Stereospecific Synthesis of 1,3-Oxazolidines from Allenic and Acetylenic Sulphones

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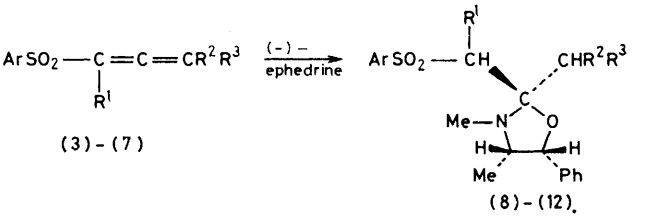
Reaction of allenic, α-acetylenic, and propargylic sulphones with (−)-ephedrine affords enantiomerically pure 1,3-oxazolidine; the reaction proceeds *via* formation of the conjugated enamine and subsequent cyclization.

A NUMBER of 1,3-oxazolidines have been prepared by reaction of carbonyl compounds with amino-alcohols.[1] The condensation of aromatic aldehydes with (−)-ephedrine (1) and (+)-pseudoephedrine (2) is a stereospecific reaction leading to enantiomerically pure oxazolidines.[2] Ketones, however, failed to react with (−)-ephedrine,[2] thus making impossible the stereospecific synthesis of 1,3-oxazolidines bearing two substituents (other than hydrogen) at the 2-carbon atom. We report that the allenic system, a masked ketonic function, can be used to circumvent this problem. From allenic sulphones and (−)-ephedrine, 1,3-oxazolidines are formed in a stereospecific reaction.

RESULTS AND DISCUSSION

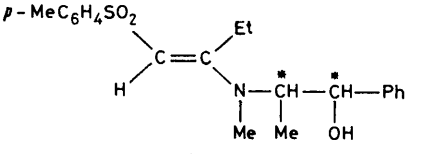
The allenic sulphones (3)—(7) are easily obtained by rearrangement of the corresponding propargylic sulphinates [3] or by oxidation of the parent allenic sulphoxides.[4] Addition of amines to 1,2-dienes is a well established reaction [5,6] and affords, at least in the case of secondary amines, the thermodynamically stable (*E*)-enamine.[5] In principle, the presence of a nucleophilic group in an appropriate position in the amine can give rise to addition to the activated double bond of the enamine thus formed, with resulting cyclization. This should lead, for example, to the formation of oxazolidines from activated allenes and β-amino-alcohols. When equimolar amounts of the allenic sulphones (3)—(7) and (−)-ephedrine are allowed to react in anhydrous benzene, the oxazolidines (8)—(12) are formed in high yield. The intermediate enamine (13) was isolated, starting from 1-*p*-toluenesulphonylbuta-1,2-diene (5), as a white solid $\{[\alpha]_D^{25} +104°$ $(CHCl_3)\}$. When set aside in chloroform solution, (13) was converted into oxazolidine (10), the reaction being followed by ^1H n.m.r. or i.r. spectroscopy, or by variation of the optical rotation.

The most striking feature of the reaction of allenes (3)—(7) with (−)-ephedrine is its stereospecificity. Indeed from phenylsulphonylpropa-1,2-diene (3), *p*-toluenesulphonylpropa-1,2-diene (4), and *p*-toluenesulphonylbuta-1,2-diene (5),† only one of the two possible diastereoisomeric oxazolidines is obtained. Starting from sulphone (6), another asymmetric centre is formed in the oxazolidine. The reaction retains its stereospecificity, and only two of the four possible diastereomers, *i.e.* (11a and b), were obtained, in unequal amounts (ratio 3 : 1, by ^1H n.m.r. spectroscopy). A similar situation is met with when two γ-substituents are present in the allenic sulphone: *e.g.* from (7) an inseparable mixture of two diastereomers (12a and b) was formed.

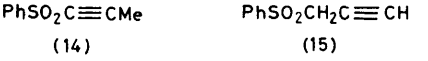


(3)-(7) (8)-(12).

