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Synthesis of α-Diazo-β-Oxo Sulfoxides

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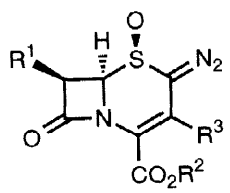
Abstract: Diazo transfer adjacent to sulfoxides to form stable α-diazo-β-oxo sulfoxides has been achieved in cyclic systems.

The synthetic versatility of α-diazocarbonyl derivatives has been widely exploited in recent years;[1] the analogous α-diazosulfones and α-diazophosphonates have also been explored.[2] However, reports of α-diazosulfoxides have been sparse despite their potential application in stereoselective synthesis. While diazo transfer adjacent to sulfoxides has been achieved in cephalosporin derivatives,[3] and there have been reports of formation of unstable diazosulfoxides as intermediates,[4] for example by treatment of sulfinyl chlorides with diazomethane,[5] synthesis of simple stable isolable diazosulfoxides has not been reported to the best of our knowledge. In particular it has been demonstrated[6] that diazo transfer to β-keto sulfoxides using tosyl azide under conditions which successfully produce α-diazo-β-keto sulfones does not lead to stable α-diazo-β-keto sulfoxides. We wish to report successful diazo transfer adjacent to sulfoxides in lactone derivatives leading to stable isolable α-diazo-β-oxo sulfoxides.



Examination of the only reported stable diazosulfoxides, the cephalosporin derivatives reported by Campbell and Rosati and co-workers,[3] led us to two possible explanations for their stability; either vinylogous conjugation to the ester conferred additional stability on the diazo derivatives (Hodson and Holt had attempted diazo transfer to α-sulfinyl ketones not α-sulfinyl ester derivatives), or the cyclic system stabilised the compounds, possibly by reduced conformational mobility thereby hindering the decomposition pathway *via* oxygen transfer.[6] To test these proposals diazo transfer to simple acyclic α-sulfinyl esters using tosyl azide was attempted and, while the starting materials were consumed, isolation of diazosulfoxide derivatives did not prove possible. Accordingly, lactones bearing α-sulfinyl substituents were prepared to examine the effect of restricting the conformational mobility in a cyclic framework. Both mono- and more rigid bicyclic systems were selected for investigation.

The *cis* and *trans* fused bicyclic sulfide lactones **1** and **4** were oxidised to the analogous sulfoxides **2**, **5** and **6** using oxone® or mCPBA.[7-9] While the *cis* fused sulfoxide **2** was formed as a single diastereomer, a mixture of diastereomeric sulfoxides **5** and **6** was obtained. Similarly, with the monocyclic lactones oxidation of the *cis* disubstituted sulfide **9** was stereospecific, while a mixture of diastereomers was formed on oxidation of the *trans* disubstituted analogue **12**. With the sulfoxides **2**, **5**, **6**, **10** and **13** in hand, examination of diazo transfer was undertaken; due to the varying structural properties of these sulfoxides investigation of the influence of stereoelectronic effects on the stability of any resulting diazosulfoxides was envisaged.

