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Synthesis of Styryl Tetrahydrofurans and Tetrahydropyrans via Addition of Radicals to Unsaturated Sulfimides.

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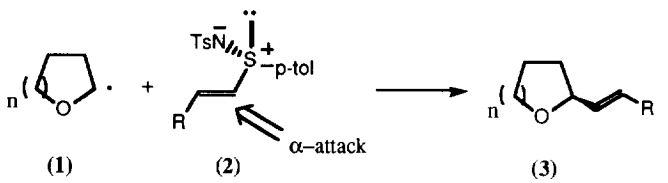
Abstract: The addition of tetrahydrofuranyl or tetrahydropyranyl radicals to (E)-styryl sulfimide derivatives furnishes the corresponding (E)-styryl tetrahydrofurans or tetrahydropyrans respectively. The corresponding radical reactions with (Z)-styryl sulfimides gives rise to a mixture of (E) and (Z) isomers, this is in contrast to the Et_3B mediated reaction, which is stereoselective.

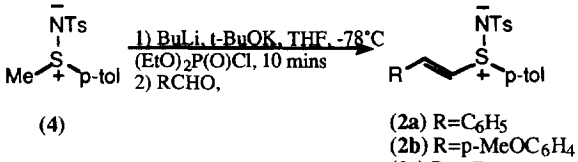
The ability to form carbon-carbon bonds is one of the primary tasks in the construction of organic molecules. In the last two decades this has been increasingly achieved by the addition of carbon centered radicals to carbon-carbon multiple bonds.[1] The addition of simple alkyl radicals to vinyl stannanes,[2] vinyl sulfides, vinyl sulfoxides and vinyl sulfones[3] to give functionalised alkenes via an addition/elimination sequence has been investigated by both Baldwin and Russell. Interestingly, with stereodefined substrates substitution with partial retention often occurs. However, this has been shown to be dependent upon the leaving radical.[4] The addition of radicals to unsaturated sulfimides has not yet been investigated. As part of an ongoing programme developing asymmetric radical reactions involving the addition of radicals to alkenes bearing chiral sulfur auxiliaries, we have recently studied the addition of heterosubstituted radicals to racemic vinyl sulfimides. We report in this paper the results of our initial studies on the addition of α-heterosubstituted radicals (**1**) to racemic sulfimides (**2**) to give styryl heterocycles (**3**) (Scheme 1).



(**1**) (**2**) (**3**)

Scheme 1

In order to investigate the intermolecular addition/elimination sequence of radicals to vinyl sulfimides radical attack must take place at the α-carbon of (**2**). The steric deactivating effect of the sulfur moiety must therefore be overcome. This in theory can be accomplished either by steric factors (i.e. making R large) or by electronic considerations (making R=Ph or CO_2Et). Consequently, we have prepared and investigated the reactions of the three sulfimides (**2a-c**).



(4)

(2a) R=C_6H_5
(2b) R=p-$MeOC_6H_4$
(2c) R=t-Bu

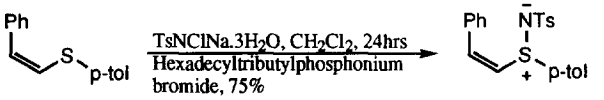
Scheme 2

Product	E/Z	Yield[a]
(2a)	95/5	38%
(2b)	87/13	58%
(2c)	>98/2	40%

a) yield of isolated (E)-isomer

Table 1

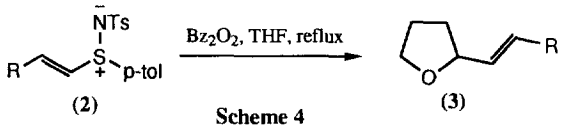
The (E)-sulfimide precursors **(2a-c)** were prepared from tosyl sulfimide **(4)** by adaption of Craig's procedure for the synthesis of sulfoximide analogues.[5] Hence, reaction of **(4)** sequentially with 1eq of BuLi and then 1eq of t-BuOK in THF at -78°C, followed by the addition of diethylchlorophosphate and the appropriate aldehyde, leads to the unsaturated sulfimides **(2a-c)** as E/Z mixtures[6] (Scheme 2). Careful chromatography allowed separation of the (E)-isomers in the yields shown in **Table 1**. The (Z)-sulfimide **(2d)** was prepared from the corresponding (Z)-sulfide[7] **(5)** by reaction with chloramine-T[8] (Scheme 3).



