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Full Paper

N-Aryl Atropisomerism Induces Facial Selectivity in Benzonitrile Oxide Cycloadditions with Exocyclic Methylene Benzosultams

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N-aryl methylene benzo-fused sultams (2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxides) underwent [3+2] cycloaddition with benzonitrile oxide to give 5-spiro isoxazoline adducts with complete regioselectivity. Steric hindrance by atropisomerism around the *N*-aryl bond induced facial selectivity in these cycloadditions.

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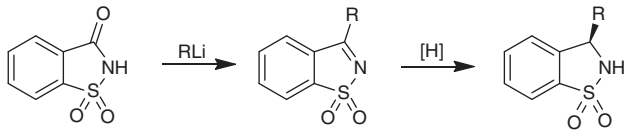
Introduction

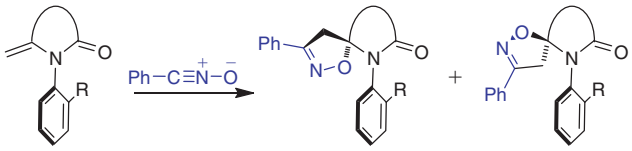
Cyclic sulfonamides, or sultams, are an important class of chiral auxiliary for π-facial discrimination in asymmetric reactions.[1] Benzosultam (2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide) chiral auxiliaries **1** are readily prepared from saccharine (Scheme 1) by the addition of organometallic reagents followed by asymmetric hydrogenation.[2,3] Since the first discovery of the antibacterial dye Prontosil,[4] sulfonamides and sultams[5–9] have also been incorporated into a wide range of biologically active compounds as carboxylic acid and amide isosteres.[10]

Hanson and coworkers recently described[11] the synthesis of 3-methylene benzosultams **5**, and these compounds caught our attention as potential dipolarophiles for 1,3-dipolar nitrile oxide cycloaddition (NOC) reactions. We have previously reported the construction of spiro heterocycles using NOC reactions with exocyclic methylene compounds[12–18] as part of an ongoing program to introduce novelty, diversity, and non-planar compounds into our medicinal chemistry screening library.[19–21] Nitrile oxides react readily with carbon-carbon double bonds to give isoxazolines,[22,23] usually with high regioselectivity that is dominated by steric influences. In the case of exocyclic methylene dipolarophiles the resulting spiro linkage invariably ends up at the 5-position of the newly formed isoxazoline ring.[24] This characteristic of NOC reactions has been extensively exploited to control regiochemical outcomes of these reactions.[25–29] We recently reported that the steric sensitivity of NOC reactions can induce facial selectivity in 1,3-dipolar reactions with methylene pyrrolones,[16] methylene hydantoins,[17] and methylene oxazolidinones,[18] as controlled by atropisomerism due to unsymmetrical *N*-aryl substituents (Scheme 2).

Atropisomerism is a relatively overlooked source of asymmetry, with important implications in the pharmaceutical industry.[30] Hence, in addition to our interest in the inherent novelty of potential NOC adducts with the 3-methylene sultams, we sought to determine if the facial selectivity of cycloaddition



Scheme 1.



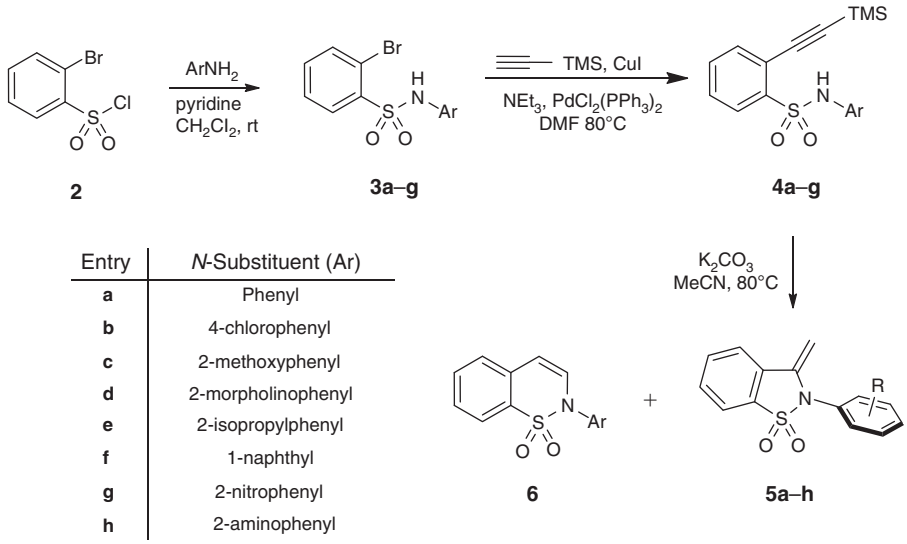
Scheme 2.

would be influenced by atropisomeric diastereoselectivity. The 2*H*,4′*H*-spiro[benzo[*d*]isothiazole-3,5′-isoxazole] 1,1-dioxide ring system expected from cycloaddition to benzosultams **5** has only been reported once previously, and that was via condensation between dilithiated oximes and methyl 2-(aminosulfonyl)benzoate.[31]

Herein we describe the nitrile oxide cycloaddition of *N*-aryl 3-methylene benzosultams **5** to generate 2*H*,4′*H*-spiro[benzo[*d*]isothiazole-3,5′-isoxazole] 1,1-dioxide systems, and the effect on facial selectivity engendered by atropisomeric asymmetry.

Results and Discussion

The 3-methylene benzosultams **5** were prepared by a procedure adapted from that of Hanson and coworkers (Scheme 3).[11] Commercially available 2-bromobenzenesulfonyl chloride **2** was reacted with the appropriate aniline derivate in pyridine and dichloromethane at room temperature to give the 2-bromosulfonamides **3**, generally in high yields.[32] The reaction with 2-nitroaniline did not proceed at room temperature



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

Scheme 3.

