HOMOLOGATION OF ACIDS via CARBON RADICALS GENERATED FROM THE ACYL DERIVATIVES OF N-HYDROXY-2-THIOPYRIDONE. (THE TWO-CARBON PROBLEM).

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Abstract: Reaction of suitably substituted olefins with carbon radicals generated from the acyl derivatives of N-hydroxy-2-thiopyridone results in the formation of precursors for the corresponding homo-acids. These compounds can then be transformed to the desired end-products in high yield under mild conditions.

Acyl derivatives of thiohydroxamic acids, like those of N-hydroxy-2-thiopyridone 1 are convenient sources of carbon radicals of synthetic utility^{1,2}. The explanation of the widespread and successful use of this method is related to the 'disciplined' nature of these carbon³ and other⁴ radicals and also to the mild methods of their generation (normally photolysis by visible (W) light).

As a continuation of our research in radical chemistry and functional group transformation by radical methods we have attempted to find a suitable 'two-carbon' unit⁵ for the one-carbon homologation of acids 2 *via* the carbon radicals 4 formed from their N-hydroxy-2-thiopyridone derivatives 3 (Scheme 1). We have demonstrated earlier^{5b}, that nitroethylene could be used for this purpose. However, this olefin is not easy to prepare on a large scale. As seen from Scheme 1, the known radical trap, phenyl vinyl sulfone $5a^6$ can be used as a possible two-carbon unit for homologation. We concieved, that the primary adduct 6a could be transformed to the desired carboxylic acid 9 by oxidation to the corresponding sulfoxide 7a and subsequent Pummerer rearrangement⁷ to 8. This, in turn, can be hydrolyzed to 9. In most cases the initial radical addition is a high yielding reaction (Table 1). Consequently, the overall yield of this type of homologation sequence depends on the subsequent non-radical steps. Although this method was successful in the case of three model compounds 2a-c, the four-step sequence resulted in a moderate overall yield (e.g. 57 % in the 2a to 9a reaction). Also the need to oxidize the sulfide to sulfoxide could be difficult in the presence of multiple olefinic linkages. We therefore examined the trimethylsilyl olefin 5c (X = Me₃Si) prepared according to the literature⁸. The radical addition process was efficient (Table 2) but again the only way to convert the product to the desired homo-acid was by Pummerer type chemistry.

We then examined the enol-phosphate 5b, which was readily prepared by the Perkow⁹ reaction on thiophenyl chloroacetate followed by peracid oxidation¹⁰. This olefin reacted smoothly with radicals. Thus the



Scheme 1

 Table 1 Radical homologation of primary carboxylic acids with phenyl vinyl sulphone as trap.

Acid	R	Y I E L D (%) ^c				
Acia		13	3 6a	6a 7a	7a 9	
2a	PhCH ₂ CH ₂ -	95	84	92	78 ^d	
2Ъ	CH ₃ CH ₂ CH ₂ -	90	88	96	50 ^ª	
2c ^b		95	84	93	56	

a: trapped as an anilide. b: from 11-oxo-lithocholic acid acetate. c: preparative yield. d: 57% overall yield.

overall yield for the synthesis of **8a** increased from 57% (see above) to 85%. Radicals, formed from secondary **2d** and tertiary **2e** carboxylic acids (i.e. cyclohexyl and 1-adamantyl, respectively) gave lower overall yields. The yield in the addition step was 76% for the reaction of **4d** (cyclohexyl radical) with **5b**, whereas the adamantyl radical **4e** gave the corresponding adduct **6** with **5b** in a yield of 61%. Other traps, related to **5a** gave similar results (Table 2) (Scheme 2). Hydrolysis of the bromo-derivative **6d** gave the corresponding acid in low yield.

R	Y I E L D (%)						
R'	PhCH ₂ CH ₂ -	Cyclohexyl-	1-Adamantyl-				
Me ₃ Si- (5c) (2 eq.)	90 ^b	81 ^a	75ª				
(2 eq.)	86 ^a (75) ^c	62 ^a (60)	45 ^a (42)				
(MeO) ₂ (P=O)O- (5b) (5 eq.)	97ª (90)	76ª (72)	61 ^a (60)				
(2 eq.)	65 ^b	-	-				
Br- (30) (5 eq.)	79 ^b	-	-				

Table 2Radical homologation of carboxylic acids with substituted
phenyl vinyl sulphone derivatives $(4 + 5 \longrightarrow 6)$.

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a: determined by NMR. b: preparative yield. c: the yields in parenthesis are preparative yields of the acids **9a-c.**

SO₂Ph
RCH₂CSiMe₃

$$i)$$
 MCPBA
 $i)$ RCH₂CO₂H
 $i)$ RCH₂CO₂H
 $i)$ RCH₂CO₂Ph
RCH₂COP(=O)(OMe)₂
 $i)$ RCH₂COP(=O)(OMe)₂
 $i)$ RCH₂COP(=O)(OMe)₂
 $i)$ RCH₂COP(=O)(OMe)₂
 $i)$ RCH₂CO₂H
 $MeOH$
 $i)$ RCH₂CO₂H
 $i)$ Yield: 60-90%
(depending on R)
 $i)$ RCH₂CO₂H
 $i)$ Yield: 40%
 $i)$ R = PhCH₂CH₂-

Typical procedure:

To the solution of the corresponding acyl derivative of N-hydroxy-2-thiopyridone 3 (1 mmol) in dry methylene dichloride (3 ml) was added the olefin 5 (2 or 5 mmol) under argon at 0° C and the mixture photolysed at 0-5°C (ice bath) with a 150 W tungsten lamp until decolorized. Then the reaction mixture was concentrated in vacuum and the next step was performed without isolation of 6.

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