CSIRO PUBLISHING

RESEARCH FRONT

Aust. J. Chem. **2014**, *67*, 381–388
http://dx.doi.org/10.1071/CH13444

Full Paper

Benzonitrile Oxide Cycloadditions with Exocyclic Methylene Benzothiazepine Dioxides

Sarah J. Ryan,[A] *Craig L. Francis,*[A] *and G. Paul Savage*[A,B]

[A]CSIRO Materials Science and Engineering, Private Bag 10, Clayton South MDC, Vic. 3169, Australia.
[B]Corresponding author. Email: paul.savage@csiro.au

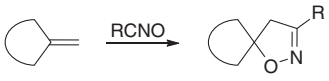
N-substituted 5-methylene-2,3,4,5-tetrahydrobenzo[*f*][1,2]thiazepine 1,1-dioxides underwent 1,3-dipolar cycloaddition with benzonitrile oxide, generated in situ, to give isoxazoline spiro adducts. The cycloadditions were completely regioselective to give the hitherto unreported 3,4-dihydro-2*H*,4′*H*-spiro[benzo[*f*][1,2]thiazepine-5,5′-isoxazole] 1,1-dioxide cycloadduct. Where the *N*-substituent on the sulfonamide cycloaddition precursor was a 2-substituted arene, the resulting atropisomerism along the *N*-aryl bond led to facial selectivity in the cycloaddition reaction, with greater than 90 % diastereoselectivity.

Manuscript received: 26 August 2013.
Manuscript accepted: 23 September 2013.
Published online: 14 October 2013.

Introduction

As part of a library enrichment program for our drug discovery endeavours,[1,2] we are interested in preparing structurally novel heterocycles. Many commercial drug-screening libraries contain an abundance of planar, aromatic heterocycles and an underrepresentation of three-dimensional structures. In contrast, the bioactive ligands typically found in nature tend to have more architectural complexity, with core structures containing a higher proportion of sp^3 centres. Screening libraries that are rich in three-dimensional compounds, with high molecular shape diversity, might be expected to display a broader range of biological activities.[3,4] 'Flatness' parameters such as the fraction of sp^3carbons as a proportion of total carbon (sp^3/C), chiral atom counts, and the difference between aromatic and sp^3 atom counts (Ar – sp^3) have all been suggested as metrics to analyse the quality of drug screening libraries.[5–7] It should be noted that these measures are somewhat simplistic in that they value the contribution of all sp^3 centres equally. In reality, the molecular three-dimensionality contribution of, for example, an sp^3 methyl substituent on a benzene ring is insignificant compared with that of an sp^3 bridgehead carbon. A more sophisticated metric for compound shape is the principal moments of inertia (PMI), which describes the shape of a molecule normalized to the molecule's longest dimension.[8]

One convenient method for introducing three-dimensionality into molecules is with spiro linkages, and to that end, we have pursued the construction of spiro heterocycles using 1,3-dipolar nitrile oxide cycloaddition (NOC) reactions[9,10] with exocyclic methylene compounds.[11–17] These reactions are highly regioselective, with the resulting spiro linkage appearing at the 5-position of the newly formed isoxazoline ring (Scheme 1).[18] The steric sensitivity of the NOC process has been extensively exploited to control the regiochemical outcomes of these reactions.[19–23] The resulting spiro-isoxazoline substructure is itself a structural motif that is found in several biologically active natural products.[24,25]



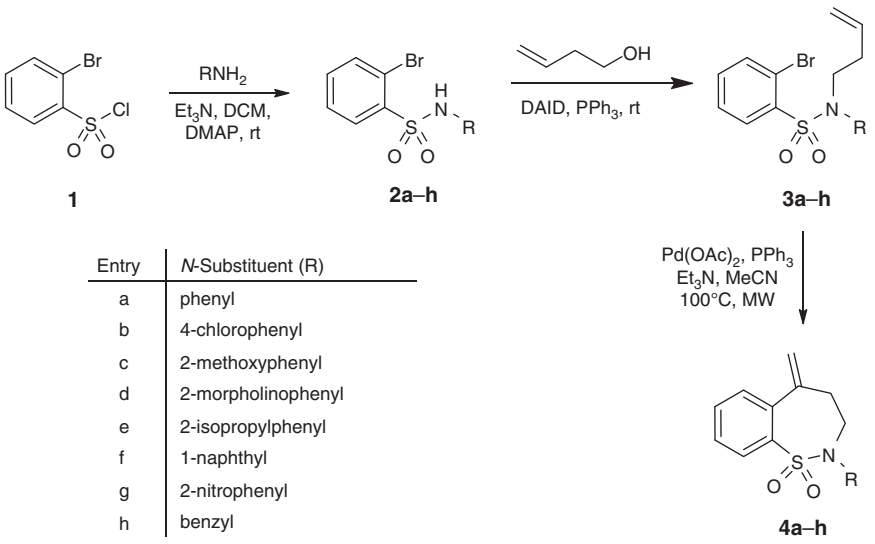
Scheme 1.

Benzo-fused cyclic sulfonamide (sultam) ring systems have been described as 'privileged structures' in medicinal chemistry.[26,27] Following the discovery of the antibacterial sulfonamide dye Prontosil,[28] this functionality has been incorporated into a wide range of biologically active compounds as carboxylic acid and amide isosteres.[29] The benzo-fused seven-membered sultam partial structure has appeared in HIV-1 protease inhibitors,[30] hypolipidemic agents,[31] antiproliferative[32,33] and proapoptotic[34] anticancer compounds, and in the antidepressant drug tianeptine.[35] Hanson and coworkers recently described[36] the synthesis of 5-methylene-2,3,4,5-tetrahydrobenzo[*f*][1,2]thiazepine 1,1-dioxides **4**, and these compounds caught our attention as potential dipolarophiles for 1,3-dipolar NOC reactions. These exocyclic methylene seven-membered sultams bear some resemblance to our previously reported NOC reactions with five-membered sultams,[37] and we were particularly interested to see if the pattern of reactivity and facial selectivity was maintained.

Herein, we describe the NOC of *N*-substituted 5-methylene-2,3,4,5-tetrahydrobenzo[*f*][1,2]thiazepine 1,1-dioxides **4** to generate the previously unreported ring system 3,4-dihydro-2*H*, 4′*H*-spiro[benzo[*f*][1,2]thiazepine-5,5′-isoxazole] 1,1-dioxide **5**.

Results and Discussion

The 5-methylene benzothiazepines **4** were prepared by a procedure adapted from that of Hanson and coworkers (Scheme 2).[36] Commercially available 2-bromobenzenesulfonyl chloride **1** was reacted with the appropriate amine in pyridine and dichloromethane (DCM) at room temperature to give the



Entry	*N*-Substituent (R)
a	phenyl
b	4-chlorophenyl
c	2-methoxyphenyl
d	2-morpholinophenyl
e	2-isopropylphenyl
f	1-naphthyl
g	2-nitrophenyl
h	benzyl

Scheme 2.

2-bromosulfonamides **2**, generally in high yields.[37,38] The 2-bromosulfonamides **2** thus obtained were subjected to a Mitsunobu reaction with 3-butenol, using triphenylphosphine and diisopropyl azodicarboxylate (DIAD), to give the *N*-homoallyl sulfonamides **3**. In turn, the *N*-homoallyl sulfonamides **3** underwent an intramolecular Heck cyclization at 100°C under microwave irradiation, using palladium acetate and triphenyl phosphine in acetonitrile, to give 5-methylene benzothiazepines **4**. For three of these compounds (the 2-morpholinophenyl derivative **4d**, the isopropylphenyl derivative **4e**, and the 1-naphthyl derivative **4f**), additional resonances in the ^{1}H NMR spectra were observed, which appeared to be consistent with diastereomeric isomers. These may be due to atropisomerism around the *N*-aryl bond or slow interconversion (on the NMR time-scale) of pseudo-boat conformations of the seven-membered ring,[39–43] or a combination of both. A variable-temperature ^{1}H NMR analysis of the *N*-(2-isopropyl)phenyl benzothiazepine **4e**, with spectra recorded at 20, 45, 85, 105, and 125°C in deuterated trichloroethane, revealed that the resonances of the isomers fully coalesced by 125°C (see Supplementary Material). Seven-membered rings are known to be more flexible than five- and six-membered rings. They can exist in complex pseudorotational equilibria, characterized by numerous conformations of similar energy with low pseudorotational barriers. However, these conformational interconversions can be significantly impeded by fused benzene rings and sp^2 centres in the ring.[43,44]

A single-crystal X-ray structure of 5-methylene-2-(naphthalen-1-yl)-2,3,4,5-tetrahydrobenzo[*f*][1,2]thiazepine 1,1-dioxide **4f** was obtained (Fig. 1). It can be seen that the seven-membered ring resides in a chair conformation in the solid state,[44] and the sulfonamide nitrogen is relatively flat. The exocyclic methylene group protrudes below the plane of the fused benzene ring such that one face is somewhat shielded by the axial hydrogen on C(1) and one of the sulfonamide oxygen atoms O(2). The other face is relatively unhindered.

