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Asymmetric 1,3-dipolar reactions of 3-sulfinylfuran-2(5*H*)-ones with 11*H*-dibenzo[*b,e*]azepine 5-oxide. Synthesis of pyrroloazepines via isoxazoloazepines ☆

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This paper is dedicated to Professor José Luis Soto

Abstract—The addition of morphanthridine *N*-oxide (**1**) to homochiral 3-*p*-tolylsulfinylfuran-2(5*H*)-ones (**2a** and **2b**) under mild conditions affords furoisoxazoloazepines (**3a** and **3b**) in high yields and with complete regioselectivity. The π-facial and *endo*-selectivities are also complete from **2a**, which yields *anti*-**3a**-*endo* as the only diastereoisomer, whereas cycloreversion determines that the *anti*-**3b**-*endo* adduct can be almost exclusively isolated from **2b**. Proper manipulation of the furoisoxazoloazepines allows the synthesis of the optically pure isoxazoloazepines and pyrroloazepines.

The biological activity of molecules containing a modified azepine ring has been intensively tested, both in vitro and in vivo, against various diseases.[1] In this context, 2-(aminoalkyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]-isoxazolo[2,3-*a*]azepines have been recently reported as 5-$HT_{2A/2C}$ receptor antagonists,[2] and pyrroloazepines have displayed interesting biological activities,[3] which confers relevance to the search of short and highly stereoselective methods to prepare them. 1,3-Dipolar cycloadditions involving the use of nitrones as dipoles is one of the best reported methods to build the isoxazolidine skeleton.[4] It was used to prepare 2-(aminoalkyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepines starting from 11*H*-dibenzo[*b,e*]azepine 5-oxide (**1**).[2a] Therefore we envisaged that the use of a proper enantiomerically pure dipolarophile would allow the asymmetric synthesis of the isoxazoloazepines, which in turn could be used to prepare pyrroloazepines.

In our continuing interest in developing strategies to afford homochiral organic compounds using sulfoxides as chiral auxiliaries,[5] we have reported the efficiency of 3-*p*-tolylsulfinyl-5-alkoxyfuran-2(5*H*)-ones (**2a** and **2b**[6]) as chiral dipolarophiles in reactions with diazoalkanes,[7] nitrile oxides[8] and azomethine ylides.[9] In all these reactions, the sulfinyl group has shown its ability to improve the dipolarophilic features of the substrates. It prompted us to study the behaviour of furanones **2a** and **2b** with nitrone **1** to obtain the optically pure furoisoxazoloazepines **3**, which have the proper substituents to be transformed into highly functionalized isoxazoloazepines and pyrroloazepines (Scheme 1). The synthetic results obtained in this study are reported in this paper.

Results obtained in reactions of nitrones with vinyl sulfoxides[10] and 5-menthyloxyfuran-2(5*H*)-one[11] have been reported previously. However, none of these studies dealt with reactions of the nitrone **1**, which has

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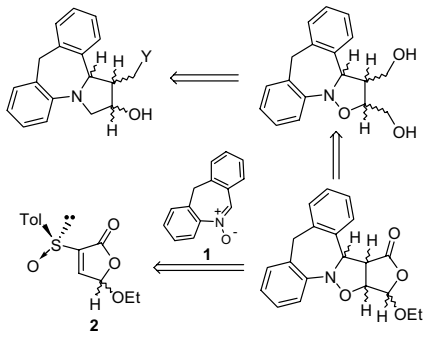
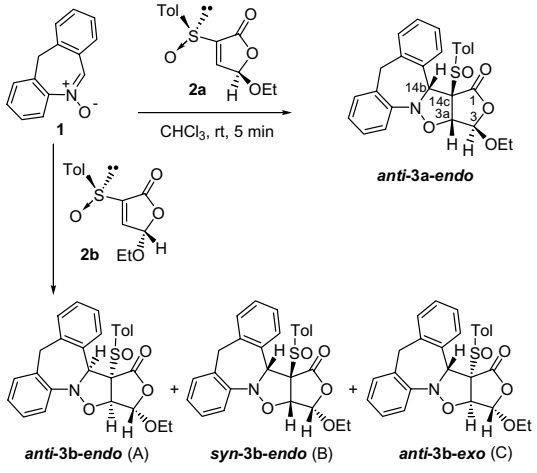


