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X=Y-ZH Systems as Potential 1,3-Dipoles. Part 46.[1] Cascade 1,3-Dipolar Cycloaddition Reactions of Cephalosporin Imines.

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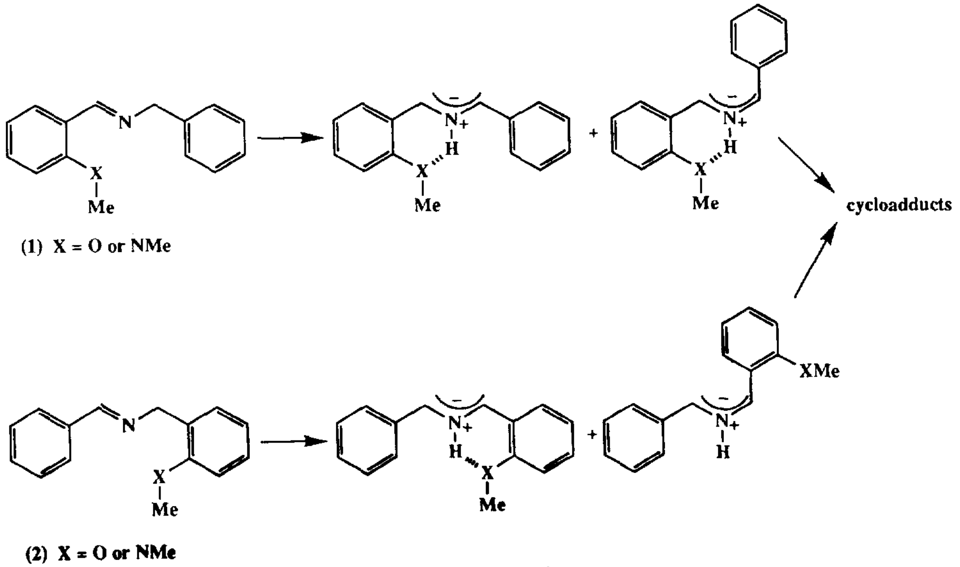
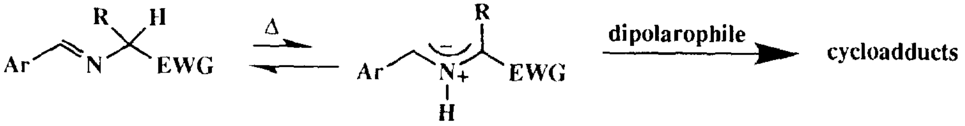
Abstract: Proton sponge effects in ortho-OMe and -NMe$_2$ arylidene imines of 7-aminocephalosporins promote thermal (toluene, 110°C) 1,2-prototropy to give mixtures of E,E- and E,Z-azomethine ylides which undergo diastereofacially specific (α-face) cycloaddition to N-phenylmaleimide to give mixtures of mainly endo-cycloadducts in excellent yield.

In the preceding paper[1] we demonstrated the effect of a 1,5-lone pair arrangement in promoting 1,2-prototropy in arylidene arylamines leading to stereospecific or stereoselective formation of E,E- or syn-azomethine ylides and their subsequent trapping in 1,3-dipolar cycloaddition reactions giving mixtures of endo- and exo-cycloadducts in excellent yield. Although (1) and (2) give rise to the same syn-dipole (Scheme 1), the corresponding anti-dipoles, if formed, have different configurations (Scheme 1) and hence furnish different cycloadducts.



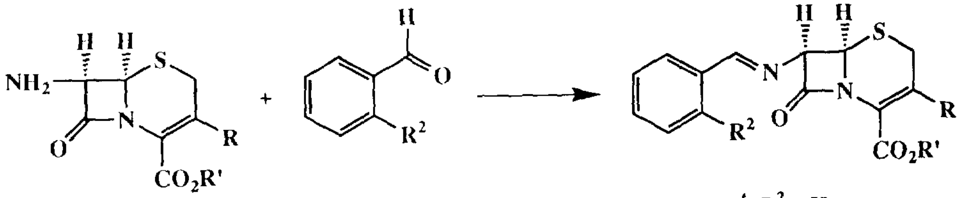
Scheme 1

Imines (1) and (2) undergo formal 1,2-prototropy on heating in boiling xylene whilst replacement of the XMe moiety by H results in an imine which does not undergo azomethine ylide formation in boiling xylene. We have previously shown that a wide range of electron withdrawing groups (EWG) promote 1,2-prototropy in simple benzylidene imines (3) at temperatures of 80 - 110°C (benzene, toluene) (Scheme 2) with stereospecific formation of the E,E-azomethine ylide.[2] Subsequently we showed that such processes can be effected at ambient temperature or below using a metal salt in combination with a tertiary amine.[3]



