Multiple Radical Additions: an Expedient Entry into Complex Frameworks

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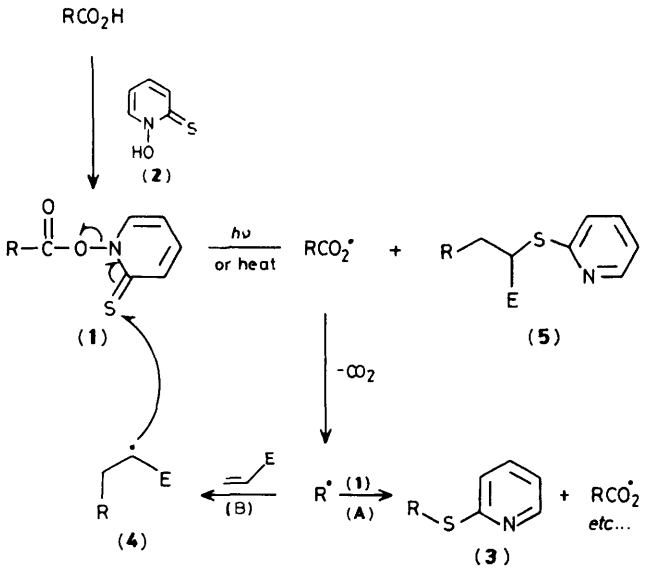
Irradiation of *N*-hydroxy-2-thiopyridone esters of suitable γ,δ-unsaturated carboxylic acids in the presence of an electron deficient alkene produces complex bicyclic systems by a multiple radical addition chain mechanism.

As part of our work on a novel radical decarboxylation reaction of carboxylic acids *via* their thiohydroxamate esters,[1] we have shown that the first formed carbon radical may be easily captured by an electron deficient alkene. A new carbon–carbon bond is created in the process which leads to compounds of general structure (**5**) as outlined in Scheme 1. Over the past few years, carbon–carbon bond formation by external radical addition to an internal or external alkene has proved to be of outstanding value in synthesis.[2] We now describe a simple modification which allows the swift assemblage of complex carbon frameworks.

The reaction sequence in Scheme 1 proceeds efficiently in the desired direction (path B) if substituent E is a strongly electron withdrawing group. This speeds up the addition of the nucleophilic alkyl or cycloalkyl radical R• and impedes the polymerisation of the alkene. In contrast to R•, radical (**4**) is now electrophilic in character and will preferentially interact with the electron rich sulphur of the thiocarbonyl group. These polar factors, which can be expressed in frontier orbital terms, play a dominant role in sterically unhindered systems (especially with regard to the alkene trap).[2,3]