Scheme 1.

only been confronted to alkenylamines.[2] The addition of nitrone **1** (prepared as indicated in Ref. 2a) to enantiomerically pure furanone **2a** required less than 5 min at room temperature to afford *anti*-**3a**-*endo*[12] as the sole product (Scheme 2), which was isolated in 85% yield after crystallization from acetone. The same adduct was exclusively detected when the reaction was conducted in refluxing toluene.

The reaction 11*H*-dibenzo[*b*,*e*]azepine 5-oxide (**1**) (1.2 equiv) with sulfoxide **2b** (1 equiv) afforded **3b** as a mixture of three stereoisomers (Scheme 2) in proportions dependent on the temperature and the reaction time, as it is indicated in Table 1. All the chromatographic attempts to separate the adducts **3b** where unsuccessful and decomposition into the starting material was observed even at room temperature. This fact



Scheme 2.

Table 1. Stereoisomeric ratios obtained under different conditions in the reaction of **1** with **2b**

Entry	Solvent	*T*	Time	Stereoisomer ratio[a] A:B:C
1	$CHCl_3$	Rt	10 min	43:38:19
2	$CHCl_3$	Rt	1 h	54:34:12
3	$CHCl_3$	Rt	18 h	70:22:8
4	Toluene	100 °C	5 min	72:19:9

[a] Determined by ^1H NMR on the reaction crudes.

suggested that cycloreversion was very easy. Thus we investigated the influence of the reaction conditions in the composition of the reaction mixture, with the results collected in Table 1. The proportion of the adduct *anti*-**3b**-*endo* grows larger as the time increases and mainly when the temperature raises. The highest stereoselectivity was observed under the conditions of the entry 4 (refluxing toluene) yielding a 72:19:9 mixture of the diastereoisomers A, B and C (Scheme 2). The fact that the *anti*-**3b**-*endo*-adduct was obtained in a 77% isolated yield after several crystallizations from this reaction mixture additionally supports the easy cycloreversion during the purification process. Cycloreversion has been reported just occasionally for 1,3-dipolar reactions of nitrones,[13] which suggests that the sulfinyl group could play a significant role in making this process easier, although the possible influence of the dibenzazepine ring cannot be ignored. The relative role of both factors on the easiness of the cycloreversion, which has allowed us to use it with synthetic purposes by increasing the stereoselectivity under proper conditions, is now being investigated by theoretical methods as well as by studying the behaviour of **2a** and **2b** with other nitrones.

The absolute configuration of *anti*-**3a**-*endo* was unequivocally established by X-ray analysis (Fig. 1).[14]

The independent transformation of the adducts *anti*-**3a**-*endo* and *anti*-**3b**-*endo* into the enantiomeric diols (−)-**5** and (+)-**5** allowed the unequivocal configurational assignment of *anti*-**3b**-*endo* (Scheme 3). This transfor-

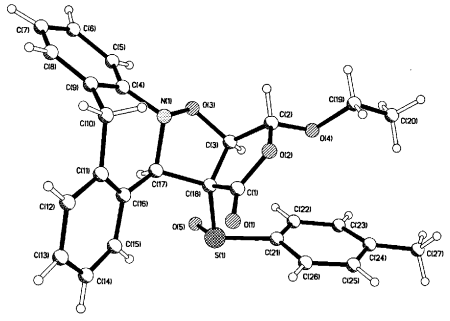
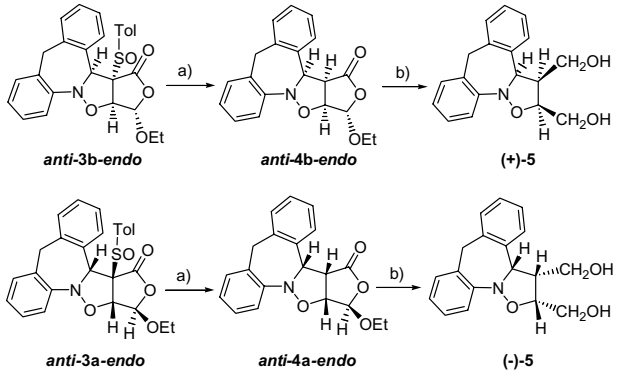


Figure 1.