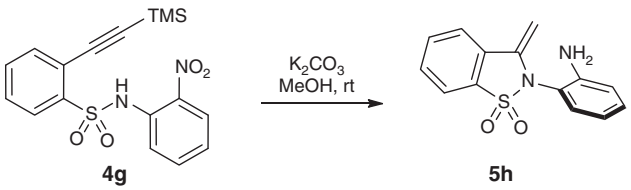
Table 1. Synthesis of methylene benzosultams 5

Entry	*N*-Substituent	Yield [%]		
		3	**4**	**5**
a	Phenyl	100	74	36
b	4-chlorophenyl	84	59	45
c	2-methoxyphenyl	92	100	56
d	2-morpholinophenyl	91	86	62
e	2-isopropylphenyl	72	56	80
f	1-naphthyl	81	76	28
g	2-nitrophenyl	49[A]	41[B]	43[C]

[A]Reflux in pyridine.
[B]2-Iodosulfonamide substrate used.
[C]Amino product.

and required heating at reflux in pyridine. Since 2-nitroaniline is no more sterically hindered than 2-isopropylaniline or 1-naphthylamine, it is likely that this sluggishness is due to reduced nucleophilicity of the amine. The 2-bromosulfonamides **3a**–**g** thus obtained were subjected to Sonogashira coupling with trimethylsilylacetylene (TMS-acetylene) in the presence of triethylamine, $PdCl_2(PPh_3)_2$, and CuI to furnish the TMS-acetylenic sulfonamides **4a**–**g** (Table 1). The only exception was the 2-nitrophenyl derivative **3g**, which failed to give any coupling product under a variety of conditions. We therefore resorted to the more reactive 2-iodo-*N*-(2-nitrophenyl)benzenesulfonamide, prepared via commercially available 2-iodobenzenesulfonyl chloride, which underwent the desired TMS-acetylene Sonogashira reaction to provide **4g** in 41 % yield.

Hanson reports cyclisation of the analogous *N*-methylbenzenesulfonamides with K_2CO_3 in acetonitrile at 50°C, over 2 h[11] and we were able to replicate that result. However, the *N*-arylbenzenesulfonamides in this work required higher temperatures to induce cyclisation. Treatment of the sulfonamides **4** with K_2CO_3 in acetonitrile at 80°C gave the methylene sultams **5** via a 5-*exo* intramolecular hydroamination-cyclisation of the acetylene functional group. Possibly as a result of the more forcing conditions, the exocyclic methylene products were contaminated with side-products, which were identified as the 6-*endo* cyclisation products **6**. These side-products, which we

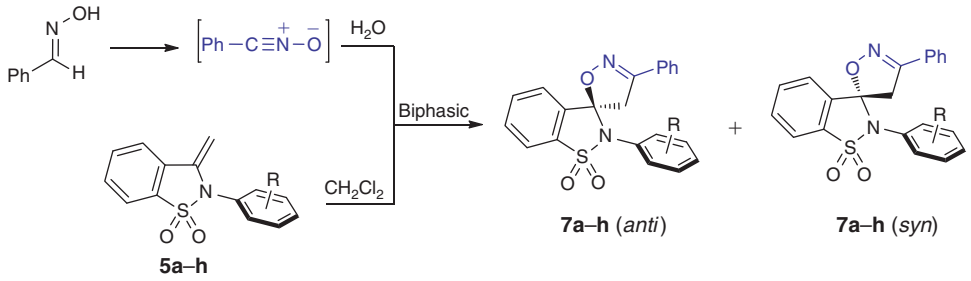


Scheme 4.

were unable to remove, were observed in the ^{1}H NMR spectra of the products in a ratio of around 1 : 4, favouring the desired product. However, the side products did not undergo the subsequent NOC reaction and were easily removed from the cycloadducts.

Unfortunately the standard conditions, and alternative bases such as pyridine, did not give **5g** by cyclisation of the nitro-substituted compound **4g**. TMS alkynes are commonly deprotected by K_2CO_3 in methanol at room temperature,[33,34] and treatment of **4g** under these conditions led to the formation of a 5-membered, exocyclic methylene sultam. Analysis revealed that the isolated product was however the 2-aminophenyl derivative **5h** (Scheme 4). The unexpected concomitant nitro reduction is presumably the result of potassium carbonate induced transfer hydrogenation with methanol in a similar fashion to the Woodward modification[35] of the Meerwein-Ponndorf-Verley reduction.[36] Similar transfer hydrogenation reactions of nitro compounds have been reported using ammonium formate as the hydrogen source.[37,38] The yield of **5h** could not be improved above 43 % with prolonged stirring at room temperature. Heating at 60°C for 2 h resulted in an increase in the undesired 6-*endo* product **6** (Ar = 2-aminophenyl).

Nitrile oxides are reactive intermediates that readily dimerise to give furoxans unless sterically hindered.[27,29] To mitigate dimerisation, nitrile oxides are usually generated in situ and trapped in the presence of olefinic dipolarophiles. Aryl nitrile oxides are typically prepared by the base-catalysed dehydrohalogenation of the corresponding hydroximoyl chlorides, which in turn are prepared by chlorination of aldoximes.[39] The chlorination and dehydrohalogenation steps can conveniently be combined in a one pot process where water-insoluble aldoximes



Scheme 5.