It is interesting to note that the four protons on the seven-membered ring of **4f** are diastereotopic. They are clearly resolved at room temperature and coupled to each other in the ^{1}H NMR spectrum. This is additional evidence of restricted *N*-aryl rotation in combination with restricted conformational interconversion of the seven-membered ring. The possibility that this phenomenon is purely due to restricted conformational interconversion of the ring cannot be discounted. However, the *N*-phenyl derivative **4a**, and the *N*-4-chlorophenyl derivative **4b**, with no asymmetry along the *N*-aryl axis, do not display such diastereotopic separation in the ^{1}H NMR. These observations are consistent with *N*-aryl restricted rotation playing some part in the conformational rigidity of these compounds. The chemical shift of one of the methylene protons on C(1) (Fig. 1) appears at 3.53 ppm, which is not unusual for a methylene adjacent to the nitrogen of an *N*-aryl sulfonamide. The other proton on C(1), however, is appreciably downfield at 4.68 ppm, which is presumably caused by significant through-space deshielding due to the proximity of the sulfonamide oxygen atom O(2) (Fig. 1).[45] In the X-ray structure, the distances between O(2) and these two methylene protons are 3.748 Å and 2.497 Å respectively.

Molecular simulation and conformational searching were carried out using a constrained optimization along the rotation of the *N*-naphthyl bond of compound **4f**, to give the rotational surface (see Supplementary Material). The calculations were of the isolated molecules in a vacuum state, carried out at the M06-2X/6-31G(d) level using the *Gaussian* package. The barrier to *N*-aryl rotation was determined to be ~160 kJ mol^{-1}.

Nitrile oxides are reactive intermediates that readily dimerize to give furoxans unless sterically hindered.[21,23] Hence, they are almost always generated in situ and trapped with olefinic dipolarophiles. Alkyl nitrile oxides are normally prepared by formal dehydration of the corresponding primary nitroalkane using the Mukaiyama procedure,[46] or one of its many variants.[10] Aryl nitrile oxides are more conveniently prepared by the base-catalyzed dehydrohalogenation of the corresponding hydroximoyl chlorides, which in turn are prepared by chlorination of aldoximes.[47] The chlorination and dehydrohalogenation steps for aryl nitrile oxides can be combined in a one-pot process where water-insoluble aldoximes are reacted under biphasic conditions with 5% sodium hypochlorite solution as both chlorinating agent and base.[48]

Using this method, benzonitrile oxide was generated in situ by mixing commercially available benzaldehyde oxime in CH_2Cl_2 with a 5% aqueous NaOCl solution at 0°C, in the presence of the 5-methylene benzothiazepines **4**. The nitrile oxide that formed was immediately trapped by the exocyclic methylene dipolarophile to give the corresponding spiro

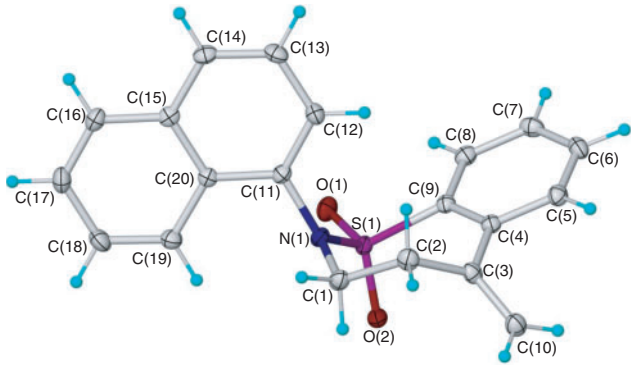
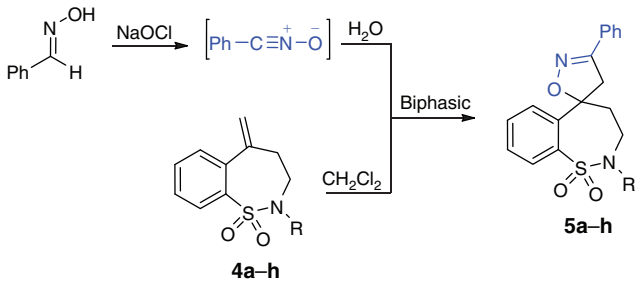


Fig. 1. Molecular diagram of 5-methylene-2-(naphthalen-1-yl)-2,3,4,5-tetrahydrobenzo[*f*][1,2]thiazepine 1,1-dioxide **4f** with non-hydrogen atoms represented by 50 % thermal ellipsoids and hydrogen atoms as spheres of arbitrary size.



Scheme 3.

Table 1. Yields for synthesis of homoallylsulfonamides 3, methylene benzothiazepines 4, and spiro isoxazolines 5

Entry	*N*-Substituent	Yield [%]		
		3	**4**	**5**
a	phenyl	68	68	58
b	4-chlorophenyl	91	46	66
c	2-methoxyphenyl	100	61	57
d	2-morpholinophenyl	100	66	87
e	2-isopropylphenyl	80	71	72
f	1-naphthyl	96	75	71
g	2-nitrophenyl	100	31	66
h	2-benzyl	52	54	71

cycloadducts **5** (Scheme 3). The reactions were generally sluggish compared with more activated carbon–carbon double-bond dipolarophiles, and a three-fold excess of nitrile oxide was required to complete the reaction. The isolated yields for the cycloadducts **5**, the dipolarophiles **4**, and the homoallylsulfonamide precursors **3** are collected in Table 1.

Nitrile oxide dipolar reactions with alkenes have been characterized as Type II cycloadditions under the Stusmann classification, which means nitrile oxides are ambiphilic dipoles capable of reacting under either HOMO or LUMO control.[49] In such cases, it is common for steric considerations to become the overriding factor in the regiochemical outcome of the reaction.[50] The dipolar cycloaddition reactions with 5-methylene benzothiazepines **4** were completely regioselective in all cases, with the oxygen of the nitrile oxide adding to the thiazepine ring end of the dipolarophile double bond. This regiochemical outcome is consistent with previous observations,[18] and could

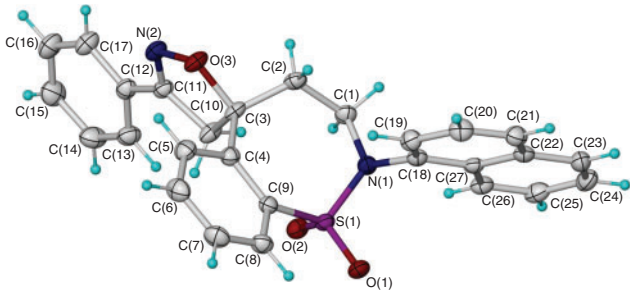


Fig. 2. Molecular diagram of 2-(naphthalen-1-yl)-3′-phenyl-3,4-dihydro-2*H*,4′*H*-spiro[benzo[*f*][1,2]thiazepine-5,5′-isoxazole] 1,1-dioxide **5f** with non-hydrogen atoms represented by 50 % thermal ellipsoids and hydrogen atoms as spheres of arbitrary size. The molecule has chirality, being *R* at C(3); the opposite enantiomer is generated by crystallographic inversion in the centrosymmetric space group.

be clearly ascertained by examination of the ^{1}H NMR spectra of the products. The chemical shifts for the characteristic AB system of the diastereotopic methylene protons on the newly formed isoxazoline rings appeared at 3.6–4.0 ppm. This chemical shift range is indicative of protons on C-4 of the isoxazoline ring. For the alternative possible regioisomer, the newly formed isoxazoline methylene protons would be at C-5, and would be expected to fall in the range of 4.5–5.0 ppm.[11] Hence, the regiochemistry of cycloaddition is as shown in Scheme 3. The X-ray crystal structure of a representative product **5f** (Fig. 2) was consistent with this assignment.

