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A new, practical access to amidyl radicals

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Amidyl radicals are readily generated from *N*-allylsulfonimides by the action of a xanthate and a small amount of a peroxide as initiator. The process involves extrusion of sulfur dioxide from an *N*-amidosulfonyl radical by rupture of the nitrogen-sulfur bond; in some cases, the *N*-amidosulfonyl radical is prematurely captured by the internal olefinic trap.

We have developed over the past few years several processes for the generation and capture of nitrogen centred radicals[1,2] and illustrated their potential for N–C bond formation by the total synthesis of various complex alkaloids.[3] We now describe yet another process for the creation of amidyls, which does not involve the use of organotin hydride but relies on the extrusion of sulfur dioxide from *N*-amidosulfonyl radicals.

As outlined in Scheme 1, step **A**, *N*-amidosulfonyl radicals **2** could be produced by an addition–fragmentation sequence onto the corresponding *N*-allylsulfonylamides **1**.[4] Loss of sulfur dioxide would then furnish the desired amidyl radical, which would then rapidly cyclise to give **4**. As the source of the initial radicals, we opted for a xanthate since the reversible transfer of a xanthate group in the last propagation step **D** would not only introduce a useful functionality into the product **5** but would also regenerate the first radical to perpetuate the chain process.[5]

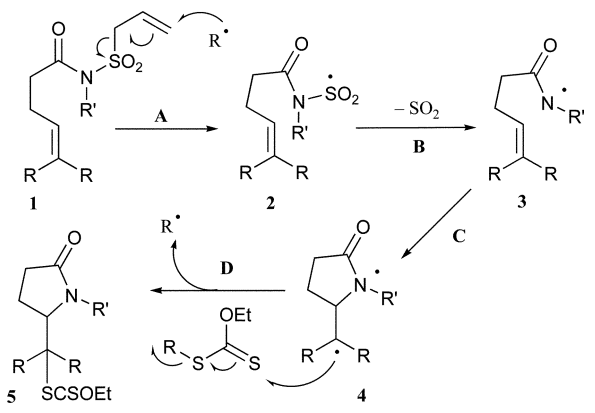
The very few earlier studies on *N*-amidosulfonyl radicals[6] indicated that extrusion of sulfur dioxide (step **B**) is not a fast process and could in fact prove to be problematic in our context. The *N*-amidosulfonyl radicals could, for example, abstract a hydrogen atom from the solvent or undergo addition to the internal olefin. The former unwanted reaction could be curtailed by choosing a solvent with poor hydrogen atom donating capability and the latter could perhaps be overcome by the inherent reversibility of the process.

We first prepared the typical substrates **8a** and **8b**, in 80 and 65% yield respectively, by reacting the mixed anhydride **6**, generated *in situ* from commercially available cyclopentenecarboxylic acid and isobutyl chloroformate in the presence of one equivalent of triethylamine, with the lithium salt of *N*-ethyl- and *N*-phenethyl-allylsulfonamide **7a** and **7b**.† The parent sulfonamides were obtained by treating allylsulfonyl chloride[7] with the requisite amine. When compound **8a** was subjected to the action of xanthate **9** and a sub-stoichiometric quantity of lauroyl peroxide, a major product was formed, which in fact turned out to be cyclic sulfonamide **13a**. It exhibited an NMR spectrum that was initially misleading since it resembled that expected for the desired compound, resulting from the amidyl radical cyclisation. The mass spectrum, however, showed a molecular ion peak that was 64 units higher than that calculated, indicating the presence of an SO_2 motif, and this was corroborated by the IR spectrum where peaks at 1360 and 1150 cm^{-1} typical of sulfonamides were observed.