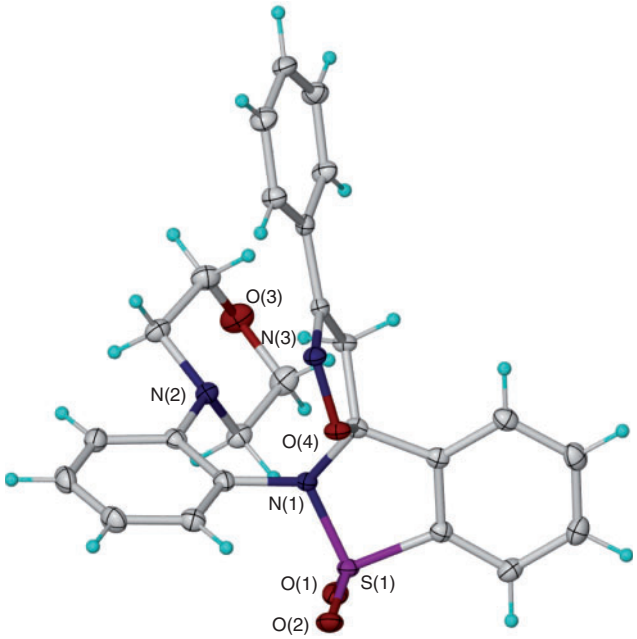


Fig. 1. Molecular diagram of **7d** with non-hydrogen atoms represented by 50 % thermal ellipsoids and hydrogen atoms as spheres of arbitrary size.

are reacted under biphasic conditions with 5 % sodium hypochlorite solution as both chlorinating agent and base.[40]

Using this method, benzonitrile oxide was generated in situ by mixing commercially available benzaldehyde oxime in dichloromethane with a 5 % aqueous NaOCl solution at 0°C, in the presence of the 3-methylene sultams **5a**–**h**. The nitrile oxide that formed was immediately trapped by the dipolarophile to give the corresponding spiro cycloadducts **7** (Scheme 5). The crude product mixtures were examined by ^{1}H NMR spectroscopy. In each case the dipolar cycloaddition reaction was completely regioselective in that the oxygen of the nitrile oxide became attached to the sultam end of the dipolarophile double bond, as expected.[24] The ^{1}H NMR chemical shifts for the characteristic AB system of the diastereotopic methylene protons on the newly formed isoxazoline rings fell in the range of 3.5–4.0 ppm. This chemical shift is indicative of protons on C-4 of the isoxazoline ring rather than C-5 (4.5–5.0 ppm),[12] hence establishing the regiochemistry of cycloaddition as shown in Scheme 5. X-ray crystallography of one of the products (Fig. 1) was consistent with this assignment.

The methylene sultams **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

Table 2. Diastereomeric product ratios for benzonitrile oxide cycloadducts 7a–h

Entry	*N*-Substituent	**7** Yield [%]	*anti* : *syn* ratio[A]
a	Phenyl	68	N/A
b	4-chlorophenyl	61	N/A
c	2-methoxyphenyl	66	>50 : 1
d	2-morpholinophenyl	51	>50 : 1
e	2-isopropylphenyl	69	2 : 1
f	1-naphthyl	52	4 : 1
h	2-aminophenyl	68	4 : 1

[A]Determined by ^{1}H NMR.

with respect to the substituent on the *N*-aryl group. ^{1}H NMR spectra of the crude reaction mixtures, before purification, were recorded and the diastereomeric ratios determined (Table 2). In three cases (**7e**, **7f**, and **7h**) diastereomers were evident in the ^{1}H NMR spectra and their ratios were measured (Table 2). In the other two cases (**7c** and **7d**) only a single diastereomer could be detected by ^{1}H NMR spectroscopy, which indicates a high degree of diastereoselectivity in the cycloaddition reaction. The cycloadducts were then purified on neutral alumina as they were less stable on silica. We were unable to separate the diastereomers using column chromatography.

It is conceivable that in the case of **7c** and **7d**, the observation of a single set of resonances in the respective ^{1}H NMR spectra is due to free rotation around the *N*-aryl bond, leading to an averaged spectrum on the NMR timescale. This is unlikely given the evident diastereomers for the other cycloadducts, but nevertheless to dispel this possibility the ^{1}H NMR spectrum of the 2-methoxyphenyl cycloadduct **7c** was recorded at −20°C and −50°C. The spectra at the two lower temperatures were unchanged from that at room temperature. From this it can be deduced that compound **7c**, and by implication the more hindered **7d**, are single atropisomeric diastereomers that are locked into a single conformation rather than a time-averaged mixture of diastereomers.

Based on previous observations with analogous systems,[17,18] the *anti* cycloaddition product is likely to predominate because the *syn* face is more sterically hindered. The ^{1}H NMR data supported this hypothesis. When there was a mixture of diastereomers (**7e**, **7f**, and **7h**) the ^{1}H resonance for the isoxazoline ring methylene AB system of the major isomer always appeared upfield from the corresponding AB system in the minor isomer. This observation is consistent with the isoxazoline methylene protons of the major cycloadducts being shielded by the substituent on the *N*-aryl group, in comparison to the corresponding isoxazoline methylene protons of the minor isomer. In the case of the morpholino derivative **7d**, where only a single diastereomer was observed, crystals grown from ethyl acetate were suitable to

obtain a single crystal structure by X-ray crystallography (Fig. 1). From this structure it can be seen that the nitrile oxide has added to the dipolarophile from the face opposite the 2-morpholino substituent on the *N*-aryl group. All of these data are consistent with preferential cycloaddition to the *anti* face of the dipolarophile, controlled by atropisomeric induction.

