A versatile synthesis of 2,4-substituted oxazoles†

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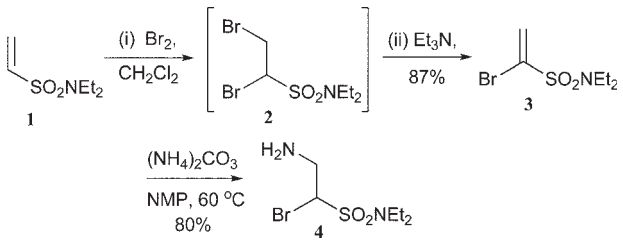
Received (in Cambridge, UK) 2nd April 2008, Accepted 8th May 2008
First published as an Advance Article on the web 16th June 2008
DOI: 10.1039/b805430d

A variety of five-membered ring oxazoles have been synthesised with complete regiocontrol and without the requirement for ring oxidation *via* a reaction sequence based on a vinyl sulfonamide template.

Five-membered ring aromatic heterocycles are important molecules that have found application throughout the chemical sciences.[1] In particular, oxazoles are important peptidomimetics,[2,3] agrochemicals[4] and are found in many natural products.[5] Imidazoles have become important constituents of ionic liquids,[6] *N*-heterocyclic carbene complexes[7] and are important organocatalytic moieties.[8] Thiazoles have found recent application as organic metals[9] and magnets.[10] In addition to this, these compounds as well as the classic heterocyclic units (pyrrole, furan and thiophene) have been and continue to be highly significant medicinal compounds, with most new drugs containing at least one heterocyclic ring.[1,11] Occasionally, simple heterocyclic compounds are commercially available and can be manipulated directly to yield the target molecule. More usually, however, it is necessary to prepare the heterocyclic compound *de novo*. Classic routes to heterocyclic compounds involve condensation reactions of 1,4-dicarbonyl compounds. Although these reactions are usually reliable and high yielding, preparation of the intermediate 1,4-diketone or aldehyde can be difficult and achieving the desired substitution pattern raises other synthetic and regiochemical issues.[12] New reliable routes to such heterocyclic systems are continually being sought, particularly for the preparation of compounds with more unusual substitution patterns.[13] Following the work in our laboratory on the chemistry of sulfonamides and sulfonate esters,[14] we here report a new synthesis of disubstituted oxazoles with the potential to be expanded to the synthesis of numerous other heterocyclic systems.

The synthesis begins with the vinyl sulfonamide **1** which is routinely transformed into vinyl bromide **3**. 1,4-Addition of ammonia to this species then proceeds smoothly to give the highly functionalised species **4** (Scheme 1).

We were struck by the regioselectivity that was observed in the formation of **4**, no displacement of the bromine atom in the alpha-position being observed (our previous experience with these systems indicates that intermolecular S_N2 reactions of these species are difficult). Acylation of the free amine with various acid chlorides then proceeds to yield an array of amides which on treatment with sodium *tert*-butoxide in DMF gave the corresponding oxazolines (**6a–e**) in excellent yields (Scheme 2, Table 1).



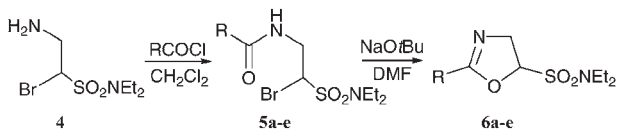
Scheme 1

It was then found that treatment of the oxazolines with aqueous sodium hydroxide in NMP or DMF resulted in the 2-substituted oxazoles (**7a–e**) in excellent yields (Scheme 4, Table 2). This approach therefore represents an efficient synthesis of 2-substituted oxazoles. It is interesting to note that aqueous basic conditions are required for the aromatisation of the oxazolines which implies a mechanism which relies on ring opening followed by elimination of SO_2 rather than an E1 elimination of the sulfonamide (Scheme 3).

Having established the generality of our approach in the synthesis of 2-substituted oxazoles, we proceeded to explore how the approach might be modified to allow the preparation of 2-, 4- and 2,4-substituted oxazoles.

It occurred to us that vinyl sulfonamide **1** might be a suitable coupling partner for palladium catalysed 'Heck' arylations. Indeed, the literature contains numerous examples of vinyl sulfonamides participating in such reactions (although often yields are low).[15] Arylation with iodobenzene proceeded without incident and the vinyl bromide species was also readily isolated. We were, however, disappointed to observe that exposure of the vinyl bromide to ammonia resulted in no 1,4-addition product being formed and only starting materials being recovered. Various reaction conditions and solvents were examined, however the olefin remained intact in all cases (Scheme 5).