The methylene benzothiazepines **5c**–**h** bearing an *ortho*-substituted *N*-aryl group, including 1-naphthyl, are potentially atropisomeric via restricted rotation around the *N*-aryl bond. Hence, the faces of the dipolarophile are non-equivalent, leading to the possibility of diastereomeric cycloadducts due to either *syn* or *anti* addition with respect to the substituent on the *N*-aryl group. We have observed this behaviour previously with a range of exocyclic methylene heterocycles, where the facial selectivity ranged from complete to as little as 2 : 1.[15–17] In the present study, however, only the resonances corresponding to a single diastereomer, or at most a trace of the other diastereomer, were observed in the ^{1}H and ^{13}C NMR spectra of the cycloadducts (see Supplementary Material). This could be the result of either a high degree of facial selectivity for the cycloaddition, or a conformational change in the products leading to free rotation around the *N*-aryl bond. To test for the latter, a ^{1}H NMR spectrum of the isopropyl derivative **5e** was recorded at −50°C and compared with the room-temperature spectrum. No change was observed at the lower temperature, which indicates that the room-temperature spectrum does not represent a time-averaged, freely interconverting mixture of diastereomers. Hence, the products are most likely single diastereomers due to a high degree of facial selectivity. An X-ray structure for the spiro adduct **5f** was obtained (Fig. 2) and the nitrile oxide appears to have added to the more exposed face of **4f** (see Fig. 1), as would be expected.

A sample of the cycloadduct **5f** was subjected to analytical chiral HPLC. Two equal peaks corresponding to the major diastereomeric enantiomer pair, and two equal peaks due to the minor diastereomeric enantiomer pair, were clearly resolved. The minor diastereomeric compounds were present in ∼5 % each (see Supplementary Material).

As with the olefinic dipolarophiles **4**, the four methylene protons of the seven-membered ring of cycloadducts **5** were all clearly resolved at room temperature in the ^{1}H NMR spectra.

The protons on the methylene carbon adjacent to the spiro linkage appeared between 2 and 3 ppm. One of the methylene protons adjacent to the sulfonamide nitrogen appeared at ~3.5–3.7 ppm while the other appeared considerably downfield at 4.6–4.8 ppm. As with the dipolarophile precursor, this is presumably caused by through-space deshielding by one of the proximate sulfonamide oxygen atoms. In the X-ray structure of cycloadduct **5f** (Fig. 2), one of the methylene protons on C(1) is almost *syn*-periplanar with sulfonamide oxygen O(2) and at a distance of ~2.47 Å. The other methylene proton on C(1) (Fig. 2) points away from the sulfonamide group and is 3.73 Å away, which accounts for the large observed difference in chemical shifts.

All of this evidence is consistent with a constrained dipolarophile having an exposed face that leads to diastereofacial selectivity of benzonitrile oxide 1,3-dipolar cycloaddition. Given the remoteness of the *N*-aryl substituent from the dipolarophile, it is unlikely that steric hindrance from that group alone is responsible for the diastereofacial selectivity of the cycloaddition reactions. Based on the X-ray structure and NMR evidence, it appears that in addition to the *N*-aryl restricted rotation, an additional constrained, non-planar conformation of the seven-membered ring leads to one face of the exocyclic methylene dipolarophile being more exposed than the other, which results in a high degree of diastereofacial selectivity in the NOC reactions.

Conclusion

N-Aryl-5-methylene-2,3,4,5-tetrahydrobenzo[*f*][1,2]thiazepine 1,1-dioxides participate in 1,3-dipolar cycloaddition reactions with benzonitrile oxide at the exocyclic methylene function. The 5-spiro isoxazoline adducts are formed with complete regioselectivity, and high diastereofacial selectivity in those cases where unsymmetrical *N*-aryl substituents engender atropisomerism around the *N*-aryl axis.

Experimental

General

Melting points were determined on a Büchi B-545 instrument and are uncorrected. Flash column chromatography was performed on silica gel (Merck, 230–400 mesh ASTM, Kieselgel 60) or aluminium oxide (Merck, 70–230 mesh ASTM, Kieselgel; 90 active neutral) using the appropriate combination of ethyl acetate and light petroleum as eluent, with compressed air. Thin-layer chromatography was performed using aluminium-backed plates coated with 0.2 mm silica (Merck, DC-Platten, Kieselgel; 60 F254 plates). Eluted plates were visualized using a 254-nm UV lamp. Starting materials and reagents were purchased from Sigma–Aldrich, Oakwood Chemicals, and Merck, and were used as supplied. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Biospin AV400 spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei, using $CDCl_3$ as solvent and internal reference. Variable-temperature ^{1}H NMR spectra were recorded on a Bruker DRX 500 spectrometer operating at 500 MHz, using either $CDCl_3$ or CD_3CCl_3 as solvent. Infrared spectra were recorded neat using a Smart iTR accessory on a Thermo Nicolet 6700 Fourier-transform (FT)IR spectrometer. Electrospray ionization (ESI) high-resolution mass spectrometric (HR-MS) analyses were performed on a Thermo Scientific Q Exactive mass spectrometer fitted with a HESI ion source. Positive and negative ions were recorded in an appropriate mass range at 140000 mass resolution. The probe was used with 0.6 mL min^{-1} flow of solvent (usually methanol), and a solution of reserpine was also introduced into the probe during the experiments to serve as a lock mass in both positive- and negative-ion modes. The nitrogen nebulising, desolvation gas used for vaporization was heated to 100°C in these experiments. The sheath-gas flow rate was set to 25 and the auxiliary gas flow rate to 7 (both arbitrary units). The spray voltage was 3.8 kV and the capillary temperature was 300°C. The Cambridge Crystallographic Data Centre (CCDC) contains the supplementary crystallographic data for this paper. The data for 5-methylene-2-(naphthalen-1-yl)-2,3,4,5-tetrahydrobenzo[*f*][1,2]thiazepine 1,1-dioxide **4f** (deposition number CCDC954979) and 2-(naphthalen-1-yl)-3′-phenyl-3,4-dihydro-2*H*,4′*H*-spiro[benzo[*f*][1,2]thiazepine-5,5′-isoxazole] 1,1-dioxide **5f** (deposition number CCDC954980) can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; email: deposit@ccdc.cam.ac.uk.

General Synthesis Procedure for Homoallylsulfonamides *3*

Homoallylsulfonamides **3** were prepared according to the procedure of Hanson.[36] The appropriate sulfonamide **2** (10 mmol) was dissolved in anhydrous CH_2Cl_2 (50 mL) in an oven-dried round-bottom flask. Triphenylphosphine (2.89 g, 11 mmol) and but-3-en-1-ol (0.95 mL, 11 mmol) were then added, and the reaction mixture was stirred for 5 min. After this time, DIAD (2.17 mL, 11 mmol) was slowly added over a period of 10 min. The reaction mixture was stirred at room temperature for 3 h, then concentrated under vacuum. The residue was purified by flash column chromatography over silica to afford the title compounds. Benzyl homoallyl sulfonamide **3h** has been previously reported.[36]

*2-Bromo-N-(but-3-en-1-yl)-N-phenylbenzenesulfonamide (**3a**)*

The *title compound* was isolated as a white solid. Mp 89.2–91.2°C. R_f 0.3 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 1488 (m), 1447 (m), 1330 (s), 1146 (s), 1085 (s), 895 (s), 760 (s), 697 (s). δ_H 7.80 (dd, *J* 7.6, 1.6, 1H), 7.69 (dd, *J* 7.6, 1.6, 1H), 7.31–7.18 (m, 7H), 5.80–5.70 (m, 1H), 5.05–5.01 (m, 2H), 3.93 (t, *J* 7.2, 2H), 2.26 (q, *J* 7.2, 2H). δ_C 138.3, 138.1, 135.3, 134.4, 133.6, 132.9, 129.2, 129.1, 128.0, 127.3, 120.2, 117.3, 51.9, 33.3. *m*/*z* (HR-MS ESI) 387.9977; $[M + Na]^+$ requires 387.9983.