(3) EWG = CO_2R', COR', $P(O)(OEt)_2$, 2 - pyridyl, 2 - thiazolyl

Scheme 2

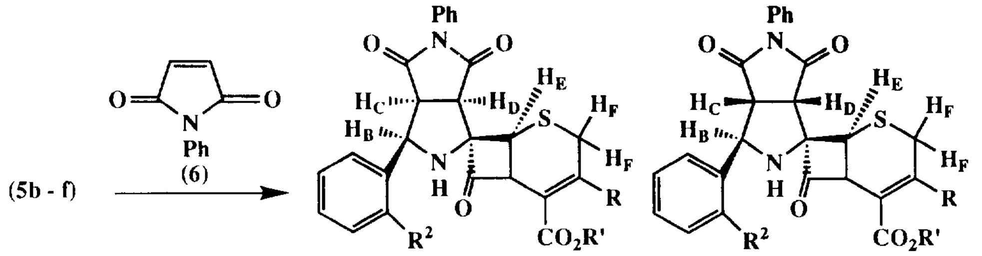


(4) a. R = CH_2OAc, R' = Bu^t
b. R = CH_2OCONH_2, R' = $CHPh_2$
c. R = Me, R' = 4 - $O_2NC_6H_4CH_2$

(5) a. R = CH_2OAc, R' = Bu^t, R^2 = H
b. R = CH_2OAc, R' = Bu^t, R^2 = OMe
c. R = CH_2OCONH_2, R' = $CHPh_2$, R^2 = OMe
d. R = CH_2OCONH_2, R' = $CHPh_2$, R^2 = NMe_2
e. R = Me, R' = 4 - $O_2NC_6H_4CH_2$, R^2 = OMe
f. R = Me, R' = 4 - $O_2NC_6H_4CH_2$, R^2 = NMe_2

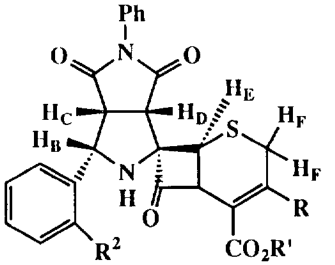
It was of interest to study the stereoelectronic effect of incorporating a β-lactam ring as the EWG in the imine (3) (Scheme 2) on the thermal 1,2-prototropic generation of azomethine ylides. A series of imines (5a-f) of 7-aminocephalosporanic esters (4a-c) was prepared by condensation of (4a-c) with the appropriate aryl aldehyde.

Heating imine (5a) and N-phenylmaleimide (6) in boiling toluene failed to yield any cycloadduct. However, when a solution of imine (5b) and (10) in toluene was boiled under reflux for 4h cycloaddition occurred. Although the imine (5b) utilised in this experiment was impure (see experimental) it proved possible to isolate a cycloadduct, formulated as (7a) by preparative t.l.c. Analogous reactions were subsequently carried out on imines (5c-f) and in all cases cycloaddition occurred to give mixtures of two [(7) and (9)] or three [(7) - (9)] cycloadducts (Table 1). Thus these cephalosporin aryl imines bearing ortho- OMe or -NMe_2 substituents display the same rate enhancing "proton sponge" effects for 1,2-prototropic azomethine ylide formation discussed in the preceding paper.[1]



(7) (8)

(7) - (9) a. R = CH_2OAc, R' = ^tBu, R^2 = OMe
b. R = CH_2OCONH_2, R' = $CHPh_2$, R^2 = OMe
c. R = CH_2OCONH_2, R' = $CHPh_2$, R^2 = NMe_2
d. R = Me, R' = 4 - $O_2NC_6H_4CH_2$, R^2 = OMe
e. R = Me, R' = 4 - $O_2NC_6H_4CH_2$, R^2 = NMe_2



(9)

Table 1. Cycloadducts from reaction of (5b-f) with (6) in toluene at 110°C.

Imine	**Reaction Time (h)**	**Yield(%)**[a]	**Isomer Ratio**	**Dipole Ratio (10) : (11)**
5b	4	40[b]	(7a)[c]	
5c	36	87	2(7b):1(8b):2(9b)	3:2
5d	12	100	3(7c):1(8c):2(9c)	2:1
5e	22	100	2(7d): - :1(9d)	2:1
5f	12	93	2(7e): - :1(9e)	2:1

a. Yield of mixed isomers before separation.
b. Isolated (preparative t.l.c.) yield of a single cycloadduct.
c. Impure imine (80%) used. Other isomers may be present.

