Alkylation Studies of 5-*exo*-Methylene Substituted Isoxazolidines

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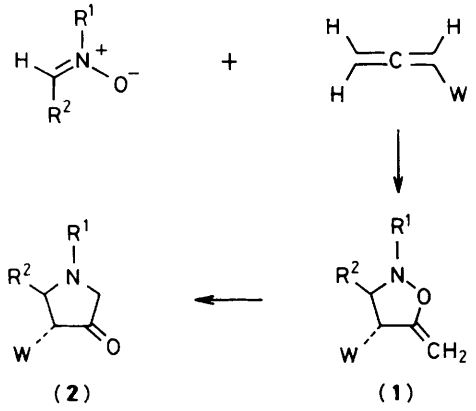
1,3-Dipolar cycloaddition of nitrones to phenylsulphonylallene gives in high yield and with complete regiospecificity 5-methyleneisoxazolidines. These on treatment with base and subsequent reaction with electrophiles afford both α- and γ-substituted products. With methyl iodide as the electrophile, only the α-methylated product was isolated. In contrast, reaction of the 5-*exo*-methylene-4-phenylsulphonylisoxazolidine with allyl bromide afforded the γ-allylated product. Formation of this was shown to be *via* direct γ-attack, rather than by α-attack, followed by a 3,3-sigmatropic rearrangement. Further studies show that the product ratio is controlled by a sensitive interplay between thermodynamic and steric factors and is very dependent on the nature of the electrophile used.

The development of procedures for efficiently constructing pyrrolidine, piperidine, and perhydroazepine ring systems with simultaneous functionalization α to the nitrogen atom is of crucial importance in alkaloid synthesis.[1,2] In this connection[3] we have investigated the 1,3-dipolar cycloadditions of nitrones with allenes[4] followed by their thermal rearrangements.[5–8] The 1,3-sigmatropic reorganization of 5-methyleneisoxazolidines seemed to us to have potential for developing a new pyrrolidine synthesis.[5,8] To this end we have studied the dipolar–cycloaddition behaviour of phenylsulphonylallene with various nitrones in the expectation that the resulting 5-methyleneisoxazolidines should be of value in synthesis (Scheme 1).

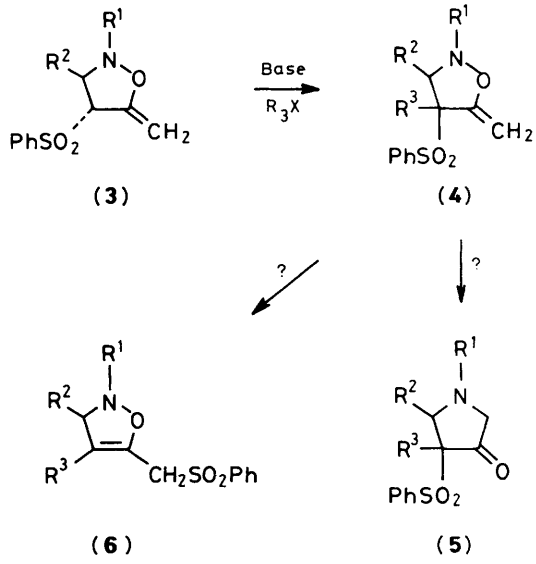


Scheme 1. W = $PhSO_2$

Stabilization of carbanion centres by adjacent sulphonyl groups is well recognized in organic synthesis[9–11] and allylic sulphones have been increasingly used for the preparation of natural products.[12,13] This increased use stems from the recognition that sulphones used to stabilize anions,[9] may be removed reductively[14] and, where appropriate, eliminated to form olefins.[15] Lately, reports in the literature indicate that substituted allylic sulphones can undergo a 1,3-rearrangement.[16–25] We have recently been involved in the preparation and utilization of allyl sulphones of the general type (**3**), with the objective of performing a metallation–alkylation followed by either a 1,3-rearrangement of the sulphonyl or nitrogen group (Scheme 2). Here we report the results of these studies.

Results and Discussion

Lithiated allylic sulphones react with alkyl halides in a synthetically useful process leading to α-alkylation.[26] Thus, the

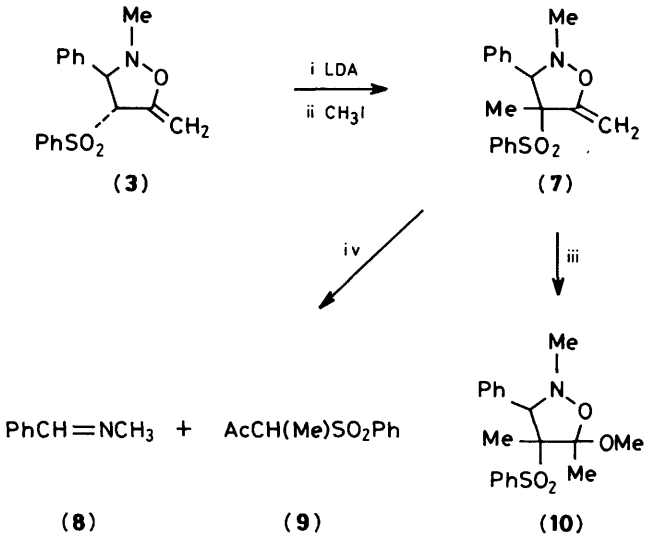


Scheme 2.

reaction of lithium di-isopropylamide (LDA) followed by addition of methyl iodide gave compound (**7**) (Scheme 3). Hydrogenation of this material resulted in cleavage of the N–O bond followed by a retro-aldol type reaction to give the imine (**8**) and the acetyl sulphone (**9**). Treatment of (**7**) with methanol in the presence of a Lewis acid afforded the 5-methoxyisoxazolidine (**10**) in high yield.

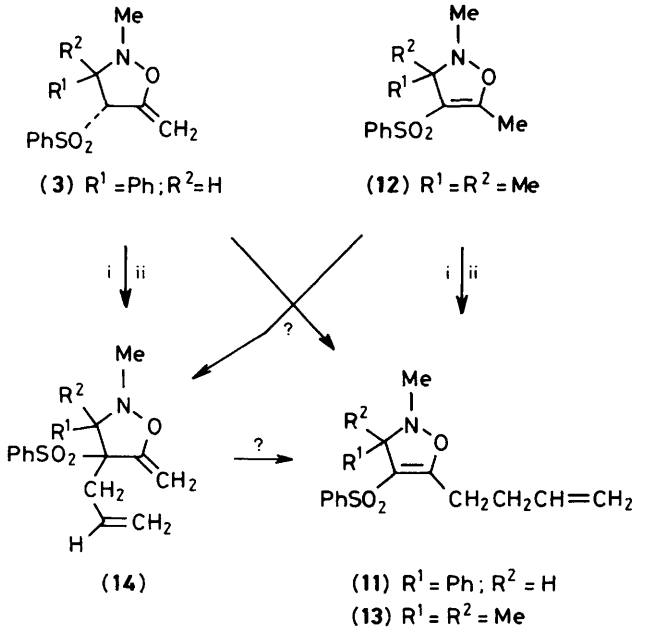
Sulphonyl groups show a high tendency to deconjugate from alkene groups during equilibration, in contrast with the conjugative tendencies of cyano and carbonyl containing groups.[27] Early work by Stirling[28] and others[29] has demonstrated that β,γ-unsaturated sulphones are more stable than their α,β-isomers by *ca.* 2.5 kcal mol^{-1}. More recently, Steele and co-workers determined accurate heats of formation for a series of sulphones in order to probe the conjugative stabilizing properties of the sulphonyl group.[30] The data obtained support the earlier conclusion of Stirling regarding thermodynamic stability. It would seem that thermodynamic factors are responsible for the preferred α-alkylation of simple systems.

