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Homologation of Carboxylic Acids by Improved Methods Based on Radical Chain Chemistry of Acyl Derivatives of N-Hydroxy-2-thiopyridone

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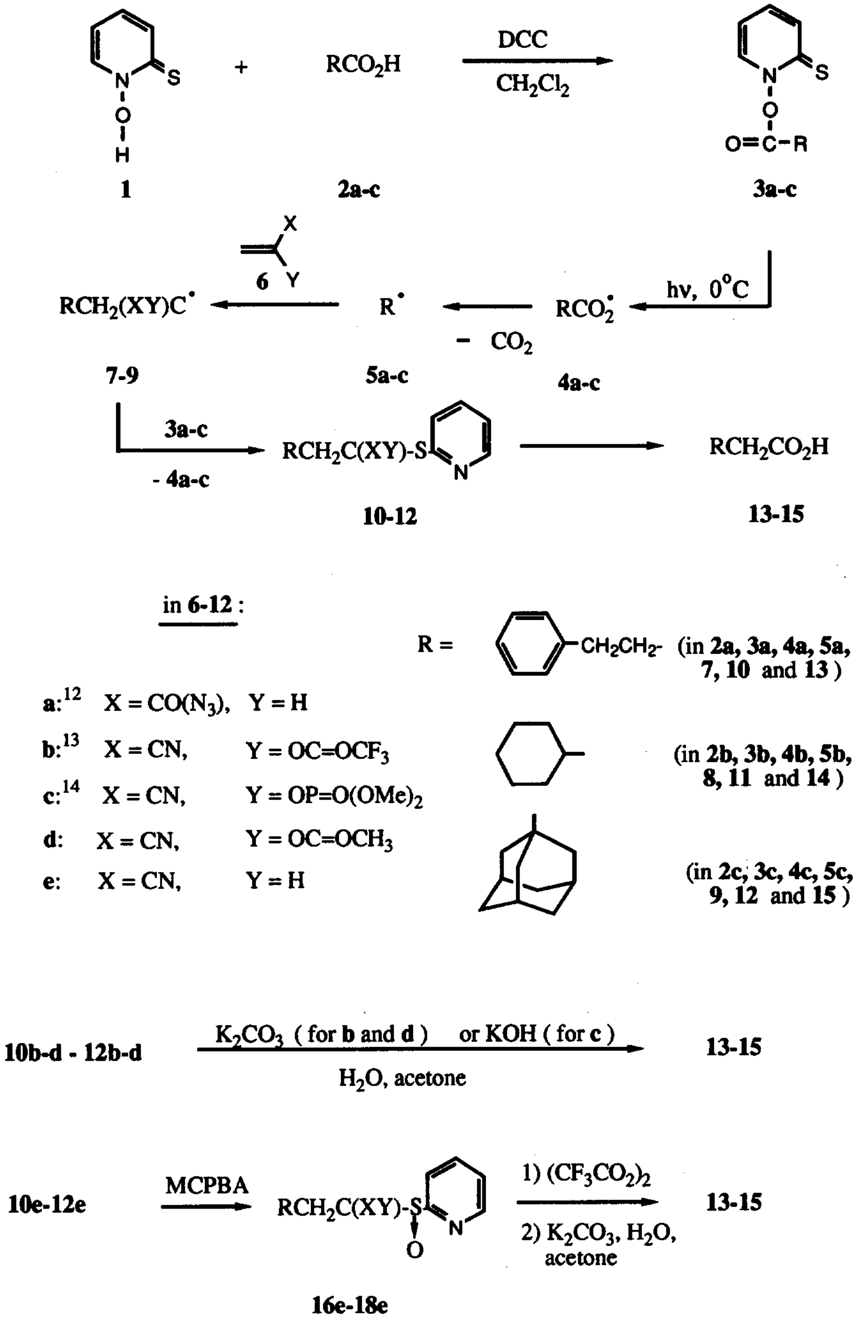
Abstract: Reaction of substituted terminal olefins with carbon radicals generated from carboxylic acids gives adducts that can be transformed to one carbon atom longer homo-acids in high overall yield. With **6b** yields are very good and the conditions of hydrolysis exceptionally mild.

