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Two Carbon Homologation of Carboxylic Acids Using Acrylamide as a Radical Trap

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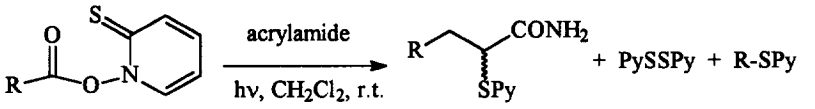
Abstract: Photolysis of *O*-acyl derivatives of *N*-hydroxy-2-thiopyridone in the presence of acrylamide in dichloromethane furnished crystalline 2-(pyridine-2-thiyl)-carboxamides. Desulfurization of the latter by nickel boride afforded primary amides in excellent yields. © 1997 Elsevier Science Ltd.

The increasing use of radical chemistry in organic synthesis is the result of the mild reaction conditions afforded by a plenitude of convenient radical sources.[1] The *O*-acyl derivatives of *N*-hydroxy-2-thiopyridone (Barton esters) have played an important role as sources of disciplined radicals.[2] Numerous olefins have been used as radical traps to form carbon-carbon bonds.[3] Using acrylate esters and derivatives as radical traps, we successfully applied this chemistry to the homologation of carboxylic acids,[4] including the synthesis of the biologically important α-keto acids.[5] As a continuation of our research, we studied the use of acrylamide as a radical trap. This has not been used before and would lead to a convenient synthesis of primary amides from carboxylic acids with two-carbon homologation. The versatile amide function can readily be converted to other derivatives.[6]

Derivatives of primary, secondary, and tertiary carboxylic acids, **1a-e**, were readily synthesized as lime-yellow crystals.[7] Due to the limited solubility of acrylamide in organic solvents, the photo-reactions were carried out in dichloromethane at room temperature. The decarboxylation of Barton esters in the presence of acrylamide was initiated either by a tungsten lamp (150 W, Q-beam) or by ordinary laboratory lighting. Although initiation with the latter demanded longer reaction times, the two methods inevitably afforded a comparable yield of products (Table 1, Entries 2-5). The 2-(pyridine-2-thiyl)-carboxamides **2a-e** were isolated as crystalline solids. The lower yields compared to those using acrylate esters[5] as the radical trap could be due

to the background rearrangement or to oligomerization of acrylamide. The more reactive primary carbon radical resulted in a larger amount of rearrangement product (Entry 1). The steric-hindered tertiary carbon radicals such as those produced by the *t*-butyl and 1-adamantyl derivatives were more prone to produce oligomerization of the olefin and, correspondingly, lower yields (Entries 6,7). The isolation of 2,2′-dipyridine disulfide (PySSPy) and rearrangement products (RSPy) in relatively small amounts supported this hypothesis. The oligomers of acrylamide were presumably more polar and more soluble in water, and thus were lost during aqueous work-up. These facts considered, we conclude that acrylamide is an effective radical trap for radicals from Barton esters.



1a-e **2a-e**

R = **a**: $Ph(CH_2)_2$; **b:** $(CH_3)_2CH$; **c**: c-C_6H_{11}; **d**: $(CH_3)_3C$; **e**: 1-adamantyl.

Table 1. Products and yields of Barton-ester radical chain reactions.

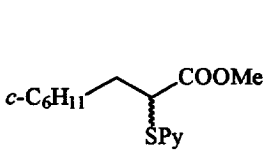
entry	substrate	photolysis conditions	product[a] (yield %)	m. p.[b] (°C)	PySSPy (%)	R-SPy (%)
1	**1a**	Q-beam, 6 min	**2a** (62)	82-83	14	17
2	**1b**	lab light, 7 h	**2b** (60)	95-96	5	2
3	**1b**	Q-beam, 5 min	**2b** (63)		9	2
4	**1c**	lab light, 7 h	**2c** (73)	141-142	10	10
5	**1c**	Q-beam, 5 min	**2c** (71)		12	9
6	**1d**	Q-beam, 20 min	**2d** (54)	88-89	trace	1
7	**1e**	Q-beam, 30 min	**2e** (56)	170-171	trace	trace

[a] All new compounds gave satisfactory NMR and microanalytical data.