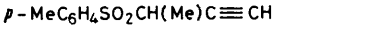
(3), (8) Ar = Ph, $R^1 = R^2 = R^3 = H$
(4), (9) Ar = *p*-MeC_6H_4, $R^1 = R^2 = R^3 = H$
(5), (10) Ar = *p*-MeC_6H_4, $R^1 = R^2 = H$, $R^3 = Me$
(6), (11a,b) Ar = *p*-MeC_6H_4, $R^1 = Me$, $R^2 = R^3 = H$
(7), (12a,b) Ar = *p*-MeC_6H_4, $R^1 = H$, $R^2 = Me$, $R^3 = Ph$



(13)



(14) (15)



(16)

Addition of amines to phenylsulphonylacetylenes (14) and (15) and to phenylsulphonylpropadiene (3) has been shown [5,7] to afford the same sulphonyl-enamine. When sulphones (14) and (15) were treated with (−)-ephedrine, optically pure oxazolidine (8) was obtained.‡

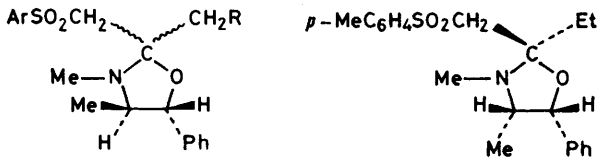
Similarly sulphone (16) afforded a mixture of (11a and b), in the same ratio as when obtained from allenic sulphone (6), which implies that reaction of the propargylic derivatives (15) and (16) involves isomerization to the allenic counterparts before addition. By monitoring the reaction of (16) with ephedrine by ^1H n.m.r.

† Reaction of (5) with (−)-ephedrine does not involve kinetic resolution: when the sulphone was treated with 0.5 molar equivalents of (−)-ephedrine, the recovered (5) was optically inactive. Different behaviour has been reported [6] for other chiral amines.

‡ The stereospecific formation of oxazolidines from an acetylenic diester has recently been reported.[8]

spectroscopy, the formation of (6) from (16) could be clearly detected.

The reaction of allenic sulphones (3) and (5) with (+)-ψ-ephedrine was also investigated. A mixture of the diastereoisomeric oxazolidines (17a, b) and (18a, b)



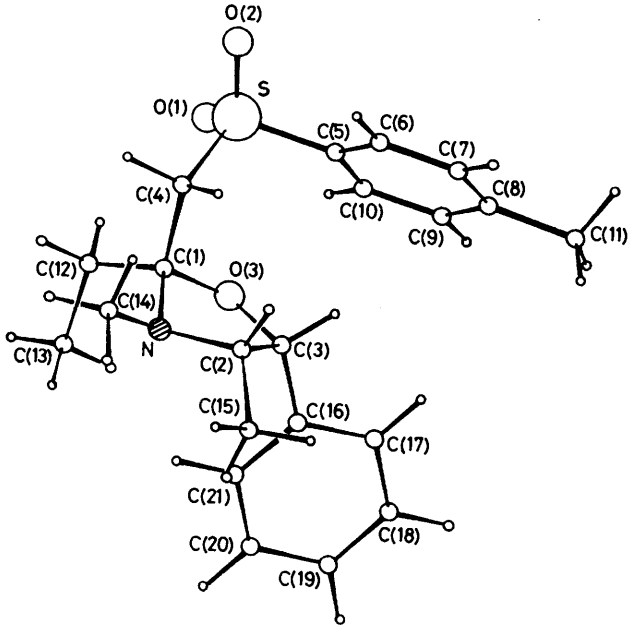
(17a,b) Ar = Ph, R = H
(18a,b) Ar = p-MeC6H4, R = Me

(10)

was obtained from (3) and (5), respectively (see Experimental section).

The stereochemical course of the reaction of allenic derivatives with β-amino-alcohols thus seems to be strictly connected with the chirality of the latter.