It is noteworthy that steric hindrance alone is insufficient to account for the observed facial selectivity in the NOC reactions with the atropisomeric methylene benzosultams **5**. The 2-isopropylphenyl (**5e**) and 1-naphthyl (**5f**) substituents only induced modest facial selectivity compared with the 2-methoxyphenyl derivative **5c**. We have previously noted that a combination of steric hindrance and electrostatic repulsion appears to influence the incoming nitrile oxide in NOC reactions,[17,18] and this again appears to be the case with the benzosultam ring system. Coulombic repulsive interactions of this type have previously been postulated as a rationale for diastereofacial differentiation in NOC reactions,[41,42] as a generalised extension of the 'inside alkoxy effect'.[43]

Conclusion

N-aryl methylene benzo-fused sultams (2,3-dihydrobenzo[*d*] isothiazole 1,1-dioxides) participate in 1,3-dipolar cycloaddition reactions with benzonitrile oxide to give 5-spiro isoxazoline adducts with complete regioselectivity. In cases where unsymmetrical *N*-aryl substituents engender atropisomerism around the *N*-aryl bond, facial selectivity for the less hindered face vary from a modest ratio of 2 : 1 to complete selectivity within the limits of NMR detection. While steric hindrance certainly carries some responsibility for this facial selectivity, it appears that electrostatic repulsions are also involved.

Experimental

General

Melting points were determined on a Buchi 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) with the appropriate combination of ethyl acetate and light petroleum as eluant, using compressed air for elution. 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 visualised using a 254 nm ultraviolet (UV) lamp. Starting materials and reagents were purchased from Sigma-Aldrich, Oakwood Chemicals, and Merck, and were used as supplied; where specified dichloromethane and THF were dried through a solvent purification system (SPS). ^{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 $CDCl_3$ as solvent. Infrared spectra were recorded using a Smart iTR accessory on a Thermo Nicolet 6700 Fourier transform infrared (FTIR) spectrometer. FT-IR spectra were recorded on a Bruker Equinox 55/S FT-IR spectrometer with neat samples in KBr disks. Electron impact (EI) mass spectra were recorded on a ThermoQuest MAT95XP mass spectrometer using ionisation energy of 70 eV. Accurate mass measurements were obtained on the same instrument with a resolution of 5000–10000 using perfluorokerosene (PFK) as the reference compound. The Cambridge Crystallographic Data Centre contains the supplementary crystallographic data for this paper. The data for 2-(2-morpholinophenyl)-3′-phenyl-2*H*,4′*H*-spiro[benzo[*d*] isothiazole-3,5′-isoxazole] 1,1-dioxide **7d** (deposition number CCDC 939831) 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; fax: +44(0)1223–336033; email: deposit@ccdc.cam.ac.uk.

General Method for Benzenesulfonamides *3*

Following the procedure of Park,[44] 2-bromobenzenesulfonyl chloride **2** (25 mmol) was added to a stirred solution of the appropriate aniline (25 mmol) and pyridine (8.1 mL, 100 mmol) in CH_2Cl_2 (70 mL). The reaction mixture was stirred for 2 h at room temperature. Following this time it was washed with a 5 % aqueous solution of HCl (3 × 20 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated under vacuum. This method was used to prepare benzenesulfonamides **3a**–**d**. For compounds **3e** and **3f** the reaction was stirred overnight at room temperature. 2-Bromo-*N*-(2-nitrophenyl)benzenesulfonamide **3g**, and its iodo-analogue, were prepared following the procedure of Njar,[45] whereby 2-iodo- or 2-bromobenzenesulfonyl chloride (20 mmol) was slowly added to a stirred solution of 2-nitroaniline (2.68 g, 20 mmol) in pyridine (10 mL). The reaction flask was fitted with a reflux condenser and the reaction mixture was heated at reflux for 6 h. After this time the solution was cooled to room temperature and diluted with CH_2Cl_2 (50 mL). The organic material was washed with a 5 % aqueous solution of HCl (3 × 10 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude benzenesulfonamides were used immediately without further purification.

General Method for Synthesis of TMS Alkynes *4*

TMS alkynes **4** were prepared according to the procedure of Hanson,[11] from the corresponding 2-bromobenzenesulfonamide **3**. Triethylamine (4.2 mL, 30 mmol), triphenylphosphine (315 mg, 1.2 mmol), copper(I) iodide (95 mg, 0.5 mmol), and $PdCl_2(PPh_3)_2$ (211 mg, 0.3 mmol) were added to a stirred solution of the appropriate 2-bromobenzenesulfonamide **3** (10 mmol) in DMF (50 mL). TMS acetylene (4.3 mL, 30 mmol) was then added and the reaction vessel was fitted with a reflux condenser and heated to 80°C overnight. The mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by flash column chromatography to afford the title compounds. Compounds **4a** and **4b** have previously been reported.[32]

N-*(2-Methoxyphenyl)-2-((trimethylsilyl)ethynyl) benzenesulfonamide (**4c**)*

This compound was prepared from sulfonamide **3c** and isolated as a pale yellow oil. R_f 0.31 (1 : 9, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 2956 (w), 2161 (w), 1501 (m), 1345 (s), 1249 (s), 1161 (s), 1111 (m), 843 (s), 748 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, J = 8.0, 1.2 Hz, 1H), 7.74 (br s, 1H), 7.56 (dd, J = 7.6, 1.2 Hz, 1H), 7.46 (dd, J = 7.6, 1.2 Hz, 1H), 7.41 (td, J = 7.6, 1.2 Hz, 1H), 7.31 (td, J = 7.6, 1.2 Hz, 1H), 6.97 (td, J = 8.0, 1.2 Hz, 1H), 6.82 (td, J = 8.0, 1.2 Hz, 1H), 6.74 (dd, J = 8.0, 1.2 Hz, 1H), 3.73 (s, 3H), −0.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 141.1, 134.5, 132.3, 129.5, 128.2, 126.0, 124.8, 121.3, 121.0, 120.1, 110.7, 104.2, 101.0, 55.7, 0.3. *m*/*z* (HR-MS ESI) 382.0905; $[M+Na]^+$ requires 382.0909.