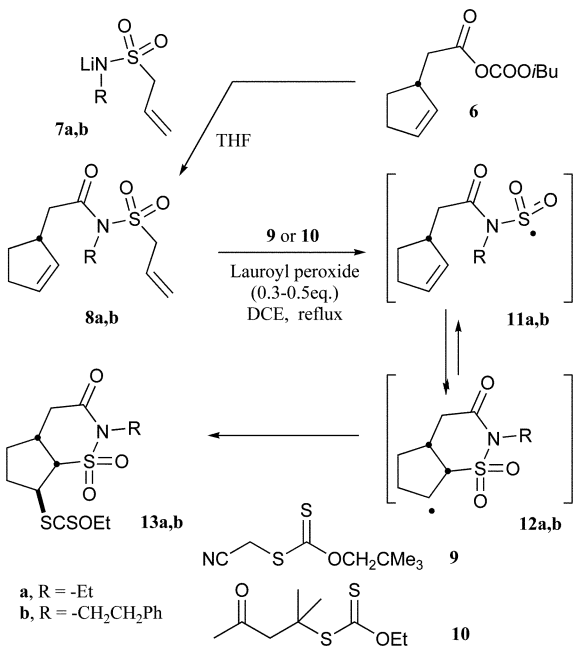
Clearly, the loss of sulfur dioxide represented by step **B** in the mechanism delineated in Scheme 1 did not occur fast enough to compete with cyclisation of the *N*-amidosulfonyl radical. The yield of **13a**, obtained as a single diastereoisomer, was a modest 36%. It could be improved to 62% by using xanthate **10**,[8] which produces a tertiary radical with a nucleophilic character and hence exhibits a better reactivity towards the mildly electrophilic allylsulfonyl group in the substrate. We therefore used this xanthate throughout the rest of the study. Modification of the concentration from 0.3 M (in **8a**) to 0.6 M did not significantly alter the yield (58%). Replacing the ethyl group on the nitrogen by the bulkier but nevertheless primary phenethyl group caused a decrease in the efficiency. Compound **13b** was thus obtained in only 39% yield from **8b** under the same reaction conditions.

When substrate **14** was subjected to the same conditions, two compounds **15** and **16** were formed, with the desired lactam predominating (55%). Compound **17** produced a similar mixture of *N*-sulfonylamide **18** (25%) and lactam **19** (51%). The slight change in the geometric constraints in these two substrates is thus sufficient to push the reaction in the desired direction.

In stark contrast to the above results, no complications were observed from the premature cyclisation of the *N*-amidosulfonyl radical when the ethyl group on the nitrogen was replaced by a phenyl. Loss of sulfur dioxide is speeded up by the greater stability



Scheme 1 Chain reaction for the generation of amidyl radicals.



Scheme 2 Formation of cyclic *N*-sulfonylamides.

