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The Reaction of Carbon Radicals with Sulfur. A Convenient Synthesis of Thiols from Carboxylic Acids.

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Abstract: A new synthesis of thiols in high yield utilizing carbon radicals and elemental sulfur is demonstrated. The procedure is applicable to 1°, 2° and 3° carboxylic acids.

Thiols have been prepared in a wide variety of ways, however, many of these procedures suffer from the disadvantage of being specific only to certain organic substrates or form unwanted sulfur containing by-products.[1] For example, treatment of alkyl halides with sodium hydrogen sulfide (NaSH) is a commonly used procedure, but fails completely for tertiary halides due to competing elimination. [1,2]

Among the other more useful methods for the formation of thiols are the reaction of Grignard reagents with controlled quantities of sulfur,[1] the reduction of sulfonyl halides,[1] sulfonic acids[3] and disulfides[4] or the addition of hydrogen sulfide to alkenes.[1] Reduction of di- and polysulfides with $LiAlH_4$ formed from the reaction of carbon radicals with sulfur monochloride has also been employed as a synthesis of thiols of limited utility.[5]

The acyl derivatives of N-hydroxy-2-thiopyridone (Barton PTOC esters) are a convenient and inexpensive source of carbon radicals. Recently we showed[6] that radicals obtained by photolysis of these derivatives reacted with white phosphorous to furnish, after oxidation with H_2O_2, a new method for the conversion of carboxylic acids into the corresponding phosphonic acids. We now report the same reaction with elemental sulfur.

Barton PTOC esters of phenethyl, cyclohexyl and 1-adamantyl carboxylic acids were prepared according to the general procedure outlined.[7] Photolysis of these esters in the presence of elemental sulfur afforded after reduction of the products with sodium borohydride the corresponding thiols in excellent yield as depicted in Table 1. As can be seen the method is applicable to primary, secondary and tertiary carboxylic acids.

The intermediate products formed from the photolysis of the Barton PTOC esters in the presence of S_8 were also analyzed for all three examples in order to investigate the mechanism of the reaction of carbon centered radicals with S_8. The products isolated, normalized to 100% are displayed in Table 2. The products were identified by comparison with authentic samples or characterized by standard procedures.[8]

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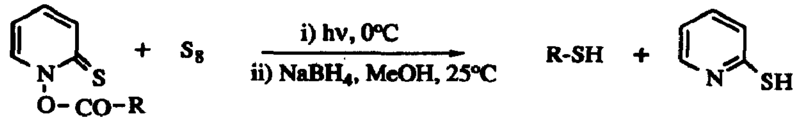
Table 1. Synthesis of thiols from carboxylic acids.



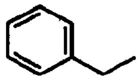
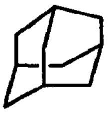
R	Yield of thiol (R-SH)
	98%
	94%
 (tert.)	88%

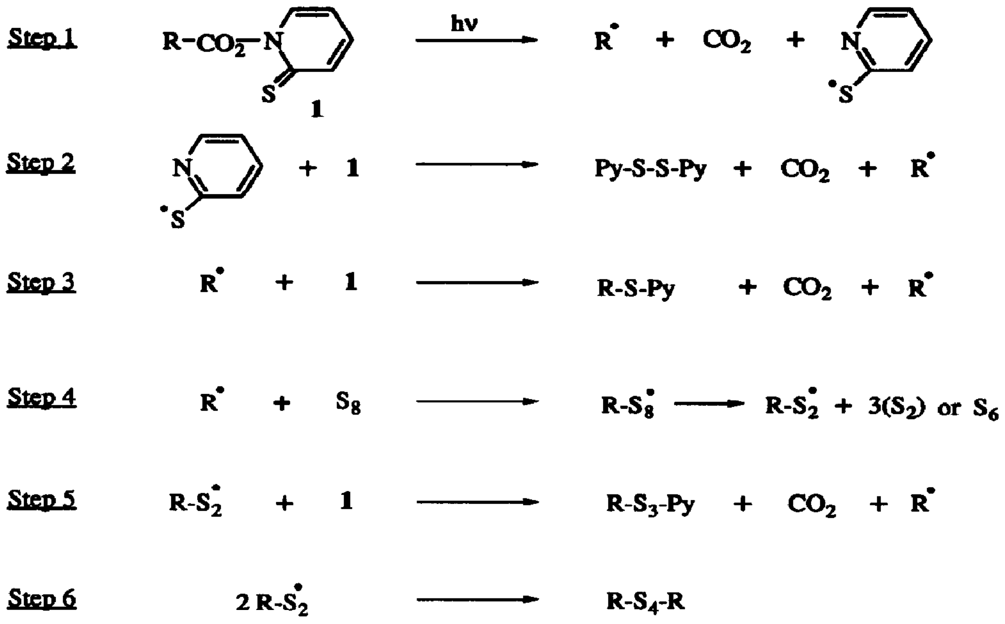
Table 2. Products (%, normalized to 100%) isolated after photolysis of Barton PTOC esters in the presence of elemental sulfur.