In order to obtain further information about the behaviour of allyl sulphonyl carbanions derived from 5-methyleneisoxazolidines, we investigated the reaction of (**3**) with allyl bromide. The only product formed (87%) from this reaction (using LDA as the base) corresponded to the γ-allylated



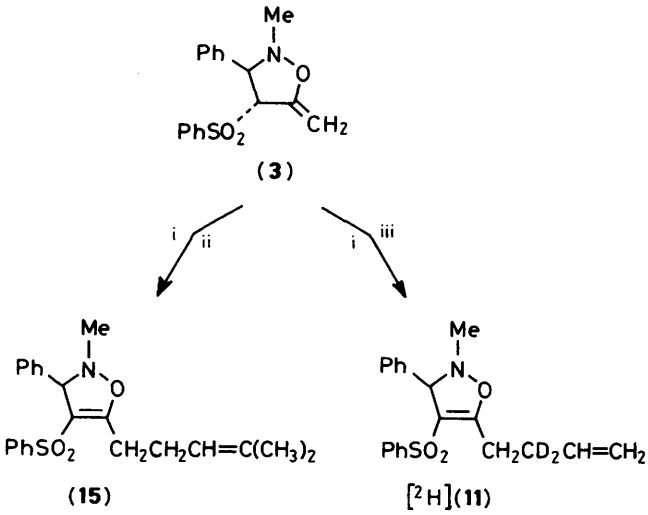
Scheme 3. *Reagents:* i, LDA; ii, MeI; iii, MeOH, H^+; iv, H_2 (Pd/C)

product (**11**). An analogous reaction occurred with 2,3-dihydroisoxazole (**12**) using LDA as the base. These results are quite surprising since, in most cases, allyl sulphonyl anions undergo exclusive α-alkylation.[9,26] Two fundamentally different mechanisms can explain the formation of (**11**) (Scheme 4). One



Scheme 4. *Reagents:* i, LDA; ii, CH_2=$CHCH_2Br$

route involves γ-alkylation, possibly owing to the steric environment about the α-site. The alternative path involves α-alkylation to give structure (**14**) as a transient intermediate which rapidly undergoes a subsequent Cope rearrangement to the observed product. In order to distinguish between these two possibilities, we have investigated the reaction of (**3**) with LDA and several allylic halides. Treatment of (**3**) with LDA and 3-bromo[3,3-$^2H_2$]prop-1-ene[31] produced [^{2}H]-(**11**) where the deuterium atoms were located at the β-position of the side chain. No detectable quantities of the Cope product could be found since there was no incorporation of deuterium into the olefinic entity. We also examined the LDA-induced alkylation reaction of (**3**) with 4-bromo-2-methylbut-2-ene. The location of the methyl substituents in the allyl side-chain was easily determined by examination of the n.m.r. spectrum of the γ-alkylated product. The formation of the 5-(4-methylpent-3-enyl)-2,3-dihydroisoxazole system is only compatible with the direct γ-alkylation route. Evidently, the sulphone reaction

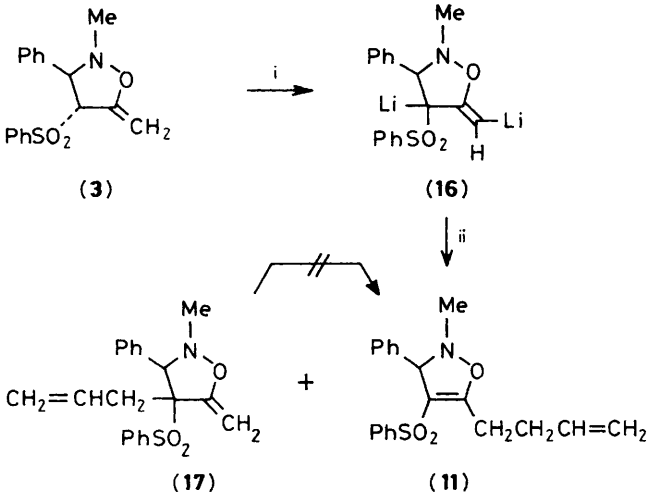


Scheme 5. *Reagents:* i, LDA; ii, $BrCH_2CH=C(CH_3)_2$; iii, $BrCD_2CH=CH_2$

proceeds *via* selective γ-alkylation, perhaps as a consequence of steric hindrance to attack at the α-site. An alternative explanation which could also rationalize the site specificity is that the α,β-unsaturated sulphone actually corresponds to the more stable isomer since the π-bond is part of the 2,3-dihydroisoxazole ring. The Hammond postulate suggests that endothermic reactions have late, product-like transition states: hence the anion derived from (**3**) might well prefer to alkylate at the methylene carbon (γ-site) with developing dihydroisoxazole character, rather than at the α-site.

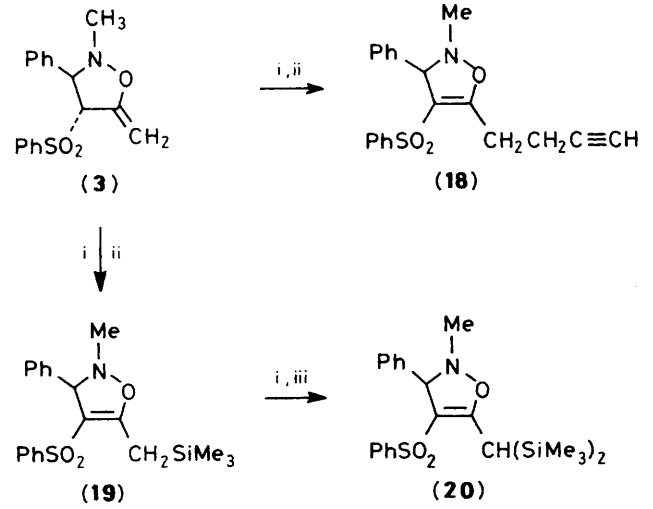
α,β-Unsaturated carboxylic acids[32] and secondary amides[33] undergo alkylation *via* their dianions and one can anticipate that similar polyionized species could also be generated from allylic sulphones.[34,35] Accordingly, we treated the isoxazolidine (**3**) with an excess of several lithiate bases and found that a significant amount of α-alkylation occurred (10—50%). At −100 °C in THF the following trend in γ:α alkylation was observed: s-butyl-lithium (5:1), phenyl-lithium (8:1), and t-butyl-lithium (1:1) (using allyl bromide as the electrophile). Apparently, the use of strong alkyl-lithium bases results in the formation of the dilithio species (**16**) (Scheme 6), where some stabilization is provided by lithium chelation with the oxygen atom of the isoxazolidine ring. The ratio of α:γ products does not seem to vary significantly with the solvent systems used. However, when methyl iodide was employed as the electrophile, only the α-alkylated product [*i.e.* (**7**)] was formed. We also investigated the thermal behaviour of the α-allyl substituted isoxazolidine (**17**) and found that it did not undergo a Cope rearrangement, even under forcing conditions (120 °C, 48 h).