*2-Bromo-N-(but-3-en-1-yl)-N-(4-chlorophenyl) benzenesulfonamide (**3b**)*

The *title compound* was isolated as a yellow solid. Mp 75.3–75.6°C. R_f 0.3 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 1487 (m), 1334 (s), 1150 (s), 1081 (s), 914 (s), 743 (s), 718 (s). δ_H 7.82 (dd, *J* 7.6, 2.0, 1H), 7.70 (dd, *J* 7.6, 2.0, 1H), 7.33–7.14 (m, 6H), 5.78–5.68 (m, 1H), 5.06–5.01 (m, 2H), 3.90 (t, *J* 7.2, 2H), 2.24 (q, *J* 7.2, 2H). δ_C 138.2, 136.9, 135.6, 134.3, 133.9, 133.1, 130.7, 129.5, 127.6, 120.3, 117.6, 52.1, 33.4 (one aromatic signal overlapping). *m*/*z* (HR-MS ESI) 421.9588; $[M + Na]^+$ requires 421.9593.

*2-Bromo-N-(but-3-en-1-yl)-N-(2-methoxyphenyl) benzenesulfonamide (**3c**)*

The *title compound* was isolated as a yellow solid. Mp 68.9–70.9°C. R_f 0.2 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2978 (w), 1494 (m), 1343 (s), 1259 (m), 1168 (s), 1023 (s),

903 (m), 758 (s). δ_H 7.68 (dd, *J* 8.0, 1.6, 1H), 7.65 (dd, *J* 8.0, 1.6, 1H), 7.31 (dd, *J* 8.0, 1.6, 1H), 7.23–7.15 (m, 3H), 6.86 (td, *J* 8.0, 1.6, 1H), 6.65 (dd, *J* 8.0, 1.6, 1H), 5.78–5.68 (m, 1H), 5.02–4.97 (m, 2H), 3.90 (br s, 2H), 3.31 (s, 3H), 2.18 (q, *J* 7.2, 2H). δ_C 156.6, 140.0, 135.0, 134.9, 134.1, 132.8, 132.3, 130.0, 126.7, 125.3, 120.5, 120.4, 116.9, 111.4, 54.7, 50.3, 33.4. *m/z* (HR-MS ESI) 418.0083; $[M + Na]^+$ requires 418.0089.

*2-Bromo-N-(but-3-en-1-yl)-N-(2-morpholinophenyl) benzenesulfonamide (**3d**)*

The *title compound* was isolated as a yellow solid. Mp 67.2–71.8°C. R_f 0.3 (1 : 4 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2956 (w), 1490 (m), 1447 (m), 1343 (s), 1255 (m), 1162 (s), 1111 (s), 1024 (m), 901 (m), 754 (s). δ_H 7.94–7.91 (m, 1H), 7.74–7.72 (m, 1H), 7.36–7.32 (m, 2H), 7.28 (td, *J* 7.2, 1.6, 1H), 7.17 (dd, *J* 8.0, 1.6, 1H), 7.11 (dd, *J* 8.0 1.6, 1H), 7.02 (td, *J* 7.2, 1.6, 1H), 5.67–5.56 (m, 1H), 4.97–4.89 (m, 2H), 4.09–4.04 (m, 2H), 3.74 (t, *J* 4.4, 4H), 2.78 (br s, 4H), 2.07 (t, *J* 7.2, 2H). δ_C 151.1, 141.0, 135.9, 134.6, 133.7, 133.4, 132.5, 132.3, 129.5, 127.6, 125.0, 123.5, 120.2, 117.1, 70.1, 67.4, 53.2, 49.9, 33.1, 22.1. *m/z* (HR-MS ESI) 473.0505; $[M + Na]^+$ requires 473.0510.

*2-Bromo-N-(but-3-en-1-yl)-N-(2-isopropylphenyl) benzenesulfonamide (**3e**)*

The *title compound* was isolated as a yellow waxy solid. R_f 0.3 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2965 (w), 1487 (m), 1447 (m), 1342 (s), 1161 (s), 1100 (m), 1067 (m), 1025 (m), 906 (m), 751 (s). δ_H 7.73 (dd, *J* 7.6, 1.6, 2H), 7.30 (td, *J* 7.6, 1.6, 1H), 7.26–7.23 (m, 3H), 7.06–7.02 (m, 1H), 6.97 (d, *J* 7.6, 1H), 5.78–5.68 (m, 1H), 5.07–5.02 (m, 2H), 4.09–4.01 (m, 1H), 3.97–3.72 (m, 1H), 3.26 (sept., *J* 6.8, 1H), 2.25 (q, *J* 7.2, 2H), 1.12 (d, *J* 6.8, 3H), 0.84 (d, *J* 6.8, 3H). δ_C 149.8, 139.5, 135.8, 135.0, 134.5, 133.5, 133.2, 131.3, 129.2, 127.5, 127.4, 126.2, 120.4, 117.3, 53.0, 33.5, 27.5, 24.9, 23.5. *m/z* (HR-MS ESI) 430.0445; $[M + Na]^+$ requires 430.0452.

*2-Bromo-N-(but-3-en-1-yl)-N-(naphthalene-1-yl) benzenesulfonamide (**3f**)*

The *title compound* was isolated as a yellow waxy solid. R_f 0.3 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2936 (w), 1572 (m), 1445 (m), 1393 (m), 1333 (s), 1158 (s), 1101 (m), 1067 (m), 1027 (m), 1006 (m), 898 (m), 758 (s). δ_H 8.06–8.03 (m, 1H), 7.81–7.78 (m, 2H), 7.69 (td, *J* 8.0, 1.2, 1H), 7.45–7.39 (m, 2H), 7.34 (t, *J* 8.0, 1H), 7.83–7.23 (m, 2H), 7.14 (td *J* 8.0, 1.2, 1H), 5.75–5.65 (m, 1H), 5.02–4.97 (m, 2H), 4.14–4.00 (m, 2H), 2.31–2.26 (m, 1H), 1.26–1.22 (m, 1H). δ_C 138.9, 135.6, 134.7, 134.4, 133.5, 132.9, 132.3, 129.4, 129.1, 128.3, 127.4, 126.8, 126.4, 125.2, 123.7, 120.2, 117.3, 52.9, 33.8 (one aromatic signal overlapping). *m/z* (HR-MS ESI) 438.0132; $[M + Na]^+$ requires 438.0139.

*2-Bromo-N-(but-3-en-1-yl)-N-(2-nitrophenyl) benzenesulfonamide (**3g**)*

The *title compound* was isolated as a yellow solid. Mp 94.5–95.6°C. R_f 0.3 (1 : 4 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 1447 (m), 1333 (s), 1160 (s), 911 (m), 759 (s), 692 (s). δ_H 7.82–7.71 (m, 3H), 7.58–7.46 (m, 2H), 7.40–7.29 (m, 3H), 5.79–5.69 (m, 1H), 5.09–5.03 (m, 2H), 3.99 (br s, 2H), 2.43 (q, *J* 7.2, 2H). δ_C 149.3, 138.6, 136.0, 134.3, 134.1, 134.0, 133.1, 132.3, 131.5, 129.7, 127.6, 125.5, 120.4, 117.6, 52.4, 33.5. *m/z* (HR-MS ESI) 432.9828; $[M + Na]^+$ requires 432.9834.

*General Synthesis Procedure for Methylene Benzothiazepines **4***

Methylene benzothiazepines **4** were prepared according to the method of Hanson.[36] The appropriate homoallylsulfonamide **3** (4.4 mmol) was weighed into a 20-mL microwave vial, to which was added MeCN (15 mL), triethylamine (1.8 mL, 13 mmol), PPh_3 (230 mg, 0.88 mmol), and $Pd(OAc)_2$ (98 mg, 0.44 mmol). The vial was sealed and stirred at room temperature for 5 min, followed by heating to 100°C in a microwave reactor for 1.5 h. The reaction mixture was cooled to room temperature, then filtered through a plug of Celite, rinsing with CH_2Cl_2. The filtrate was concentrated under vacuum and the residue was purified via flash column chromatography to afford the title compounds. The *N*-benzyl 5-methylene benzothiazepine **4h** has been previously reported.[36]

*5-Methylene-2-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2] thiazepine 1,1-Dioxide (**4a**)*

The *title compound* was isolated as a waxy yellow solid. R_f 0.3 (1 : 4 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 1595 (m), 1491 (m), 1335 (s), 1158 (s), 911 (s), 728 (s), 694 (s). δ_H 7.88 (dd, *J* 7.6, 1.2, 1H), 7.53 (td, *J* 7.6, 1.2, 1H), 7.44 (dd, *J* 7.6, 1.2, 1H), 7.37 (td, *J* 7.6, 1.2, 1H), 7.26–7.21 (m, 3H), 7.09–7.03 (m, 2H), 5.39 (d, *J* 0.8, 1H), 5.33 (d, *J* 0.8, 1H), 4.09–4.07 (m, 2H), 2.66 (t, *J* 5.6, 2H). δ_C 147.3, 141.2, 140.2, 132.8, 130.8, 129.4, 127.8, 127.7, 127.5, 127.2, 121.3, 120.2, 54.6, 34.5. *m/z* (HR-MS ESI) 308.0716; $[M + Na]^+$ requires 308.0721.