(5) **Scheme 3** (2d)

Radical additions to sulfimides.

Initial investigations involved addition of the tetrahydrofuranyl radical **(1)** [n=1] to each of the (E)-sulfimides **(2a-c)**. The desired radical **(1)** [n=1] was prepared from THF by heating in the presence of a radical initiator such as benzoyl peroxide or t-butyl peroxide. Reaction with either **(2a)** or **(2b)** proceeded as expected to give the desired heterocyclic products **(3a)** and **(3b)** in yields of 45% and 84% respectively. On the other hand reaction of **(1)** [n=1] with **(2c)** under identical conditions led to no detected product **(3c)**. Presumably an intermediate stabilised benzylic radical is neccessary for successful activation. The overall yield of the reactions could be increased ((**3a**) from 45% to 77%) if t-butyl peroxide (20mol%) was used as initiator instead of benzoyl peroxide. However, due to the harsher conditions required (150°C at 20 atm in an autoclave) all further reactions were conducted using benzoyl peroxide as initiator. In the above cases only (E)-products were detected. Interestingly, reaction of the (Z)-sulfimide **(2d)** was not stereoselective, giving a mixture of (E) and (Z)-styryl heterocycles (E/Z 50/50).



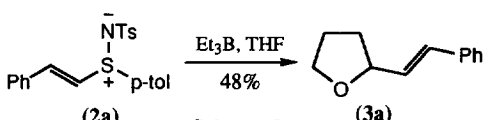
(2) **Scheme 4** (3)

Sulfimide	Yield (3)
(2a)	45%
(2b)	84%
(2c)	-

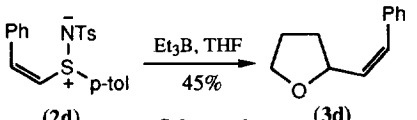
A typical procedure is as follows: benzoyl peroxide (10 mol%) was added to the sulfimide **(2a)** dissolved in dry deoxygenated THF (5 ml). The mixture was then refluxed for 24 hrs (additional portions of radical initiator were added after every 6 hrs). The solvent was evaporated and the crude mixture was chromatographed to give the (E)-styryl tetrahydrofuran **(3a)** in 45% yield.[9]

Triethylborane mediated reactions.

The synthesis of styryl heterocycles from styryl sulfoxides has been reported using Et3B.[10] Consequently, we investigated the Et3B mediated reaction of both the (E) and (Z)-sulfimide **(2a)** and **(2d)** with THF. Hence, reaction of a THF solution of the (E)-sulfimide **(2a)** with Et3B for 18 hrs at room temperature furnished the desired (E)-styryl heterocyclic product **(3a)** (48%) as expected. However, treatment of the (Z)-sulfimide **(2d)** under identical conditions led almost exclusively to the (Z)-styryl heterocycle **(3d)**, (45%, E/Z = 8/92). This is contrary to the results reported for the additions of the corresponding sulfoxides and sulfones which give exclusively the (E)-products, irrespective of their starting geometry[10]. Although the yields were lower than for the benzoyl peroxide initiated procedure, this method allows easy preparation of the (Z)-isomer and is complementary to the benzoyl peroxide initiated procedure. Work is in progress to confirm the mechanism of the Et3B mediated process.

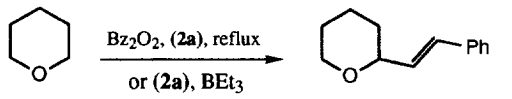


(2a) Scheme 5 (3a)



(2d) Scheme 6 (3d)

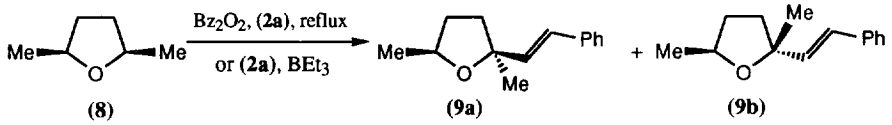
Both described procedures were applicable to the synthesis of other types of heterocyclic derivatives. For example, the tetrahydropyran derivative **(7)** could be produced in good yield by either the benzoyl peroxide (90%) or the Et3B (61%) method, as could functionalised tetrahydrofurans such as **(9a)** and **(9b)**. In this latter case both methods gave similar diastereoselectivities **(9a)/(9b)** = 29/71 (Bz_2O_2), 33/67 (Et3B). Alternatively, the corresponding (Z)-styryl tetrahydrofuran derivatives **(10a)/(10b)** could be prepared by the Et3B mediated addition of **(8)** to the (Z)-sulfimide **(2d)**. In this case a minor amount of the corresponding (E)-isomers **(9a)/(9b)** was detected (E/Z 23/77). The diastereoselectivities of both (E)- and (Z)- products were similar (**(10a)/(10b)**=(32/68), **(9a)/(9b)**=(34/66)).