Imines (5c) and (5d) both give mixtures of three cycloadducts. Thus (5c) gives a 2:1:2 mixture of (7b), (8b) and (9b) respectively whilst (5d) gives a 3:1:2 mixture of (7c), (8c) and (9c). The mixtures of cycloadducts were separated by flash chromatography (SiO_2) and the stereochemistry of the individual isomers assigned by n.O.e. studies (Table 2) and by comparison with the products from (5e) and (5f).

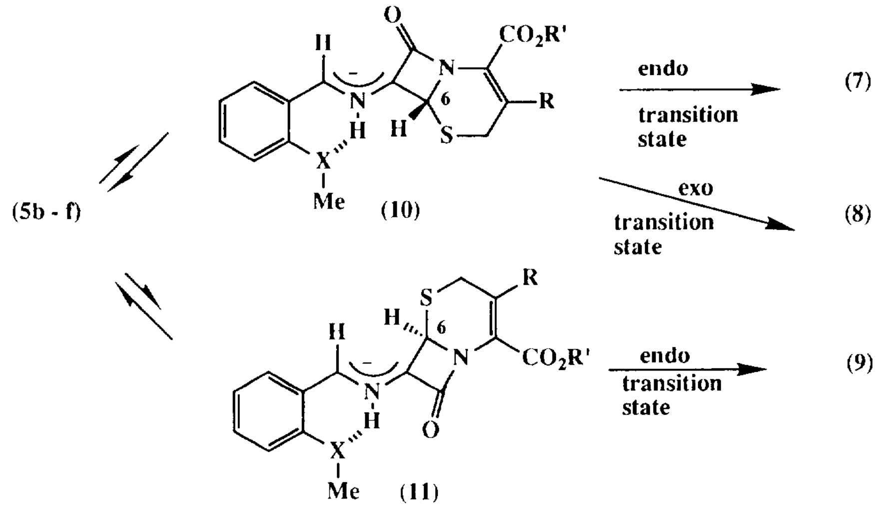
Table 2. Selected n.O.e. data ($CDCl_3$) for cycloadducts (7b) - (9b) and (7c) - (9c).

Cycloadduct	**Proton irradiated**	**n.O.e.(%)**			
		H_B	H_C	H_D	H_E
7b	H_B	-	22	4	-
	H_D	-	17	-	7
	H_E	-	-	6	-
8b[a]	H_B	-	-	-	-
	H_E	-	-	12	-
9b[b]	H_C	10	-	-	-
	H_E	-	-	12	-
7c	H_B	-	9	-	
	H_C	8	-	15	-
	H_E	-	-	6	-
8c[a]	H_E	-	-	11	-
9c[c]	H_E	-	-	12	-

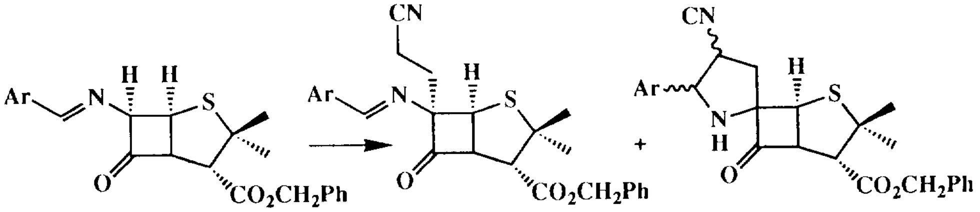
a. H_C and H_D obscured by other signals.
b. H_B and H_D observed by other signals.
c. H_C obscured by other signals.

Cycloadducts (7) and (8) are derived from the azomethine ylide (10) via endo- and exo-transition states respectively, whilst cycloadduct (9) is derived from azomethine ylide (11) via and endo-transition state (Scheme 3).