*2-(4-Chlorophenyl)-5-methylene-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-Dioxide (**4b**)*

The *title compound* was isolated as a yellow oil. R_f 0.35 (1 : 4 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 1488 (s), 1342 (s), 1160 (s), 1089 (m), 906 (s), 739 (s). δ_H 7.84 (dd, *J* 7.6, 0.8, 1H), 7.53 (td, *J* 7.6, 1.2, 1H), 7.43 (dd, *J* 7.6, 0.8, 1H), 7.38 (td, *J* 7.6, 1.2, 1H), 7.19 (d, *J* 8.8, 2H), 6.98 (d, *J* 8.8, 2H), 5.39 (s, 1H), 5.33 (s, 1H), 4.04 (br s, 2H), 2.65 (t, *J* 5.6, 2H). δ_C 147.0, 140.2, 139.9, 139.5, 133.4, 133.0, 130.9, 129.5, 128.8, 127.9, 127.2, 120.4, 54.4, 34.6. *m/z* (HR-MS ESI) 342.0327; $[M + Na]^+$ requires 342.0331.

*2-(2-Methoxyphenyl)-5-methylene-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-Dioxide (**4c**)*

The *title compound* was isolated as a yellow solid. Mp 118.0–120.2°C (dec.). R_f 0.3 (1 : 4 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2903 (w), 1497 (m), 1465 (m), 1339 (s), 1255 (m), 1159 (s), 1114 (m), 1099 (m), 1024 (m), 919 (m), 752 (s). δ_H 7.91 (dd, *J* 7.6, 1.2, 1H), 7.52 (td, *J* 7.6, 1.2, 1H), 7.44 (dd, *J* 7.6, 1.2, 1H), 7.40 (td, *J* 7.6, 1.2, 1H), 7.26–7.21 (m, 1H), 6.90–6.87 (m, 2H), 6.79 (td, *J* 7.6, 1.2, 1H), 5.37 (s, 1H), 5.34 (d, *J* 1.2, 1H), 3.99 (br s, 2H), 3.63 (s, 3H), 2.67 (t, *J* 5.6, 2H). δ_C 156.3, 148.1, 141.3, 140.2, 132.3, 130.7, 130.2, 129.5, 129.4, 127.6, 126.6, 120.8, 119.9, 112.5, 55.6, 53.9, 35.2. *m/z* (HR-MS ESI) 338.0821; $[M + Na]^+$ requires 338.0827.

*5-Methylene-2-(2-morpholinophenyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-Dioxide (**4d**)*

The *title compound* was isolated as a yellow solid. Mp 136.7–138.0°C. R_f 0.3 (1 : 4 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 3245 (w), 2964 (w), 1687 (m), 1490 (m), 1441 (m), 1341 (s), 1254 (m), 1227 (m), 1162 (s), 1112 (s), 923 (m), 758 (s). δ_H 7.99 (d, *J* 7.2, 1H), 7.58 (td, *J* 7.2, 0.8, 1H), 7.49–7.46 (m, 2H), 7.21 (td, *J* 7.2, 0.8, 1H), 7.03 (d, *J* 7.2, 1H), 6.81 (td, *J* 7.2, 0.8, 1H), 6.64 (dd, *J* 7.2, 0.8, 1H), 5.38 (s, 1H), 5.34 (s, 1H), 4.98 (quint.,

J 6.4, 1H), 4.42–4.38 (m, 1H), 3.89–3.86 (m, 4H), 3.55–3.48 (m, 2H), 2.86–2.79 (m, 2H), 2.59–2.56 (m, 2H). δ_C 148.7, 147.6, 141.1, 140.2, 134.6, 132.8, 131.0, 128.5, 128.0, 127.7, 126.6, 123.0, 120.3, 120.0, 69.9, 67.6, 52.5, 51.8, 34.2, 22.0. *m/z* (HR-MS ESI) 393.1244; $[M + Na]^+$ requires 392.1249.

*2-(2-Isopropylphenyl)-5-methylene-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-Dioxide (**4e**)*

The *title compound* was isolated as a yellow waxy solid. R_f 0.25 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2958 (w), 1486 (m), 1445 (m), 1344 (s), 1165 (s), 1129 (m), 1101 (m), 1087 (m), 1045 (m), 906 (s), 842 (m), 758 (s). δ_H 7.87 (dd, *J* 8.0, 1.2, 1H), 7.56 (td, *J* 8.0, 1.2, 1H), 7.48 (dd, *J* 8.0, 1.2, 1H), 7.42–7.38 (m, 2H), 7.28 (td, *J* 8.0, 1.2, 1H), 6.95 (td, *J* 8.0, 1.2, 1H), 6.59 (dd, *J* 8.0, 1.2, 1H), 5.42 (s, 1H), 5.38 (s, 1H), 4.52 (ddd, *J* 14.4, 11.6, 2.8, 1H), 3.54 (sept., *J* 6.8, 1H), 3.39 (dt, *J* 14.4, 4.0, 1H), 2.76 (tdd, *J* 14.4, 4.0, 0.8, 1H), 2.64 (dt, *J* 14.4, 4.0, 1H) 1.30 (d, *J* 6.8, 3H), 1.24 (d, *J* 6.8, 3H). δ_C 148.9, 147.6, 140.3, 140.1, 138.5, 132.8, 130.9, 129.1, 127.8, 127.6, 127.5, 127.3, 126.2, 120.3, 54.3, 34.4, 27.8, 24.1, 24.0. *m/z* (HR-MS ESI) 350.1185; $[M + Na]^+$ requires 350.1191.

*5-Methylene-2-(naphthalen-1-yl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-Dioxide (**4f**)*

The *title compound* was isolated as a yellow waxy solid. R_f 0.2 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2980 (w), 1706 (m), 1466 (m), 1339 (s), 1159 (s), 1107 (m), 914 (m), 757 (s). δ_H 8.31 (d, *J* 8.0, 1H), 7.91 (dd, *J* 7.6, 1.2, 1H), 7.86 (d, *J* 8.0, 1H), 7.80 (d, *J* 8.0, 1H), 7.65–7.51 (m, 4H), 7.44 (td, *J* 7.6, 1.2, 1H), 7.22 (t, *J* 8.0, 1H), 6.81 (dd, *J* 7.6, 1.2, 1H), 5.45 (s, 1H), 5.42 (d, *J* 1.2, 1H), 4.68 (ddd, *J* 14.4, 11.6, 2.8, 1H), 3.53 (dt, *J* 14.4, 4.0, 1H), 2.76 (tdd, *J* 14.4, 4.0, 1.2, 1H), 2.65 (dt, *J* 14.4, 4.0, 1H). δ_C 147.6, 140.4, 140.2, 137.3, 135.0, 133.0, 131.9, 131.1, 130.0, 128.4, 127.9, 127.5, 127.4, 126.9, 125.0, 124.8, 123.5, 120.5, 53.9, 34.7. *m/z* (HR-MS ESI) 358.0871; $[M + Na]^+$ requires 358.0878.

*5-Methylene-2-(2-nitrophenyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-Dioxide (**4g**)*

The *title compound* was isolated as a white solid. Mp 189.3–190.9°C (dec.). R_f 0.3 (3 : 7, v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 1526 (m), 1351 (s), 1166 (s), 923 (m), 766 (m), 724 (s). δ_H 7.85 (dd, *J* 7.6, 1.6, 1H), 7.81 (d, *J* 7.6, 1H), 7.57 (td, *J* 7.6, 1.6, 1H), 7.50–7.38 (m, 4H), 6.94 (dd, *J* 7.6, 1.6, 1H), 5.45 (s, 1H), 5.41 (s, 1H), 4.38–3.80 (m, 2H), 2.77 (t, *J* 5.6, 2H). δ_C 149.5, 146.8, 140.1, 139.6, 134.1, 133.2, 133.1, 130.9, 130.1, 129.5, 128.0, 127.0, 125.3, 120.6, 54.4, 35.1. *m/z* (HR-MS ESI) 353.0566; $[M + Na]^+$ requires 353.0572.

