for $C_{19}H_{25}NO_5$ C, 65.69; H, 7.25; N, 4.03. Found: C, 65.39; H, 7.10; N, 4.19. IR (neat): 1740, 1725, 1610, 1580. ^1H nmr: 1.11 (t, 6H, J = 7.0, $CH_2C\underline{H}_3$); 1.64 (s, 9H, ^{t}Bu); 3.47 (m, 1H, $C\underline{H}_2CH_3$); 3.71 (m, 1H, $C\underline{H}_2CH_3$); 6.06 (s, 1H, CH); 7.42 (m, 3H, Ph); 7.96 (m, 2H, Ph).^{13}C nmr: 14.9 ($CH_2\underline{C}H_3$); 28.1 (CH_3, ^{t}Bu); 63.3 ($\underline{C}H_2CH_3$); 84.4 (C, ^{t}Bu); 95.8 ($C_{Ac}H$); 121.1 (C-4); 127.9, 128.7 and 129.5 (Ar); 156.5 (C-5); 157.9 (C=O); 162.8 (C-3).

***tert*-Butyl 5-diethoxymethyl-3-phenylisoxazole-4-carboxylate (7A).** This could not be isolated as a pure compound. The signals were assigned from the NMR spectrum of the isomeric mixture. ^1H nmr: 1.29 (t, 3H, J = 7.0, $CH_2C\underline{H}_3$,); 1.41 (s, 9H, ^{t}Bu); 3.78 (m, 2H, $C\underline{H}_2CH_3$); 6.13 (s, 1H, CH).

3.1.2. To a stirred mixture of 10% sodium hydroxide solution (2.5 mL) and ether (2.5 mL) was added portionwise during 10 min at 0 °C the benzaldehyde chloroxime (583 mg, 3.75 mmol). The ethereal layer was separated, quickly dried over magnesium sulfate and added to a solution of the (S_5,S_S)- or (R_5,S_S)-5-ethoxy-3-*p*-tolylsulfinyl-2(5*H*)-furanone (**6a** or **6b**) (200 mg, 0.75 mmol) in ether (8 mL). After stirring for 5 min at 0 °C the reaction mixture contained the diastereoisomeric isoxazolines (**14a** and **15a** or **14b** and **15b**) in a 3:1 or 1.5:1 ratio, respectively (determined by ^1H nmr). The adduct **14a** was filtered off. A second crop of **14a** was obtained from the ethereal solution. All attempts to separate the isoxazolines (**14a** and **15a** or **14b** and **15b**) by column chromatography on silica gel were unsuccessful.

(S_{3a},S_4,R_{6a},S_S)-4-Ethoxy-3-phenyl-6a-*p*-tolylsulfinyl-*3a*,6a-dihydrofuro[3,4-*d*]isoxazol-6(4*H*)-one (14a). Yellow solid, mp 84-85 °C. $[\alpha]_D$ +274.7 (c = 1, $CHCl_3$). Yield 55% (157 mg). Anal. Calcd for $C_{20}H_{19}NO_5S$: C, 62.32; H, 4.97; N, 3.63; S, 8.32. Found: C, 62.10; H, 4.63; N, 3.49; S, 8.02. IR (KBr): 1776, 1716, 1698, 1608, 1594. ^{1}H nmr: 0.86 (t, 3H, J = 7.0, $CH_2C\underline{H}_3$); 2.46 (s, 3H, CH_3); 3.42 (m, 1H, $C\underline{H}_2CH_3$); 3.71 (m, 1H, $C\underline{H}_2CH_3$); 5.03 (d, 1H, J = 6.9, H-3a); 5.28 (d, 1H, J = 6.9, H-4); 7.41 (m, 4H, Ar); 7.63 (m, 5H, Ar).^{13}C nmr: 14.2 ($CH_2\underline{C}H_3$); 21.6 (CH_3-Ar.); 54.1 (C-3a); 66.9 ($\underline{C}H_2CH_3$); 101.9 (C-4); 125.3, 127.4, 128.5, 130.3, and 130.7 (CH, Ar).

(R_{3a},S_4,S_{6a},S_S)-4-Ethoxy-3-phenyl-6a-*p*-tolylsulfinyl-*3a*,6a-dihydrofuro[3,4-*d*]isoxazol-6(4*H*)-one (15a). This could not be isolated as a pure compound. The signals were assigned from the NMR spectrum of the isomeric mixture. ^{1}H nmr: 1.32 (t, 3H, J = 7.0, $CH_2C\underline{H}_3$); 2.27 (s, 3H, CH_3); 3.72 (m, 1H, $C\underline{H}_2CH_3$); 3.99 (m, 1H, $C\underline{H}_2CH_3$); 4.55 (d, 1H, J = 2.7, H-3a); 5.48 (d, 1H, J = 2.7, H-4).