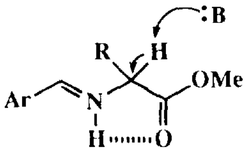
The cycloadditions are diastereofacially specific with addition occurring cis to the C(6)-H. This selectivity parallels that observed for alkylation[4] and radical coupling,[5] of azaallyl anions and radicals respectively, derived from imines of 6-aminopenicillins and 7-aminocephalosporins and is steric in origin. The conversion of (5) → (7) - (9) are the first examples of thermal prototropic azomethine ylide generation from β-lactam imines and provide interesting conformationally restricted analogues. An early study[6]of the Michael addition of imine (12) to acrylonitrile catalysed by diisopropyl ethylamine reports the formation (13)(18%) together with two stereoisomers of (14) (14 and 8%, stereochemistry undetermined). The mechanism of formation of (14) was not discussed. These two isomers could have arisen via a [$4\pi + 2\pi$]-azaallyl anion cycloaddition of the type pioneered by Kauffmann[7] and later further developed by Pearson[8] or may have arisen from base catalysed prototropy generating small amounts of NH azomethine ylides. Pyrrolidines can also be generated as stereoisomeric mixtures by a two step Michael addition-cyclisation sequence of azaallyl anions.[9]



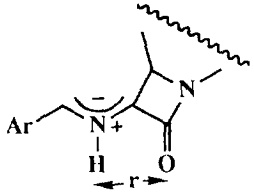
Scheme 3


(12) Ar = 4 - $O_2NC_6H_4$ (13) (14)

Azomethine Ylide Stereochemistry. Thermal 1,2-prototropic generation of azomethine ylides from arylidene imines of α-amino esters results in stereospecific formation of the E,E-azomethine ylides (Scheme 2). When these E,E-azomethine ylides are generated in the presence of a reactive dipolarophile (maleimides) they are rapidly trapped before any dipole stereomutation can occur. The results obtained with cephalosporin imines indicate that azomethine ylides (10) and (11) are formed concurrently and that the factors favouring the E,E-azomethine ylides (Scheme 2) are absent or of reduced importance in the cephalosporin imines. The major factor favouring the E,E-azomethine ylide as the kinetic isomer is the transition state stabilisation occurring from the hydrogen bonding (15) [Note that the 5-membered H-bond in (15) may involve a bridging water molecule giving a more stable 7-membered H-bond]. There are several factors which could contribute to a substantial reduction in the kinetic preference for the E,E-azomethine ylide. Thus (i) the β-lactam carbonyl oxygen atom is less basic than the carbonyl oxygen atom in conventional esters and amides due to the inhibition of normal amide resonance (ii) the H-bonding in the "expected" kinetic dipole (16) is not possible even with an additional water molecule due to the ca 90° bond angles in the β-lactam ring which substantially increases the distance r between the carbonyl oxygen atom and HN moiety. It is this latter factor, we believe, which is responsible for lack of selectivity for (16). Thus both (10) and (11) are generated concurrently with only a slight preference for (10) (Table 1).



(15)



(16)

Experimental. General experimental details were as previously described.[10]

Imines.

Imine (5b). 2-Methoxybenzaldehyde (1.36g, 0.01mol) and the cephalosporin (4a) (3.8g, 0.012mol, this material was judged to be approximately 80% pure) were mixed in anhydrous methylene chloride (100ml) and the solution stirred at room temperature for 2 dy. The solution was then washed with water, dried (Na_2SO_4) and concentrated to afford the crude imine as a thick red oil (2.2g, 50%) which could not be distilled. This material was used for cycloaddition reactions without further purification. δ 8.9(s, 1H, CH=N), 7.9-6.7(4H, ArH), 5.2(d, 1H, CH=NCH), 5.0(d, 1H, CHN), 4.8(d, 2H, CH_2OAc), 3.4(d, 2H, CH_2S), 2.0(s, 3H, Me) and 1.5(s, 9H, t-Bu); ν_{max} 1780, 1710-1740(br), 1630, 1600 and 1490 cm^{-1}

Imine (5c). 2-Methoxybenzaldehyde (1.36g, 0.01mol) and the cephalosporin (4b) (4.39g, 0.01 mol) were reacted over 18h as described above. Work up followed by crystallisation from ethyl acetate-hexane afforded the **product** (4.91g, 88%) as colourless plates, m.p. 78-80°C (Found: C, 64.15; H, 4.85; N, 7.4; S, 5.75. $C_{30}H_{27}N_3O_6S$ requires C, 64.6; H, 4.9; N, 7.55; S, 5.75%); m/z(%) 397(0.2), 184(25), 183(17), 168(35), 167(100), 105(52) and 44(79); ν_{max} ($CHBr_3$) 3520, 3410, 1775 (C=O, β-lactam), 1727 (C=O, ester) and 1638 (C=N) cm^{-1}; δ (DMSO) 8.91(s, 1H, HC=N), 7.83-6.93(m, 15H, ArH), 6.67(br s, 2H, NH_2), 5.76(d, 1H, H_D, J4Hz), 5.37(d, 1H, H_E, J4.2Hz), 4.80 and 4.11(2xd, 2H, CH_2O, J11.5Hz), 3.88(s, 3H, OMe), and 3.65 and 3.43(2xd, 2H, SCH_2, J16Hz).