General Procedure for Nitrile Oxide Cycloaddition Reactions

Nitrile oxide cycloaddition reactions were carried out using our previously reported method.[16] The appropriate methylene benzothiazepine **4** (1 mmol) was dissolved in CH_2Cl_2 (5 mL). Benzaldehyde oxime (363 mg, 3 mmol) was added and the vigorously stirred solution was cooled to 0°C in an ice bath. NaOCl (5.5 mL of an 5 % aqueous solution, 6 mmol) was added slowly over a period of 30 min. The reaction mixture was stirred vigorously overnight, then diluted with CH_2Cl_2 (5 mL) and brine (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified via flash column chromatography (EtOAc/light petroleum) over neutral alumina to afford the title compounds.

*2,3′-Diphenyl-3,4-dihydro-2H,4′H-spiro[benzo[f][1,2]thiazepine-5,5′-isoxazole] 1,1-Dioxide (**5a**)*

The *title compound* was isolated as a white solid. Mp 204.9–206.6°C. R_f 0.3 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 1489 (m), 1443 (m), 1330 (s), 1165 (s), 1125 (m), 923 (m), 885 (m), 758 (s), 686 (s). δ_H 8.04 (d, *J* 7.6, 1H), 8.00 (d, *J* 7.6, 1H), 7.69–7.61 (m, 3H), 7.41–7.26 (m, 7H), 6.99 (br s, 2H), 4.74 (t, *J* 14.0, 2.4, 1H), 3.93 (d, *J* 17.6, 1H), 3.85 (d, *J* 17.6, 1H), 3.62 (d, *J* 14.8, 1H), 2.63 (t, *J* 14.0, 1H), 2.15 (d, *J* 14.0, 1H). δ_C 157.1, 140.8, 140.7, 138.6, 133.5, 130.5, 129.7, 129.2, 128.9, 128.6, 128.3, 128.2, 127.7, 126.9, 91.0, 49.2, 46.6, 36.0. *m/z* (HR-MS ESI) 427.1087; $[M + Na]^+$ requires 427.1092.

*2-(4-Chlorophenyl)-3′-phenyl-3,4-dihydro-2H,4′H-spiro[benzo[f][1,2]thiazepine-5,5′-isoxazole] 1,1-Dioxide (**5b**)*

The *title compound* was isolated as a white solid. Mp 178.9–180.2°C. R_f 0.3 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 1490 (m), 1342 (s), 1167 (s), 865 (m), 837 (m), 750 (s). δ_H 8.06 (d, *J* 8.0, 1H), 8.00 (dd, *J* 7.6, 1.2, 1H), 7.71–7.69 (m, 2H), 7.64 (td, *J* 7.6, 1.2, 1H), 7.46–7.39 (m, 4H), 7.25 (d, *J* 8.8, 2H), 6.95 (d, *J* 8.8, 2H), 4.74 (td, *J* 14.0, 2.4, 1H), 3.95 (d, *J* 18.0, 1H), 3.85 (d, *J* 18.0, 1H), 3.60 (dt, *J* 15.6, 3.6, 1H), 2.61 (td, *J* 14.0, 3.6, 1H), 2.19 (dt, *J* 15.6, 2.4, 1H). δ_C 157.1, 140.8, 139.1, 138.1, 134.2, 133.7, 130.6, 129.9, 129.3, 129.1, 128.9, 128.7, 128.3, 126.9, 90.9, 49.2, 46.7, 36.1 (one aromatic signal overlapping). *m/z* (HR-MS ESI) 461.0697; $[M + Na]^+$ requires 461.0703.

*2-(2-Methoxyphenyl)-3′-phenyl-3,4-dihydro-2H,4′H-spiro[benzo[f][1,2]thiazepine-5,5′-isoxazole] 1,1-Dioxide (**5c**)*

The *title compound* was isolated as a white solid. Mp 146.8–152.1°C. R_f 0.2 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2947 (w), 1500 (m), 1343 (s), 1254 (m), 1159 (s), 1055 (m), 1024 (m), 903 (m), 756 (s). δ_H 8.00 (d, *J* 8.0, 2H), 7.70–7.68 (m, 2H), 7.58 (td, *J* 8.0, 0.8, 1H), 7.42–7.37 (m, 4H), 7.24 (td, *J* 8.0, 0.8, 1H), 6.89–6.78 (m, 3H), 4.66 (td, *J* 13.6, 0.4, 1H), 3.92 (d, *J* 18.0, 1H), 3.83 (d, *J* 18.0, 1H), 3.57–3.51 (m, 4H), 2.66 (td, *J* 13.6, 3.2, 1H), 2.11 (dt, *J* 13.6, 1.2, 1H). δ_C 157.1, 156.2, 140.6, 140.0, 132.9, 130.5, 129.8, 129.7, 129.6, 129.5, 129.3, 128.9, 128.2, 127.9, 126.9, 120.9, 112.4, 91.3, 55.6, 48.4, 46.6, 36.6. *m/z* (HR-MS ESI) 457.1192; $[M + Na]^+$ requires 457.1198.

*2-(2-Morpholinophenyl)-3′-phenyl-3,4-dihydro-2H,4′H-spiro[benzo[f][1,2]thiazepine-5,5′-isoxazole] 1,1-Dioxide (**5d**)*

The title compound was isolated as a white solid. Mp 199.3–200.0°C (dec.). R_f 0.3 (1 : 4 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2957 (w), 1737 (m), 1596 (m), 1494 (m), 1444 (m), 1338 (s), 1232 (m), 1166 (m), 1115 (s), 935 (m), 909 (m), 761 (s). δ_H 8.10 (dd, *J* 7.6, 1.2, 1H), 8.03 (dd, *J* 7.6, 1.2, 1H), 7.70–7.68 (m, 2H), 7.63 (td, *J* 7.6, 1.2, 1H), 7.49 (td, *J* 7.6, 1.2, 1H), 7.40–7.36 (m, 3H), 7.21 (td, *J* 7.6, 1.2, 1H), 7.01 (dd, *J* 7.6, 1.2, 1H), 6.78 (td, *J* 7.6, 1.2, 1H), 6.45–6.32 (m, 1H), 4.60 (t, *J* 14.4, 1H), 3.95–3.80 (m, 5H), 3.93 (d, *J* 18.0, 1H), 3.83 (d, *J* 18.0, 1H), 3.54–3.51 (m, 2H), 2.84–2.79 (m, 2H), 2.46 (t, *J* 15.6, 1H), 2.08 (d, *J* 15.6, 1H). δ_C 157.0, 148.8, 140.7, 139.8, 133.9, 133.5, 130.5, 129.2, 129.0, 128.9, 128.8, 128.5, 128.3, 127.6, 126.9, 123.3, 120.6, 91.1, 67.8, 60.5, 52.0, 46.9, 46.5, 35.5, 22.5. *m/z* (HR-MS ESI) 512.1618; $[M + Na]^+$ requires 512.1620.

*2-(2-Isopropylphenyl)-3′-phenyl-3,4-dihydro-2*H*, 4′*H*-spiro[benzo[f][1,2]thiazepine-5,5′-isoxazole] 1,1-Dioxide (**5e**)*

The *title compound* was isolated as a white solid. Mp 204.5–205.6°C. R_f 0.15 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2961 (w), 1488 (m), 1446 (m), 1341 (s), 1305 (m), 1174 (s), 1129 (m), 924 (m), 753 (s). δ_H 8.07 (d, *J* 8.0, 1H), 7.98 (d, *J* 8.0, 1H), 7.72–7.70 (m, 2H), 7.64 (t, *J* 8.0, 1H), 7.44–7.40 (m, 5H), 7.30 (t, *J* 8.0, 1H), 6.92 (td, *J* 8.0, 1.6, 1H), 6.41 (d, *J* 8.0, 1H), 4.75 (td, *J* 14.4, 1.6, 1H), 3.97 (d, *J* 18.0, 1H), 3.89 (d, *J* 18.0, 1H), 3.56 (sept., *J* 6.8, 1H), 3.38 (dt, *J* 15.6, 3.6, 1H), 2.69 (td, *J* 14.4, 3.6, 1H), 2.14 (dd, 15.6, 3.6, 1H), 1.34 (d, *J* 6.8, 3H), 1.26 (d, *J* 6.8, 3H). δ_C 157.1, 148.7, 140.5, 138.8, 137.7, 133.4, 130.5, 129.4, 129.2, 128.9, 128.8, 128.5, 128.2, 127.7, 127.1, 126.9, 126.3, 91.1, 48.8, 46.6, 35.5, 27.9, 24.1, 23.9. *m/z* (HR-MS ESI) 469.1559; $[M + Na]^+$ requires 469.1562.