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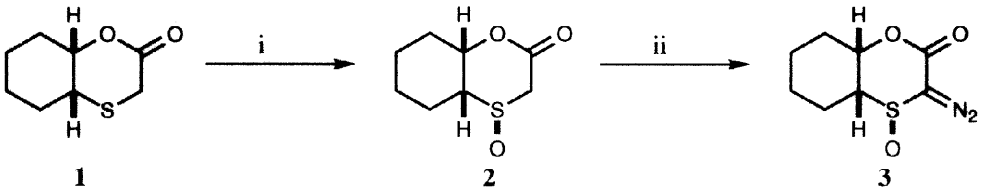
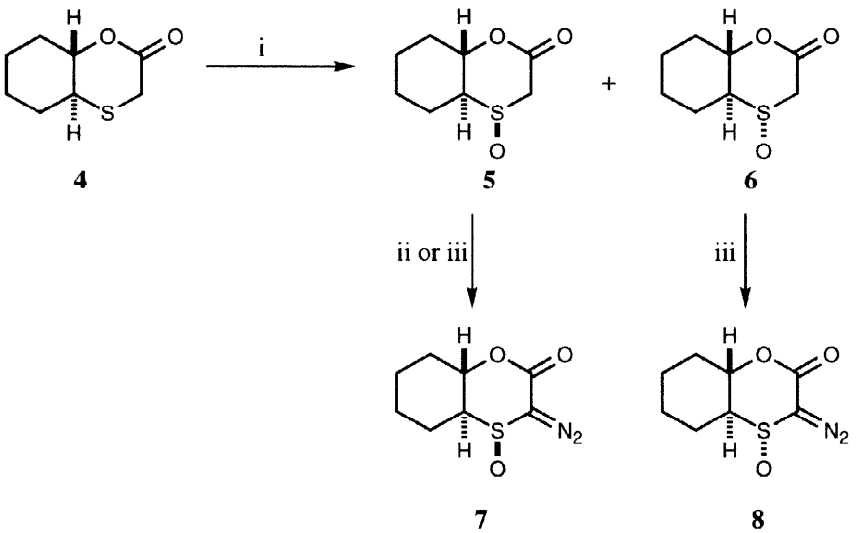


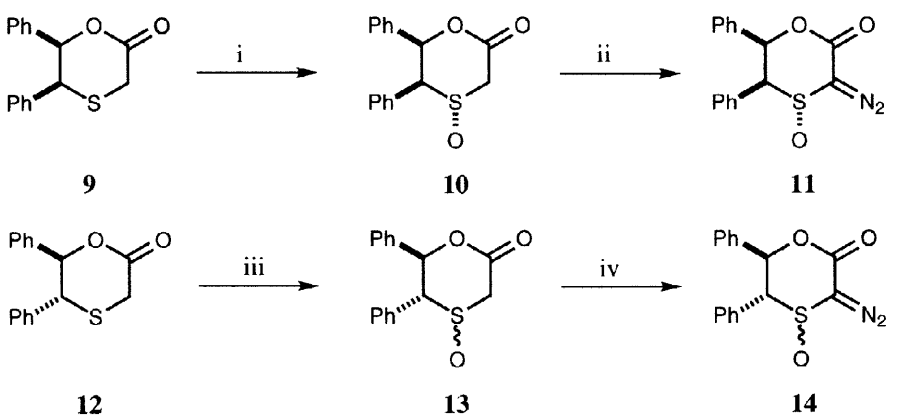
i, oxone®, aq. acetone[8] ; ii, dodecylbenzenesulfonyl azides, Et_3N, CH_2Cl_2, 40%.

Scheme 1



i, mCPBA, CH_2Cl_2, 44%, equimolar mixture of **5** and **6** ; ii, TsN_3, Et_3N, CH_2Cl_2, **7** 63%; iii, dodecylbenzenesulfonyl azides, Et_3N, CH_2Cl_2, **7** 40%; **8** 17%

Scheme 2



i, mCPBA, CH_2Cl_2, 75% ; ii, TsN_3, K_2CO_3, CH_3CN, 43%; iii, oxone®, aq. acetone, 53% ; iv, dodecylbenzenesulfonyl azides, K_2CO_3, CH_3CN, 10% . **13** and **14** were isolated as diastereomeric mixtures.

Scheme 3

Gratifyingly, diazo transfer to the bicyclic sulfoxide **2** with dodecylbenzenesulfonyl azides[10] proved successful with the diazosulfoxide **3** isolated as a yellow crystalline solid in modest yield (Scheme 1).[7] Unambiguous structural confirmation by X-ray crystallography[12] proved possible, indicating the relative stability of the diazo derivative **3**. There are two molecules in the asymmetric unit which differ significantly from one another as can be evidenced by an examination of the torsion angles for molecules A and B; C41x-S4x-C3x-C2x 29.2(5)° and 16.5(5)° and O4x-S4x-C3x-C2x, -78.6(5)° and -91.9(5)° where x = A and B respectively. The six membered rings in both molecules (A) and (B) have an envelope {S4, C3, C2, O1, C81, C41} and chair conformation {C41, C5, C6, C7, C8, C81} respectively.