(S_{3a},R_4,R_{6a},S_S)-4-Ethoxy-3-phenyl-6a-*p*-tolylsulfinyl-*3a*,6a-dihydrofuro[3,4-*d*]isoxazol-6(4*H*)-one (14b). This could not be isolated as a pure compound. The signals were assigned from the NMR spectrum of the isomeric mixture. ^{1}H nmr: 0.98 (t, 3H, J = 7.0, $CH_2C\underline{H}_3$); 2.44 (s, 3H, CH_3); 3.43 (q, 2H, J = 7.0, $C\underline{H}_2CH_3$); 4.65 (d, 1H, J = 1.8, H-3a); 5.38 (d, 1H, J = 1.8, H-4).

(R_{3a},R_4,S_{6a},S_S)-4-Ethoxy-3-phenyl-6a-*p*-tolylsulfinyl-*3a*,6a-dihydrofuro[3,4-*d*]isoxazol-6(4*H*)-one (15b). This could not be isolated as a pure compound. The signals were assigned from the NMR spectrum of the isomeric mixture.^{1}H nmr: 0.93 (t, 3H, J=7.0, $CH_2C\underline{H}_3$); 2.23 (s, 3H, CH_3); 3.54 (m, 1H, $C\underline{H}_2CH_3$); 3.82 (m, 1H, $C\underline{H}_2CH_3$); 4.84 (d, 1H, J=6.7, H-3a); 5.80 (d, 1H, J=6.7, H-4).

3.2. Cycloaddition of acetonitrile oxide

To a solution of *tert*-butyl (*E*)-4,4-diethoxy-2-*p*-tolylsulfinylbut-2-enoate (**5**) (200 mg, 0.54 mmol), phenyl isocyanate (236 μl, 2.17 mmol) and triethylamine (0.1 mL) in anhydrous toluene (5 mL), was added dropwise nitroethane (97 μl, 1.36 mmol). The mixture was stirred at room temperature for 23 h. The precipitated N,N-diphenylurea was filtered off. Evaporation of the solvent gave a residue, in which ^{1}H nmr showed the presence of **8B** and **8A** in a 14:1 ratio. It was chromatographed on silica gel (hexane / ethyl acetate, 18:1) to give the pure isoxazole **8B** as a colourless oil in 69 % yield.

***tert*-Butyl 4-diethoxymethyl-3-methylisoxazole-5-carboxylate (8B).** Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.95; H, 8.07; N, 4.91. Found: C, 59.20; H, 8.35; N, 4.92. IR (neat): 1740, 1725, 1623. ^{1}H nmr: 1.21 (t, 6H, J = 7.0, $CH_2C\underline{H}_3$); 1.59 (s, 9H, ^{t}Bu); 2.42 (s, 3H, CH_3); 3.48 (m, 2H, $C\underline{H}_2CH_3$); 3.71 (m, 2H, $C\underline{H}_2CH_3$); 5.93 (s, 1H, CH). ^{13}C nmr: 11.3 (CH_3); 14.9 ($CH_2\underline{C}H_3$); 27.9 (CH_3, ^{t}Bu); 63.0 ($\underline{C}H_2CH_3$); 84.0 (C, ^{t}Bu); 95.9 ($C_{Ac}H$); 121.5 (C-4); 156.1 and 156.3 (C-3 and/or C-5); 160.2 (C=O).

***tert*-Butyl 5-diethoxymethyl-3-methylisoxazole-4-carboxylate (8A).** This could not be isolated as a pure compound. The signals were assigned from the NMR spectrum of the isomeric mixture. ^{1}H nmr: 1.23 (t, 6H, J = 7.0, $CH_2C\underline{H}_3$); 1.56 (s, 9H, ^{t}Bu); 6.10 (s, 1H, CH).

3.3. Cycloaddition of bromoformonitrile oxide

To a vigorously stirred mixture of *tert*-butyl (*E*)-4,4-diethoxy-2-*p*-tolylsulfinylbut-2-enoate (**5**) (300 mg, 0.81 mmol), ethyl acetate (5 mL), potassium bicarbonate (811 mg, 8.10 mmol), and water (1.5 mL), was added solid dibromoformaldoxime (821 mg, 4.05 mmol) in small portions. After 30 min at room temperature, a further portion of potassium bicarbonate (811 mg, 8.10 mmol) and dibromoformaldoxime (821 mg, 4.05 mmol) was added and the mixture was allowed to stand for 30 min. The precipitated salts were filtered off, the

filtrate was dried ($MgSO_4$) and the solvent was removed under reduced pressure. ^1H nmr analysis of the crude product showed the presence of **9B** and **9A** in a 14:1 ratio. The crude product was chromatographied on silica gel (hexane-ethyl acetate, 45:1) to afford the isoxazole **9B** with traces of **9A**.