*2-(Naphthalen-1-yl)-3′-phenyl-3,4-dihydro-2*H*, 4′*H*-spiro[benzo[f][1,2]thiazepine-5,5′-isoxazole] 1,1-Dioxide (**5f**)*

The *title compound* was isolated as a white solid. Mp 260.3–262.1°C. R_f 0.25 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 2961 (w), 1488 (m), 1446 (m), 1341 (s), 1305 (m), 1174 (s), 1129 (m), 924 (m), 753 (s). δ_H 8.33 (d, *J* 8.0, 1H), 8.12 (dd, *J* 8.0, 1.2, 1H), 8.03 (dd, *J* 8.0, 1.2, 1H), 7.87 (d, *J* 8.0, 1H), 7.81 (d, *J* 8.0, 1H), 7.75–7.72 (m, 2H), 7.69 (dd, *J* 8.0, 1.2, 1H), 7.65 (dd, *J* 8.0, 1.2, 1H), 7.57 (td, *J* 8.0, 1.2, 1H), 7.46 (td, *J* 8.0, 1.2, 1H), 7.44–7.41 (m, 3H), 7.20 (t, *J* 8.0, 1H), 6.65 (dd, *J* 8.0, 1.2, 1H), 4.90 (ddd, *J* 15.6, 13.6, 2.0, 1H), 4.03 (d, *J* 18.0, 1H), 3.95 (d, *J* 18.0, 1H), 3.54 (td, *J* 15.6, 3.2, 1H), 2.72 (td, *J* 13.6, 2.0, 1H), 2.17 (ddd, *J* 15.6, 3.2, 2.0, 1H). δ_C 157.1, 140.8, 138.8, 136.4, 135.1, 133.5, 132.1, 130.6, 129.3, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.7, 127.0, 126.9, 125.1, 124.6, 123.2, 91.1, 48.4, 46.7, 35.8. *m/z* (HR-MS ESI) 477.1243; $[M + Na]^+$ requires 477.1249.

*2-(2-Nitrophenyl)-3′-phenyl-3,4-dihydro-2*H*, 4′*H*-spiro[benzo[f][1,2]thiazepine-5,5′-isoxazole] 1,1-Dioxide (**5g**)*

The *title compound* was isolated as a white solid. Mp 208.7–209.0°C. R_f 0.25 (1 : 4 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 1524 (s), 1341 (s), 1170 (m), 1158 (m), 910 (m), 847 (m), 762 (s), 740 (s), 695 (s). δ_H 8.10 (d, *J* 8.0, 1H), 7.93 (dd, *J* 7.6, 1.2, 1H), 7.88 (d, *J* 7.6, 1H), 7.71–7.69 (m, 2H), 7.66 (td, *J* 8.0, 1.2, 1H), 7.49 (td, *J* 7.6, 1.2, 1H), 7.45–7.39 (m, 6H), 4.76 (t, *J* 14.4, 1H), 3.98 (d, *J* 18.0, 1H), 3.86 (d, *J* 18.0, 1H), 3.73 (dt, *J* 16.0, 3.6, 1H), 2.66 (td, *J* 14.4, 3.6, 1H), 2.28 (ddd, *J* 16.0, 3.6, 2.4, 1H). δ_C 157.2, 140.7, 138.2, 133.8, 133.2, 130.6, 129.9, 129.7, 129.1, 128.9, 128.6, 128.4, 126.9, 125.6, 90.8, 77.5, 48.9, 46.5 (3 aromatic signals overlapping). *m/z* (HR-MS ESI) 472.0938; $[M + Na]^+$ requires 472.0943.

*2-Benzyl-3′-phenyl-3,4-dihydro-2*H*,4′*H*-spiro[benzo[f][1,2]thiazepine-5,5′-isoxazole] 1,1-Dioxide (**5h**)*

The *title compound* was isolated as a white solid. Mp 77.6–79.5°C. R_f 0.2 (1 : 9 v/v EtOAc/light petroleum). ν_{max}/cm^{-1} 1336 (s), 1161 (s), 910 (m), 759 (s), 721 (s), 691 (s). δ_H 8.14 (dd, *J* 8.0, 1.6, 1H), 7.98 (dd, *J* 8.0, 1.2, 1H), 7.67–7.64 (m, 2H), 7.59 (td, *J* 8.0, 1.6, 1H) 7.45 (td, *J* 7.6, 1.2, 1H), 7.38–7.24 (m, 8H), 4.56 (d, *J* 14.4, 1H), 4.17 (td, *J* 14.0, 1.2, 1H), 3.83 (d, *J* 18.0, 1H), 3.76 (d, *J* 18.0, 1H), 3.62 (d, *J* 14.4, 1H), 3.12 (dt, *J* 15.6, 3.2, 1H), 2.52 (td, *J* 14.0, 3.2, 1H), 1.96 (ddd, *J* 15.6, 3.2, 2.4, 1H). δ_C 157.1, 141.3, 136.1, 135.3, 133.5, 130.5, 130.3, 129.2, 128.9, 128.8, 128.5, 128.4, 128.3, 128.0, 126.9, 90.7, 50.0, 46.5, 42.3, 32.7. *m/z* (HR-MS ESI) 441.1244; $[M + Na]^+$ requires 441.1249.

Supplementary Material

Variable-temperature ^{1}H NMR experiments of the *N*-(2-isopropyl)phenyl benzothiazepine **4e**, a plot of the of *N*-aryl rotational energy for compound **4f** (molecular simulation), chiral HPLC chromatogram for **5f**, and the ^{1}H and ^{13}C NMR spectra of cycloadducts are available on the Journal's website.

Acknowledgements

The authors wish to thank Dr Roger Mulder of CSIRO for assistance with NMR spectroscopy, Dr Leaf Lin and Professor Michelle Coote of The Australian National University for rotational barrier calculations, Professor James De Voss of the University of Queensland for chiral HPLC, and Dr Craig Forsyth of Monash University for the X-ray crystallographic structure determination.

References

[1] T. S. Peat, D. I. Rhodes, N. Vandegraaff, G. Le, J. A. Smith, L. J. Clark, E. D. Jones, J. A. V. Coates, N. Thienthong, J. Newman, O. Dolezal, R. Mulder, J. H. Ryan, G. P. Savage, C. L. Francis, J. J. Deadman, *PLoS ONE* **2012**, *7*, e40147. doi:10.1371/JOURNAL.PONE.0040147

[2] D. I. Rhodes, T. S. Peat, N. Vandegraaff, D. Jeevarajah, G. Le, E. D. Jones, J. A. Smith, J. A. V. Coates, L. J. Winfield, N. Thienthong, J. Newman, D. Lucent, J. H. Ryan, G. P. Savage, C. L. Francis, J. J. Deadman, *Antivir. Chem. Chemother.* **2011**, *21*, 155. doi:10.3851/IMP1716

[3] J. Clardy, C. Walsh, *Nature* **2004**, *432*, 829. doi:10.1038/NATURE03194

[4] A. D. Morley, A. Pugliese, K. Birchall, J. Bower, P. Brennan, N. Brown, T. Chapman, M. Drysdale, I. H. Gilbert, S. Hoelder, A. Jordan, S. V. Ley, A. Merritt, D. Miller, M. E. Swarbrick, P. G. Wyatt, *Drug Discov. Today* **2013**, in press. doi:10.1016/J.DRUDIS.2013.07.011

[5] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752. doi:10.1021/JM901241E

[6] P. D. Leeson, S. A. St-Gallay, M. C. Wenlock, *Med. Chem. Commun.* **2011**, *2*, 91. doi:10.1039/C0MD00157K

[7] T. J. Ritchie, S. J. F. Macdonald, R. J. Young, S. D. Pickett, *Drug Discov. Today* **2011**, *16*, 164. doi:10.1016/J.DRUDIS.2010.11.014

[8] W. H. B. Sauer, M. K. Schwarz, *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 987. doi:10.1021/CI025599W

[9] P. Grunanger, P. Vita-Finzi, *Isoxazoles – Part 1* (Eds A. Weissberger, E. C. Taylor) The Chemistry of Heterocyclic Compounds **1991**, Vol. 49 (Wiley: New York, NY).

