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A new synthesis of pyrroles

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Received (in Cambridge, UK) 18th July 2002, Accepted 8th August 2002
First published as an Advance Article on the web 3rd September 2002

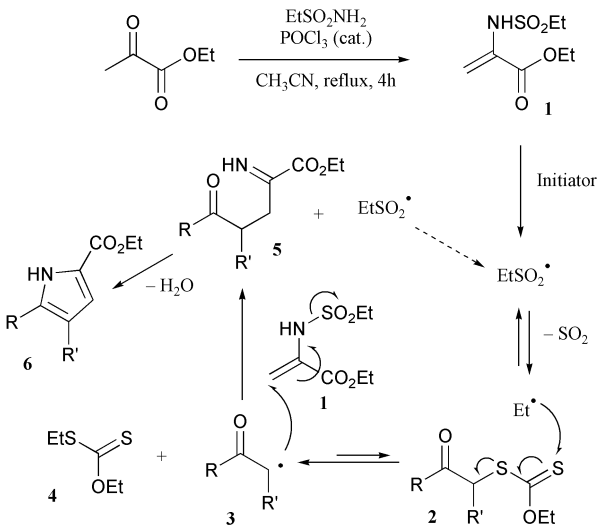
The radical reaction between an *N*-ethylsulfonylenamide and an α-xanthyl ketone gives an intermediate γ-keto imine which spontaneously ring-closes to the pyrrole.

The pyrrole ring corresponds to one of the more basic heteroaromatic structures. It is an essential building block for the construction of porphyrins and a key element in a number of biologically active compounds.[1] It is not surprising therefore that, over the years, much effort has been invested in the design and development of synthetic routes to pyrroles.[1,2] As part of our ongoing studies on the radical chemistry of xanthates and of sulfonyl radicals,[3] we have found a new access to this fundamental ring system which complements existing synthetic pathways.

The reaction sequence outlined in Scheme 1 summarises our approach. Ethylsulfonyl radicals generated by the action of an initiator on enesulfonamide **1** can undergo loss of sulfur dioxide to give ethyl radicals, which can undergo a reversible sequence of addition–fragmentation to a xanthate such as **2** to provide an acetonyl radical **3** and diethyl xanthate **4** as co-product. In turn, addition of radical **3** to enesulfonamide **1** gives imine **5** after the expulsion of an ethylsulfonyl radical, thus closing the radical chain loop. The iminyl group in intermediate **5** is ideally located with respect to the carbonyl of the ketone to ensure a spontaneous ring closure to the pyrrole **6** with the concomitant formation of a water molecule.

The synthesis of the enesulfonamide **1** was readily accomplished starting with ethyl pyruvate and ethylsulfonamide by an adaptation of a literature procedure.[4]‡ We had previously exploited the loss of sulfur dioxide from alkylsulfonyl radicals as a means for the tin-free allylation and vinylation of aliphatic xanthates and iodides,[5] and the present extension seemed initially quite straightforward. In practice, however, we encountered some unexpected difficulty in implementing the desired radical chain process.

Initial experiments with xanthate **2a** (Table 1) were disappointing. The yield of pyrrole was low and extensive decomposition of enesulfonamide **1** was observed under conditions which proved satisfactory in our previous studies with sulfones.[5]



Scheme 1 Reaction pathway to pyrroles.

Table 1 Synthesis of pyrroles[a]

Xanthate **2**	Pyrrole **6**
2a	**6a** 54% (70%)
2b	**6b** 62% (81%)
2c	**6c** 47% (70%)
2d	**6d** 36% (50%)
2e	**6e** 38% (54%)
2f	**6f** 49% (54%)
2g	**6g** 67% (71%)
2h	**6h** 50% (65%)

[a] Yields in parenthesis are based on recovered starting material.