Scheme 3. Reagents and conditions: (a) AI/Hg, THF/H_2O (9:1), rt, 30 min; (b) $LiAlH_4$, THF, 30 min, rt.

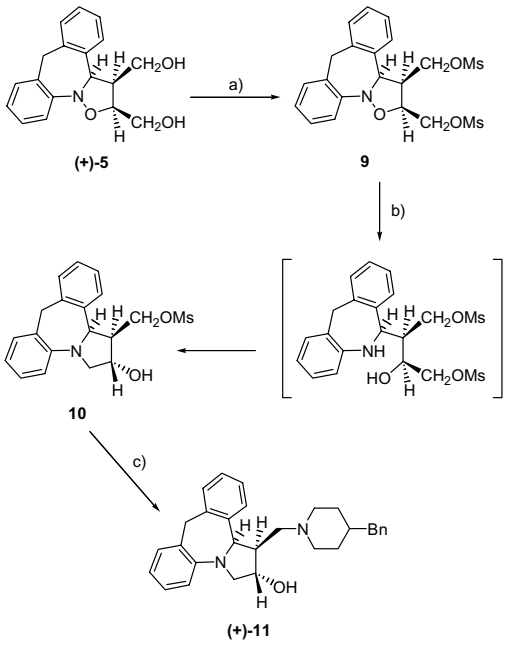
mation involved the hydrogenolysis of the C–S bond with Al/Hg and the reduction of the lactone ring into the diol system with $LiAlH_4$ at room temperature. The 1,3-dipolar cycloaddition of nitrone **1** to **2a** and **2b** and the subsequent transformation of the adducts affords one of the most efficient methods to prepare highly functionalized isoxazoloazepines in optically pure form.

Once unequivocally assigned the absolute configuration of the major adducts, the configuration of *syn*-**3b**-*endo* was established by its transformation into the diol (−)-**5** by using a sequence identical to that depicted in Scheme 3. As the two adducts identified in the mixture obtained from **2b** have the *endo*-stereochemistry, the third one must exhibit the *exo*-stereochemistry. Its assignment as *anti*-**3b**-*exo* was established on the base of the zero value of its coupling constant $J_{3,3a}$, indicative of the *anti*-spatial arrangement (values ranging between 0 and 2 Hz were measured for the *anti*-adducts and 5.0 Hz for the *syn*-ones).

In order to establish the role of the sulfinyl group on the course of the reactions of the nitrone **1** with **2** we have studied the reaction of **1** with (±)-**6**,[15] which is the furanone bearing no sulfinyl group. The reaction required 2 h at room temperature (Scheme 4) to yield the *anti*-**7**-*exo*-adduct exclusively. This stereochemistry was assigned on the base of the coupling constant $J_{3,3a}$ (0), indicative of the *trans*-spatial arrangement of the involved protons, as well as its chemical correlation with diols **5**. The adduct *anti*-**7**-*exo* was transformed into isoxazoloazepine (±)-**8** by reaction with $LiAlH_4$. Compound (±)-**8** proved to be diastereoisomer of **5**; therefore, protons $H_{14\,b}$ and $H_{14\,c}$ must exhibit a *trans*-arrangement.

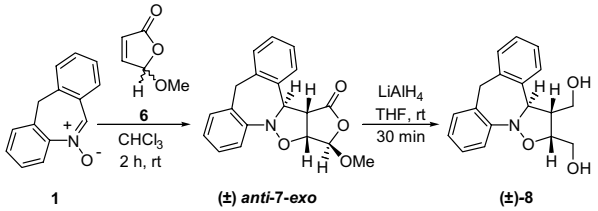
The comparison of the results obtained in the reactions shown in Schemes 2 and 4, indicates that the sulfinyl group significantly increases the reactivity (it reduces the reaction times), is the main controller of the *endo*/*exo*-selectivity, which is just the opposite for sulfinylated (*endo*) and nonsulfinylated (*exo*)-5-alkoxy-2(5*H*)furanones and modulates the π-facial selectivity, which is mainly governed by the configuration at C-5 [only *anti*-adducts were obtained from **2a** and (±)-**6** but mixtures containing the *syn*-adduct as a minor component were obtained from **2b**].

