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Sulfur oxidation in supercritical carbon dioxide: dramatic pressure dependant enhancement of diastereoselectivity for sulfoxidation of cysteine derivatives

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The diastereoselective sulfoxidation of chiral sulfides derived from methionine and cysteine has been investigated in conventional solvents and in supercritical carbon dioxide ($scCO_2$); use of *tert*-butyl hydroperoxide and Amberlyst™ 15 ion exchange resin is particularly effective for sulfoxide formation, and with cysteine derivatives shows a dramatic pressure-dependant increase in diastereoselectivity (up to > 95% de) in $scCO_2$ compared with conventional solvents, where no diastereoselectivity is observed; the stereochemical configuration of the major product of the oxidation of Cbz-CysSMe-OMe has been confirmed as *anti* using X-ray crystallography.

The development of new methods for addressing environmental problems associated with organic synthetic procedures continues to be one of the major challenges facing synthetic organic chemists, and will remain so for the foreseeable future. Supercritical carbon dioxide ($scCO_2$) is currently being investigated as an environmentally friendly solvent by a number of research groups, and has been demonstrated as being an effective medium for a limited number of organic transformations (*vide infra*). Supercritical fluids are substances above their critical temperatures and pressures, whose properties are intermediate between those of gases and liquids, and which can be controlled by both temperature and pressure.[1] Pure carbon dioxide has a critical temperature of 31 °C and critical pressure of 74 atmospheres, both of which are readily achievable using commercially available equipment. Advantages include: low toxicity, ready availability, ease of removal and disposal and/or recycling. Other advantages which are particularly relevant for carrying out reactions in $scCO_2$ are: fine control of solvent properties by changes in temperature and pressure; the ability to homogenise reaction substrates, electrically neutral metal complexes and gases like oxygen and hydrogen; enhanced diffusion rates; and potential for product processing.[2]

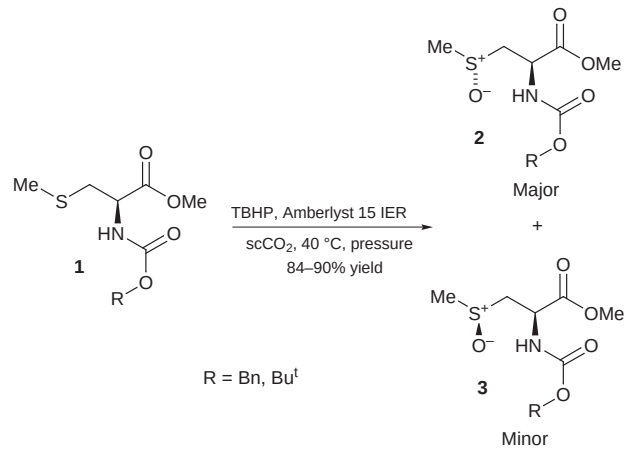
Supercritical fluids have also been shown to be excellent media for a number of reactions.[3] In our laboratories, we have recently shown that it is possible to fine tune the *endo*/*exo* selectivity of the Diels–Alder reaction between cyclopentadiene and methyl acrylate by controlling the density of the reaction medium by varying the temperature and pressure of the $scCO_2$.[4] However, in this case, the changes observed were modest, and gave no real preparative advantage. We now report some results which clearly show definite advantages of carrying out reactions in $scCO_2$ in addition to the environmental and processing reasons stated above.

We have recently developed a new method for the oxidation of simple sulfides to sulfoxides in conventional solvents and $scCO_2$[5] using *tert*-butyl hydroperoxide (TBHP) as oxidant with Amberlyst 15 ion exchange resin catalyst (Scheme 1).[6] High yields and excellent selectivity for sulfoxide formation are obtained, even with an excess of oxidant, and this method provides an attractive alternative to procedures currently available for use under conventional conditions as well as in $scCO_2$.[7]

We now report the results of studies on the oxidation of more complex substrates, which have potential for diastereoselective oxidation, to see whether using $scCO_2$ as solvent has any particular advantages in addition to the environmental and product processing benefits mentioned above.

