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NEW ROUTES TO HETEROCYCLES VIA SULPHENYLATION OF UNSATURATED AMIDES

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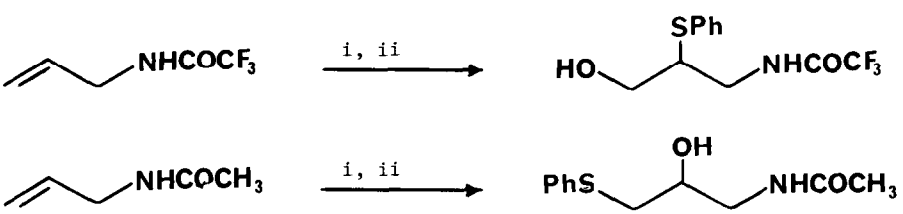
Abstract Reaction of manganic acetate with organic disulphides in dichloromethane-trifluoroacetic acid in the presence of a variety of unsaturated amides leads to intramolecular cyclisation with formation of sulphenylated oxazolines, oxazines or tetrahydropyrroles.

The addition of aryl sulphenyl halides and of aryl selenenyl halides to alkenes has been used to give both simple adducts[1] without participation of any neighbouring group in the alkene, and to give cyclic adducts[2-5] with participation of such a neighbouring group. At an early point in the study of such cyclisations it was recognised[2] that owing to both the poorer stability of sulphenyl chlorides relative to selenenyl chlorides, and other drawbacks, phenylsulphenyl lactonisation was inferior to phenylselenenyl lactonisation. Subsequently, in spite of the occasional report[6,7] of sulphenyllactonisation, the selenium based methodology[8] has become much more widely used. Similarly the recent systematic study of the addition of benzene selenenyl halides to unsaturated amides[9] leading to the synthesis of a number of heterocyclic systems highlights the absence of any such methodology leading to sulphenylated heterocyclic systems. We now describe an alternative methodology which permits the conversion of unsaturated amides to a variety of sulphenylated heterocyclic systems. This methodology is based on the procedure for hydroxysulphenylation of alkenes using organic sulphides developed by Trost et al.[10] We have recently used a modification,[11,12] employing manganic acetate rather than lead tetraacetate, to give sulphenylated adducts of unsaturated nitriles, esters and amides. In these additions only acyclic adducts were obtained. Here we describe reactions of unsaturated amides which proceed via participation of the amide group to create heterocyclic products.



Reagents: i, PhSSPh, $Mn(OAc)_3$, CH_2Cl_2, CF_3CO_2H. ii, Na_2CO_3

Scheme

Table

Sulphenocyclisation of unsaturated acids and amides via Mn^{3+} oxidation of organic disulphides

Entry	Alkene	Disulphide	Product	Yield(%)[a]
1	CH_2=$CHCH_2NHCOPh$	PhSSPh	(1)	76
2	CH_2=$CHCH_2NHCOPh$	nPrSSnPr	(2)	67
3	CH_2=$C(Me)CH_2NHCOPh$	PhSSPh	(3)	85
4	CH_2=$C(Me)CH_2NHCOPh$	nPrSSnPr	(4)	78
5	CH_2=$C(Me)CH_2NHCOCH_3$	PhSSPh	(5)	10
			(6)	60
6	CH_2=$CHCH_2CH_2NHCOPh$	PhSSPh	(7)	67
7	CH_2=$CHCH_2CH_2NHCOCH_3$	PhSSPh	(8)	42
8	CH_2=$CH(CH_2)_3NHCOPh$	PhSSPh	(9)	54
9	CH_2=$CH(CH_2)_3NHCOC_6H_4OMe$	PhSSPh	(10)	48
10	CH_2=$CHCH_2CH(Me)CH_2NHCOPh$	PhSSPh	(11)[b]	71
11	CH_2=$CH(CH_2)_4NHCOPh$	PhSSPh	(12)	60
12	CH_2=$CHCH_2CH_2CPNHPh$	PhSSPh	(13)	66
13	CH_2=$CHCH_2CH_2CONHnBu$	PhSSPh	(13)	52
14	CH_2=$CHCH_2CH_2CO_2H$	PhSSPh	(13)	88
15	CH_2=$CHCH_2CH_2CO_2H$	nPrSSnPr	(14)	91
16	CH_2=$CH(CH_2)_3CO_2H$	PhSSPh	(15)	85
17	CH_2=$CH(CH_2)_3CO_2H$	nPrSSnPr	(16)	84

[a] Isolated yields after chromatographic separation. All new compounds were characterised spectroscopically (i.r., ^1H and ^{13}C n.m.r.) and gave satisfactory analyses (m.s. or microanalysis).