The synthesis of pyrroloazepines from the corresponding isoxazolines could be achieved following the protocol previously described for the transformation of hexahydropyrrolo[1,2-*b*]isoxazole to hexahydropyrrolizines.[16] It involved the conversion of the adduct **3** into the corresponding diol **5** (see Scheme 3) and mesylation of the two hydroxyl groups as a previous step to the hydrogenolysis of the N–O bond with H_2/Pd in ethanol (Scheme 5). The aminoalcohol formed in the opening of the isoxazolidine ring evolved spontaneously into the {2-hydroxy-2,3,9,13b-tetrahydro-1*H*-dibenzo[*c*,*f*]pyrrolo[2,1-*a*]azepin-1-yl}methylethanesulfonate **10**, which subsequently reacted with 4-benzylpiperidine to afford the corresponding aminoalcohol (+)-**11** in high overall yield (79% from (+)-**5**).



Scheme 5. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (b) H_2 (40 psi), Pd/C, EtOH, rt, 2 h; (c) 4-benzylpiperidine, 70 °C, 1.5 h.

Other dibenzopyrroloazepines could also prepared by the synthetic method described above, and they were screened in several in vitro assays to evaluate their affinity with different G-protein-coupled receptors (GPCRs). Thus, their affinities for a set of adrenergic, dopaminergic and serotonergic receptors were measured by standard procedures.[17] Some compounds showed weak to moderate binding activity for a few of those receptors. In that respect, the most relevant results were obtained for the piperidine and the 4-ethoxycarbonylpiperidine derivatives **12** and **13** (Fig. 2) that showed K_i values for the H_1 receptor of 9 and 13 nM, respectively.



Scheme 4.

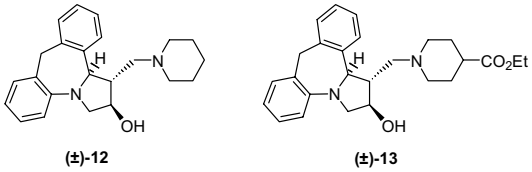


Figure 2.

In summary, we have demonstrated the high efficiency of the reactions of 11*H*-dibenzo[*b*,*e*]azepine-5 oxide (**1**) with the sulfinylfuranones **2a** and **2b** in the asymmetric synthesis of highly functionalized isoxazoloazepines and pyrroloazepines. The significant role of the sulfinyl group improving the dipolarophilic features of the 5-alkoxy-3-furanones is also evident from the results herein presented.

Supplementary material

Experimental procedures as well as spectroscopic data of compound **3**–**5**, **7**–**8** and **11** are available. This material is available online with the paper in ScienceDirect.

Acknowledgements

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12. The *syn*- or *anti*-character of the adducts that indicates the *cis*- or *trans*-relationship between H_3 and H_{3a} (Scheme 2), is related to the face of the dipolarophile, which is attacked by the dipole, using as a reference the spatial arrangement of the ethoxy group. The *endo*- or *exo*-terms, indicative of the *cis*- or *trans*-arrangement exhibited by furanone and azepine moieties at the isoxazolidine ring, are related to the *endo*- and *exo*-addition modes of the dipole, using the ester group at the furanone ring as a reference.
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14. Crystallographic data (excluding structure factors) for *anti*-**3a**-*endo* have been deposited with the Cambridge Crystallographic Data Centre as suplementary publication number CCDC 190809. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-366033 or e-mail: deposit@ccdc.cam.ac.uk].
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17. The in vitro screening of the compounds was performed at Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen Pharmaceutica N.V., Turnhoutsweg 30, B2340 Beerse, Belgium. The authors would like to acknowledge support from this company.