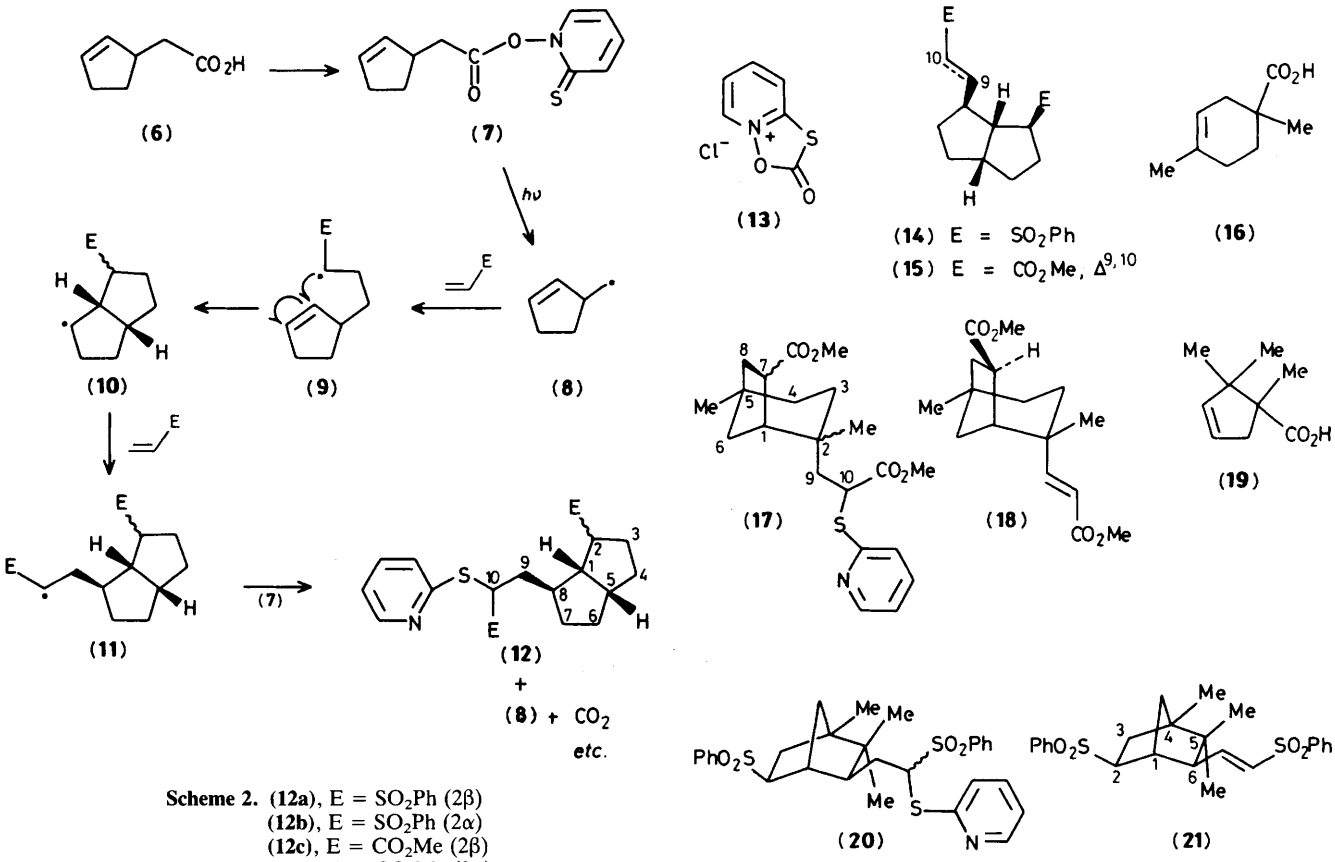


Scheme 1

Using such a rationale, the behaviour of a γ,δ-unsaturated carboxylic acid can be easily delineated as illustrated in Scheme 2 for cyclopent-2-enylacetic acid (**6**). In this case, the first radical addition to the activated alkene should be rapidly followed by cyclisation to give (**10**). Unlike its precursor, this radical is nucleophilic in character; it should therefore preferentially add to the electron poor alkene producing this time an electrophilic radical (**11**) [*cf.* (**4**)]. The sequence is eventually terminated by attack at the thiocarbonyl group of the starting ester (**7**) to give compound (**12**) and, concomitantly, propagate the chain. Overall, three carbon–carbon bonds would therefore be introduced in one operation.

This proposal was easily confirmed for the commercially available acid (**6**) using phenyl vinyl sulphone (E = SO_2Ph) as the non-polymerisable external alkene. The corresponding ester (**7**) was prepared and used *in situ*, either by the reaction of the acid chloride with the sodium salt of (**2**) or, more conveniently, from the acid itself and the phosgene-derived (**13**)[4] in the presence of triethylamine. Irradiation with a 250 W projector lamp of a mixture of (**7**) and phenyl vinyl sulphone afforded cleanly (**12a**) and (**12b**) in a combined yield of 74%, based on the starting acid. This mixture of isomers could easily be changed to one compound by treatment with Bu^tO^- in Bu^tOH, which converted the minor isomer (**12b**) into (**12a**) by epimerisation at C-2. Desulphurisation with nickel boride finally gave (**14**) as a single crystalline isomer†

† All final single isomers have been fully characterised by spectroscopic and microelemental analysis.



Scheme 2. **(12a)**, E = SO_2Ph (2β)
(12b), E = SO_2Ph (2α)
(12c), E = CO_2Me (2β)
(12d), E = CO_2Me (2α)

(m.p. 130—133 °C) in 94% yield, thereby eliminating the terminal asymmetric centre, the stereochemistry of which is difficult to control.

Very simply, therefore, a complex, functionalised bicyclic structure could be rapidly constructed with almost perfect control of stereochemistry of the ring carbon atoms.[6] Had acid (**6**) been optically pure, this sequence would have led to chiral (**14**) with excellent asymmetric induction. The fact that γ,δ-unsaturated carboxylic acids such as (**6**) may be prepared from an allylic alcohol by the stereospecific Claisen orthoester rearrangement[7] makes this approach attractive for enantiospecific syntheses.

In a similar manner, irradiation of the ester (**7**) in the presence of the less reactive methyl acrylate furnished (**12c**) (major) and (**12d**) in a combined yield of 43%. In this case the mixture was oxidised to the sulphoxide using MCPBA (*m*-chloroperbenzoic acid) and heated in boiling toluene; epimerisation at C-2 with DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene) in methanol then provided the unsaturated ester (**15**)† as the sole product in 60% overall yield.

A different type of carbon skeleton may be assembled by simply varying the relative position of the double bond and acid group with respect to the ring. Thus, starting from 1,4-dimethylcyclohex-3-enecarboxylic acid (**16**), a similar sequence of radical additions to methyl acrylate led to the bridged bicyclic [3.2.1] derivative (**17**) as a mixture of isomers in 43% yield. As before, *syn*-elimination *via* the sulphoxide and exposure to DBU in methanol reduced the number of diastereoisomers to one major product (**18**)† (69%) accompanied by *ca.* 5—10% of what appears to be its C-2 epimer. The C-2 position cannot be epimerised with base and the ~9:1 ratio reflects therefore the stereoselectivity of the second radical addition step. The proposed stereochemistry of the major product is supported by a nuclear Overhauser correlation between the signal of the C-2 methyl and that of the hydrogen at C-7 (NOESY). The fact that, in this example, two quaternary centres (C-2 and C-5) are introduced in one operation emphasises some of the advantages attending the use of radical processes.

A further illustration of the flexibility of this approach is given by the transformation of the acid (**19**) which is readily available from camphoric acid.[9] In this case, and using phenyl vinyl sulphone as the activated alkene, the reaction produces (**20**) (59% yield) with the important bicyclo [2.2.1] framework. Interestingly, compound (**20**) is a mixture of only two epimers with respect to the terminal asymmetric carbon, the configuration of which cannot be controlled. As before, this chiral centre was eliminated by oxidation to the sulphoxide (MCPBA) followed by thermolysis in boiling toluene. This gave the expected product (**21**) as a single crystalline isomer† (m.p. 131—133 °C) in 72% yield. The bridgehead hydrogen appears as a slightly broadened singlet in the n.m.r. spectrum indicating that the two vicinal hydrogens at C-2 and C-6 are both *endo*.[10]

These preliminary results clearly demonstrate that by controlling the sequence of radical additions, an expedient entry into complex systems may be readily achieved. This approach combines simplicity, flexibility, and resonable yields considering the number of discrete steps involved in each operation. In addition, some of the bicyclic structures

elaborated in the foregoing examples are subunits in many terpenes.

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