[b] The compounds were recrystallized from hexanes-dichloromethane.

When acrylamide was photolyzed in dichloromethane with a tungsten lamp at room temperature, it was recovered unchanged after 30 minutes. This confirms that the acrylamide is not involved in the initiation step of the radical chain reactions.

For comparison, when **1c** was photolyzed in the presence of methyl acrylate at 0°C, methyl 3-cyclohexyl-2-(pyridine-2-thiyl)-propionate **3** and the double addition product **4** were obtained in isolated yields of 83 and 11%, respectively.



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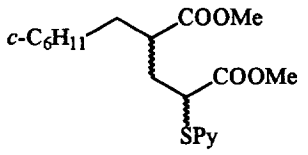

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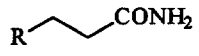
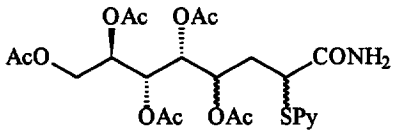


5a: R = c-C_6H_{11}

5b: R = 1-adamanyl



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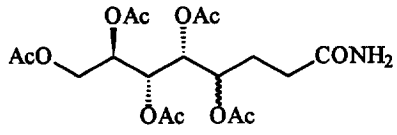

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The combination of nickel(II) chloride and sodium borohydride ('nickel boride'[8]) was found to be very effective for desulfurization of pyridine sulfide compounds. The 3-cyclohexyl-propionamide **5a** (m.p. 119-120°C, lit.[9] m.p. 119-120°C) was obtained in quantitative yield from the reduction of **2c**, and under the same conditions, the 3-adamantyl-propionamide **5b** (m.p. 145-146°C) was obtained in 94% yield from **2e**.

When the derivative of 2,3,4,5,6-penta-*O*-acetyl-D-gluconic acid,[10] prepared *in situ* due to its instability, was photolyzed in the presence of acrylamide, the eight-carbon sugar compound **6** and the corresponding background rearrangement product were isolated in 40 and 41% yields, respectively. Reduction of **6** by nickel boride at room temperature afforded **7** as a mixture of two diastereomers in 75% yield.

In conclusion, the two-carbon homologation of carboxylic acids to primary amides through Barton esters can be achieved using acrylamide as the radical trap followed by desulfurization with nickel boride.

Typical Procedures: *Photo-reaction*. To a solution of acrylamide (142 mg, 2 mmol) in dichloromethane (20 ml) was added **1c** (231 mg, 1 mmol) under an argon atmosphere at room temperature. The yellow solution was irradiated with a tungsten lamp (150 W) for five minutes. After stirring for 30 minutes at room temperature, the white suspension was filtered and the precipitate was washed with dichloromethane. The filtrate was diluted with dichloromethane, washed with distilled water, and dried with anhydrous magnesium sulfate. After removal of the solvent, isolation by a short silica gel column (Et_2O-hexanes 2:1) afforded **2c** as white crystals (193 mg, 71%).

Desulfurization: To a mixture of **2c** (52 mg, 0.2 mmol) and $NiCl_2$ (650 mg, 5 mmol) in ethanol (35 ml) was added slowly a solution of $NaBH_4$ (378 mg, 10 mmol) in EtOH-H_2O (5ml:5ml) under an argon atmosphere. After stirring for five hours at room temperature, the reaction mixture was filtered through Celite® 545 and

washed with dichloromethane. The filtrate was diluted with dichloromethane, washed with distilled water, and dried with anhydrous magnesium sulfate. Removal of the solvent furnished pure compound **5a** as colorless crystals (31 mg, 100%).

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