As far as the absolute configuration of oxazolidines (8)—(12) at C-2 is concerned, it can be assumed that reaction of allenic and acetylenic sulphones with (—)-ephedrine leads to those diastereoisomers where the steric interactions between *cis*-oriented substituents are minimized, and thus to (2*R*, 4*S*, 5*R*)-oxazolidines (on the assumption that the configuration of ephedrine is main-



tained in the cyclization). The absolute configuration at C-2 has been unequivocally established as *R* in the case of oxazolidine (10) by *X*-ray diffraction analysis.[9]

EXPERIMENTAL

General.—Light petroleum had b.p. 40—60 °C. Ether and benzene were dried over sodium, and dichloromethane was distilled from $CaCl_2$. Extractions were performed with dichloromethane and extracts were dried over Na_2SO_4. ^1H N.m.r. spectra were recorded with a Varian A-60 and/or a Varian HA 100 instrument; i.r. spectra were recorded with a Perkin-Elmer 377 spectrometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. (—)-(1*R*,2*S*)-Ephedrine, $[\alpha]_D^{25}$ —34.6° (*c* 4.0 in 50% aqueous HCl), was a commercial product; (+)-1*S*,2*S*)-ψ-ephedrine, prepared following the literature method,[10] had $[\alpha]_D^{25}$ +53.0° (*c* 4.0, EtOH) {lit.,[10] $[\alpha]_D^{20}$ +51.6° (*c* 5.0, EtOH)}.

Allenic and Acetylenic Sulphones.—The following compounds were prepared following literature methods; propa-1,2-dienyl phenyl sulphone (3), m.p. 43—44 °C (lit.,[7] m.p. 44—45 °C); propa-1,2-dienyl *p*-tolyl sulphone (4), m.p. 86—87 °C (lit.,[3] m.p. 86—87 °C); buta-1,2-dienyl *p*-tolyl sulphine (5), m.p. 47—48 °C (lit.,[3] m.p. 47—48 °C); 3-*p*-toluenesulphonylbuta-1,2-diene (6), m.p. 64—65 °C (lit.,[4] m.p. 64—65 °C); 3-phenylbuta-1,2-dienyl *p*-tolyl sulphone (7), m.p. 99—100 °C (lit.,[6] m.p. 99—100 °C); 1-phenylsulphonylpropyne (14), m.p. 68—69 °C (lit.,[7] m.p. 68—69 °C); 3-phenylsulphonylpropyne (15), m.p. 93 °C (lit.,[7] m.p. 93 °C); 3-*p*-toluenesulphonylbut-1-yne (16), m.p. 88—89 °C (lit.,[4] m.p. 88—89 °C).

Synthesis of Oxazolidines (8), (9), (11), *and* (12) *from Allenic Sulphones* (3), (4), (6), *and* (7).—In a typical run 0.165 g (1 mmol) of (—)-ephedrine was added to a stirred solution of the allenic sulphone (1 mmol) in anhydrous benzene (3 ml). The mixture was set aside at 25 °C for 12 h in the case of sulphones (3) and (4), and for 72 h in the case of (6) and (7). The solvent was evaporated off and the crude product purified by column cromatography (silica; anhydrous light petroleum–anhydrous diethyl ether). Oxazolidine (8) (100% yield) had m.p. 98—99 °C, $[\alpha]_D^{25}$ +54.4° (*c* 1.0, acetone) (Found: C, 66.2; H, 6.6; N, 4.0. $C_{19}H_{23}NO_3S$ requires C, 66.1; H, 6.7; N, 4.05%). Oxazolidine (9) (100% yield) had m.p. 113—114 °C, $[\alpha]_D^{25}$ +54.0° (*c* 1.0, acetone) (Found: C, 66.6; H, 7.0; N, 3.9. $C_{20}H_{25}NO_3S$ requires C, 66.8; H, 7.0; N, 3.9%). Oxazolidine (11a) was a viscous oil, $[\alpha]_D^{25}$ —89.0° (*c* 1.0, acetone); (11b), m.p. 121—123 °C, $[\alpha]_D^{25}$ —66.7° (*c* 1.0, acetone) [Found for (11a): C, 67.5; H, 7.3; N, 3.75; found for (11b): C, 67.5; H, 7.3; N, 3.75. $C_{21}H_{27}NO_3S$ requires C, 67.5; H, 7.3; N, 3.75%]; relative ratio (11a) : (11b) 3 : 1 (by ^1H n.m.r.); overall yield 70%; separated by column chromatography. Oxazolidines (12a and b), m.p. 122—138 °C, $[\alpha]_D^{25}$ +31.1° (*c* 1.0, acetone) (Found: C, 72.1; H, 6.9; N, 3.0. $C_{26}H_{31}NO_3S$ requires C, 72.1; H, 6.95; N, 3.1%) were obtained as an inseparable mixture in 65% yield.