[10] C. J. Easton, C. M. M. Hughes, G. P. Savage, G. W. Simpson, in *Cycloaddition Reactions of Nitrile Oxides with Alkenes* (Ed. A. R. Katritzky) **1994**, Vol. 60, pp. 261–327 (Academic Press: San Diego, CA.).

[11] S. M. Pereira, G. P. Savage, G. W. Simpson, R. J. Greenwood, M. F. Mackay, *Aust. J. Chem.* **1993**, *46*, 1401. doi:10.1071/CH9931401

[12] B. M. Kelly-Basetti, M. F. Mackay, S. M. Pereira, G. P. Savage, G. W. Simpson, *Heterocycles* **1994**, *37*, 529. doi:10.3987/COM-93-S49

[13] C. K. Y. Lee, C. J. Easton, G. P. Savage, G. W. Simpson, *ARKIVOC* **2006**, *3*, 175.

[14] R. Newton, G. P. Savage, *Aust. J. Chem.* **2008**, *61*, 432. doi:10.1071/CH08111

[15] N. J. Beattie, C. L. Francis, A. J. Liepa, G. P. Savage, *Aust. J. Chem.* **2010**, *63*, 445. doi:10.1071/CH09479

[16] A. M. Said, G. P. Savage, *J. Org. Chem.* **2011**, *76*, 6946. doi:10.1021/JO2011818

[17] S. L. Harding, G. P. Savage, *Org. Biomol. Chem.* **2012**, *10*, 4759. doi:10.1039/C2OB25271F

[18] G. P. Savage, *Curr. Org. Chem.* **2010**, *14*, 1478. doi:10.2174/138527210791616812
[19] J. Xu, A. T. Hamme II, *Synlett* **2008**, 919. doi:10.1055/S-2008-1042906
[20] S. Dadiboyena, J. Xu, A. T. Hamme II, *Tetrahedron Lett.* **2007**, *48*, 1295. doi:10.1016/J.TETLET.2006.12.005
[21] G. P. Savage, G. T. Wernert, *Aust. J. Chem.* **2005**, *58*, 877. doi:10.1071/CH05189
[22] C. J. Easton, C. M. M. Hughes, E. R. T. Tiekink, C. E. Lubin, G. P. Savage, G. W. Simpson, *Tetrahedron Lett.* **1994**, *35*, 3589. doi:10.1016/S0040-4039(00)73248-5
[23] S. J. Barrow, C. J. Easton, G. P. Savage, G. W. Simpson, *Tetrahedron Lett.* **1997**, *38*, 2175. doi:10.1016/S0040-4039(97)00275-X
[24] W.-C. Cheng, Y. Liu, M. Wong, M. M. Olmstead, K. S. Lam, M. J. Kurth, *J. Org. Chem.* **2002**, *67*, 5673. doi:10.1021/JO025611J
[25] K. G. Guggenheim, J. D. Butler, P. P. Painter, B. A. Lorsbach, D. J. Tantillo, M. J. Kurth, *J. Org. Chem.* **2011**, *76*, 5803. doi:10.1021/JO200924Y
[26] B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, *J. Med. Chem.* **1988**, *31*, 2235. doi:10.1021/JM00120A002
[27] M. Altamura, V. Fedi, D. Giannotti, P. Paoli, P. Rossi, *New J. Chem.* **2009**, *33*, 2219. doi:10.1039/B9NJ00279K
[28] M. Wainwright, J. E. Kristiansen, *Dyes Pigments* **2011**, *88*, 231. doi:10.1016/J.DYEPIG.2010.08.012
[29] D. B. A. de Bont, K. M. Sliedregt-Bol, L. J. F. Hofmeyer, R. M. J. Liskamp, *Bioorg. Med. Chem.* **1999**, *7*, 1043. doi:10.1016/S0968-0896(99)00021-8
[30] A. K. Ganguly, S. S. Alluri, D. Caroccia, D. Biswas, C.-H. Wang, E. Kang, Y. Zhang, A. T. McPhail, S. S. Carroll, C. Burlein, V. Munshi, P. Orth, C. Strickland, *J. Med. Chem.* **2011**, *54*, 7176. doi:10.1021/JM200778Q
[31] M. B. Tollefson, S. A. Kolodziej, T. R. Fletcher, W. F. Vernier, J. A. Beaudry, B. T. Keller, D. B. Reitz, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3727. doi:10.1016/J.BMCL.2003.08.004
[32] G. Laconde, P. Depreux, P. Berthelot, N. Pommery, J.-P. Hénichart, *Eur. J. Med. Chem.* **2005**, *40*, 167. doi:10.1016/J.EJMECH.2004.10.008
[33] N. Lebegue, S. Gallet, N. Flouquet, P. Carato, B. Pfeiffer, P. Renard, S. Léonce, A. Pierré, P. Chavatte, P. Berthelot, *J. Med. Chem.* **2005**, *48*, 7363. doi:10.1021/JM0503897
[34] R. Silvestri, G. Marfè, M. Artico, G. La Regina, A. Lavecchia, E. Novellino, M. Morgante, C. Di Stefano, G. Catalano, G. Filomeni, E. Abruzzese, M. R. Ciriolo, M. A. Russo, S. Amadori, R. Cirilli, F. La Torre, P. Sinibaldi Salimei, *J. Med. Chem.* **2006**, *49*, 5840. doi:10.1021/JM0602716
[35] P. Pacher, E. Kohegyi, V. Kecskemeti, S. Furst, *Curr. Med. Chem.* **2001**, *8*, 89. doi:10.2174/0929867013373796
[36] D. K. Rayabarapu, A. Zhou, K. O. Jeon, T. Samarakoon, A. Rolfe, H. Siddiqui, P. R. Hanson, *Tetrahedron* **2009**, *65*, 3180. doi:10.1016/J.TET.2008.11.053
[37] S. J. Ryan, C. L. Francis, G. P. Savage, *Aust. J. Chem.* **2013**, *66*, 874. doi:10.1071/CH13270
[38] Y. Ohta, H. Chiba, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2009**, *74*, 7052. doi:10.1021/JO901328Q
[39] K. Ackermann, J. Chapuis, D. E. Horning, G. Lacasse, J. M. Muchowski, *Can. J. Chem.* **1969**, *47*, 4327. doi:10.1139/V69-717
[40] N. Platzer, J. P. Bouchet, C. Malen, C. Labrid, E. Mocaer, *Magn. Reson. Chem.* **1992**, *30*, 1212. doi:10.1002/MRC.1260301210
[41] M. Raban, E. H. Carlson, J. Szmuszkovicz, G. Slomp, C. G. Chidester, D. J. Duchamp, *Tetrahedron Lett.* **1975**, *16*, 139. doi:10.1016/S0040-4039(00)72491-9
[42] M. Sarrazin, M. Bourdeaux-Pontier, C. Briand, E.-J. Vincent, *Org. Magn. Resonance* **1975**, *7*, 89. doi:10.1002/MRC.1270070209
[43] R. Benassi, P. Lazzeretti, F. Taddei, D. Nardi, A. Tajana, *Org. Magn. Resonance* **1976**, *8*, 387. doi:10.1002/MRC.1270080715
[44] A. Entrena, J. M. Campos, M. A. Gallo, A. Espinosa, *ARKIVOC* **2005**, *2005*, 88. doi:10.3998/ARK.5550190.0006.608
[45] N. H. Martin, J. D. Brown, K. H. Nance, H. F. Schaefer, P. R. Schleyer, Z.-X. Wang, H. L. Woodcock, *Org. Lett.* **2001**, *3*, 3823. doi:10.1021/OL016500U
[46] T. Mukaiyama, T. Hoshino, *J. Am. Chem. Soc.* **1960**, *82*, 5339. doi:10.1021/JA01505A017
[47] H. Feuer, K. Torssell, *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis* **2008** (John Wiley and Sons: Hoboken, NJ).
[48] G. A. Lee, *Synthesis* **1982**, 508. doi:10.1055/S-1982-29860
[49] R. Sustmann, *Pure Appl. Chem.* **1974**, *40*, 569. doi:10.1351/PAC197440040569
[50] R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 633. doi:10.1002/ANIE.196306331