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Tin-Free Radical Carbonylation: Thiol Ester Synthesis Using Alkyl Allyl Sulfone Precursors, Phenyl Benzenethiosulfonate, and CO**

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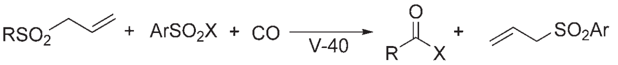
Free-radical carbonylation is synthetically very useful in preparing various carbonyl compounds.[1] Synthetic methods based on free-radical carbonylation utilize mainly highly toxic organotin reagents as mediators.[2] In our efforts to address the problems associated with toxic organotin reagents, we reported that the use of alkyl allyl sulfone precursors is one of the most useful and reliable methods for the generation of alkyl radicals under tin-free conditions and are very effective in radical carbon–carbon bond-formation reactions.[3,4] In our continued efforts to achieve tin-free radical carbon–carbon bond formations,[5] we have recently focused on tin-free radical carbonylations that use alkyl allyl sulfone precursors to prepare thiol esters [Eq. (1)].



(1)

Radical carboxylations were reported by Kharasch et al. in the 1940s,[6] but no significant progress in this area was made in the subsequent 50 years. Direct radical carboxylation of alkyl radicals with carbon dioxide is an extremely difficult process because decarboxylation is a greatly favored process.[7] Thus, radical carboxylations using highly reactive radical trapping agents such as oxalyl acid derivatives[8] and *S*-phenyl chlorothioformate[9] have recently been reported along with an indirect approach involving carbonylation and iodine atom transfer.[10] For the synthesis of thiol esters, radical reactions of aldehydes with disulfides are used.[11]

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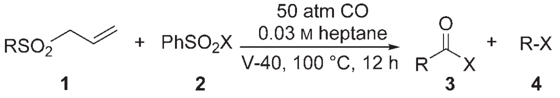
To uncover efficient radical-trapping agents of acyl radicals,[12,13] we screened several phenylsulfonyl derivatives as shown in Table 1. When 4-phenoxybutyl allyl sulfone (**1**) was treated with phenylsulfonyl bromide (**2b**) in the presence of V-40 (1,1′-azobis(cyclohexane-1-carbonitrile)) as initiator under pressurized CO (50 atm, 0.03 M, autoclave) in heptane at 100 °C for 12 h, 4-phenoxybutyl bromide (**4b**) was obtained in 75 % yield along with recovery of the starting material **1** (20 %) while no acid bromide was obtained. The use of phenyl benzeneselenosulfonate (**2c**) gave 4-phenoxybutyl phenyl selenide (**4c**) in 84 % yield, whereas the use of phenylsulfonyl chloride (**2a**) yielded a small amount of the acid chloride (10 %). Apparently, phenylsulfonyl bromide and phenyl benzeneselenosulfonate react with the alkyl radical prior to the carbonylation of the alkyl radical, whereas phenylsulfonyl chloride is too unreactive toward the alkyl radical. When the reaction was attempted using phenyl benzenethiosulfonate (**2d**) under the same conditions, a mixture of thiol ester **3d** (75 %) and alkyl sulfide **4d** (12 %) was isolated along with some starting material (7 %). Furthermore, the use of diphenyl disulfide as a trapping agent under the same conditions was not effective and **3d** was obtained in 15 % yield along with 80 % recovery of **1**.

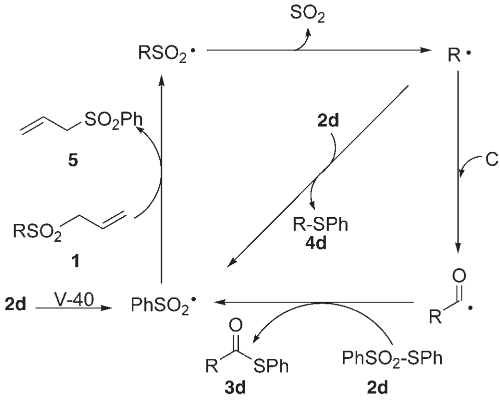
Table 1: Radical carbonylation of alkyl allyl sulfone **1** (R = PhO(CH$_2$)$_4$) with arylsulfonyl derivatives **2**.



2: X =	Yield [%] **3**	**4**	**1**
a: Cl	10[a]	0	76
b: Br	0	75	20
c: SePh	0	84	0
d: SPh	75	12	7

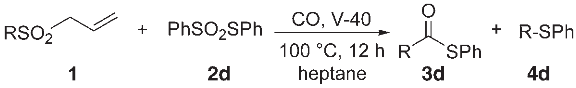
[a] Isolated as the methyl ester.