N-*(2-Morpholinophenyl)-2-((trimethylsilyl)ethynyl) benzenesulfonamide (**4d**)*

This compound was prepared from sulfonamide **3d** and isolated as a brown oil. R_f 0.3 (1 : 4, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 3148 (w), 2969 (w), 2161 (w), 1491 (m), 1383 (m), 1333 (m), 1253 (m), 1171 (s), 1115 (s), 840 (s), 755 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.96 (dd, J = 7.6, 1.2 Hz, 1H), 7.59 (dd, J = 7.6, 1.2 Hz, 1H), 7.47–7.42 (m, 2H), 7.36 (td, J = 7.6, 1.2 Hz, 1H), 7.12–7.01 (m, 3H), 3.86 (t, J = 4.8 Hz, 4H), 2.68 (t, J = 4.8 Hz, 4H), 0.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.3, 135.2, 133.0, 132.4, 129.2, 128.5, 126.0, 124.6, 121.7, 121.4, 119.4, 104.8, 101.4, 67.4, 53.0, 0.0. *m/z* (HR-MS ESI) 437.1325; $[M+Na]^+$ requires 437.1331.

N-*(2-Isopropylphenyl)-2-((trimethylsilyl)ethynyl) benzenesulfonamide (**4e**)*

This compound was prepared from sulfonamide **3e** and isolated as a yellow oil. R_f 0.3 (1 : 9, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 2962 (w), 2157 (w), 1492 (w), 1387 (m), 1250 (m), 1168 (s), 909 (m), 860 (s), 842 (s), 755 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 1H), 7.65 (dd, J = 7.6, 0.4 Hz, 1H), 7.46 (td, J = 7.6, 0.4 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.08–6.98 (m, 3H), 3.36 (sept, J = 6.8 Hz, 1H), 1.10 (d, J = 6.8 Hz, 6H), 0.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 141.9, 134.7, 132.8, 132.3, 129.3, 128.8, 127.2, 126.4, 125.3, 120.8, 104.7, 101.8, 27.5, 23.6, 0.2 (one aromatic signal overlapping). *m/z* (HR-MS ESI) 394.1268; $[M+Na]^+$ requires 394.1273.

N-*(Naphthalen-1-yl)-2-((trimethylsilyl)ethynyl) benzenesulfonamide (**4f**)*

This compound was prepared from sulfonamide **3f** and isolated as a yellow oil. R_f 0.3 (1 : 9, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 2956 (w), 2156 (w), 1465 (w), 1351 (w), 1249 (m), 1164 (s), 1126 (m), 1066 (m), 840 (s), 759 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.4 Hz, 1H), 7.82 (dd, J = 8.4, 0.8 Hz, 1H), 7.79 (dd, J = 8.4, 0.8 Hz, 1H), 7.68–7.65 (m, 2H), 7.55–7.46 (m, 4H), 7.45 (td, J = 8.2, 0.8 Hz, 1H), 7.32–7.24 (m, 2H), 0.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 134.7, 134.4, 132.4, 131.7, 129.4, 129.3, 128.8, 128.4, 127.3, 126.7, 126.5, 125.4, 122.4, 121.8, 120.8, 105.0, 102.1, 0.2. *m/z* (HR-MS ESI) 402.0955; $[M+Na]^+$ requires 402.0960.

N-*(2-Nitrophenyl)-2-((trimethylsilyl)ethynyl) benzenesulfonamide (**4g**)*

This compound was prepared from 2-iodo-*N*-(2-nitrophenyl) benzenesulfonamide and isolated as a brown waxy solid. R_f 0.25 (1 : 9, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 3262 (w), 2956 (w), 2163 (w), 1531 (m), 1487 (m), 1350 (s), 1248 (s), 1174 (s), 814 (s), 758 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (br s, 1H), 8.14–8.13 (m, 2H), 7.67 (dd, J = 8.4, 1.2 Hz, 1H), 7.60 (dd, J = 7.6, 1.2 Hz, 1H), 7.51 (td, J = 7.6, 1.2 Hz, 1H), 7.49–7.43 (m, 2H), 7.07 (td, J = 7.6, 1.2 Hz, 1H), −0.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 136.2, 135.8, 135.7, 134.1, 133.2, 130.0, 128.4, 126.5, 122.9, 122.0, 118.7, 106.5, 99.4, 0.4. *m/z* (HR-MS ESI) 397.0649; $[M+Na]^+$ requires 397.0654.

*General Synthesis Procedure for Methylene Sultams **5***

In a modification of Hanson's procedure,[11] K_2CO_3 (5.5 g, 40 mmol) was added to a stirred solution of the appropriate TMS alkyne **4** (5 mmol) in MeCN (50 mL). The reaction vessel was fitted with a reflux condenser and heated to 80°C for 3 h. The mixture was allowed to cool to room temperature then filtered through a plug of silica, which was then rinsed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography to afford the title compounds. The products were isolated as a 4 : 1 mixture with the corresponding 6-*endo-dig* isomer. We were unable to separate these materials but the unwanted side-product product did not affect the subsequent nitrile oxide cycloaddition reaction.