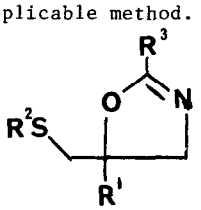
[b] Mixture of diastereoisomers

Earlier we reported[11] that the major pathway in addition of diphenyl disulphide to N-allyl trifluoroacetamide was as reported in the Scheme but that due to the control of the neighbouring group the reverse regiochemistry was observed in addition to N-allyl acetamide. Addition to N-allyl benzamide takes a different course (Table; entry 1). The more electron releasing phenyl substituent facilitates formation of an oxazoline product (1) which can be isolated in 76% yield. Hence addition to unsaturated amides can take two courses, formation of trifluoroacetoxy sulphides, which on work up can give hydroxysulphides, or cyclisation to afford a heterocyclic product. Results in the Table establish that by use of the benzoyl amides derived from unsaturated amines the addition can be controlled to give heterocyclic products. Thus entries 2-4 establish the generality of formation of oxazolines from N-allylbenzamides. The advantage of use of a benzamide derivative is emphasised by the contrasting course of use of an acetamide (entry 5). It is found in the above additions to N-allyl-acetamides and benzamides that optimum yields of cyclic products are obtained with relatively short reaction times and in the absence of a large excess of trifluoroacetic acid. Either prolonged reaction times or the presence of a large excess of trifluoroacetic acid favours isolation of non-cyclic products. These results suggest that the oxazolines are formed under kinetic control and can react further to give the vicinal trifluoroacetoxysulphides. Isolation of kinetically unstable products in related additions[13] is well known.

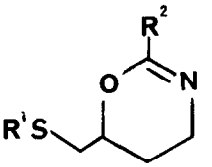
Homoallylic amides behave in a similar manner and afford oxazines (entries 6 and 7). Further chain extension offers the competition between formation of a 7-membered ring through cyclisation through oxygen, or formation of a tetrahydropyrrole through cyclisation through nitrogen. The preference for the latter pathway is shown in entries 8-10. In contrast further chain extension does not permit isolation of substituted piperidines. Instead the hydroxysulphide (12) is isolated as the sole product (entry 11).

Entries 12 and 13 give the outcome of the reaction of amides which might afford lactams. Instead cyclisation through oxygen gives lactones as products. From entries 14-17 it is clear that this alternative procedure for preparation of related sulphenylated lactones, using manganese salts to promote addition of organic disulphides, further illustrates the advantages of this method relative to the use of sulphenyl halides.

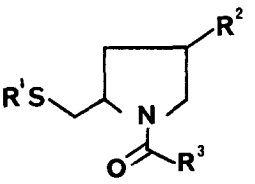
A number of interesting points emerge in the comparison of the results in the Table with other procedures described in the literature. Although the formation of sulphenylated oxazolines and oxazines (Table, entries 1-7) has not been studied related cyclisations of N-allyl amides have been reported with other electrophiles. A close parallel is the recent work[9] with benzeneselenenyl halides but earlier studies report cyclisation under acidic conditions[14] or on halogenation.[15] Similarly although our report of the direct formation of sulphenylated tetrahydropyrroles from amides (entries 8-10) is novel there are many recent reports[9,16] of the synthesis of functionalised tetrahydropyrroles via cyclofunctionalisation, of which the closest analogy is the two step sulphenylcycloamination procedure[17] of Kametani et al. The isolation of a lactone (13) (entries 12 and 13) has a precedent in the related cyclofunctionalisation[18] with benzene selenenyl chloride. Finally the synthesis of sulphenylated lactones from carboxylic acids (entries 14-17) suggests that by comparison with alternative methods,[19] our route using oxidation of organic disulphides is the most generally applicable method.



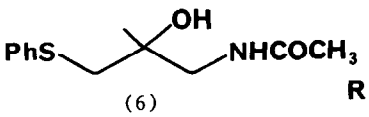
(1) R^1=H; R^2=R^3=Ph
(2) R^1=H; R^2=nPr; R^3=Ph
(3) R^1=Me; R^2=R^3=Ph
(4) R^1=Me; R^2=nPr; R^3=Ph
(5) R^1=R^3=Me; R^2=Ph



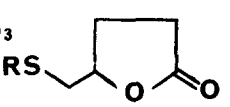
(7) R^1=R^2=Ph
(8) R^1=Ph; R^2=Me

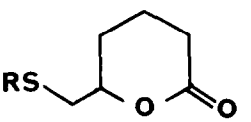


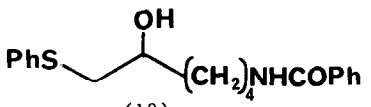
(9) R^1=R^3=Ph; R^2=H
(10) R^1=Ph; R^2=H; R^3=pC_6H_4OMe
(11) R^1=R^3=Ph; R^2=Me



(6)







(12)

(13) R=Ph
(14) R=nPr

(15) R=Ph
(16) R=nPr

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