(6) (7)

Bz2O2 method = 90%
BEt3 method = 61%

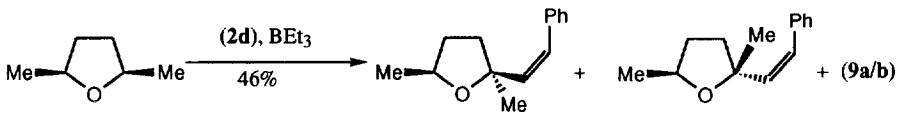
Scheme 7



(8) (9a) (9b)

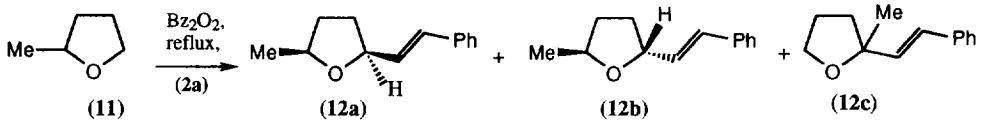
Scheme 8

Bz2O2 method = 42%
BEt3 method = 58%



(8) Scheme 9 (10a) (10b)

The regioselectivity of the addition of unsymmetrical heterocycles was probed by investigating the Bz_2O_2 mediated reaction of 2-methyl tetrahydrofuran (**11**) with (**2a**). In this case three products were produced in 74% overall yield in the ratio shown. No regioselectivity was observed, but the diastereomeric ratio of (**12a**)/(**12b**) (25/75) was similar to that observed with (**9**), (major isomer proven by nOe studies).



(**11**) (**12a**) (**12b**) (**12c**)

Scheme 10 (**12a**)/(**12b**)/(**12c**) = 1.0/2.9/3.9

In conclusion we have reported the first study on the addition of radicals to unsaturated sulfimides and have shown that for styryl sulfimides an addition/elimination mechanism occurs to give functionalised styrene derivatives. In addition, if Et_3B is used to mediate the reactions, the eliminations proceed with a high degree of retention unlike the corresponding sulfoxides and sulfones. Future work will investigate additions to optically pure sulfimides to determine if this route is applicable to the synthesis of optically active heterocycles.
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9. Selected spectroscopic data: (**2a**) δ_H (400MHz, $CDCl_3$) δ 7.76 (d, 2H, J=8.4Hz), 7.55 (d, 2H, J=8.2Hz), 7.35 (m, 5H), 7.32 (d, J=15.2Hz), 7.26 (d, 2H, J=8.4Hz), 7.14 (d, 2H, J=8.2Hz), 6.55 (d, 1H, J=15.2Hz), 2.37 (s, 3H), 2.30 (s, 3H). (**2d**) δ_H (400MHz, $CDCl_3$) δ 7.69 (d, 2H, J=8.3Hz) 7.53 (d, 2H, J=8.3Hz), 7.36 (m, 5H), 7.25 (d, 2H, J=8.3Hz), 7.13 (d, 1H, J=10.2Hz), 7.09 (d, 2H, J=8.3Hz), 6.34 (d, 1H, J=10.2Hz), 2.36 (s, 3H), 2.32 (s, 3H). (**3a**) δ_H (400MHz, $CDCl_3$) δ 7.27 (m, 5H), 6.57 (d, 1H, J=15.9Hz), 6.20 (dd, 1H, J=15.9, 6.1Hz), 4.47 (dq, 1H, J=6.1, 1Hz), 3.96 (ddd, 1H, J=14.0, 7.0, 6.6Hz), 3.83 (ddd, 1H, J=14.0, 7.8, 6.2Hz), 2.12 (m, 1H), 1.95 (m, 2H), 1.71 (m, 1H).
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