Imine (5d). 2-Dimethylaminobenzaldehyde (1.49g, 0.01mol) and cephalosporin (4b) (4.39g, 0.01mol) were reacted over 18h as described above. The **product** (4.67g, 82%) crystallised from ethyl acetate-hexane as colourless needles, m.p. 38-41°C (Found: N, 9.55. $C_{31}H_{30}N_4O_5S$ requires N, 9.8%); m/z(%) 383(1), 184(37), 183(22), 167(50), 105(100), 77(32) and 44(88); ν_{max} ($CHBr_3$) 3500-3200 (NH_2), 1770 (C=O, β-lactam) and 1724 (C=O, ester) cm^{-1}; δ 8.83(s, 1H, HC=N), 7.82-6.80(m, 15H, ArH), 6.62(br s, 2H, NH_2), 5.81(d, 1H, H_D, J3Hz), 5.42(d, 1H, H_E, J4Hz), 4.84 and 4.62(2xd, 2H, CH_2O, J12.7Hz), 3.61 and 3.50(2xd, 2H, SCH_2, J10Hz) and 3.03(s, 6H, NMe_2).

Imine (5e). 2-Methoxybenzaldehyde (2.72g, 0.02mol) and cephalosporin (4c) (6.99g, 0.02mol) were reacted over 18h as described above. Work up followed by crystallisation from ethyl acetate-hexane afforded the **product** (7.9g, 85%) as fine colourless needles, m.p. 210-212°C (decomp). (Found: C, 58.65; H, 4.95; N, 8.55. $C_{23}H_{21}N_3O_6S$ requires C, 59.1; H, 4.5; N, 9.0%); m/z(%) 467(M^+,5), 293(21), 192(31), 177(22), 112(100) and 77(15); ν_{max} ($CHBr_3$) 1770(C=O, β-lactam), 1723 (C=O, ester), 1688 (C=N) and 1520 (NO_2) cm^{-1}; δ (DMSO) 8.90(s, 1H, HC=N), 8.27-7.02(m, 8H, ArH), 5.68(d, 1H, H_D, J4Hz), 5.40(s, 2H, $ArCH_2$), 5.31(d, 1H, H_E, J5Hz), 3.87(s, 3H, OMe), 3.67 and 3.39(2xd, 2H, SCH_2, J16Hz) and 2.06(s, 3H, Me).

Imine (5f). 2-Dimethylaminobenzaldehyde (2.98g, 0.02mol) and cephalosporin (4c) (6.99g, 0.02mol) were reacted over 20h as described above. The resulting yellow solid (8.93g, 93%) was crystallised from ethyl acetate-hexane to afford the **product** as pale yellow plates, m.p. 175-177°C (decomp) (Found: N, 11.75. $C_{24}H_{24}N_4O_5S$ requires N, 11.7%); m/z(%) 480(M^+,0.3), 260(30), 156(19), 153(16), 134(54), 132(100), 124(43) and 120(32); ν_{max} ($CHBr_3$) 3500-3200 (NH_2), 1770 (C=O, β-lactam) and 1724 (C=O, ester) cm.$^{-1}$; δ 8.93(s, 1H, HC=N), 8.25-7.0(m, 8H, ArH) 5.45-5.25(m, 3H, H_D and $ArCH_2$), 4.75(d, 1H, H_E, J5Hz), 3.57 and 3.25(d, 1H, SCH_2, J15Hz), 2.70(s, 6H, NMe_2) and 2.17(s, 3H, Me).

Cephalosporin Imine Cycloadducts.