*3-Methylene-2-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**5a**)*

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} 1592 (m), 1490 (m), 1471 (m), 1301 (s), 1160 (s), 748 (s), 696 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 7.2, 1.2 Hz, 1H), 7.75 (dd, J = 7.2, 1.2 Hz, 1H), 7.69–7.59 (m, 2H), 7.52–7.38 (m, 5H), 4.99 (d, J = 2.8 Hz, 1H), 4.29 (d, J = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 133.2, 130.8, 130.3, 130.1, 129.7, 129.5, 128.4, 127.1, 121.7, 121.2, 86.7. *m/z* (HR-MS ESI) 280.0403; $[M+Na]^+$ requires 280.0408.

*2-(4-Chlorophenyl)-3-methylene-2,3-dihydrobenzo[*d*] isothiazole 1,1-dioxide (**5b**)*

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} 1489 (m), 1303 (s), 1175 (s), 1162 (s), 1091 (m), 749 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 7.2, 0.8 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.76–7.60 (m, 2H), 7.51–7.37 (m, 2H), 7.38 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 5.01 (d, J = 2.8 Hz, 1H), 4.28 (d, J = 2.8 Hz, 1H). *m/z* (HR-MS ESI) 314.0013; $[M+Na]^+$ requires 314.0018.

*2-(2-Methoxyphenyl)-3-methylene-2,3-dihydrobenzo[*d*] isothiazole 1,1-dioxide (**5c**)*

The title compound was isolated as a yellow oil. R_f 0.2 (1 : 4, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 1595 (m), 1500 (s), 1474 (m), 1304 (s), 1282 (s), 1162 (s), 1023 (s), 763 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.52–7.44 (m, 2H), 7.09–7.05 (m, 2H), 4.93 (d, J = 2.4 Hz, 1H), 4.10 (d, J = 2.4 Hz, 1H), 3.81 (s, 3H). *m/z* (HR-MS ESI) 310.0508; $[M+Na]^+$ requires 310.0514.

*3-Methylene-2-(2-morpholinophenyl)-2,3-dihydrobenzo [*d*]isothiazole 1,1-dioxide (**5d**)*

The title compound was isolated as a brown solid. R_f 0.3 (1 : 4, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 2820 (w), 1493 (m), 1448 (m), 1310 (s), 1270 (m), 1176 (s), 1159 (s), 1112 (s), 919 (m), 760 (s), 728 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.68 (td, J = 7.6, 0.8 Hz, 1H), 7.62 (dd, J = 7.6, 0.8 Hz, 1H), 7.52 (dd, J = 7.6, 0.8 Hz, 1H), 7.48–7.41 (m, 1H), 7.16–7.11 (m, 2H), 5.03 (d, J = 2.4 Hz, 1H), 4.18 (d, J = 2.4 Hz, 1H), 3.63–3.61 (m, 4H), 3.20–3.15 (m, 2H), 2.96–2.91 (m, 2H). *m/z* (HR-MS ESI) 314.0013; $[M+Na]^+$ requires 314.0018.

*2-(2-Isopropylphenyl)-3-methylene-2,3-dihydrobenzo[*d*] isothiazole 1,1-dioxide (**5e**)*

The title compound was isolated as a yellow solid. R_f 0.2 (1 : 9, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 2961 (w), 1487 (m), 1469 (m), 1446 (m), 1306 (s), 1181 (s), 1155 (s), 1028 (m), 768 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.67 (td, J = 7.6, 0.8 Hz, 1H), 7.63 (td, J = 7.6, 0.8 Hz, 1H), 7.51–7.48 (m, 2H), 7.43–7.40 (m, 2H), 4.94 (d, J = 2.4 Hz, 1H), 4.02 (d, J = 2.4 Hz, 1H), 3.14 (sept, J = 6.8 Hz, 1H), 1.26 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 140.4, 133.1, 131.8, 130.8, 130.7, 130.3, 128.1, 127.7, 127.3, 126.9, 121.8, 121.3, 86.2, 28.2, 24.4, 24.2. *m/z* (HR-MS ESI) 322.0873; $[M+Na]^+$ requires 322.0878.

*3-Methylene-2-(naphthalen-1-yl)-2,3-dihydrobenzo[*d*] isothiazole 1,1-dioxide (**5f**)*

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} 3066 (w), 1635 (m), 1467 (m), 1393 (m), 1309 (s), 1175 (s), 1155 (s), 1030 (m), 768 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.93–7.91 (m, 2H), 7.82–7.58 (m, 5H), 7.53–7.50 (m, 3H), 4.94 (d, J = 2.4 Hz, 1H), 3.97 (d, J = 2.4 Hz, 1H). *m/z* (HR-MS ESI) 330.0559; $[M+Na]^+$ requires 330.0565.

*2-(2-Aminophenyl)-3-methylene-2,3-dihydrobenzo[*d*] isothiazole 1,1-dioxide (**5h**)*

K_2CO_3 (3.96 g, 30 mmol) was added to a stirred solution of the TMS-alkyne **4 g** (1.12 g, 3 mmol) in methanol (6 mL). The reaction mixture was stirred overnight at room temperature. The mixture was diluted with diethyl ether and filtered through a plug of silica. The filtrate was concentrated under vacuum and the residue was purified by flash column chromatography (1 : 4 v/v EtOAc : light petroleum) to afford the title compound as a yellow solid. R_f 0.3 (1 : 4, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 3379 (w), 1620 (m), 1486 (m), 1469 (m), 1303 (s), 1256 (m), 1176 (s), 1159 (s), 726 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.68 (td, J = 7.6, 0.8 Hz, 1H), 7.62 (td, J = 7.6, 0.8 Hz, 1H), 7.29–7.24 (m, 2H), 6.88–6.82 (m, 2H), 4.99 (d, J = 2.4 Hz, 1H), 4.22 (d, J = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 139.7, 134.3, 134.1, 133.8, 130.5, 125.7, 123.8, 122.6, 121.8, 118.1, 113.1, 87.6 (one signal overlapping). *m/z* (HR-MS ESI) 295.0511; $[M+Na]^+$ requires 295.0517.