Recent studies on the sulfoxidation of cysteine derivatives have shown that, although in general they may be expected to give diastereoselective oxidation, this can in practice be difficult to achieve without significant substituent modification, requiring preparation of the MEM esters of *S*-benzyl (or larger) derivatives for good results, with no significant selectivity being observed with the methyl esters[8] or reported for *S*-methyl derivatives.[8,9] With this in mind, we chose to investigate the oxidation of a range of conventionally protected cysteine and methionine derivatives, firstly as more complex examples of substrates for oxidation, but also to determine if carrying out the reaction in $scCO_2$ had any significant effect on the diastereoselectivity of the reaction.

Initial studies using our TBHP/Amberlyst reagent system showed that oxidation of Cbz-methionine methyl ester proceeded efficiently in either toluene or $scCO_2$, but with no diastereoselectivity as determined by ^1H NMR analysis, presumably due to the remote nature of the existing chiral centre and the sulfur atom in the substrate.‡ A potentially more promising substrate, CBz methyl cysteine methyl ester, was oxidised in high yield, but also gave no appreciable diastereoselectivity in toluene or CH_2Cl_2 in accord with previous literature results.[8] On attempting the reaction in $scCO_2$ (200 bar, 40 °C), high yields were obtained (Scheme 1), but also significant diastereoselectivity (Fig. 1). As from our previous work on the Diels–Alder reaction,[4] we were aware that the density of the medium, controlled by varying either temperature or pressure, can have an effect on reaction selectivity, and it may be possible to fine tune the reaction conditions to optimise such selectivity. In this case, by varying the pressure at a constant temperature of 40 °C, we were able to optimise the diastereoselectivity of the reaction to > 95% de (Fig. 1). This is a particularly dramatic enhancement considering that no selectivity was observed under conventional reaction conditions.



Scheme 1

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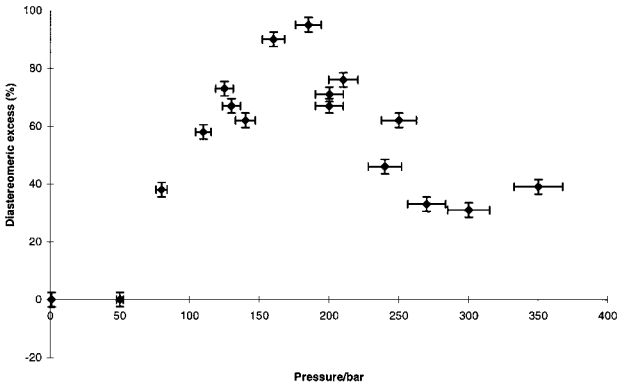

Fig. 1 Variation of diastereoselectivity for oxidation of Cbz-CysSMe-OMe.

Similar effects were also observed in the case of Boc methyl cysteine methyl ester, although with less impressive selectivities (up to 31% de). Note that in both cases, at a constant temperature, the selectivity rises to a maximum at around 180 bar then falls off as pressure is increased further. The relative stereochemistry of the major isomer for the oxidation of Cbz-CysSMe-OMe has been confirmed as the *anti* isomer **2** (R = Bn) by X-ray crystallography§ (Fig. 2).

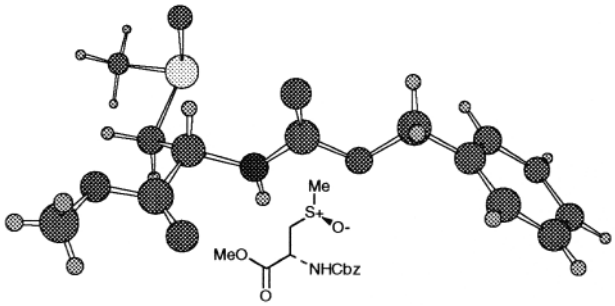

Fig. 2 X-Ray crystal structure of major diastereomer from oxidation of Cbz-CysSMe-OMe in $scCO_2$.