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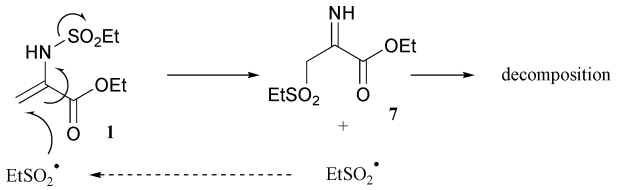
DOI: 10.1039/b207061h



Scheme 2 Isomerisation and decomposition of *N*-sulfonylenamide **1**.

Our problems appeared to be due to a competing chain reaction, pictured in Scheme 2, causing an irreversible isomerisation of **1** into the highly reactive imine **7**.§ Such rearrangements involving *N*-arylsulfonylenamides were observed by Hertler some years ago.[6] Further uncontrolled condensation reactions of imine **7** can lead to the liberation of ammonia, which in turn causes the destruction of the starting xanthate and chain inhibition.

In the light of this reasoning, we had to keep the temperature as high as possible in order to speed up the unimolecular loss of sulfur dioxide from ethyl sulfonyl radicals without causing thermal decomposition of the reactants. At the same time, we increased the dilution and added sulfonylenamide **1** in portions as the reaction progressed in order to slow down the unwanted rearrangement. With these experimental modifications,‡ the yield of pyrrole became acceptable, as shown by the examples compiled in Table 1. Various functional groups are tolerated and both aromatic or heteroaromatic (*e.g.* thiophene in example **6e**) and aliphatic substituents may be incorporated.

Even though the procedure has not been completely optimised in this preliminary study and room for improvement certainly exists, the present radical based, tin-free approach provides an expedient route to pyrroles with a useful substitution pattern, using readily available starting materials and reagents.

We thank Rhodia and the CNRS for generous financial support to one of us (FW) and Dr Virginie Pevere for many friendly discussions.

Notes and references

‡ Synthesis of sulfonylenamide **1**: Ethyl pyruvate (3.5 g, 29.8 mmol) and phosphorus oxychloride (1.9 g, 20.4 mmol) were added to a solution of ethanesulfonamide (3.9 g, 35.8 mmol) in anhydrous acetonitrile (44 ml) under an inert atmosphere and the resulting solution heated to reflux for 4 h. After cooling, the medium was diluted with dichloromethane and washed with aqueous sodium bicarbonate solution until neutral pH. The aqueous phases were extracted once more with dichloromethane and the combined organic phases dried over sodium sulfate and concentrated under partial vacuum. Purification of the residue by column chromatography over silica gel using a heptane : ethyl acetate gradient gave pure ethylsulfonylenamide **1** as a pale yellow oil (2.7 g, 44%); IR (film, cm^{-1}): 3277, 1715, 1635; ^1H NMR (300 MHz; $CDCl_3$) δ ppm: 6.95 (bs, 1H), 5.73 (dd, J = 1.2 Hz, J' = 16.1 Hz, 2H), 4.32 (q, J = 7.0 Hz, 2H), 3.17 (q, J = 7.4 Hz, 2H), 1.37 (t, J = 7.4 Hz, 3H), 1.36 (t, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) δ ppm: 163.1, 131.5, 106,5, 64.3, 50.5, 13.9, 8.3. Calc. For $C_7H_{13}NO_4S$: C, 40.57; H, 6.32. Found: C, 40.61; H, 6.38.

Typical experimental procedure for the synthesis of pyrroles: A solution of ehylsulfonylamide 1 (2 mmol) and xanthate 3 (1 mmol) in a 5 : 1 mixture of heptane and chlorobenzene (3 ml) were heated to reflux under argon for 15 min. Solid AIBN (2.5 mol%) was added every hour and, when TLC indicated the consumption of the sulfonylenamide **1**, a further portion (2 mmol) was added (this process was in some cases repeated once again; the total reaction time did not exceed 10–11 h). The mixture was then cooled, concentrated under partial vacuum and the residue purified by column chromatography over silica gel.

§ Unlike the present case, the addition of ethyl sulfonyl radicals to ethyl allyl sulfone and related reagents used in ref. 5 is *reversible and degenerate* and does not therefore interfere with the desired process.

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