



Radical cyclizations of carboxylic mixed anhydrides

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Abstract

Carboxylic mixed anhydrides are moderately reactive toward alkyl radicals and can be used as radical acceptors in the radical cyclizations, although carboxylic esters and amides are generally unreactive toward alkyl radicals. © 2000 Elsevier Science Ltd. All rights reserved.

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Additions of alkyl radicals onto carbonyl groups are reversible and energetically unfavorable due to strong π -bond strengths of carbonyl bonds. The reverse reactions (β -fragmentation reactions of alkoxy radicals) are faster than additions of alkyl radicals onto carbonyl groups.¹ Thus, it is anticipated that carbonyl derivatives can not be used as efficient radical acceptors. The use of carboxylic acid derivatives as radical acceptors in intermolecular addition reactions is uncommon and only several reports have appeared to date.² Similarly, only several carbonyl derivatives are effective in radical cyclizations to some extent.³

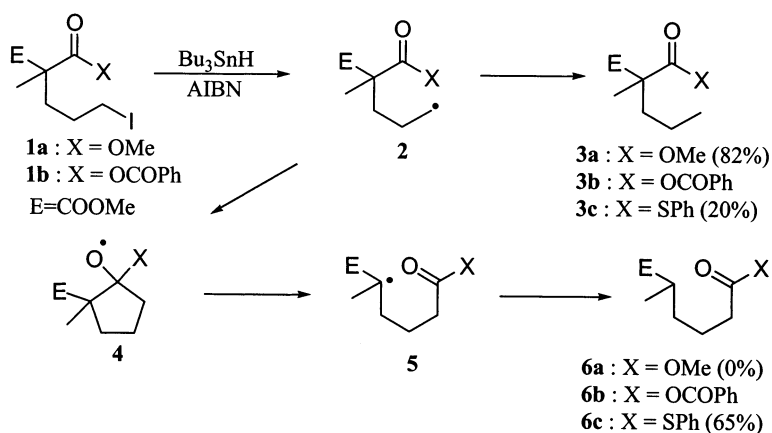


Carboxylic esters and amides are generally unreactive toward carbon-centered radicals and have not been used as radical acceptors although two exceptions have been reported to date.⁴ We assumed that the low reactivity of carboxylic acid derivatives such as esters and amides would be due to the π -bond delocalization of the carbonyl groups with non-bonding electrons of heteroatoms such as oxygen and nitrogen. Thus, the C=O bonds of esters and amides would be something less than the C=O bonds of aldehydes and ketones. If this idea might be true, one can expect that resonance stabilization should be greatly reduced by introducing an electron-

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withdrawing group. The introduction of an electron-withdrawing group should lower the energy of the LUMO of a radical acceptor,⁵ thereby increasing the rate of addition. We have studied this intriguing possibility of using carboxylic acid derivatives such as mixed anhydrides as radical acceptors.

We initially studied the radical reaction of ester **1a** with Bu₃SnH/AIBN in refluxing benzene under a high dilution and direct reduction product **3a** was isolated in 82% yield without yielding β-cleavage product **6a** as shown in Scheme 1. However, radical reaction of mixed anhydride **1b** with Bu₃SnH/AIBN under the same condition resulted in the formation of a mixture of **3b** and **6b**. Since **3b** and **6b** were unstable on silica gel, the mixed anhydride products **3b** and **6b** were treated with thiophenol and dicyclohexylcarbodiimide in the presence of a catalytic amount of 4-dimethyl-aminopyridine⁶ to afford the thioester **3c** and **6c** in 20 and 65% yields, respectively. Apparently, 1,4-migration product **6b** was formed by the addition of the alkyl radical to mixed anhydride **1b**, subsequent β-cleavage and reduction by Bu₃SnH. We also briefly studied 1,2-migration of mixed anhydride group via 3-*exo* cyclization (Scheme 2). Radical reaction of mixed anhydride **7** under the same conditions followed by treatment with thiophenol and DCC-DMAP provided a mixture of **8** and **9** in 15 and 61% yields, apparently resulting from 1,2-migration and the direct reduction, respectively. As we anticipated, the results obtained here clearly indicate that mixed anhydrides could be used as radical acceptors, although the efficiency of this process would depend very much on the nature of the substrate.