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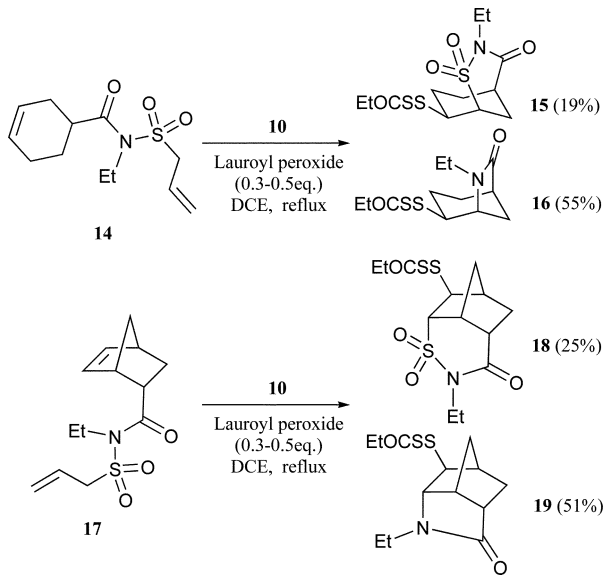
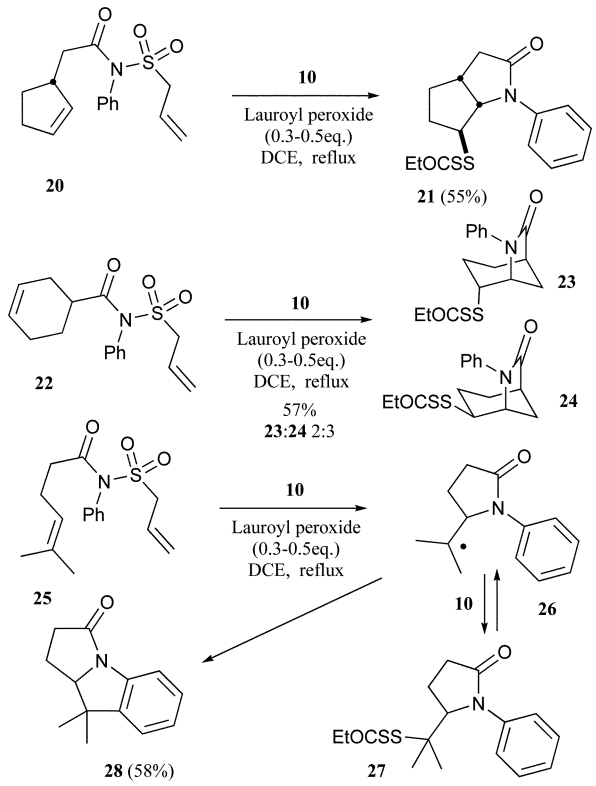
of the nitrogen centred radical created in this case. Only lactam **21** (55%) was produced from allylsulfonamide **20**, and substrate **22** gave rise to 2 : 3 mixture of epimeric lactams **23** and **24** in 57% yield. This latter example contrasts with that of **14** which gave **16** as only one epimer. The presence of the aromatic ring allowed one further twist in the radical sequence when the open chain precursor **25** was subjected to the same reaction conditions. The reaction produced polycyclic derivative **28** in 58% yield. The "normal" lactam **27** was not observed even though it could be formed during the reaction but then converted into **28** through the reversible exchange of the xanthate group. The presence of the xanthate group is a powerful asset in view of the numerous possible further transformations.[4,5]



Scheme 3 Generation and cyclisation of amidyl radicals.



Scheme 4 Generation and cyclisation of *N*-phenylamidyl radicals.

In summary, these preliminary results demonstrate the potential of this process for generating amidyl and perhaps other types of nitrogen centred radicals. The precursors are readily available and stable and the cyclisation can be easily incorporated into various tandem sequences, thus opening a straightforward access to a variety of complex structures. Further studies aimed at improving the yield and extending the scope are under way.

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Notes and references

† Typical experimental procedure:

Synthesis of N-allylsulfonamides: Triethylamine (1–1.2 eq.) and isobutyl chloroformate (1–1.2 eq.) were added to an ice cold solution of the carboxylic acid (1 eq.) in dry THF (5.0 ml per mmole of acid) under an inert atmosphere. In parallel, a solution of butyllithium in hexanes (1.25 M; 1.05–1.2 eq.) was added to a cold (−78°C) solution of the allysulfonamide (1.0 eq.) in dry THF (5.0 ml per mmole) under an inert atmosphere. After 15 minutes, the second solution was cannulated into the first. The resulting mixture was allowed to warm to room temperature and then left stirring for 18 hours. Water and ether were then added and the layers separated. The aqueous layer was further extracted with ether and the combined organic layers combined, washed with brine, and dried over magnesium sulfate. Filtration and evaporation gave a residue that was purified by flash chromatography on silica (eluent: ether–petroleum ether mixtures) to give the respective *N*-allylsulfonylamides.

Radical cyclisation: a solution of the *N*-allylsulfonylamide in 1,2-dichloroethane (0.5 M) and xanthate **10** (1.2 eq.) was refluxed for 15 minutes under an inert atmosphere. Lauroyl peroxide was added in small portions every 90 minutes (first 0.1 eq. then 0.05 eq.), until almost complete disappearance of the starting material. Evaporation of the solvent and purification of the residue by chromatography on silica gel (elutent: ether–petroleum ether mixtures) gave the lactams and/or cyclic *N*-sulfonyl lactams.

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