Cycloadduct (7a). The crude imine (5b) (0.446g, 1mmol) and N-phenylmaleimide (0.173g, 1mmol) were dissolved in dry toluene and boiled under reflux for 4h. Removal of the solvent afforded a thick oil which was purified by preparative t.l.c. ($SiO_2/CHCl_3$). The **product** (0.28g, 40%) was obtained as pale yellow prisms from ether - 40-60° petroleum ether, m.p. 135-138°C. (Found: N, 6.55. $C_{32}H_{34}N_3O_8S$ requires N, 6.8%); δ 7.12(m, ArH, 9H), 5.91(s, 1H, H_E), 5.6(d, 1H. H_B, J8.8Hz), 5.0, 4.78(2xd, 2x1H, CH_2OAc, J13Hz), 3.97 (t, 1H, H_C, J7.9Hz), 3.88(s, 3H, OMe), 3.74(d, 1H, H_D, J7.85Hz), 3.61, 3.34(2xd, 2H, CH_2S, J18.4Hz), 2.10(s, 3H, Me), 1.58(s, 9H, tBu) and 2.8 (br, s, 1H, NH); ν_{max} 3400, 1760, 1500 and 1400 cm.$^{-1}$; m/z(%) 619(M^+,1), 475(1), 430(1), 365(1.5), 334(1), 223(2), 216(3), 56(57), and 44(81).

Cycloadducts (7b) - (9b). Imine (5c) (2.78g, 5mmol) and N-phenylmaleimide (0.86g, 5mmol) were heated in boiling toluene (100ml) for 36h. The solvent was removed under reduced pressure to furnish a yellow solid (87%) whose ^1H n.m.r. spectrum showed it to comprise a 2:1:2 mixture of (7b), (8b) and (9b). The isomers were separated by flash chromatography using 5:1 v/v toluene - ethyl acetate as elutant. [Found (mixed isomers): C, 65.45; H, 5.05; N, 7.85; S, 3.9. $C_{40}H_{34}N_4O_8S$ requires C, 65.75; H, 4.7, N, 7.65; S, 4.4%].

7b. Obtained as pale yellow plates, m.p. 109-111°C (EtOAc-toluene); m/z(%) 365(5), 168(57), 167(100), 165(35) and 44(28); ν_{max} ($CHBr_3$) 3525/3415/3330 (NH/NH_2), 2840 (OMe), 1773(C=O, β-lactam) and 1718 (C=O, ester + maleimide) cm.$^{-1}$; δ (C_6D_6) 7.8-7.5(m, 20H, ArH and Ar_2CH), 5.93(s, 1H, H_E), 5.44(d, 1H, H_B, J8Hz), 4.89 and 4.60 (2xd, 2H, CH_2O J13.5Hz), 4.06(br s, 2H, NH_2), 3.6(t, 1H, H_C, J7Hz), 3.45(s, 3H, OMe), 2.94(d, 1H, HCHS, J14Hz), 2.84(d, 1H, H_D, J7Hz) and 2.36(br s, 1H, NH).

8b. Obtained as pale yellow plates, m.p. 138-141°C (EtOAc-toluene); m/z(%) 564(2), 168(51), 167(100), 165(38), 105(18) and 44(20); ν_{max} ($CHBr_3$), 3525/3410/3325 (NH/NH_2), 2825, 1789 (C=O, β-lactam), 1720 (C=O, carbamate) and 1577 (C=C) cm.$^{-1}$; δ (C_6D_6) 7.85-6.56 (m, 20H, ArH and Ar_2CH), 5.19(d, 1H, NH or H_B, J11Hz), 4.76(d, 1H, NH or H_B, J11Hz), 4.91 and 4.63 (2xd, 2H, CH_2O, J10Hz), 4.23(s, 1H, H_E), 4.00(br s, 2H, NH_2), 3.41(s, 3H, OMe), and 3.39-3.25(m, 4H, H_C, H_D and SCH_2).

9b. Obtained as colourless plates, m.p. 126-128°C (EtOAc-toluene); m/z(%) 320(14), 168(57), 167(100), 165(34), 119(26) and 91(38); ν_{max} ($CHBr_3$) 3530/3420/3320 (NH/NH_2), 1780 (C=O, β-lactam), 1738 (C=O, ester) and 1720 (C=O, maleimide) cm.$^{-1}$; δ (C_6D_6) 7.7-6.5(m, 20H, ArH and Ar_2CH), 4.71 and 4.39(2xd, 2H, CH_2O, J12Hz), 4.88(s, 1H, H_E), 4.48(d, 1H, H_B, J4Hz), 4.02(br s, 2H, NH_2), 3.42(s/d, 4H, OMe and H_D), 3.29(t, 1H, H_C, J6Hz) and 3.1-3.0(m, 3H, NH and SCH2).