A convenient method for generating carbon radicals from carboxylic acids *via* O-acyl derivatives of N-hydroxy-2-thiopyridone[1,2] has become a widely used synthetic tool.[2-4] This is because the nucleophilic carbon radicals generated by visible light photolysis can be trapped efficiently by electron-deficient (usually terminal) olefins.[5]

The strategy for homologation of carboxylic acids is shown in Scheme 1. Based on earlier findings, various electron-deficient olefins can be used as radical traps to solve the one-carbon homologation of carboxylic acids (this is the two carbon problem, since we remove one carbon when the radical is generated and then add two carbon atoms, the terminal one being used as the precursor of the new carboxyl function).[6,7] We studied earlier the use of vinyl sulfones[8] to provide an alternative to the Arndt-Eistert-Wolff synthesis.[9] Thus, N-hydroxy-2-thiopyridone **1** was transformed to the corresponding O-acyl-N-hydroxy-2-thiopyridone derivative **3** with selected carboxylic acids **2a-c**. These carboxylic acids were selected to generate primary, secondary and tertiary radicals, respectively. The known visible light photolysis in an ice bath with a commercial 150 W tungsten lamp generated the corresponding acyloxy radicals **4a-c**. In the case of the acids selected these radicals decarboxylate smoothly to the corresponding nucleophilic carbon radicals **5a-c** which were trapped by olefin **6** to furnish adduct radicals **7-9**. These radicals carry the radical chain by reacting with the starting **3** to form the corresponding trapped product **10-12** and acyloxy radical **4**. The latter then re-enters the radical cycle described above (Table 1).

Although trapping with various vinyl sulfones was efficient the conditions for transforming the terminal carbon to carbonyl were less satisfactory. In the present study we first used the known acryloyl azide **6a**. The trapping was efficient, but the rearrangement of the products to isocyanates was unsatisfactory. The olefin **6b**, on the other hand, was the best reagent. Addition of radicals was efficient and hydrolysis to homo-acid was


1
RCO2H
2a-c
DCC
CH2Cl2
3a-c
O=C-R
hv, 0°C
RCO2•
4a-c
- CO2
R•
5a-c
6
X
Y
RCH2(XY)C•
7-9
3a-c
- 4a-c
RCH2C(XY)-S
10-12
RCH2CO2H
13-15
in 6-12 :
R =
-CH2CH2- (in 2a, 3a, 4a, 5a, 7, 10 and 13)
(in 2b, 3b, 4b, 5b, 8, 11 and 14)
(in 2c, 3c, 4c, 5c, 9, 12 and 15)
a:12 X = CO(N3), Y = H
b:13 X = CN, Y = OC=OCF3
c:14 X = CN, Y = OP=O(OMe)2
d: X = CN, Y = OC=OCH3
e: X = CN, Y = H
10b-d - 12b-d
K2CO3 (for b and d) or KOH (for c)
H2O, acetone
13-15
10e-12e
MCPBA
RCH2C(XY)-S
O
16e-18e
1) (CF3CO2)2
2) K2CO3, H2O, acetone
13-15

Scheme 1

also easy. The corresponding acetate 6d was not such a good trap, but the hydrolysis to homo-acid was also easy. The enol phosphate 6c, made by a Perkow reaction, was not such a good trap and did not merit further study. Acrylonitrile 6e was, as expected, an excellent trap, but conversion to the homo-acid would require the same Pummerer type rearrangement[10,11] that we have already described.[8]

Table 1 Radical homologation of carboxylic acids with substituted ethylene derivatives (**5a-c** + **6** $\longrightarrow$ **10-12**).

R / Radical trap		YIELD(%)[a]		
		$PhCH_2CH_2$- (**10**)	Cyclohexyl- (**11**)	1-Adamantyl- (**12**)
6a	(2 eq.)	89	79	40
6b	(2 eq.)	90 (81)[b]	80 (71)[b]	75 (52)[b]
	(5 eq.)	95 (86)[b]	83 (75)[b]	79 (56)[b]
6c	(2 eq.)	55	33	36
	(5 eq.)	65	52	38
6d	(2 eq.)	74 (52)[b]	54 (41)[b]	30 (26)[b]
	(5 eq.)	75	60	33
6e	(2 eq.)	97	94	87

[a] determined by ^{1}H NMR. [b] preparative yield of the corresponding homo-acids.

Typical procedure:

To the solution of the corresponding acyl derivative of N-hydroxy-2-thiopyridone (**3a-c**) (1 mmol) in dry methylene dichloride (3 ml) was added the olefin (**6b**)[13] (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 adduct **10-12**. Water (10 ml), acetone (10 ml) and potassium carbonate (10 equiv.) were added to the evaporation residue and the solution was stirred for 12 h at 25°C. Then the acetone was removed under vacuum and the aqueous layer was washed with mehylene dichloride (20 ml) to remove non-polar impurities. The aqueous layer was then acidified with 1M HCl to pH =1 and extracted with ethyl acetate (3 x 10 ml). The ethyl acetate solution was then washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated in vacuum. The product (**13-15**) was crystallized from CH_2Cl_2/hexanes.

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