Most unsymmetrical allyl metallic compounds react with electrophiles at the more substituted end of the allyl group because the metal spends most of its time at the less substituted end.[36—40] With large electrophiles and hindered ketones, however, the allyl metallic compound generally reacts at the less substituted end, presumably as a result of a reversible 1,3-shift of the metal to the more substituted position followed by attack by the electrophile at the sterically less crowded end. Our results with the allyl sulphonyl carbanion derived from (**3**) suggest that



Scheme 6. *Reagents:* i, RLi, 2.2 equiv.; ii, CH_2=$CHCH_2Br$

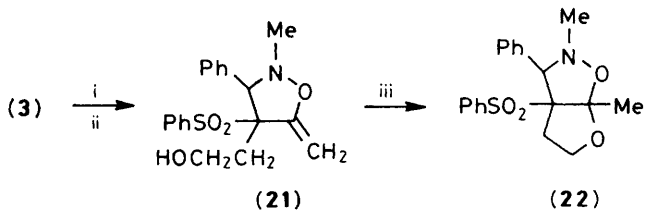
the product ratios are controlled by a sensitive interplay between thermodynamic and steric factors. With a small electrophile such as methyl iodide, α-alkylation is the only path followed. As the bulk of the electrophile increases, γ-alkylation becomes the dominant or exclusive path. This was demonstrated by studying the reaction of (**3**) with prop-2-ynyl bromide or trimethylsilyl chloride (using LDA as the base) and finding that the γ-alkylation product was formed in high yield (Scheme 7). If



Scheme 7. *Reagents:* i, LDA; ii, $BrCH_2C{\equiv}CH$; iii, Me_3SiCl

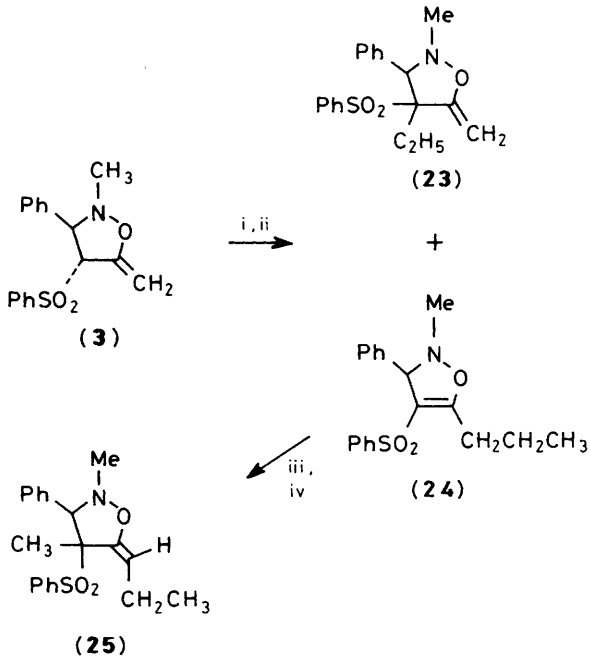
an excess of LDA was used, the initially formed γ-silylated 2,3-dihydroisoxazole (**19**) was further converted into the disilylated derivative (**20**). Interestingly, the addition of ethylene oxide to the lithium salt of (**3**) (THF with added HMPA) at −78 °C followed by quenching with methanol afforded the mono α-alkylated product (**21**) in 80% yield (Scheme 8). This material was readily converted into the cyclic ether (**22**) on silica gel chromatography or by treatment with a trace of acid.

Alkylation of the isoxazolidine (**3**) with ethyl iodide (using LDA as the base in THF) afforded a 1:3 mixture of the α and γ-alkylation products (**23**) and (**24**). The α-/γ-alkylation ratios were obtained by integration of the vinylic and allylic proton signals and are estimated to be accurate to within 5%. We also carried out a variety of ethylation experiments using different solvents (ether, DMF), additives (TMEDA, HMPA), and bases



Scheme 8. *Reagents:* i, LDA; ii, ethylene oxide; iii, H^+

(Bu^sLi, Bu^tLi, NaH, KH) without noting a major difference in product distribution. Methylation of the lithium salt of (**24**) in THF (Bu^tLi) occurred in high yield and again favoured α-attack (Scheme 9). From these results it is clear that steric factors play



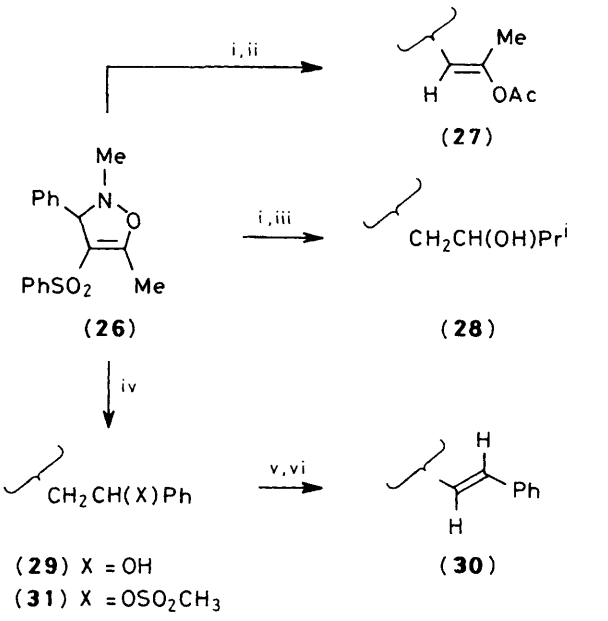
Scheme 9. *Reagents:* i, Base; ii, EtI; iii, Bu^tLi; iv, MeI

an important role in controlling the α/γ-alkylation ratios. The results are of some interest when compared with the overwhelming α-selectivity observed with numerous simple allyl sulphones.

We also examined the reaction of the carbanion derived from dihydroisoxazole (**26**) with several carbonyl compounds and found that only γ-attack had occurred. Thus, treatment of (**26**) with LDA followed by reaction with an excess of acetyl chloride gave the enol ester (**27**). Reaction of (**26**) with LDA and α-methyl propionaldehyde afforded alcohol (**28**). The benzaldehyde adduct (**29**) was readily converted into the styryl derivative (**30**) *via* the mesylate (**31**) (Scheme 10).