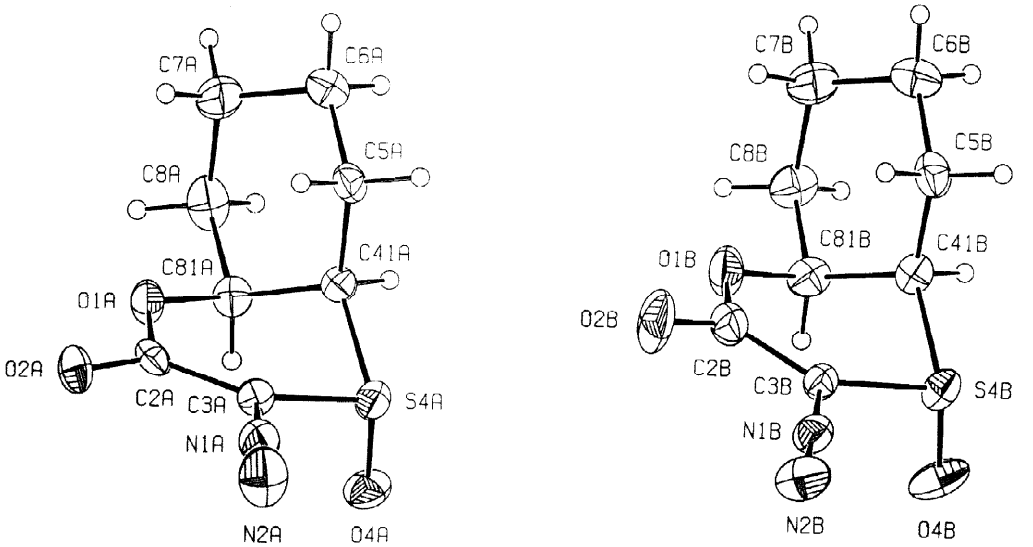


Figure 1: A view of molecules A and B in **3** with all non-hydrogen atoms drawn with thermal ellipsoids at the 30% probability level. The hydrogen atoms are drawn as spheres of an arbitrary size for clarity.

Encouraged by this result, diazo transfer to the remaining sulfoxides was examined using a range of diazo transfer agents[10] - tosyl, mesyl and dodecylbenzenesulfonyl azides - and conditions *e.g.* potassium carbonate and triethylamine were employed as bases, and ethanol, dichloromethane and acetonitrile as solvents. As illustrated in Scheme 2, diazo transfer to the *trans* fused sulfoxides **5** and **6** provided the analogous diazosulfoxides **7** and **8**.[7,11] Formation of the diazo derivative of the axial sulfoxide **7** was in general more efficient, and indeed **7** appears to be more stable than the equatorial sulfoxide **8**, *e.g.* recoveries of **7** following chromatography are higher than those of **8**, indicating that the relative stereochemistry of the diazo and sulfoxide groups has a significant effect on their stability. Diazo transfer to the mixture of diastereomeric sulfoxides **5** and **6** can also be effected producing mixed diazo derivatives **7** and **8**; yields of the diazo derivatives **7** and **8** varied somewhat from different experiments. Diazo transfer to the monocyclic sulfoxides also proved possible[7] : **11** was isolated in 43% yield as a yellow crystalline solid by treatment of the sulfoxide **10** with tosyl azide and potassium carbonate in acetonitrile, while **14** was isolated as a mixture of diastereomers, albeit in very low yield, using dodecylbenzenesulfonyl azides as the transfer agent.

These results indicate that stable isolable α-diazo-β-oxo sulfoxides can be synthesised by diazo transfer to sulfinyl lactones, while the analogous acyclic ester derivatives are not sufficiently stable to isolate. The stability of the diazosulfoxides appears to be influenced by stereochemical features, in particular the relative orientation of the sulfoxide and diazo groups. Further investigation of the structural features which allow isolation of diazosulfoxide derivatives is underway.