It was reasoned that the sulfonamide motif is not sufficiently electron withdrawing for the addition of ammonia (and concomitant loss of extended conjugation) to be thermodynamically viable. If this rationale was correct then a more electron withdrawing sulfonate moiety should alleviate this problem and allow us to proceed further with the synthesis. The well defined phenyl vinylsulfonate was therefore chosen as the new starting

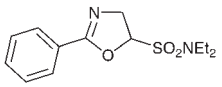
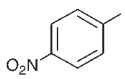
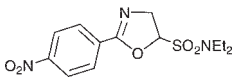
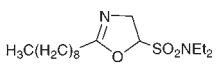
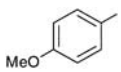
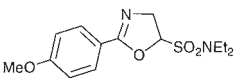
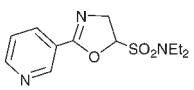


Scheme 2

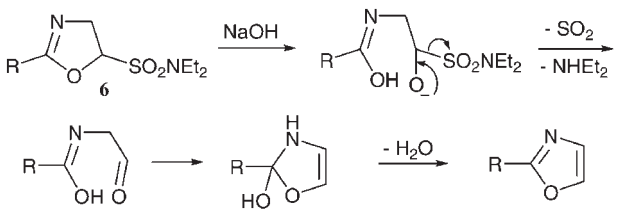
The Christopher Ingold Laboratories, University College London, 20 Gordon Street, London, UK WC1H 0AJ. E-mail: j.wilden@ucl.ac.uk; Fax: +44 (0)20 7679 7463; Tel: +44 (0)20 7679 3395

† Electronic supplementary information (ESI) available: Full characterisation data for all compounds quoted. See DOI: 10.1039/b805430d

Table 1

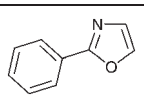
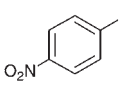
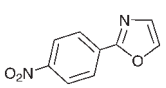
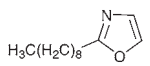
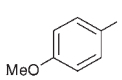
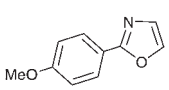
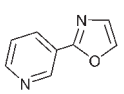
Entry	R	Amide yield %	Oxazoline	Isolated yield %
1		93 **5a**		89 **6a**
2		83 **5b**		92 **6b**
3	$CH_3(CH_2)_8$–	68 **5c**		62 **6c**
4		55 **5d**		57 **6d**
5		80 **5e**		50 **6e**

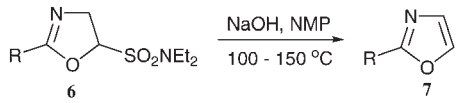
material and it was expected that this species would be routinely elaborated *via* Heck chemistry. However, only one comparable reaction of this species was found in the literature (which utilised a palladium catalyst derived from a tetraphosphine).[16]



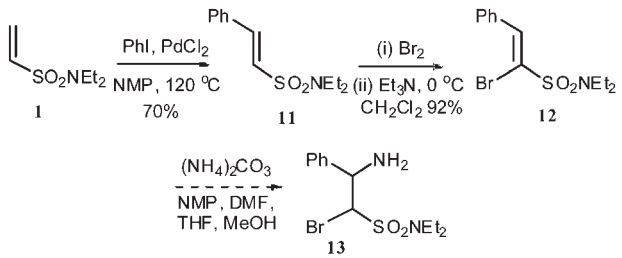
Scheme 3

Table 2

Entry	R	Oxazole	Isolated yield %
1			68 **7a**
2			70 **7b**
3	$CH_3(CH_2)_8$–		62 **7c**
4			92 **7d**
5			83 **7e**