Reductive cleavage of the isoxazolidine ring is known to produce γ-amino alcohols.[41–45] We had hoped that the initially formed enone (**32**) derived from N–O bond cleavage of (**30**) would undergo intramolecular conjugate addition to give the piperidone (**33**) (Scheme 11). Instead, a retro-aldol type reaction occurred to produce *N*-methyl *C*-phenylimine and (**34**) which was further reduced to 1-phenyl-4-phenylsulphonylbutan-3-one (**35**) under the hydrogenation conditions used.

At this stage of our studies we decided to investigate the photochemical behaviour of the 5-methyleneisoxazolidine ring (Scheme 12). We were particularly interested in determining whether this ring system would undergo a photochemically induced 1,3-sigmatropic sulphonyl shift as had been encountered



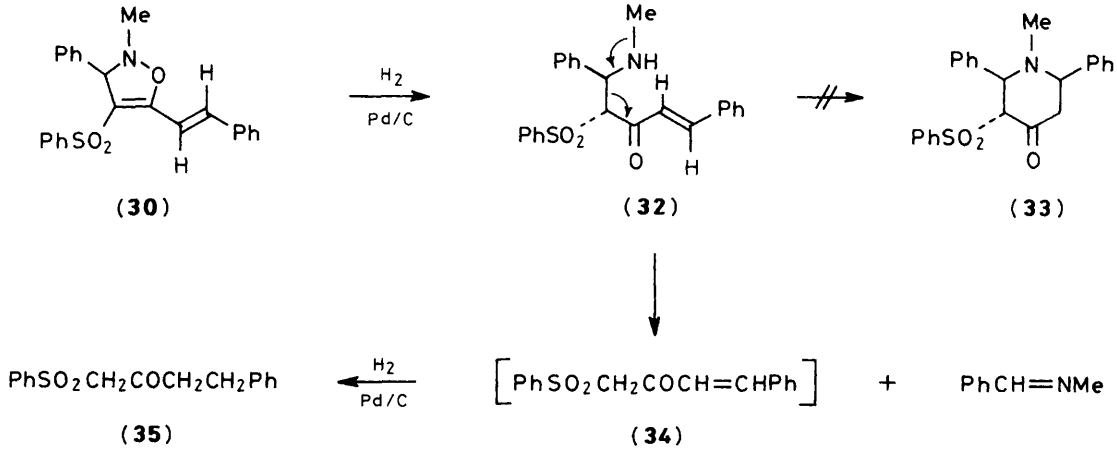
Scheme 10. *Reagents:* i, Base, ii, MeCOCl, iii, $(Me)_2CHCHO$; iv, PhCHO; v, MeSCl; vi, DBU

with related systems.[22] Unfortunately, all attempts to induce this rearrangement with several isoxazolidines failed to give characterizable material and consequently this approach was abandoned. The only material that was isolated (52%) on extended irradiation of (**3**) corresponded to enamide (**36**). The formation of this material can be attributed to N–O bond scission followed by internal disproportonation and double bond isomerization.

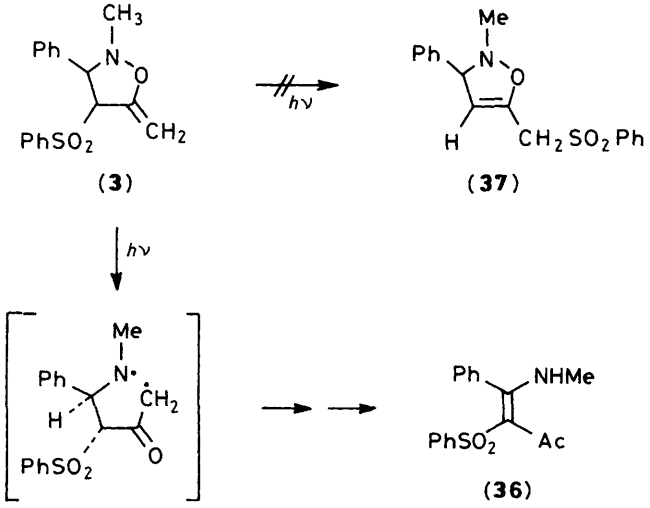
In summary, the reaction of 5-methylene-4-phenylsulphonylisoxazolidines with base followed by alkylation affords both α- and γ-substituted products. The product ratio is controlled by a sensitive interplay between thermodynamic and steric factors and is very dependent on the nature of the electrophile used. Further generalizations of these findings and their implications for the synthesis of various heterocyclic compounds are the object of ongoing investigations.

Experimental

M.p.s were determined on a Thomas-Hoover capillary m.p. apparatus and are uncorrected. I.r. spectra were run on a Perkin-Elmer Model 283 spectrometer. ^1H N.m.r. spectra were obtained on a Varian EM-390 and Nicolet NMC-360 MHz spectrometer. ^{13}C N.m.r. spectra were recorded on an IBM NB 200 SY FT spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, Ga. Mass spectra were determined



Scheme 11.



Scheme 12.

with a VG MM-7070S mass spectrometer at an ionizing voltage of 70 eV.

Alkylation Studies of 2-Methyl-5-methylene-3-phenyl-4-phenylsulphonylisoxazolidine (**3**).—To a solution of di-isopropylamine (1.9 ml) and butyl-lithium (1.6 mmol) in THF (20 ml) at −78 °C was added a solution of isoxazolidine (**3**)[3] (1 mmol) THF (1 ml). The solution was stirred for 45 min and then the appropriate electrophile (1.2 mmol) was added and the reaction mixture warmed to 0 °C and stirred for 1 h. The mixture was poured into 10% aqueous ammonium chloride and extracted with ether. The ethereal extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure and the residue chromatographed (silica; 10% ethyl acetate–hexane) to afford the alkylated product. Use of methyl iodide as the electrophile gave crystalline 2,4-dimethyl-5-methylene-3-phenyl-4-phenylsulphonylisoxazolidine (**7**) (78%); m.p. 129—130 °C; $\nu_{max.}$(KBr) 3 085, 3 040, 2 990, 2 890, 1 670, 1 605, 1 300, 1 150, 760, and 690 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz) 1.30 (s, 3 H), 2.58 (s, 3 H), 4.30 (d, 1 H, *J* 2.6 Hz), 4.42 (s, 1 H), 4.70 (d, 1 H, *J* 2.6 Hz), 7.32—7.38 (m, 3 H), 7.42—7.47 (m, 2 H), 7.55—7.63 (m, 2

H), 7.68—7.75 (m, 1 H), and 7.97—8.04 (m, 2 H); $\delta_C(CDCl_3)$ 18.1, 43.8, 74.4, 76.8, 87.8, 128.4, 128.7, 129.2, 131.6, 134.2, and 157.7 p.p.m.; *m/z* 329 (M^+), 187, 118, and 77 (Found: C, 65.7; H, 5.85; N, 4.15. Calc. for $C_{18}H_{19}NO_3S$: C, 65.64; H, 5.82, N, 4.25%).