General Procedure for Nitrile Oxide Cycloaddition Reactions

According to the procedure of Savage,[16] the appropriate methylene sultam **5** (1 mmol) and benzaldehyde oxime (363 mg, 3 mmol) were dissolved in CH_2Cl_2 (5 mL). The solution was cooled to 0°C in an ice bath with vigorous stirring and NaOCl (5.5 mL of an 8 % aqueous solution, 6 mmol) was then slowly added over a period of 30 min. The reaction mixture was then stirred vigorously overnight. After this time the mixture was diluted with CH_2Cl_2 and brine was added. The layers were separated and 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 by flash column chromatography (EtOAc : light petroleum) over neutral alumina to afford the title compounds.

*2,3′-Diphenyl-2*H*,4′*H*-spiro[benzo[*d*]isothiazole-3,5′-isoxazole] 1,1-dioxide (**7a**)*

Isolated as a white solid. Mp 231.4–234.1°C. R_f 0.25 (3 : 7, v/v EtOAc : light petroleum); ν_{max}/cm^{-1} 1362 (w), 1301 (s), 1173 (m), 1156 (s), 759 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 1H), 7.77–7.63 (m, 5H), 7.46–7.32 (m, 8H), 3.86 (d, J = 18.4 Hz, 1H), 3.70 (d, J = 18.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 136.2, 134.8, 134.0, 132.0, 131.5, 130.8, 130.2, 130.0, 129.9, 128.9, 128.2, 126.6, 124.1, 121.5, 99.1, 43.3. *m/z* (HR-MS ESI) 399.0775; $[M+Na]^+$ requires 399.0779.

*2-(4-Chlorophenyl)-3′-phenyl-2*H*,4′*H*-spiro[benzo[*d*] isothiazole-3,5′-isoxazole] 1,1-dioxide (**7b**)*

Isolated as a white solid. Mp182.9–183.8°C. R_f 0.15 (1 : 4, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 1488 (m), 1304 (s), 1171 (s), 759 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.6 Hz, 1H), 7.77–7.72 (m, 2H), 7.66–7.60 (m, 3H), 7.49–7.37 (m, 7H), 3.88 (d, J = 18.4 Hz, 1H), 3.66 (d, J = 18.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 136.5, 136.2, 134.6, 134.2, 133.2, 131.6, 131.0, 130.2, 129.1, 128.6, 128.1, 126.6, 124.1, 121.6, 99.1, 43.5. *m/z* (HR-MS ESI) 433.0383; $[M+Na]^+$ requires 433.0390.

*2-(2-Methoxyphenyl)-3′-phenyl-2*H*,4′*H*-spiro[benzo[*d*] isothiazole-3,5′-isoxazole] 1,1-dioxide (**7c**)*

Isolated as a yellow waxy solid. R_f 0.2 (1 : 4, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 1497 (m), 1307 (s), 1168 (s), 1021 (m), 902 (m), 754 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 1H), 7.76–7.64 (m, 4H), 7.45–7.43 (m, 2H), 7.40–7.32 (m, 4H), 7.04 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 4.07 (d, J = 18.4 Hz, 1H), 3.81 (s, 3H), 3.80 (d, J = 18.4 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.4, 156.7, 136.0, 135.5, 133.8, 131.9, 131.3, 130.7, 128.9, 128.5, 126.6, 124.2, 122.0, 121.6, 117.8, 112.9, 99.5, 56.4, 43.0 (one aromatic signal overlapping). *m/z* (HR-MS ESI) 429.0879; $[M+Na]^+$ requires 429.0885.

*2-(2-Morpholinophenyl)-3′-phenyl-2*H*,4′*H*-spiro[benzo[*d*] isothiazole-3,5′-isoxazole] 1,1-dioxide (**7d**)*

Isolated as a white solid. Mp 204.5–208.1°C (decomp.). R_f 0.2 (3 : 7, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 2958 (w), 1491 (m), 1304 (s), 1172 (s), 1115 (m), 848 (m), 757 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 1H), 7.84 (dd, J = 7.6, 1.2 Hz, 1H), 7.77–7.67 (m, 3H), 7.36–7.27 (m, 6H), 7.19 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 5.13 (d, J = 17.6 Hz, 1H), 3.83 (d, J = 17.6 Hz, 1H), 3.78–3.67 (m, 4H), 3.54–3.51 (m, 2H), 2.49–2.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 152.3, 136.1, 135.9, 135.2, 133.9, 131.5, 131.1, 130.8, 128.9, 128.6, 126.4, 125.3, 124.9, 124.4, 121.5, 121.0, 100.4, 67.5, 53.0, 43.3. *m/z* (HR-MS ESI) 484.1303; $[M+Na]^+$ requires 484.1307.

*2-(2-Isopropylphenyl)-3′-phenyl-2*H*,4′*H*-spiro[benzo[*d*] isothiazole-3,5′-isoxazole] 1,1-dioxide (**7e**)*

The title compound was formed as a 2 : 1 mixture of diastereomers, as determined by integration of suitable peaks in the ^{1}H NMR spectrum of the crude product. These diastereomers could not be separated by standard purification techniques. The mixture of products was a white solid. Mp 197.1–199.9°C. R_f 0.2 (1 : 4, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 2962 (w), 1450 (m), 1363 (m), 1309 (s), 1164 (s), 895 (m), 753 (s). *major diastereomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.6 Hz, 1H), 7.82–7.64 (m, 4H), 7.47–7.30 (m, 8H), 3.89 (d, J = 18.4 Hz, 1H), 3.60 (d, J = 18.4 Hz, 1H), 3.39 (sept, J = 6.8 Hz, 1H), 1.30 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H); *minor diastereomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 1H), 7.82–7.64 (m, 3H), 7.47–7.30 (m, 8H), 7.15 (td, J = 7.6, 1.6 Hz, 1H), 3.95 (d, J = 18.0 Hz, 1H), 3.75 (d, J = 18.0 Hz, 1H),