We had previously rationalised this kind of fine-tuning of reaction conditions by the adjustment of the nearest neighbour solvent molecules with respect to the transition states.[4] This would be particularly important for processes with highly ordered transition states such as Diels–Alder reactions. In the case of this work, the situation is less clear and factors such as hydrogen bonding and/or conformation[10] may also play an important role. The fact that essentially no diastereoselectivity is observed in conventional solvents, however, strongly suggests that the nature of the reaction medium is playing a crucial role in inducing the stereoselective reaction.

Whilst the actual reasons for this effect may be the subject of some debate, there is no doubt that it is potentially very important in the area of stereoselective synthesis, particularly if it can be shown to be applicable to other types of reaction, with similar levels of amplification of stereoselectivity. We are currently investigating both the causes and generality of this effect, and the results of these studies will be reported in due course.

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Notes and references

‡ Experimental procedure: As with all reactions under high pressure, adequate safety precautions must be taken. For carrying out reactions in $scCO_2$, a stainless steel cyclindrical vessel was used with a volume of 20 ml. The seal between vessel and lid is maintained by a Viton high pressure 'O'-ring. Stirring is accomplished using a remote magnetic stirrer. A Swagelok pressure relief valve with a release pressure of 6000 psi is employed as a safety precaution. The pressure is measured utilising a Farnells Electronics™ pressure transducer (0–5000 psi). Reagents can be injected into the system *via* a Rheodyne injector valve. The system is pressurised using a Varian™ 8500 syringe pump, which draws from a BOC 100.00 CP grade CO_2 cylinder (*ca*. 50 bar head pressure), and has a cooled pump head. Temperature control is achieved by locating the vessel in a modified GC oven. Diastereomeric ratios were determined by ^{1}H NMR analysis to ±2.5% de. Errors along the pressure axis were set at 5% to allow for inaccuracies in other variables such as temperature, reagent quantities and volumes, and pressure.

Amberlyst™ 15 resin (0.5 g), the sulfide (up to 4.0 mmol) and a magnetic stirrer were placed in the reaction vessel described above, at room temperature. The vessel was sealed and pressurised to *ca*. 50 bar with CO_2 and the oven temperature maintained at 40 °C. Agitation was started at a rate of 600 rpm. The pressure was increased to *ca*. 100–120 bar, at which point the TBHP (1.1 equiv. of *ca*. 4.0 M solution in toluene) was injected and the pressure further increased to the desired reading. Agitation was maintained at this temperature and pressure for 24 h. On completion, the pressure was released slowly *via* a vent into a CH_2Cl_2 trap (20 ml). When atmospheric pressure was reached, the reaction vessel was washed through with CH_2Cl_2 (2 × 1 ml, at 50 bar). The vessel was opened and the Amberlyst™ 15 washed with MeOH (2 × 5 ml) and removed by filtration. The solutions were combined and the solvent was removed *in vacuo*. Column chromatography of the residue gave the desired sulfoxides in 82–97% yield.

§ *Crystal data* for **2** (R = Bn) (ref. 11): $C_{13}H_{17}NO_5S$, M = 299.34, orthorhombic, space group $P2_12_12_1$, a = 7.87930(10), b = 8.19550(10), c = 22.0906(4) Å, V = 1426.50(4) Å^3, T = 100(2) K, Z = 4, D_c = 1.394 Mg m^{-3}, μ(MoKα) = 0.245 mm^{-1}, 27208 reflections collected, 2747 independent reflections, R(int) = 0.0282, all non-H atoms anisotropic, all H-atoms constrained to idealised positions. Final R indices [based on 2724 reflections with $I > 2\sigma(I)$], R_1 = 0.0256, wR_2 = 0.0706. The absolute structure of the molecule was confirmed by the refinement of an enantiopole parameter to −0.02(6). CCDC 182/1113. Crystallographic data is available in CIF format from the RSC web site, see: http://www.rsc.org/suppdata/cc/1999/247/

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