A solution containing (**7**) (130 mg) and aluminium trichloride (53 mg) in methanol (25 ml) was heated at reflux under a nitrogen atmosphere for 16 h. It was then concentrated under reduced pressure, poured into water (50 ml), and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil which crystallized with time. Recrystallization from methylene dichloride–ether–hexane gave 5-methoxy-2,4,5-trimethyl-3-phenyl-4-phenylsulphonylisoxazolidine (**10**) (90%), m.p. 188—189 °C; $\nu_{max.}$(KBr) 3 080, 2 995, 2 985, 2 940, 2 885, 1 500, 1 445, 1 305, 1 130, 770, and 695 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz) 0.98 (s, 3 H), 1.30 (s, 3 H), 2.80 (s, 3 H), 3.38 (s, 3 H), 5.25 (s, 1 H), 7.30—7.40 (m, 3 H), 7.40—7.48 (m, 2 H), 7.52—7.63 (m, 3 H), and 7.70—7.80 (m, 2 H) (Found: C, 63.05; H, 6.45; N, 3.85. Calc. for $C_{19}H_{23}NO_4S$: C, 63.14; H, 6.42; N, 3.88%).

A sample of the isoxazolidine (**7**) (150 mg) in dry methanol (20 ml) was hydrogenated at atmospheric pressure and room temperature for 6 h using palladium on carbon (4 mg) as catalyst. The mixture was filtered through Celite and concentrated under reduced pressure. Chromatography of the crude residue (silica; 15% ethyl acetate–hexane) gave 3-phenylsulphonylbutan-2-one (**9**) (75%), m.p. 96—97 °C; $\delta_H(CDCl_3$; 90 MHz) 1.40 (d, *J* 7 Hz, 3 H), 2.42 (s, 3 H), 4.13 (q, *J* 7 Hz, 1 H), and 7.31—7.72 (m, 5 H).

Alkylation of 2-Methyl-5-methylene-3-phenyl-4-phenylsulphonylisoxazolidine (**3**) *with Allyl Bromide.*—To a solution of compound (**3**) (1.0 mmol) in THF (10 ml) at −78 °C was added butyl-lithium (2.2:1 mmol). The solution was stirred for 5 min and then allyl bromide (1.0 mmol) was added. The mixture was warmed to room temperature and then quenched with saturated aqueous ammonium chloride. The solution was extracted with ether and the ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure and the residue chromatographed (silica; 10% ethyl acetate–hexane) to give a mixture of 5-but-3-enyl-2-methyl-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**11**) (52% yield) and 4-allyl-2-methyl-5-methylene-3-phenyl-4-phenylsulphonylisoxazolidine (**17**) (10%). The major product (**11**) was isolated as a colourless oil; $\nu_{max.}$(neat) 3 070, 3 040, 2 980, 2 960, 2 920, 2 880, 2 855, 1 630, 1 590, 1 500, 1 450, 1 310, 1 160, 930, 730, and 700 cm^{-1}; $\delta_H(CDCl_3$; 300 MHz) 2.33—2.98 (m, 2 H), 2.75—3.00 (m, 2 H), 2.85 (s, 3 H), 4.90 (s, 1 H), 5.05—5.09 (m, 1 H), 5.10—5.18 (m, 1 H), 5.75—5.90 (m, 1 H), 7.00—7.23 (m, 7 H) and 7.30—7.40 (m, 3 H); *m/z* 355 (M^+), 278, 214, 141, 84, and 77 (Found: M^+, 355.1240. Calc. for $C_{20}H_{21}NO_3S$: *M*, 355.1242).

The minor product (**17**) exhibited the following properties: m.p. 105—106 °C; $\nu_{max.}$(KBr) 3 080, 3 060, 3 000, 2 980, 2 920, 2 880, 2 860, 1 645, 1 590, 1 500, 1 480, 1 455, 1 310, 1 155, 930, 770, 750, 710, and 690 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz) 2.40 (s, 3 H), 2.65 (dd, 1 H, *J* 14.9 and 6.5 Hz), 2.75 (dd, 1 H, *J* 14.9 and 6.0 Hz), 4.35 (s, 1 H), 4.38 (d, 1 H, *J* 2.6 Hz), 4.67 (dd, 1 H, *J* 17.0 and 1.4 Hz), 4.72 (d, 1 H, *J* 2.6 Hz), 4.83 (dd, 1 H, *J* 9.7 and 1.4 Hz), 5.56 (dddd, 1 H, *J* 17.0, 9.7, 6.5, and 6.0 Hz), 7.28—7.32 (m, 3 H), 7.42—7.50 (m, 2 H), 7.53 (d, 2 H, *J* 7.7 Hz), 7.63 (t, 1 H, *J* 7.7 Hz), and 8.00 (d, 2 H, *J* 7.7 Hz); *m/z* 355 (M^+), 278, 214, 118, and 77 (Found: *M*, 355.1218. Calc. for $C_{20}H_{21}NO_3S$: *M*, 355.1242).

Using the general procedure described above, 5-[2-$^2H_2$]but-3-enyl-2-methyl-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole [$^2H_2$]-(**11**) was obtained, from the reaction of (**3**) with 1-bromo[1-$^2H_2$]prop-2-ene,[31] as a viscous yellow oil (78%); $\nu_{max.}$(neat) 3 070, 2 970, 1 590, 1 535, 1 450, 1 310, and 1 160 cm^{-1}; $\delta_H(CCl_4$; 90 MHz) 2.45 (d, 1 H, *J* 7.0 Hz), 2.70 (d, 1 H, *J* 7.0 Hz), 2.80 (s, 3 H), 4.85 (s, 1 H), 4.95 (1 H, *J* 2.0 Hz), 5.10 (dd, 1 H, *J* 12.0 and 2.0 Hz), 5.80 (dd, 1 H, *J* 15.0 and 12.0 Hz), and 6.85—7.40 (m, 10 H).

Alkylation of 2,3,3,5-Tetramethyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**12**) *with Allyl Bromide.*—Compound (**12**) (1 mmol) was added to a solution of LDA (1.2 mmol) in THF (20 ml) at −78 °C. The solution was stirred for 1 h and then allyl bromide (1.2 mmol) was added. The reaction mixture was allowed to warm to 0 °C over 1 h. Work-up as previously described gave 5-but-3-enyl-2,3,3-trimethyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**13**) in 78% yield as a viscous yellow oil; $\nu_{max.}$(neat) 3 080, 2 980, 2 940, 1 625, 1 450, 1 310, 1 160, 1 070, and 930 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz) 1.20 (s, 6 H), 2.25—2.42 (m, 2 H), 2.50 (s, 3 H), 2.80—2.90 (m, 2 H), 4.95—5.15 (m, 2 H), 5.70—5.87 (m, 1 H), 7.43—7.58 (m, 3 H), and 7.80—7.90 (m, 2 H); *m/z* 307 (M^+), 292, 125, 91, 77, and 56 (Found: M^+, 307.1236. Calc. for $C_{16}H_{21}NO_3S$: *M*, 307.1242).

