JOC Note

Palladium-Catalyzed Ring-Opening Thiocarbonylation of Vinylcyclopropanes with Thiols and Carbon Monoxide

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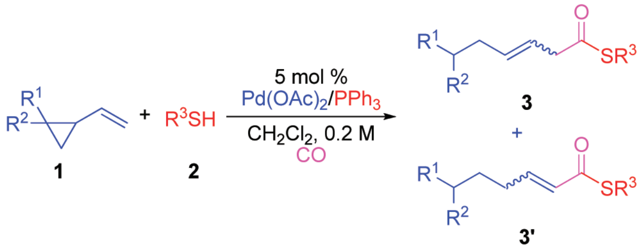

Palladium-catalyzed ring-opening thiocarbonylation of vinylcyclopropanes (VCPs) with thiols and carbon monoxide affords the corresponding unsaturated thioesters in moderate to excellent yields. This reaction provides a general method for the ring-opening thiocarbonylation of VCPs. It further demonstrates the utility of transition metal catalysts for the synthesis of organosulfur compounds.

Transition-metal-catalyzed carbonylation is widely recognized as one of the most important carbonyl-forming reactions in organic synthesis.[1] Formation of a thiocarbonyl unit and employing organosulfur compounds, especially thiols and thiophenols, as a direct substrate represents a challenging subject in transition-metal-catalyzed reactions. We and others have investigated some interesting transformations employing organosulfur compounds as substrates.[2] Those results and others such as thioboration,[3] thiosilylation,[4] thiophosphorylation,[5] thioesterification,[6]thiopropargylation,[7] and carbothiolation[8] of unsaturated compounds developed in the past few years have corrected the widely accepted concept that “sulfur compounds are poisons to transition metal catalysts”.[9] The chemistry of vinylcyclopropanes (VCPs) has attracted interest in synthetic chemistry.[10] Containing an olefinic moiety and a cyclopropane ring, these species demonstrate high reactivity. The ring opening of VCPs can be catalyzed by complexes of transition metal catalysts such as those containing palladium, rhodium, zirconium, chromium, nickel, and gold.[11] However, there are no reports of the ring-opening thiocarbonylation of VCPs. We previously demonstrated that palladium complexes can catalyze thiocarbonylation reactions of unsaturated species for the synthesis of unsaturated thioesters.[12] We now report a novel palladium-catalyzed ring-opening thiocarbonylation reaction of VCPs with thiols and carbon monoxide to give a new class of unsaturated thioesters.

The palladium-catalyzed reaction of 1,1-dimethoxycarbonyl 2-vinylcyclopropane (**1a**) with thiophenol (**2a**) and carbon monoxide was chosen as a model reaction to determine the

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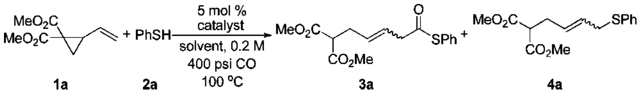
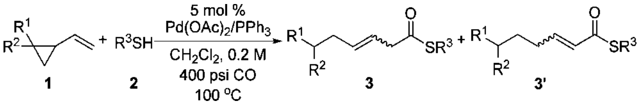
TABLE 1. Ring-Opening Thiocarbonylation of 1,1-Dimethoxycarbonyl 2-Vinylcyclopropane (1a) with Thiophenol (2a) under Various Conditions[a]

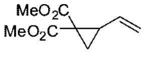
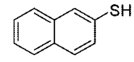
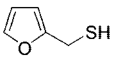
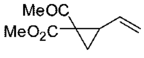
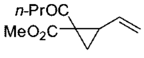
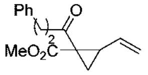
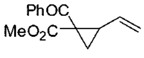
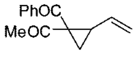
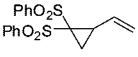
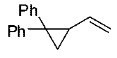


entry	catalyst	solvent	time (h)	yield (%)[b]	
				3a	4a
1	$Pd(OAc)_2$/dppb	CH_2Cl_2	48	22	53
2	$Pd(OAc)_2$/dppp	CH_2Cl_2	72	0	12
3	$Pd(OAc)_2/Cy_3P$	CH_2Cl_2	48	trace	25
4	$Pd(OAc)_2/Bu_3P$	CH_2Cl_2	48	trace	31
5	$Pd(OAc)_2/PPh_3$	CH_2Cl_2	48	77	0
6	$Pd(PPh_3)_4/PPh_3$	CH_2Cl_2	72	70	6
7	$Pd_2(dba)\cdot CHCl_3/PPh_3$	CH_2Cl_2	48	46	9
8	$RhCl(PPh_3)_3/PPh_3$	CH_2Cl_2	48	trace	16
9	$Pd(OAc)_2$	CH_2Cl_2	48	0	trace
10	$Pd(OAc)_2/PPh_3$	THF	48	16	9
11	$Pd(OAc)_2/PPh_3$	toluene	48	56	0
12	$Pd(OAc)_2/PPh_3$	CH_3CN	48	trace	16
13	$Pd(OAc)_2/PPh_3$	Et_2O	48	trace	2
14[c]	$Pd(OAc)_2/PPh_3$	CH_2Cl_2	48	41	15

[a] Reaction conditions: 1,1-dimethoxycarbonyl 2-vinylcyclopropane (**1a**, 2 mmol), thiophenol (**2a**, 1 mmol), catalyst (0.05 mmol), PPh_3 (22.5 mol %, if used), 400 psi of CO, solvent (5 mL). [b] Isolated yield. [c] 1.0 equiv of **1a** was used.