Entry	R	$R\text{-}S_4\text{-}R$	$R\text{-}S_3\text{-}Py$	R-S-Py	Py-S-S-Py
1	Phenethyl	28	37	10	25
2	Cyclohexyl	29	32	11	28
3	1-Adamantyl	32	26	15	27
4	1-Adamantyl[a]	26	<1	47	26

[a] Performed at 120°C with four equivalents S_8.

Scrutiny of the product yields (Table 2, Entries 1-3) indicates that the formation of the sulfur containing products is unaffected by steric factors for primary, secondary and tertiary substrates. A radical chain mechanism which accounts for all the observed products is depicted in Scheme 1.

Initiation (Step 1) results from the irradiation of the Barton PTOC esters causing homolysis of the oxygen-nitrogen bond affording the alkyl radical (R·), carbon dioxide and the thiopyridyl radical. Steps 2-5 represent propagation steps and account for the formation of three of the sulfur containing products, namely, Py-S-S-Py, R-S-Py and $R\text{-}S_3\text{-}Py$. The key step in this mechanism is step 4 which involves the reaction of a carbon-centered radical with S_8. Elemental sulfur being an eight-membered ring at ambient temperature is readily cleaved by carbon radicals due to the weak sulfur-sulfur bond strength (*c.a.* 33 kcal mol^{-1}),[9] and the high thiophilicity of the carbon radical. The intermediate $R\text{-}S_8\cdot$ radical breaks down to afford the perthiyl radical ($R\text{-}S_2\cdot$) which does not fragment further due to the stronger carbon-sulfur bond.



Scheme 1.

Finally, step 6 represents a termination process and accounts for the formation of the dialkyl tetrasulfide (R-S_4-R). The lack of formation of dialkyl disulfide (R-S_2-R) indicates that the dialkyl tetrasulfide does not result from the combination of a R-S_4· radical with R·. Interestingly, pyrolytic decomposition of the Barton PTOC ester in the presence of four equivalents of S_8 at 120°C resulted in an increased yield of R-S-Py at the expense of R-S_3-Py. (Table 2, Entry 4). The formation and reactions of S_2 have been extensively studied by Steliou and by other investigators.[10]

In conclusion, the sulfur containing products resulting from the reaction of carbon-centered radicals (generated from Barton PTOC esters) with elemental sulfur have been identified. The formation of these products were found to be unaffected by steric effects. Furthermore, reduction with $NaBH_4$ results in the formation of thiols in excellent yield.

Typical procedure for the preparation of thiols from PTOC esters : To an ice-cooled solution of anhydrous methylene chloride (15 ml) under an inert atmosphere was added elemental sulfur (0.29 mmol, 74 mg) followed by the thiohydroxamate (1.0 mmol). Photolysis was initiated and continued until starting materials disappeared (1 hr.). The mixture was allowed to attain room temperature and an anhydrous methanolic solution (10 mL) of sodium borohydride (20 mmol) added dropwise over 15 min. The mixture was stirred for an additional hour, then poured into sulfuric acid (1N, 60 mL). The aqueous phase was extracted with methylene chloride (4 x 20 mL), dried ($MgSO_4$) and the solvent removed in vacuo. Chromatography (hexanes / ethyl acetate, 97 : 3) afforded pure thiols with physical properties in agreement with the known compounds. (phenethyl thiol[11], cyclohexyl and 1-adamantyl thiol[5]).

Procedure for the isolation of sulfur containing intermediates : The reaction was performed in an identical manner to that described above. After completion of the reaction, the volatiles were removed in vacuo and the crude products subjected to column chromatography, (hexanes / ethyl acetate, 97 : 3). Pure products were obtained as follows, (increasing retention times): RS_4R, RSPy, RS_3Py, Py_2S_2.[12]

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