As shown in Scheme 1, the addition of a phenylsulfonyl radical to **1** produces an alkyl radical through the thermal desulfonylation of the initially generated alkyl sulfonyl radical along with formation of phenyl allyl sulfone (**5**). The alkyl radical can react with CO and/or phenyl benzenethiosulfonate (**2d**) to yield the acyl radical and/or alkyl sulfide **4d**. Therefore, the success of this approach depends critically on obviating the formation of **4d**. To optimize the reaction conditions, the effect of the pressure of CO and the concentration of **1** were investigated (Table 2). As expected, the yield of thiol ester **3d** was increased at the higher pressure of CO while a lower concentration of **1** led to a reduced yield of alkyl sulfide **4d**. The best result was obtained when the reaction was carried out with **2d** (1.5 equiv) and V-40 (0.2 equiv) as initiator in a pressurized autoclave (95 atm of CO) in heptane (0.01 M) at 100 °C for 18 hours. Furthermore, when the effectiveness of alkyl benzenethiosulfonates relative to **2d** was briefly studied, methyl benzenethiosulfonate was found to be equally effective and slightly more reactive than **2d** [Eq. (2)]. Additionally, we explored the application of the present method to synthetically useful pentafluorophenyl thiol esters [Eq. (3)].[14] Treatment of **1** with pentafluorophenyl benzenethiosulfonate (**7**)[15] under the same conditions afforded pentafluorophenyl thiol ester **8** in 82 % yield along with pentafluorophenyl sulfide **9** (16 %). A similar result was also obtained with **6**.



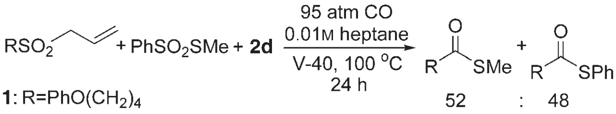
Scheme 1. Tin-free radical carbonylation of alkyl allyl sulfone **1** (R = PhO(CH$_2$)$_4$) with phenyl benzenethiosulfonate (**2d**).

Table 2: Effect of concentration of **1** (R = PhO(CH$_2$)$_4$) and pressure of CO on the tin-free radical carbonylation with **2d**.

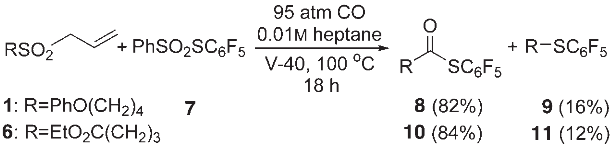


[**1**] [M]	*p*CO [atm]	Yield [%] **3d**	**4d**	**1**
0.05	95	82	11	5
0.02	95	77	3	18
0.02	50	81	8	9
0.01	50	61	3	34
0.01	95	70	0	19
0.01	95[a]	92	0	6

[a] Reaction time: 18 h.



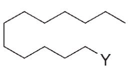
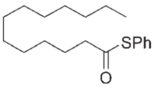
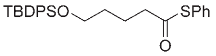
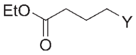
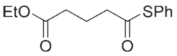
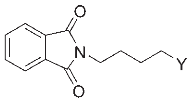
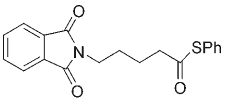
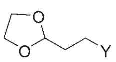
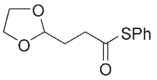
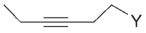
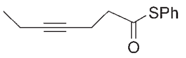
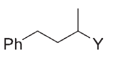
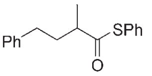
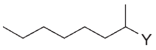
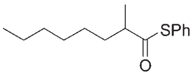
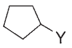
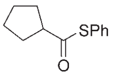
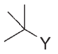
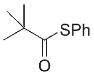
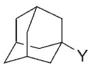
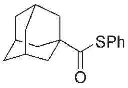
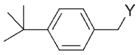
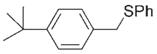
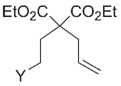
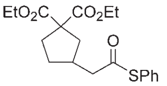
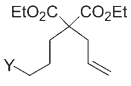
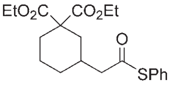
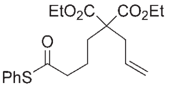
(2)



(3)

Table 3 illustrates the efficiency and the scope of the present method. Primary alkyl radicals worked well, yielding the corresponding thiol esters in high yields under the present

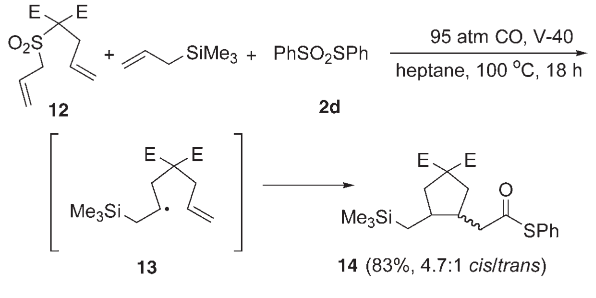
Table 3: Synthesis of thiol esters through tin-free radical carbonylation.