3.71 (sept, $J = 6.8$ Hz, 1H), 1.32 (d, $J = 6.8$ Hz, 3H), 1.24 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 156.2, 154.0, 151.1, 137.0, 136.3, 135.2, 135.0, 134.6, 134.0, 133.9, 132.7, 131.5, 131.0, 130.9, 130.8, 129.0, 128.9, 129.6, 128.4, 128.3, 127.3, 126.6, 126.5, 126.4, 126.1, 124.3, 123.0, 121.7, 121.4, 99.5, 99.4, 43.6, 42.4, 28.5, 28.1, 25.5, 25.4, 24.5, 23.9 (4 aromatic signals overlapping). *m/z* (HR-MS ESI) 441.1243; $[M+Na]^+$ requires 441.1249.

*2-(2-Naphthalen-1-yl)-3′-phenyl-2*H*,4′*H*-spiro[benzo*[d]*isothiazole-3,5′-isoxazole] 1,1-dioxide (**7f**)*

The title compound was formed as a 4 : 1 mixture of diastereomers, as determined by integration of suitable peaks in the ^{1}H NMR spectrum of the crude product. These diastereomers could not be separated by standard purification techniques. The mixture of products was a white solid. Mp 244.3–245.5°C (decomp.). R_f 0.2 (1 : 4, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 2965 (w), 1363 (m), 1321 (s), 1179 (s), 1165 (s), 897 (m), 763 (s). *major diastereomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, $J = 7.6$ Hz, 1H), 8.06 (d, $J = 7.6$ Hz, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 7.6$ Hz, 1H), 7.78–7.70 (m, 2H), 7.63 (d, $J = 7.6$ Hz, 1H), 7.57–7.46 (m, 3H), 7.29–7.18 (m, 5H), 3.82 (d, $J = 18.4$ Hz, 1H), 3.67 (d, $J = 18.4$ Hz, 1H); *minor diastereomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, $J = 7.6$ Hz, 1H), 7.95 (d, $J = 7.6$ Hz, 1H), 7.85–7.71 (m, 4H), 7.65–7.62 (m, 1H), 7.57–7.46 (m, 3H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.29–7.18 (m, 5H), 4.01 (d, $J = 18.0$ Hz, 1H), 3.78 (d, $J = 18.0$ Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.6, 156.5, 136.5, 135.2, 135.1, 134.7, 134.3, 134.0, 133.9, 133.3, 131.6, 131.5, 131.2, 131.0, 130.7, 130.6, 128.6, 128.1, 128.0, 127.7, 127.6, 127.5, 127.1, 126.9, 126.5, 126.3, 125.7, 125.6, 124.9, 124.4, 123.9, 123.4, 121.7, 121.5, 99.9, 99.7, 43.7, 42.1 (8 aromatic signals overlapping). *m/z* (HR-MS ESI) 449.0929; $[M+Na]^+$ requires 449.0936.

*2-(2-Aminophenyl)-3′-phenyl-2*H*,4′*H*-spiro[benzo*[d]*isothiazole-3,5′-isoxazole] 1,1-dioxide (**7h**)*

The title compound was formed as a 4 : 1 mixture of diastereomers, as determined by integration of suitable peaks in the ^{1}H NMR spectrum of the crude product. These diastereomers could not be separated by standard purification techniques. The mixture of products was a white solid. Mp 136.2–138.9°C R_f 0.2 (3 : 7, v/v EtOAc : light petroleum). ν_{max}/cm^{-1} 3586 (w), 3415 (w), 1620 (m), 1498 (m), 1363 (m), 1299 (s), 1170 (s), 902 (m), 792 (m), 759 (s). *major diastereomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, $J = 7.6$ Hz, 1H), 7.78–7.58 (m, 4H), 7.46 (d, $J = 7.6$ Hz, 2H), 7.38–7.31 (m, 3H), 7.13 (t, $J = 7.6$ Hz, 1H), 6.80 (t, $J = 7.6$ Hz, 1H), 6.71 (d, $J = 7.6$ Hz, 1H), 4.03 (d, $J = 18.4$ Hz, 1H), 3.80 (d, $J = 18.4$ Hz, 1H); *major diastereomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, $J = 7.6$ Hz, 1H), 7.78–7.58 (m, 4H), 7.46 (d, $J = 7.6$ Hz, 2H), 7.38–7.31 (m, 3H), 7.08 (t, $J = 7.6$ Hz, 1H), 6.73 (d, $J = 7.6$ Hz, 1H), 6.63 (t, $J = 7.6$ Hz, 1H), 3.91 (d, $J = 18.4$ Hz, 1H), 3.75 (d, $J = 18.4$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 156.9, 149.0, 147.4, 136.9, 136.1, 135.1, 135.0, 134.8, 134.0, 133.5, 131.7, 131.6, 131.4, 130.9, 130.7, 129.0, 128.9, 128.5, 128.3, 126.7, 124.2, 121.5, 121.4, 120.1, 118.1, 117.6, 117.1, 115.0, 114.1, 99.8, 99.3, 43.1, 42.7 (4 aromatic signals overlapping). *m/z* (HR-MS ESI) 414.0880; $[M+Na]^+$ requires 414.0888.

Supplementary Material

^{1}H and ^{13}C NMR spectra of all nitrile oxide cycloadducts are available on the Journal's website.

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