Synthesis of Oxazolidines (8), (9), *and* (11) *from Acetylenic Sulphones* (14), (15), *and* (16).—In a typical run 0.165 g (1 mmol) of (—)-ephedrine was added to a stirred solution of the acetylenic sulphone (1 mmol) in anhydrous benzene (3 ml). Starting from sulphones (14) and (15), after being set aside for 12 h at 25 °C, the solvent was evaporated off and the crude product was purified by washing with n-pentane, to give oxazolidine (8) in 100% yield, m.p. 98—99 °C, $[\alpha]_D^{25}$ +54.4° (*c* 1.0, acetone). Starting from sulphone (16), after being set aside for 96 h at 25 °C, the product was purified by column chromatography and oxazolidines (11a), a viscous oil, $[\alpha]_D^{25}$ —89.0° (*c* 1.0, acetone) and (11b), m.p. 121—123 °C, $[\alpha]_D^{25}$ —66.7° (*c* 1.0, acetone), were obtained in the ratio 3 : 1, overall yield 70%. After 20 h reactions ^1H n.m.r. spectra of a sample of the reaction mixture from sulphone (16) showed the following product composition: allenic sulphone (6) 50%, acetylenic sulphone (16) 10%, oxazolidine (11) 40%.

Synthesis of Enamine (13) *and Oxazolidine* (10) *from Allenic Sulphone* (5).—(−)-Ephedrine (0.165 g, 1 mmol) was added to a stirred solution of allenic sulphone (5) (0.208 g, 1 mmol) in anhydrous benzene (3 ml). After 12 h at 25 °C a white solid was isolated by filtration, m.p. 125—130 °C, $[\alpha]_D^{25}$ +104° (*c* 1.0, chloroform), and identified by ^{1}H n.m.r. spectroscopy as the enamine (13). When set aside in anhydrous dichloromethane solution (5 ml) at 25 °C for 50 h, (13) was converted into oxazolidine (10), m.p. 107—108 °C, $[\alpha]_D^{25}$ +41.0° (*c* 1.0, acetone) (Found: C, 67.55; H, 7.2; N, 3.7. $C_{21}H_{27}NO_3S$ requires C, 67.5; H, 7.3; N, 3.75%).

Synthesis of Oxazolidines (17) *and* (18) *from Allenic Sulphones* (3) *and* (5) *and* (+)-*ψ*-*Ephedrine*.—In a typical run 0.165 g (1 mmol) of (+)-*ψ*-ephedrine was added to a stirred solution of the allenic sulphone and the mixture set aside at 25 °C for 12 h. The work-up described above afforded oxazolidine (17) (100% yield), as a diastereoisomeric mixture, isomer ratio 3 : 2 (by ^{1}H n.m.r. spectroscopy), m.p. 71—78 °C, $[\alpha]_D^{25}$ +52.5° (*c* 1.0, acetone), and oxazolidine (18) (93% yield), as a diastereoisomeric mixture, ratio 1 : 1 (by ^{1}H n.m.r. spectroscopy), $[\alpha]_D^{25}$ +60.4° (*c* 1.0, acetone). Attempts to purify the product by column chromatography resulted in partial decomposition; the diastereoisomeric mixture obtained was in the ratio 2 : 1, m.p. 89—96 °C, $[\alpha]_D^{25}$ +81.3° (*c* 1.0, acetone).

[8/903 *Received*, 16*th May*, 1978]

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