Alkylation of 2-Methyl-5-methylene-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**3**) *with 4-Bromo-2-methylbut-2-ene.*—To a solution containing LDA (1.2 equiv.) and THF (10 ml) at −78 °C was added LDA compound (**3**) (319 mg). The reaction mixture was stirred at −78 °C for 1 h and then 4-bromo-2-methylbut-2-ene (1.2 equiv.) was added. The reaction mixture was warmed to room temperature and then quenched with saturated aqueous ammonium chloride. The solution was poured into water, extracted with ether and the ethereal extracts dried ($MgSO_4$), concentrated under reduced pressure, and the residue subjected to chromatography (silica; 20% ether–hexane) to give 5-(4-methylpent-3-enyl)-2-methyl-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**15**) (81%); $\nu_{max.}$(neat) 3 070, 3 040, 2 980, 2 930, 2 880, 2 860, 1 635, 1 450, 1 310, 1 165, 760, 740, and 695 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz) 1.62 (s, 3 H), 1.65 (s, 3 H), 2.30 (q, 2 H, *J* 7.0 Hz), 2.78 (t, 2 H, *J* 7.0 Hz), 2.83 (s, 3 H), 4.84 (s, 1 H), 5.08 (t, 1 H, *J* 7.0 Hz), 6.98 (t, 2 H, *J* 7.25 Hz), 7.04 (t, 2 H, *J* 7.25 Hz), 7.11 (t, 3 H, *J* 7.25 Hz), and 7.27 (d, 3 H, *J* 7.25 Hz); *m/z* 383 (M^+), 306, 242, and 77 (Found: M^+, 383.1554. Calc. for $C_{22}H_{25}NO_3S$: *M*, 383.1549).

5-But-3-ynyl-2-methyl-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**18**).—Compound (**18**) was formed as a pale yellow oil (75%) from the reaction of compound (**3**) with prop-2-ynyl bromide using LDA as the base in THF as solvent; $\nu_{max.}$(neat) 3 300, 3 070, 3 040, 2 960, 2 920, 2 880, 2 850, 1 635, 1 590, 1 500, 1 450, 1 310, 1 160, 725, and 690 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz), 1.98 (t, 1 H, *J* 2.6 Hz), 2.59 (dt, 2 H, *J* 7.4 and 2.6 Hz), 2.90 (s, 3 H), 3.07 (t, 2 H, *J* 7.4 Hz), 4.96 (s, 1 H), 7.08—7.20 (m, 7 H), and 7.32—7.42 (m, 3 H); $\delta_C(CDCl_3)$ 16.1, 24.3, 47.1, 69.9, 76.6, 82.0, 112.0, 126.9, 127.3, 127.7, 128.2, 129.2, 132.3, 139.2, 141.8, and 169.3 p.p.m.; *m/z* 353 (M^+), 314, 276, 238, 212, 141, and 77 (Found: M^+, 353.1085. Calc. for $C_{20}H_{19}NO_3S$: *M*, 353.1086).

Reaction of 2-Methyl-5-methylene-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**3**) *with Chlorotrimethylsilane.*—To a solution containing LDA (1.2 equiv.) and THF (10 ml) at −78 °C was added compound (**3**) (284 mg). The reaction mixture was stirred at −78 °C for 1 h and then chlorotrimethylsilane (1.2 equiv.) added. The reaction mixture was warmed to room temperature and then quenched with a saturated aqueous ammonium chloride. The reaction mixture was poured into water and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil which crystallized with time. Recrystallization from ether–hexane gave 2-methyl-3-phenyl-4-phenylsulphonyl-5-trimethylsilylmethyl-2,3-dihydroisoxazole (**19**) (77%), m.p. 93—94 °C; $\nu_{max.}$(KBr) 3 080, 2 960, 2 910, 2 875, 2 850, 1 620, 1 500, 1 450, 1 315, 1 305, 1 170, 845, 760, 730, 705, and 690 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz) 0.25 (s, 9 H), 2.26 (d, 1 H, *J* 12.9 Hz), 2.42

(d, 1 H, *J* 12.9 Hz), 2.87 (s, 3 H), 4.89 (s, 1 H), 7.05—7.78 (m, 7 H), 7.18 (d, 1 H, *J* 7.2 Hz), and 7.33 (d, 2 H, *J* 7.2 Hz); $\delta_C(CDCl_3)$ −0.9, 17.2, 47.3, 76.5, 107.6, 126.6, 127.7, 128.0, 128.2, 128.4, 132.1, 139.0, 142.6, and 166.4 p.p.m.; (Found: C, 62.05; H, 6.55; N, 3.58. Calc. for $C_{20}H_{25}NO_3SiS$: C, 61.97; H, 6.51; N, 3.61%).

When 2.5 equiv. of LDA was used 2-methyl-3-phenyl-4-phenylsulphonyl-5-bis(trimethylsilyl)methyl-2,3-dihydroisoxazole (45%) (**20**) was also isolated. This material exhibited the following properties: m.p. 110—111 °C; $\nu_{max.}$(KBr) 3 060, 3 040, 2 960, 2 900, 1 590, 1 450, 1 315, 1 250, 1 185, 1 150, 1 020, 850, 760, 720, and 690 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz) 0.05 (s, 9 H), 0.11 (s, 9 H), 2.65 (s, 3 H), 2.90 (s, 3 H), 5.00 (s, 1 H), and 7.18—7.38 (m, 10 H); $\delta_C(CDCl_3)$ 0.20, 20.4, 47.4, 106.0, 125.5, 127.2, 128.0, 129.3, 130.8, 133.1, 139.2, 142.9, and 169.2 p.p.m.; *m/z* 459 (M^+), 382, 315, 238, 174, 173, 135, 132, 77, and 73 (Found: M^+, 459.1708. Calc. for $C_{23}H_{34}NO_3SSi_2$: *M*, 459.1720).

Reaction of 2-Methyl-5-methylene-3-phenyl-4-phenylsulphonylisoxazolidine (**3**) *with Ethylene Oxide.*—To a solution containing LDA (1.2 equiv.) and hexamethylphosphoramide (2 ml) at −78 °C was added compound (**3**) (315 mg) in THF (10 ml). The reaction mixture was stirred at −78 °C for 1 h, after which the yellow solution was treated with an excess of ethylene oxide and warmed to 25 °C. The reaction mixture was quenched with methanol and extracted with ether. The combined ethereal extracts were washed with dilute aqueous acetic acid and brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford a yellow solid which was purified by column chromatography. The major fraction was a white solid whose structure was assigned as 4-(2-hydroxyethyl)-2-methyl-5-methylene-3-phenyl-4-phenylsulphonylisoxazolidine (**21**) (80%), m.p. 116—117 °C; $\nu_{max.}$(KBr) 3 410, 3 060, 2 970, 2 880, 1 660, 1 500, 1 450, 1 300, 1 140, 670, and 600 cm^{-1}; $\delta_H(CDCl_3$; 90 MHz) 1.70 (s, 1 H), 2.25 (m, 2 H), 2.43 (s, 3 H), 3.60 (m, 2 H), 4.35 (s, 1 H), 4.46 (d, 1 H, *J* 3.0 Hz), 4.70 (d, 1 H, *J* 3.0 Hz), 7.20—7.60 (m, 7 H), and 7.70—8.10 (m, 3 H); *m/z* 359 (M^+), 282, 217, 188, 149, 118, and 77 (Found: C, 63.38; H, 5.93; N, 3.88; S, 8.85. Calc. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.88; N, 3.89; S, 8.92%).

