Radical reaction of *S*-phenyl chlorothioformate with alkyl iodides: free radical-mediated carboxylation approach

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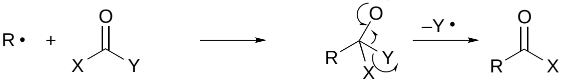
Free radical-mediated carboxylation is achieved by treatment of alkyl iodides with *S*-phenyl chlorothioformate and bis(tributyltin) with irradiation at 300 nm.

Since a free radical-mediated carboxylation reaction was reported by Kharasch and co-workers in the 1940s,[1] no further developments in this area have been noted during the last 50 years, although a free radical carboxylation approach involving carbonylation and iodine atom transfer has recently been reported.[2] This could be due to the fact that alkyl radical additions to C=O bonds are inefficient due to the reversibility of the addition step and the high π-bond strengths of C=O bonds.[3] Thus, intermolecular addition of alkyl radicals to C=O and C=N bonds[4,5] is relatively rare, as compared to C=C bonds. Recently, we have shown that alkyl radical additions to phenylsulfonyl oxime ethers are highly efficient, suggesting the importance of the substituent at the C=N bond.[6] We conceived that the success of alkyl radical additions to C=O bonds would depend very much on the nature of the substituent, which would be closely related to the LUMO energy of carbonyl derivative **1**. We have studied the possibility of developing a free radical carboxylation reaction utilizing carbonyl derivative **1** as a carboxyl equivalent radical acceptor [eqn. (1)].



X , Y = Cl, OMe, NMe$_2$, SR, CN

1 **2**

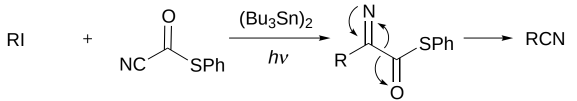
(1)

Before we began our studies with carbonyl derivatives, AM1 calculations for several carbonyl derivatives were performed, as nucleophilic alkyl radicals would react more rapidly with radical acceptors having lower LUMO energy.[7] According to the computational studies, *S*-phenyl chlorothioformate exhibited the lowest LUMO energy among carbonyl derivatives tested in this study. To see whether the computational results are in accordance with experimental results, free radical carboxylation reactions were carried out with 4-phenoxybutyl iodide, carbonyl derivative **1** and bis(tributyltin) using irradiation at 300 nm.[8] As shown in Table 1, dimethylcarbamoyl chloride, methyl chlorofomate and phosgene were totally ineffective. *S*-Phenyl chlorothioformate **1f** gave the best result, although bis(thiophenyl) carbonate **1d** and *S*-methyl chlorothioformate **1e** were effective to some extent. Furthermore, it is noteworthy

Table 1 LUMO energy of **1** and chemical yields of **2**

	Carbonyl derivative **1**	LUMO energy[a]/eV	Product **2**	Yield (%)
1a	$ClC(O)NMe_2$	0.1377	$RCONMe_2$	0
1b	$ClCO_2Me$	0.0039	RCOOMe	0
1c	$C(O)Cl_2$	−0.7740	RCOCl	0
1d	$C(O)(SPh)_2$	−1.0911	RCOSPh	31
1e	ClC(O)SMe	−1.1810	RCOSMe	32
1f	ClC(O)SPh	−1.3863	RCOSPh	60
1g	NCC(O)SPh	−1.2635	RCOCN	0[b]

[a] The LUMO energy was calculated using MOPAC. [b] 4-Phenoxybutyl cyanide (75%) was obtained.

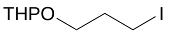
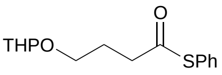
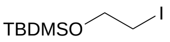
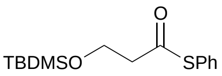
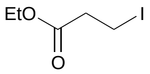
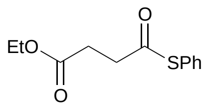
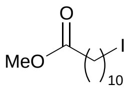
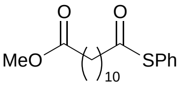
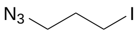
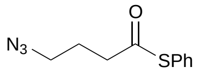
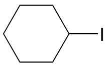
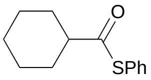
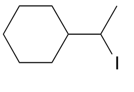
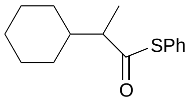
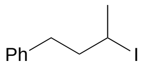
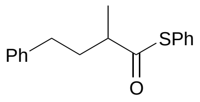
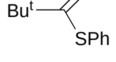
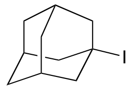
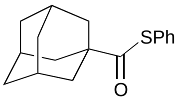


(2)

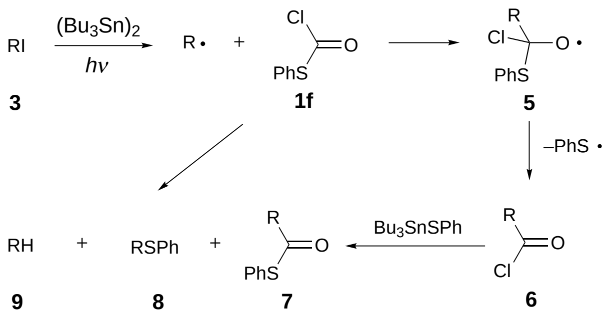
3 **1g** **10** (75%)

R = PhO(CH$_2$)$_4$

Table 2 Preparation of *S*-phenyl thioates from alkyl iodides with *S*-phenyl chlorothioformate

Substrate	Product	Yield (%)
		53 (5)[a] (20)[b]
		55 (5)[a]
		44 (11)[a]
		52 (12)[a] (27)[b]
		48 (9)[a]
		56
		51 (8)[a]
		53
Bu^{t}I		49
		56 (4)[a]

[a] Sulfide product. [b] Direct reduction product.