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6. Hodson, D.; Holt, G. *J. Chem. Soc. (C)*, 1968, 1602. Decomposition of α-diazo-β-keto sulfoxides by oxygen transfer from sulfur to carbon to form the α-keto acid thiol esters was proposed.
7. Satisfactory spectroscopic and analytical / HRMS data was obtained for all new compounds.
8. Sulfoxide **2** was synthesised by oxidation of a mixture of the *cis* and *trans* sulfides **1** and **4** with oxone®, followed by chromatographic separation of the resulting sulfoxides **2**, **5** and **6**. Sulfoxides **5** and **6** were prepared by oxidation (mCPBA) of the *trans* sulfide **4** followed by chromatographic separation. Full details of the investigation of the oxidation of the sulfides **1**, **4**, **9** and **12** will be reported elsewhere.
9. The sulfides were prepared following standard procedures: for **1** and **4** see Koskimies, J.K. *Acta Chem. Scand. B*, 1984, **3**, 101, for **9** and **12** see Garcia Ruano, J.L.; Martinez, M.C.; Rodriguez, J.H.; Olefirowicz, E.M.; Eliel, E.L. *J. Org. Chem.*, 1992, **57**, 4215.
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11. *Typical procedure:* Triethylamine (0.22 ml, 1.6 mmol) and tosyl azide (0.31 g, 1.6 mmol) were added to a solution of sulfoxide **5** (0.30 g, 1.6 mmol) in acetonitrile (31 ml) while stirring at 0°C under nitrogen. Stirring was continued for 2 h at 0°C, then the mixture was concentrated at reduced pressure. Dichloromethane (20 ml) was added and the solution was washed with water (2 x 10 ml), dried and concentrated. Chromatography on silica gel using Et_2O as eluent gave the diazosulfoxide **7** as a yellow crystalline solid (0.22 g, 63%); mp 104-106°C (recryst. from Et_2O); (Found: C, 45.03; H, 4.87; N, 13.17; S, 15.21. $C_8H_{10}N_2O_3S$ requires C, 44.85; H, 4.70; N, 13.08; S, 14.96%). υ_{max} (KBr) 2129, 1695, 1256, 1055 cm^{-1}; δ_H ($CDCl_3$) 1.20-2.18 (7H, m), 2.28-2.50 (1H, m), 2.71-2.93 (1H, ddd, *J* 5, 10, 11, CHS), 4.79-5.00 (1H, ddd, *J* 5, 11, 11, CHO); δ_C ($CDCl_3$) 22.85, 24.23, 24.82, 31.86 (CH_2 x 4), 57.91 (CHS), 71.81 (CHO), 158.68 (CO); m/z 214 (M^+, 19%), 186 ($M^+ - N_2$, 2%), 138 ($M^+ - N_2$ - SO, 8%), 41 (100%); HRMS found 214.0409, $C_8H_{10}N_2O_3S$ requires 214.0412.
12. Crystals of **3** are monoclinic, space group $P2_1/n$, with eight molecules of $C_8H_{10}N_2O_3S$ in a unit cell of dimensions, a = 10.3464(12), b = 9.2456(8), c = 20.152(5) Å, β = 95.565(12)°, V = 1918.6(5) $Å^3$, F(000) 896, μ(Mo–Kα) = 0.32 mm^{-1}, $R(F_o)$ = 0.063 for 1506 observed reflections with $I > 2\sigma(I)$, $wR_2(F^2)$ = 0.136 for all 3395 unique reflections. Data in the θ range 2 -25° were collected on a Nonius CAD4 diffractometer using monochromatic Mo–Kα radiation and corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares methods using SHELXL-93 and all F^2 data. All non-H atoms were allowed anisotropic motion. All H atoms were visible in difference maps and allowed for as riding atoms. Full details of molecular dimensions, fractional coordinates, thermal parameters and structure factor listing are available from the authors and have been deposited with the Cambridge Crystallographic Data Centre.