Synthetic Methods

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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)].

$$RSO_2$$
 + $ArSO_2X$ + $CO \longrightarrow O_{-V-40}$ + SO_2Ar (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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6183

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Communications

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

Table 1: Radical carbonylation of alkyl allyl sulfone 1 ($R = PhO(CH_2)_4$) with arylsulfonyl derivatives **2**.

RSO ₂	+ PhSO ₂ X	50 atm CO 0.03 м heptane	0 ∐ +	R-X	
1	2	V-40, 100 °C, 12 h	R X 3	4	
=	Yield [%]				
	3	4			1
	10 ^[a]	()		76
r	0	75	5		20
ePh	0	84	1		C
Ph	75	12	2		7
	RSO ₂ 1 = Ph Ph	$ \frac{1}{1} = \frac{3}{10^{[a]}} $ $ \frac{1}{10^{[a]}} $	$\begin{array}{c} \text{RSO}_2 & + \text{ PhSO}_2 X \\ \hline 0.03 \text{ M heptane} \\ \hline V-40, 100 \ ^\circ\text{C}, 12 \text{ h} \\ \hline 1 & 2 \\ \end{array}$ $= \begin{array}{c} \text{Yield} \\ \hline 3 & 4 \\ \hline 10^{[a]} & 0 \\ \text{r} & 0 & 75 \\ \text{ePh} & 0 & 84 \\ Ph & 75 & 12 \\ \end{array}$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

[a] Isolated as the methyl ester.

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.

As shown in Scheme 1, the addition of a phenylsulfonyl radical to 1 produces an alkyl radical through the thermal

RSO

PhSO₂

SO₂P

5

RSO

2d _____

SO2

2d

R-SPh 4d

PhSO₂-SPh

2d

Scheme 1. Tin-free radical carbonylation of alkyl allyl sulfone 1 $(R = PhO(CH_2)_4)$ with phenyl benzenethiosulfonate (2 d).

C

SPh 3d

6184 www.angewandte.org

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CO

C

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

Table 2: Effect of concentration of 1 ($R = PhO(CH_2)_4$) and pressure of CO on the tin-free radical carbonylation with **2d**.

RSO ₂	+ 1	PhSO ₂ SPh 2d	CO, V-40 100 °C, 12 h heptane	0	R-SPh 4d
[1] [м]	рC	O [atm]		Yield [%]	
			3 d	4 d	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.

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 (0.01m) 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.



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

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 vielded 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

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

Entry	Alkyl allyl sulfone Y=SO ₂ CH ₂ CH=CH ₂	Conditions ^[a]	Thiol ester	Yield [%] ^[b]
1	Correct of the second s	А	SPh	97
2	TBDPSO	A	TBDPSO	98
3	EtO Y	A	EtO SPh	94
4	Ny	А	SPh O O	83
5	CO Y	А	SPh SPh	95
6	<u>∖_</u> ∕_Y	А	SPh O	84 ^[c]
7 8	Ph	A B	Ph SPh	64 (26) 80 (11)
9	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	A	SPh	87 (10)
10	ζγ	А	SPh	83 (13)
11	\downarrow_{r}	А	SPh	33 (57)
12	D,	A	SPh	72 (24)
13	Y Y	А	SPh SPh	- (51) ^[d]
14	EtO ₂ C CO ₂ Et	А	EtO ₂ C CO ₂ Et	90
15	EtO ₂ C CO ₂ Et	A	EtO ₂ C CO ₂ Et 0 EtO ₂ C CO ₂ Et	24
			PhS	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, 0.01M 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



afforded thiol ester 18 according to

the scheme proposed (Scheme 3).

When 15 was subjected to the

Scheme 2. $E = CO_2 Et$.

Angew. Chem. Int. Ed. 2005, 44, 6183-6186

Communications



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 $(3 \times 10 \text{ atm})$. 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%). ¹H NMR (CDCl₃, 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, 2 H), 7.39 ppm (s, 5 H); 13 C NMR (CDCl₃, 100 MHz): δ = 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 C₁₃H₁₆O₃S: 252.0820; found: 252.0815

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