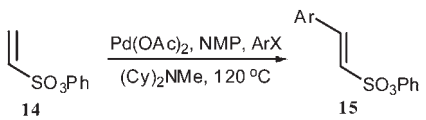
Scheme 4



Scheme 5

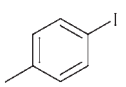
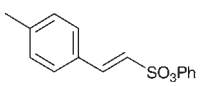
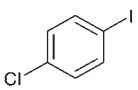
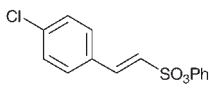
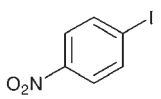
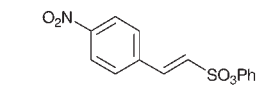
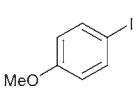
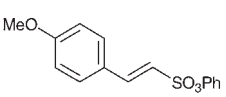
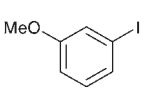
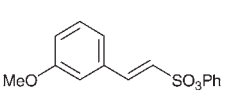
Despite the relative lack of literature precedent, sulfonate ester **14** was found to undergo palladium catalysed cross coupling with various iodides under ligand-free conditions (Scheme 6) to give the corresponding coupled products **15a–e**, Table 3. Numerous attempts were made to maximise the efficiency of these reactions (employing various catalysts, ligands and solvents), however only the combination of dicyclohexylmethylamine as base and palladium(II) acetate in DMF or NMP in the absence of classical ligands has so far given significant yields.

At this juncture we wished to test the feasibility of employing a sulfonate ester such as **16** in the preparation of a

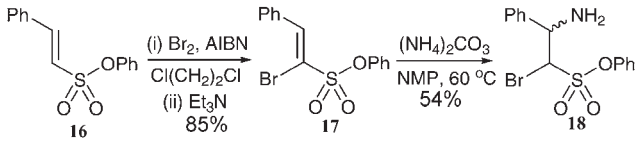


Scheme 6

Table 3

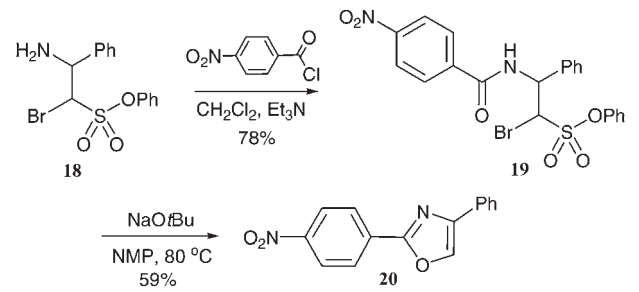
Entry	Halide	Product	Isolated yield %
1			37 **15a**
2			48 **15b**
3			26 **15c**
4			48 **15d**
5			37 **15e**

disubstituted oxazole. Using sulfonate ester **16**, a slightly modified radical bromination protocol was employed which furnished the desired product in near quantitative yield. Elimination to yield the vinyl bromide **17** similarly proceeded without incident. Treatment of **17** with ammonium carbonate in NMP then gave the amine **18** as a 1 : 1 mixture of diastereoisomers which were separable by column chromatography (Scheme 7).



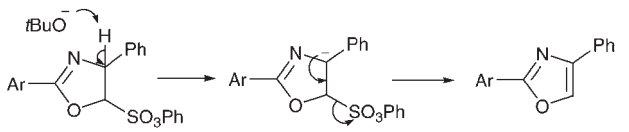
Scheme 7

Exposure of **18** to 4-nitrobenzoyl chloride led as expected to the amide **19** in good yield. It was then found that treatment of either diastereoisomer of **19** with sodium *tert*-butoxide gave the oxazole directly without isolation of the oxazoline intermediate (Scheme 8).



Scheme 8

We were intrigued by the discovery that cyclisation and elimination of the sulfonate ester were simultaneous in this case. It was reasoned that the aryl group at the 4-position of the putative oxazoline serves to lower the pK_a of the adjacent proton sufficiently to allow an E1cb elimination of the sulfonate ester (Scheme 9).



Scheme 9

In conclusion, we have described a short, regioselective synthesis of a variety of 2-substituted oxazoles and have demonstrated the potential of the synthesis in the preparation of 2,4-substituted oxazoles exploiting the unique reactivity of vinyl sulfonates and sulfonamides. In doing so, we have also developed a ligand free palladium catalysed coupling protocol that has allowed the elaboration of phenyl vinylsulfonate.

We recognise that this approach may have wider potential in the preparation of other heterocyclic systems such as imidazoles, thiazoles, isoxazoles and pyrazoles and work is currently underway in our laboratory to develop this methodology.

We thank the EPSRC and UCL for generous financial support of this work. We also gratefully acknowledge the contributions of Dr A. Aliev and Dr L. Harris.

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