Entry	Alkyl allyl sulfone Y = $SO_2CH_2CH{=}CH_2$	Conditions[a]	Thiol ester	Yield [%][b]
1		A		97
2		A		98
3		A		94
4		A		83
5		A		95
6		A		84[c]
7		A		64 (26)
8		B		80 (11)
9		A		87 (10)
10		A		83 (13)
11		A		33 (57)
12		A		72 (24)
13		A		– (51)[d]
14		A		90
15		A		24
				59

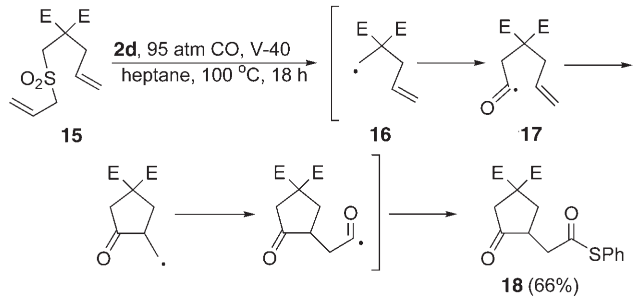
[a] A: **2d** (1.5 equiv), CO (95 atm), heptane, 100 °C, 18 h; B: **2d** (1.5 equiv), CO (130 atm), heptane, 100 °C, 18 h. TBDPS = *tert*-butyldiphenylsilyl. [b] The numbers in parentheses indicate isolated yields of alkyl phenyl sulfides. [c] Starting material (12%) was recovered. [d] Some starting material (46%) was also recovered.

conditions (95 atm of CO, 0.01 M solution of **1**). There was no indication of the formation of alkyl sulfide **4d**. In one case, a small amount of the starting material was recovered (entry 6). However, secondary alkyl radicals led to a significant amount of formation of **4d**. As the radical carbonylation of secondary alkyl radicals is less efficient than that of primary alkyl radicals, secondary alkyl radicals would have more chance to react with **5** prior to carbonylation. At 95 atm of CO, a 64:26 mixture of the thiol ester and the alkyl phenyl sulfide was isolated (entry 7). When the same reaction was repeated at a higher pressure of CO (130 atm) for 18 h, the formation of the alkyl phenyl sulfide was reduced to some extent to yield an 80:11 mixture of **3d** and **4d** (entry 8). As we anticipated, tertiary alkyl radicals gave more direct addition products (entries 11 and 12). The benzylic radical did not undergo carbonylation and reacted with **2d** to give a benzyl phenyl sulfide in 51% yield together with the recovery of some starting material (46%; entry 13). Sequential radical reaction involving cyclization and phenylthio carbonylation afforded the desired product in 90% yield (entry 14). However, in the case of 6-*exo* ring closure, a 24:59 mixture of two products was obtained in favor of the direct carbonylation product, apparently as a result of the competition between 6-*exo* ring closure and the direct carbonylation (entry 15).[16] When a four-component coupling reaction using **12**, allyl trimethylsilane, CO, and **2d** was carried out under the same conditions, a 4.7:1 diastereomeric mixture of the desired product **14** was isolated in 83% yield (Scheme 2).[17] Evidently, the electrophilic alkyl radical generated from **12** failed to undergo carbonylation and reacted with allyl trimethylsilane to yield intermediate **13**.

Next, the possibility of a double carbonylation was explored.[18] Reaction of **15** with **2d** and CO yielded acyl radical **17** through carbonylation of the radical intermediate **16**. The subsequent 5-*exo* ring closure of **17** and CO trapping followed by quenching with **2d** afforded thiol ester **18** according to the scheme proposed (Scheme 3). When **15** was subjected to the



Scheme 2. E = CO_2Et.



Scheme 3. E = CO_2Et.

standard carbonylation conditions, **18** was isolated in 66% yield.

In conclusion, we have reported that tin-free radical carbonylation is successfully achieved using alkyl allyl sulfone precursors and have developed a highly efficient method for the synthesis of thiol esters using phenyl benzenethiosulfonate as a trapping agent. This approach provides ready access to other related carbonyl derivatives.

Experimental Section

Typical procedure: Heptane (12 mL), 4-(prop-2-ene-1-sulfonyl)butyric acid ethyl ester (26 mg, 0.12 mmol), phenyl benzenethiosulfonate (**2d**; 45 mg, 0.18 mmol), and V-40 (8 mg, 0.03 mmol) were placed in a 50-mL stainless steel autoclave. The autoclave was sealed and purged with CO (3 × 10 atm). The autoclave was then pressurized with CO (95 atm) and heated, with stirring, at 100 °C for 18 h. After excess CO was discharged at room temperature, the solvent was evaporated, and the residue was purified by column chromatography on silica gel using ethyl acetate and *n*-hexane (1:20) as eluant to give 4-phenylsulfanylcarbonylbutyric acid ethyl ester (28 mg, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.24$ (t, $J = 7.1$ Hz, 3H), 2.01 (quin, $J = 7.3$ Hz, 2H), 2.38 (t, $J = 7.3$ Hz, 2H), 2.72 (t, $J = 7.3$ Hz, 2H), 4.12 (q, $J = 7.1$ Hz, 2H), 7.39 ppm (s, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.2$, 20.6, 33.0, 42.5, 60.5, 127.6, 129.2, 129.4, 134.5, 172.7, 196.8 ppm; IR (polymer): $\tilde{\nu} = 749$, 1026, 1187, 1442, 1479, 1708, 1735, 1963, 2983 cm^{-1}; HRMS [M^+] calcd for $C_{13}H_{16}O_3S$: 252.0820; found: 252.0815

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