***tert*-Butyl 3-bromo-4,4-diethoxymetylisoxazole-5-carboxylate (9B)**. Colourless oil. Yield 70%. Anal. Calcd. for $C_{13}H_{20}NO_5Br$ C, 44.59; H, 5.76; N, 4.00; Br, 22.82. Found: C, 44.40; H, 5.72; N, 4,10. IR (neat): 1740, 1730, 1610. ^1H nmr: 1.23 (t, 6H, J = 7.0, $CH_2C\underline{H}_3$); 1.60 (s, 9H, ^{t}Bu); 3.52 (m, 2H, $C\underline{H}_2CH_3$); 3.73 (m, 2H, $C\underline{H}_2CH_3$); 5.95 (s, 1H, CH). ^{13}C nmr: 14.9 ($CH_2\underline{C}H_3$); 27.9 (CH_3, ^{t}Bu); 63.2 ($\underline{C}H_2CH_3$); 85.1 (C, ^{t}Bu); 95.0 ($C_{Ac}H$,); 122.1 (C-4); 140.3 (C-3); 155.1 (C-5); 157.8 (C=O).

***tert*-Butyl 3-bromo-5-diethoxymethylisoxazole-4-carboxylate (9A).** This could not be isolated as a pure compound. The signals were assigned from the NMR spectrum of the isomeric mixture. ^1H nmr: 1.24 (t, 6H, J = 7.0, $CH_2C\underline{H}_3$); 1.58 (s, 9H, ^{t}Bu); 6.08 (s, 1H, CH).

3.4. Formolysis of ester-acetals **7B-8B**

To the ester-acetal **7B** or **8B** (0.46 mmol) was added formic acid (1.4 mL, of 99 % purity) and the mixture was allowed to stand under argon at room temperature for 16 h. After removing formic acid and formates under reduced pressure, the corresponding acid-aldehyde was obtained.

4-Formyl-3-phenylisoxazole-5-carboxylic acid (10). Recrystallized from toluene, mp 149-150 °C. Yield 87%. ^1H nmr (DMSO-d_6): 7.53 (m, 3H, Ar); 7.71 (m, 2H, Ar) 10.40 (s, 1H, CHO). ^{13}C nmr (DMSO-d_6): 119.9, 127.0, 128.6, 129.3, 130.7, 157.4, 161.5, 185.6, 185.8.

4-Formyl-3-methylisoxazole-5-carboxylic acid (11). Recrystallized from toluene, mp 118-120 °C.Yield 85 %. Anal. Calcd. for $C_6H_5NO_4$: C, 46.46; H, 3.25; N, 9.03. Found: C, 46.11; H, 3.25; N, 8.89. IR (KBr): 3576, 3526, 3300-2500, 1722, 1679, 1594. ^1H nmr (DMSO-d_6): 2.42 (s, 3H, CH_3); 10.32 (s, 1H, CHO). ^{13}C nmr (DMSO-d_6): 11.3, 120.3, 157.4, 159.5, 186.6, 186.7.

3.5. Methylation of isoxazole-acids

To a solution of acid **10** or **11** (0.1 mmol) in ether-ethanol 1:0.1 (1.1 mL) was added a 2.0 M solution of trimethylsilyldiazomethane in hexane (0.1 mL). After 30 min at room temperature, the solvent and the excess of reactant were removed *in vacuo*. The ^1H nmr spectrum of the residue showed the presence of corresponding methyl ester as a white solid.

Methyl 4-formyl-3-phenylisoxazole-5-carboxylate (12).[7] Yield 98%. Recrystallized from hexane, mp 64-65 °C. ^1H nmr: 4.11 (s, 3H, CH_3); 7.50 (m, 3H, Ar); 7.78 (m, 2H, Ar); 10.58 (s, 1H, CHO).

Methyl 4-formyl-3-methylisoxazole-5-carboxylate (13).[7] Yield 96%. Recrystallized from hexane mp 69-70 °C. ^1H nmr: 2.55 (s, 3H, CH_3); 4.07 (s, 3H, OCH_3); 10.49 (s, 1H, CHO).

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