A solution containing compound (**21**) (20 mg) and a catalytic amount of toluene-*p*-sulphonic acid in chloroform (20 ml) was stirred at room temperature for 48 h and then poured into water and extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a light yellow oil which crystallized with time. Recrystallization from chloroform–hexane gave 2,6a-dimethyl-3-phenyl-3a-phenylsulphonylhexahydrofuro[3,2-*d*]isoxazole (**22**) (90%), m.p. 134—135 °C; $\nu_{max.}$(KBr) 3 080, 2 980, 2 920, 2 880, 1 580, 1 450, 1 310, 1 300, 1 150, 1 140, 770, 720, and 700 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz) 2.00 (s, 3 H), 2.13 (dd, 1 H, *J* 13.5 and 5.0 Hz), 2.50 (s, 3 H), 2.94 (ddd, 1 H, *J* 13.5, 11.0, and 8.0 Hz), 4.16 (t, 1 H, *J* 8.0 Hz), 4.28 (s, 1 H), 4.44 (ddd, 1 H, *J* 11.0, 8.0, and 5.0 Hz), 6.95 (d, 2 H, *J* 8.0 Hz) 7.07 (t, 2 H, *J* 8.0 Hz), 7.16 (t, 1 H, *J* 8.0 Hz), 7.45 (t, 2 H, *J* 8.0 Hz), 7.57 (t, 1 H, *J* 8.0 Hz), and 7.81 (d, 2 H, *J* 8.0 Hz) (Found: C, 63.35; H, 5.95; N, 3.85. Calc. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.88; N, 3.89%).

Alkylation of 2-Methyl-5-methylene-3-phenyl-4-phenylsulphonylisoxazolidine (**3**) *with Ethyl Iodide.*—Using the LDA procedure described above, a mixture of two compounds was obtained. The major product isolated corresponded to 2-methyl-3-phenyl-4-phenylsulphonyl-5-propyl-2,3-dihydroisoxazole (**24**) as a colourless solid (67%), m.p. 59—60 °C; $\nu_{max.}$(KBr) 3 070, 3 025, 2 960, 2 930, 2 870, 1 630, 1 490, 1 470, 1 450, 1 310, 1 160, 1 150, 770, 760, 730, 700, and 695 cm^{-1}; $\delta_H(CDCl_3$; 300 MHz), 1.02 (t, 3 H, *J* 7.4 Hz), 1.62—1.80 (m, 2 H), 2.65—2.89 (m, 2 H), 2.90 (s, 3 H), 4.90 (s, 1 H), 7.00—7.20 (m, 7 H), and 7.28—7.40 (m, 3 H) (Found: C, 66.35; H, 6.2; N, 4.05. Calc. for $C_{19}H_{21}NO_3S$: C, 66.46; H, 6.16; N, 4.08%).

The minor product isolated was assigned as 4-ethyl-2-methyl-5-methylene-3-phenyl-4-phenylsulphonylisoxazolidine (**23**) (33%), m.p. 129—130 °C; $\nu_{max.}$(KBr) 3 065, 3 020, 2 965, 2 935, 2 880, 2 860, 1 650, 1 605, 1 585, 1 500, 1 450, 1 310, 1 150, 760, 730, and 695 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz) 0.84 (t, 3 H, *J* 7.4 Hz), 1.98 (m, 2 H), 2.48 (s, 3 H), 4.42 (s, 1 H), 4.46 (s, 1 H), 4.47 (s, 1 H), 7.24—7.40 (m, 3 H), 7.50—7.60 (m, 4 H), 7.64—7.70 (m, 1 H), and 8.05—8.08 (m, 2 H) (Found: C, 66.35; H, 6.2; N, 4.05. Calc. for $C_{19}H_{21}NO_3S$: C, 66.46; H, 6.16; N, 4.08%).

Methylation of 2-Methyl-3-phenyl-4-phenylsulphonyl-5-propyl-2,3-dihydroisoxazole (**24**).—To a solution of t-butyl-lithium (1.2 mmol) in ether (15 ml) at −78 °C was added 2-methyl-3-phenyl-4-phenylsulphonyl-5-propyl-2,3-dihydroisoxazole (**24**) (1 mmol) in ether (2 ml). The solution was stirred for 1 h and then methyl iodide (1.2 mmol) added. The reaction mixture was slowly warmed to −20 °C over 1 h and then quenched with water (0.5 ml). The resulting solution was poured into water (20 ml) and extracted with ether. The ethereal solution was dried ($MgSO_4$) and concentrated and the oily residue was purified by chromatography (silica; 10% ethyl acetate–hexane) to give 2,4-dimethyl-3-phenyl-4-phenylsulphonyl-5-propylideneisoxazolidine (**25**) as the major product (84%), m.p. 126—127 °C; $\nu_{max.}$(KBr) 3 070, 3 020, 2 995, 2 880, 1 660, 1 610, 1 590, 1 455, 1 310, 1 150, 1 080, 840, 790, 770, 715, and 695 cm^{-1}; $\delta_H(CDCl_3$; 90 MHz) 1.02 (t, 3 H, *J* 7.5 Hz), 2.78 (s, 3 H), 4.64 (s, 1 H), 4.80 (t, 1 H, *J* 8.0 Hz), 7.50—7.95 (m, 8 H), and 8.11—8.29 (m, 2 H); *m/z* 357 (M^+), 215, 187, 118, and 77 (Found: M^+, 357.1398. Calc. for $C_{20}H_{23}NO_3S$: *M*, 357.1393).

Reaction of 2,5-Dimethyl-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**26**) *with Acetyl Chloride.*—To a solution containing LDA (2.5 equiv.) and hexamethylphosphoramide (2 ml) at −78 °C was added compound (**26**)[3] (315 mg) in THF (10 ml). After the reaction mixture had been stirred for 1 h at −78 °C, acetyl chloride (2 ml) was added and the mixture warmed to room temperature. It was then poured into 10% aqueous ammonium chloride and extracted with ether. The ethereal extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure and the residue subjected to column chromatography (silica; 20% ethyl acetate–hexane) to give 5-(2-acetoxy-2-methylvinyl)-2-methyl-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**27**) (80%), m.p. 112—113 °C; $\nu_{max.}$(KBr) 3 080, 2 995, 2 920, 1 760, 1 680, 1 600, 1 450, 1 320, 1 200, 1 170, 1 130, 725, and 700 cm^{-1}; $\delta_H(CDCl_3$; 360 MHz) 2.15 (s, 3 H), 2.18 (s, 3 H), 2.82 (s, 3 H), 4.81 (s, 1 H), 6.72 (s, 1 H), and 7.00—7.40 (m, 10 H); *m/z* 399 (M^+), 357, 355, 280, 221, 187, 141, 139, 125, and 77 (Found: C, 63.05; H, 5.3; N, 3.5; S, 8.05. Calc. for $C_{21}H_{21}NO_5S$: C, 63.15; H, 5.29; N, 3.50; S, 8.02%).