Cycloadducts (7c-9c). Imine (5d) (3.2g, 5.4mmol) and N-phenylmaleimide (0.94g, 5.4mmol) were heated in boiling toluene (100ml) for 12h. The solution darkened considerably on heating and removal of the solvent under reduced pressure yielded a brown solid (100%) whose ^{1}H n.m.r. spectrum showed it to comprise a 3:1:2 mixture of (7c), (8c) and 9c. The isomers were separated (with dificulty) by flash chromatography using gradient elution: fractions 1-40 5:2 v/v toluene-ethyl acetate; fractions 41-62, 4:2 v/v toluene-ethyl acetate: and fractions 63-70, 1:2 v/v toluene-ethyl acetate with 15ml fractions. [Found (mixed isomers): C, 65.45; H, 5.45; N, 8.2. $C_{41}H_{37}N_5O_7.SC_4H_8O_2$ requires C, 64.95; H, 5.45; N, 8.4%].

7c. Obtained as yellow plates, m.p. 113-115°C (EtOAc-toluene); m/z(%) 346(6), 168(65), 167(100), 165(37), 105(31) and 44(45); ν_{max} ($CHBr_3$) 3530/3420/3330 (NH/NH_2), 2780, 1770 (C=O, β-lactam) and 1715 (C=O, ester + maleimide) cm.$^{-1}$; δ (C_6D_6) 7.65-6.81 (m, 20H, ArH and Ar_2CH), 5.95 (s, 1H, H_E), 5.65(d, 1H, H_B, J8Hz), 4.84 and 4.55(2xd, 2H, CH_2O, J12.5Hz), 3.68(br s, 2H, NH_2), 3.61(t, 1H, H_C, J7.5Hz), 2.90(d, 1H, HC$\underline{H}$S, J10Hz), 2.85(d, 1H, H_D, J7.5Hz), 2.76(d, 1H, $\underline{H}$CHS, J10Hz), 2.62(s, 6H, NMe_2) and 2.38(br s, 1H, NH).

8c. Obtained as colourless plates, m.p. 108-110°C (EtOAc-toluene); m/z(%) 184(8), 168(64), 167(100), 91(17) and 44(43); ν_{max} ($CHBr_3$) 3530/3420/3340 (NH/NH_2), 2780, 1779(C=O, β-lactam), 1719 (C=O, esters + maleimide) cm.$^{-1}$; δ (C_6D_6) 7.85-6.8(m, 20H, ArH and Ar_2CH), 5.04(br s, 1H, H_B), 5.18 and 4.56(2xd, 2H, CH_2O, J11Hz), 4.15(s, 1H, H_E), 3.78(br s, 2H, NH_2), 3.36(d, 1H, H_C, J6Hz), 3.24(d, 1H, HC$\underline{H}$S, J8Hz), 3.19(d, 1H, H_D, J6Hz), 2.9(br s, 1H, NH), 2.85(d, 1H, $\underline{H}$CHS, J8Hz), and 2.56(s, 6H, NMe_2).

9c. Obtained as colourless rods, m.p. 122-124°C (EtOAc-toluene); m/z(%)347(5), 346(7), 168(50), 167(100), 165(40), 105(23) and 44(38); ν_{max} ($CHBr_3$) 3535/3420/3330 (NH/NH_2), 2780, 1789(C=O, β-lactam) and 1720(C=O, esters + maleimide) cm.$^{-1}$; δ (C_6D_6) 7.65-6.8(m, 20H, ArH and Ar_2CH), 4.86(s, 1H, H_E), 4.73(d, 1H, H_B, J6Hz), 4.70 and 4.38(d, 1H, CH_2O, J12Hz), 4.40(br s, 2H, NH_2), 3.28(t, 1H, H_C, J6Hz), 3.04(d, 1H, H_D, J7Hz), 2.98(br m, 3H, NH and SCH_2), and 2.57(s, 6H, NMe_2).

Cycloadducts (7d) and (9d). Imine (5e) (3.64g, 7.8mmol) and N-phenylmaleimide (1.35g, 7.8mmol) were heated in boiling toluene (130ml) for 22h. The solvent was removed under reduced pressure to yield a yellow solid (100%) whose ^{1}H n.m.r. spectrum showed it to comprise a 2:1 mixture of (7d) and (9d). The isomers were separated by flash chromatography eluting with 5:1 v/v toluene-ethyl acetate. [Found (mixed isomers): C, 62.0; H, 4.75; N, 8.85; S, 4.5. $C_{33}H_{28}N_4O_8S$ requires C, 61.85; H, 4.4; N, 8.75; S, 5.0%].