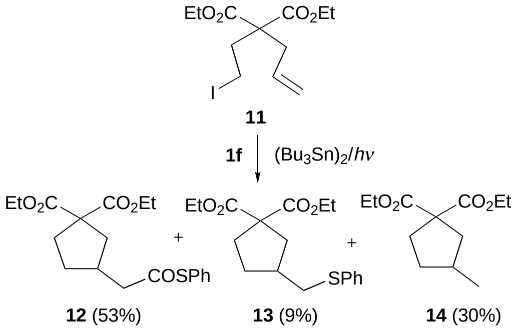


Scheme 1

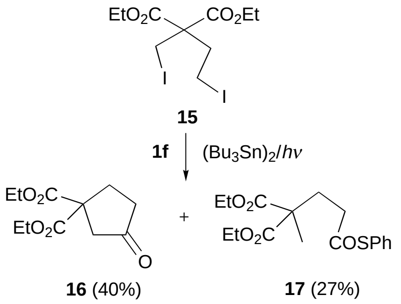
that the radical reaction with *S*-phenyl cyanothioformate **1g** afforded 4-phenoxybutyl cyanide **10** [eqn. (2)]. Apparently, the 4-phenoxybutyl radical attacked the cyano group rather than the carbonyl group. The present result clearly indicates that the LUMO energy is a very important factor in predicting and designing the radical reactions. Treatment of 4-phenoxybutyl iodide with **1f** and bis(tributyltin) in benzene with irradiation at 300 nm for 10 h afforded *S*-phenyl thioate **7** in 60% yield. In addition, 4-phenoxybutane **9** was obtained in 15% yield along with 4-phenoxybutyl phenyl sulfide **8** (8%) due to homolytic substitution by the alkyl radical at the sulfur atom.[9] When the same reaction was carried out in the presence of an equimolar amount of isobutyryl chloride, a mixture of **7** (26%) and *S*-phenyl thioisobutyrate (52%) was obtained.

According to our experimental results, the present approach involves an alkyl radical addition to the C=O bond to generate alkoxy radical **5**, which undergoes β-fragmentation to afford acid chloride **6** (Scheme 1). Reaction of acid chloride **6** with tri-*n*-butyltin phenylthiolate would provide *S*-phenyl thioate **7**.[10]

Table 2 summarizes the experimental results and illustrates the efficiency of the present method. For most of the cases observed, the reaction required 10 h for completion of the reaction and afforded the *S*-phenyl thioates in reasonably good yield. Sterically hindered tertiary alkyl iodides gave similar results. We also studied sequential radical reactions involving cyclization and carboxylation. Radical reaction of olefinic iodide **11** under similar conditions afforded the desired product **12** in 53% yield along with **13** (9%) and **14** (30%) [eqn. (3)]. When a similar reaction was carried out with **15**, cyclopentanone **16** was obtained in 40% yield along with *S*-phenyl thioate **17** (27%) [eqn. (4)]. Further studies on free radical carboxylation related reactions are underway.[11]



(3)



(4)

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Notes and References

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11 A typical procedure for the radical reaction of *S*-phenyl chlorothioformate with an alkyl iodide is as follows. A benzene solution (0.5 ml, 0.4 M in the iodide) of cyclohexyl iodide (42 mg, 0.2 mmol), *S*-phenyl chlorothioformate (70 mg, 0.4 mmol) and bis(tributyltin) (140 mg, 0.24 mmol) in a quartz tube was degassed for 10 min and then irradiated at 300 nm in a photochemical reactor for 9 h. The reaction mixture was concentrated under reduced pressure. EtOAc (3 ml), water (2–3 drops) and KF (116 mg, 2 mmol) were then added and the mixture was stirred at room temperature for 30 min. After the mixture was filtered through a short column of silica gel, the filtrate was concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography to give *S*-phenyl cyclohexanecarbothioate (25 mg, 56%) as a colorless oil: δ_H (200 MHz, $CDCl_3$) 1.23–1.54 (m, 4 H), 1.56–1.87 (m, 4 H), 1.88–2.13 (m, 2 H), 2.53–2.68 (m, 1 H), 7.38 (s, 5 H); δ_C (50 MHz, $CDCl_3$) 25.4, 25.5, 29.5, 52.4, 127.8, 129.1, 129.2, 134.4, 200.6; ν_{max}(NaCl)/cm^{-1} 2928, 1708, 1066, 950.

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