5-(2-Hydroxy-4-methylbutyl)-2-methyl-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole. (**28**).—Compound (**28**) was obtained as a colourless oil (70%) from the reaction of compound (**26**) with 2-methylpropanal in the presence of LDA; $\nu_{max.}$(neat) 3 400, 3 080, 2 960, 2 920, 2 880, 1 630, 1 540, 1 310, 1 155, 720, and 690 cm^{-1}; $\delta_H(CDCl_3$; 300 MHz) 1.01 (d, 3 H, *J* 6.7 Hz), 1.02, (d, 3 H, *J* 6.7 Hz), 1.81 (m, 1 H), 2.73 (dd, 1 H *J* 14.0 and 3.0 Hz), 2.94 (s, 3 H), 3.06 (dd, 1 H, *J* 14.0 and 10.2 Hz), 3.73 (m, 1 H), 4.80 (s, 1 H), and 7.0—7.5 (m, 10 H); *m/z* 387 (M^+), 310, 238, 105, 97, 84, and 77 (Found: *M*, 387.1498. Calc. for $C_{21}H_{25}NO_4S$: *M*, 387.1504).

Preparation and Catalytic Reduction of 2-Methyl-3-phenyl-4-phenylsulphonyl-5-styryl-2,3-dihydroisoxazole (**30**).—To a solution containing LDA (1.2 equiv.) and hexamethylphosphoramide (2 ml) at −78 °C was added 2,5-dimethyl-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**26**) (315 mg) in THF (10 ml). The reaction mixture was stirred at −78 °C for 1 h and

then benzaldehyde (1 ml) was added. After being stirred for 1 h at 0 °C, the reaction mixture was poured into 10% aqueous ammonium chloride and extracted with ether. The ethereal extracts were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure and the residue chromatographed (silica; 20% ethyl acetate–hexane) to give 5-(2-hydroxyphenethyl)-2-methyl-3-phenyl-4-phenylsulphonyl-2,3-dihydroisoxazole (**29**) (70%), m.p. 118—119 °C; $\nu_{max.}$(KBr) 3 500, 3 060, 2 920, 1 630, 1 500, 1 450, 1 310, 1 285, 1 150, 1 050, 750, 730, and 690 cm^{-1}; δ_H($CDCl_3$; 360 MHz) 2.60 (d, 1 H, *J* 4.1 Hz), 2.92 (s, 3 H), 3.25 (ddd, 1 H, *J* 14.6, 4.1, and 1.1 Hz), 3.50 (dd, 1 H, *J* 14.6 and 8.7 Hz), 4.96 (s, 1 H), 5.27 (m, 1 H), and 7.00—7.50 (m, 15 H); *m/z* 421 (M^+), 344, 280, 250, 173, 150, 141, 118, 113, 105, 91, and 77 (Found: C, 68.45; H, 5.5; N, 3.3; S, 7.55. Calc. for $C_{24}H_{23}NO_4S$: C, 68.38; H, 5.49; N, 3.32; S, 7.60%).

To a solution containing the above alcohol (160 mg) in methylene dichloride (3 ml) was added triethylamine (50 mg) followed by methanesulphonyl chloride (60 mg) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 45 min after which it was washed with 5% aqueous HCl and saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated under reduced pressure to give the expected mesylate (**31**) as a clear liquid (180 mg, 95%); $\nu_{max.}$(neat) 1 620, 1 480, 1 430, 1 300, and 1 180 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 2.8 (s, 3 H), 2.9 (s, 3 H), 3.6 (m, 2 H), 4.8 (s, 1 H), 6.0 (t, 1 H, *J* 9 Hz), and 7.0—7.5 (m, 15 H).

To a solution containing the above mesylate (189 mg) in methylene dichloride (5 ml) was added DBU (0.5 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 30 min after which it was diluted with methylene dichloride, washed with dilute HCl and 10% aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated under reduced pressure to give the title compound (**30**) (98%) as a white solid. Crystallization of this material from 10% ethyl acetate–hexane gave a pure sample, m.p. 120—121 °C: $\nu_{max.}$(KBr) 1 630, 1 600, 1 440, 1 320, 1 180, and 1 090 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 2.9 (s, 3 H), 5.0 (s, 1 H), and 7.1—7.6 (m, 17 H); $\lambda_{max.}$ (95% ethanol) 232 (ε 11 700) and 320 nm (ε 21 150) (Found: C, 71.5; H, 5.25; N, 3.4. Calc. for $C_{24}H_{21}NO_3S$: C, 71.46; H, 5.21; N, 3.47%).

To a solution containing the above material (200 mg) in methanol (20 ml) was added 10% palladium on carbon catalyst (30 mg). The mixture was stirred under an atmosphere of hydrogen for 12 h. Filtration and evaporation of the solvent under reduced pressure left a colourless residue which was purified by chromatography (silica gel; 10% ethyl acetate–hexane). A sample of pure 1-phenyl-4-phenylsulphonylbutan-3-one (**35**) (204 mg; 80%) was obtained as a colourless oil; $\nu_{max.}$(neat) 1 710, 1 500, 1 450, 1 360, and 1 180 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 2.8 (m, 4 H), 4.0 (s, 2 H), 7.2 (m, 5 H), 7.6 (m, 3 H), and 7.8 (m, 2 H) (Found: M^+, 288.0887. Calc. for $C_{16}H_{16}SO_3$: *M*, 288.0888).

Irradiation of 2-Methyl-5-methylene-3-phenyl-4-phenylsulphonylisoxazolidine (**3**).—A solution containing compound (**3**) (1.0 g) in acetonitrile (250 ml) was irradiated using a 450 W medium-pressure mercury arc lamp with a quartz filter for 90 min. Concentration of the mixture under reduced pressure followed by chromatography of the residue (silica gel; 30% ethyl acetate–hexane) afforded a light yellow oil which crystallized with time. Recrystallization of this material from ether–hexane gave (*E*)-4-methylamino-4-phenyl-3-phenylsulphonylbut-3-en-2-one (**36**) as a white solid (52%), m.p. 104—105 °C; $\nu_{max.}$(KBr) 3 400, 3 060, 2 970, 2 930, 1 610, 1 580, 1 460, 1 440, 1 400, 1 300, 1 130, 830, 770, 720, and 700 cm^{-1}; δ_H($CDCl_3$; 360 MHz) 2.50 (s, 3 H), 2.62 (d, 3 H, *J* 4.8 Hz), 6.95 (d, 2 H, *J* 7.4 Hz), 7.25—7.42 (m, 6 H), and 7.47 (d, 2 H, *J* 7.4 Hz); δ_C($CDCl_3$; 50 MHz) 31.1, 31.4, 78.0, 110.8, 126.1, 127.7, 128.0, 128.4, 128.7, 128.9, 129.0, 129.3, 129.6, 131.5, 145.1, 171.4, and 196.8 p.p.m.; *m/z* 315 (M^+), 300, 174, and 77 (Found: M^+, 315.0926. Calc. for $C_{17}H_{17}NO_3S$: *M*, 315.0925).

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