7d. Obtained as colourless rods, m.p. 112-115°C (EtOAc-toluene); m/z(%) 640(M^+,1.4), 292(46), 156(100), 139(52), 112(63) and 77(71); ν_{max} ($CHBr_3$) 3325 (NH), 1760 (C=O, β-lactam) and 1712 (C=O ester + maleimide) cm.$^{-1}$; δ (C_6D_6) 7.8-6.5(m, 13H, ArH), 5.99(s, 1H, H_E), 5.49(d, 1H, H_B, J8Hz), 5.05 and 4.95(2xd, 2H, $ArCH_2$, J11Hz), 3.62(t, 1H, H_C, J8Hz), 3.42(s, 3H, OMe), 2.97(d, 1H, H_D, J8Hz), 2.71 and 2.30(2xd, 2H, SCH_2, J14Hz), 2.48(br s, 1H, NH, exchanges with D_2O) and 1.70(s, 3H, Me).

9d. Obtained as colourless rods, m.p. 130-132°C (EtOAc-toluene); m/z(%) 640(M^+,1.8), 461(13), 320(30), 161(32), 112(100) and 106(57); ν_{max} ($CHBr_3$) 3335 (NH), 1780 (C=O, β-lactam), and 1718 (C=O ester + maleimide) cm.$^{-1}$; δ(C_6D_6) 8.5-6.5(m, 13H ArH), 5.50 and 5.23(2xd, 2H, $ArCH_2$, J10Hz), 4.80(d, 1H, H_B, J7Hz), 4.31(s, 1H, H_E), 3.42(s, 3H, OMe), 3.4(t, 1H, H_C, J7Hz), 3.14(d, 1H, H_D, J7Hz), 3.02(br s, 1H, NH, exchanges with D_2O), 2.78 and 2.43(2xd, 2H, SCH_2, J16Hz) and 1.92(s, 3H, Me).

Cycloadducts (7e) and (9e). Imine (5f) (3.0g, 6.25mmol) and N-phenylmaleimide (1.1g, 6.25mmol) were heated in boiling toluene (100ml) for 12h. The solvent was removed under reduced pressure to yield a yellow solid (93%) whose ^1H n.m.r. spectrum showed it to comprise a 2:1 mixture of (7e) and (9e). The isomers were separated using flash chromatography eluting with 5:1 v/v toluene-ethyl acetate. [Found (mixed isomers): C, 62.85; H, 5.1; N, 9.5; S, 5.15. $C_{31}H_{31}N_5O_7S$ requires C, 62.45; H, 4.8; N, 10.7; S, 4.9%].

7e. Obtained as colourless plates, m.p. 112-114°C (EtOAc-toluene); m/z(%) 653(M^+,2), 378(16), 333(43), 156(41), 136(31), and 132(100); ν_{max} ($CHBr_3$) 3335(NH), 1762(C=O, β-lactam), 1712(C=O, ester + maleimide) and 1521(NO_2) cm.$^{-1}$; δ (C_6D_6) 7.82-6.8(m, 13H, ArH), 6.04(s, 1H, H_E), 5.74(d, 1H, H_B, J10Hz), 5.07 and 4.95(2xd, 2H, $ArCH_2$, J12Hz), 3.63(t, 1H, H_C, J9Hz), 3.02(d, 1H, H_D, J11Hz), 2.59(s, 6H, NMe_2), 2.53(d, 1H, HC$\underline{H}$S, J12Hz), 2.53(br s, 1H, NH), 2.26(d, 1H, $\underline{H}$CHS, J13Hz) and 1.71(s, 3H, Me).

9e. Obtained as colourless plates, m.p. 108-110°C (EtOAc-toluene); m/z(%) 441(12), 333(50), 169(20), 144(37), 91(75) and 44(100); ν_{max} ($CHBr_3$) 3340(NH), 1782(C=O, β-lactam), 1719(C=O, ester + maleimide) and 1520(NO_2) cm.$^{-1}$; δ (C_6D_6) 8.04-6.7(m, 13H, ArH), 5.20(d, 1H, one of $ArCH_2$), 5.06(d, 1H, H_B, J8Hz), 4.85(d, 1H, one of $ArCH_2$, J10Hz), 4.25(s, 1H, H_E), 3.35(t, 1H, H_C, J7Hz), 3.10(d, 1H, H_D, J8Hz), 2.90(br s, 1H, NH), 2.74(d, 1H, HC$\underline{H}$S, J17Hz), 2.57(s, 6H, NMe), 2.37(d, 1H, $\underline{H}$CHS, J17Hz) and 1.88(s, 3H,H_C).

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