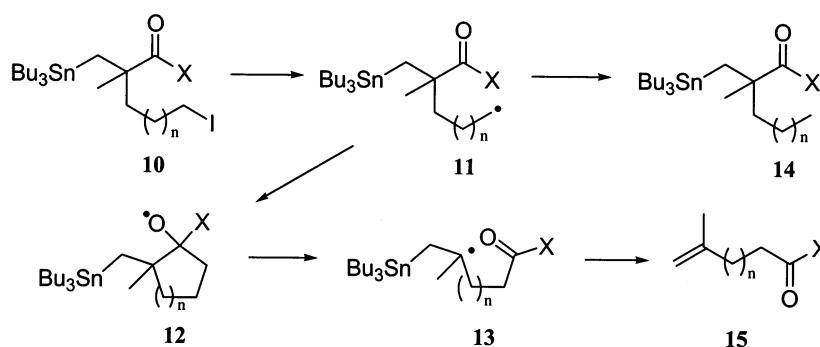
Scheme 1.



Scheme 2.

In order to study the efficiency of several different types of carboxylic mixed anhydrides as radical acceptors in the radical cyclizations, we prepared carboxylic mixed anhydride **10a**, carboxylic carbonic anhydride **10b**, carboxylic phosphinic anhydride **10c**, and carboxylic phos-

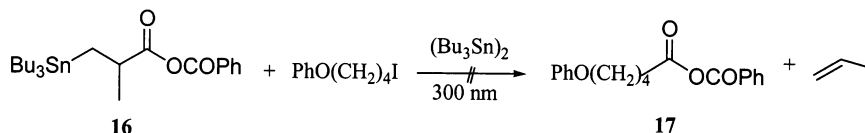
phonic anhydride **10d**. Radical cyclization of alkyl radical **11** would give rise to compound **15** via two consecutive β -cleavages of alkoxy radical **12** (Scheme 3). Treatment of mixed anhydride **10a** with a catalytic amount of hexabutylditin (0.1 equiv.) in benzene at 300 nm for 7 h followed by addition with thiophenol and DCC–DMAP afforded a mixture of **14a** and **15a** in 7 and 78% yields, respectively.⁷ Experimental results are summarized in the Table 1. The mixed anhydride products were converted into the corresponding thioesters due to instability of mixed anhydrides on silica gel. Among four different mixed anhydrides, carboxylic carbonic anhydrides **10b** seems to be the most efficient, although **10a** is equally effective. 1,4-Migration ($n=1$) via 5-*exo* ring closure was slightly more efficient than 1,5-migration ($n=2$) via 6-*exo* ring closure. Carboxylic phosphinic anhydride **10c** and phosphonic anhydride **10d** were somewhat less efficient than **10a** and **10b** but still gave 1,4- and 1,5-migration products as a major product.



Scheme 3.

Table 1
Intramolecular additions of alkyl radicals onto mixed anhydrides

Entry	Substrate	Time, h	n	Product (X=SPh), yield %	
				14	15
1	10a : X = OCOPh	9	1	7	78
2		6	2	18	69
3	10b : X = OCOOCH ₂ Ph	7	1	5	74
4		6	2	8	79
5	10c : X = OP(O)Ph ₂	13	1	21	61
6		8	2	16	53
7	10d : X = OP(O)(OPh) ₂	12	1	29	61
8		8	2	20	52



Encouraged by the results obtained here, we next studied the possibility of using mixed anhydrides as radical acceptors in the intermolecular radical carboxylation reaction. However, our attempts were unsuccessful. When a benzene solution of mixed anhydride **16** was treated with 4-phenoxybutyl iodide in the presence of hexabutylditin (0.1 equiv.) at 300 nm for 10 h, the desired mixed anhydride **17** was not detected and a small amount of 4-phenoxybutane from the direct reduction was isolated along with the starting iodide and several unidentified products.

In conclusion, we have demonstrated that carboxylic mixed anhydrides were much more reactive than carboxylic esters toward alkyl radicals and could be utilized as radical acceptors in the radical cyclizations.

Acknowledgements

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5. According to the calculation of the energy of the LUMO by MOPAC using PM3 method, acetic anhydride (0.29 eV) has lower energy than methyl acetate (1.10 eV), acetone (0.85 eV), and acetaldehyde (0.83 eV).
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7. A representative experimental procedure is as follows. A solution of **10a** ($n=1$) (61 mg, 0.1 mmol) and bis(tributyltin) (18 mg, 0.03 mmol) in benzene (2 mL) in a pyrex tube was degassed for 10 min and irradiated at 300 nm in a Rayonet photochemical reactor for 9 h. After the solution was concentrated under reduced pressure, the residue was dissolved in methylene chloride (2 mL) and then thiophenol (20 μL , 0.2 mmol), DCC (42 mg, 0.2 mmol), and DMAP (2 mg) were added to the solution. After being stirred at room temperature for 2 h, the reaction mixture was diluted with methylene chloride (20 mL), washed with 0.1 M HCl solution and Na_2CO_3 solution, dried and concentrated to dryness. The residue was subjected to the flash silica gel column chromatography to give **14a** ($n=1$) (3.5 mg, 7%) and **15a** (17 mg, 78%).