TABLE 2. Scope of the Thiocarbonylation of Vinylcyclopropanes[a]



entry	vinylcyclopropane	thiol	time (h)	yield (%)[b,c]
1	 **1a**	C_6H_5SH **(2a)**	48	77 **(3a)**
2	**1a**	4-BrC_6H_4SH **(2b)**	63	88 (**3b**:**3′b** =11:1)
3	**1a**	4-ClC_6H_4SH **(2c)**	66	78 (**3c**:**3′c** = 9:1)
4[d,f]	**1a**	4-$CH_3C_6H_4SH$ **(2d)**	68	77 (**3d**:**3′d** = 8:1)
5[e]	**1a**	 **(2e)**	96	71 (**3e**:**3′e** = 20:1)
6	**1a**	 **(2f)**	116	60 **(3f)**
7	**1a**	*i*-PrSH **(2g)**	112	55 (**3g**:**3′g** = 13:1)
8	 **1b**	**2a**	96	67 (**3h**:**3′h** = 2:1)
9[f,g]	 **1c**	**2a**	120	85 (**3i**:**3′i** = 10:1)
10[f,g]	 **1d**	**2a**	120	73 (**3j**:**3′j** = 7:1)
11[f,g]	 **1e**	**2a**	120	92 (**3k**:**3′k** = 7:1)
12	 **1f**	**2a**	72	92 (**3l**: **3′l** = 1:1)
13[f,h]	 **1g**	**2a**	96	36 (**3m**: **3′m** = 1:2)
14[i]	 **1h**	**2a**	68	*trace*

[a] Reaction conditions: 1,1-dimethoxycarbonyl 2-vinylcyclopropane (**1**, 2 mmol), thiol (**2**, 1 mmol), $Pd(OAc)_2$ (5 mol %)/PPh_3 (22.5 mol %), 400 psi of CO, CH_2Cl_2 (5 mL). [b] isolated yield. [c] The ratio of **3** and **3′** was determined by ^1H NMR. [d] 9% of the corresponding thioether **4d** was also isolated. [e] 7% of the corresponding thioether **4e** was also isolated. [f] 5 equiv of **1** was used. [g] 600 psi of CO. [h] 34% of the corresponding thioether **4m** was also isolated. [i] 150 °C.

viability of the process and the optimum reaction conditions (Table 1). A series of reactions between **1a** and **2a** were carried out under various conditions. It was shown that $Pd(OAc)_2$ with PPh_3 was the best catalyst system among those examined, and the reaction proceeded efficiently in dichloromethane (Table 1, entry 5). Using $Pd(OAc)_2$ without any ligand gave only a trace amount of the nucleophilic addition product (Table 1, entry 9). This product arises by using 1 equiv of **1a**, while the thiocarbonylated product was also formed in lower yield (Table 1, entries 5 vs 14). In accord with our observation,[12b,e,f,i] the sulfide **4a** can be suppressed by employing excess VCPs (e.g., 2 equiv relative to thiols). $Pd(PPh_3)_4$ with PPh_3 is also a good catalytic system for this reaction (Table 1, entry 6). However, other catalyst systems, such as $Pd_2(dba)_3\cdot CHCl_3$ and $RhCl(PPh_3)_3$ with PPh_3, were ineffective for this transformation (Table 1, entries 7 and 8). The nature of the solvent greatly affected the yield of β,γ-unsaturated thioester **3a** in this reaction. With the $Pd(OAc)_2/PPh_3$ catalyst system, the reaction works well at 100 °C in CH_2Cl_2 and was completed in 48 h to form the pure β,γ-unsaturated thioester.

The thiocarbonylation reactions of a series of diastereomeric mixtures of VCPs (**1a**−**h**) with thiols (**2a**−**h**) were performed by using 5 mol % of $Pd(OAc)_2$ and 22.5 mol % of PPh_3 in CH_2Cl_2 (5 mL per 1 mmol of thiol) at 400 or 600 psi of carbon monoxide for 48−120 h at 100 °C, and the results are summarized in Table 2. In most cases, the thiocarbonylation was accompanied with the isomerization process to the conjugated thioester in some extent (Table 2, entries 2−5 and 7−13). The thiophenols were found to work more effectively than alkylthiols. For examples, **1a** reacted with thiophenol (**2a**), *p*-bromobenzenethiol (**2b**), and *p*-chlorobenzenethiol (**2c**), affording the ring-opening carbonylated products in good to excellent yields (Table 2, entries 1−3), while the corresponding reaction with alkane thiols gave the carbonylated products in moderate yields (Table 2, entries 6 and 7). Reactions involving alkylthiols took longer to complete than those with arylthiols. The reactivity of the reaction was rather sensitive to both the acidity (electronic factor) and the bulkiness (steric fators) of the thiols. For example, **2d** (*p*-methylbenzenethiol), an arylthiol with an electron-donating *p*-methyl group, and **2b** (*p*-bromobenzenethiol), an arylthiol with an electron-withdrawing group, show some different behavior in this reaction. Using **2d** as the substrate gives a mixture of **3d** and **3′d** (**3d**/**3′d** = 8:1, 77% yield) and **4d** (9% yield) (Table 2, entry 4), whereas **2b** gives only the carbonylative product in 88% yield (**3b**/**3′b** = 11:1)

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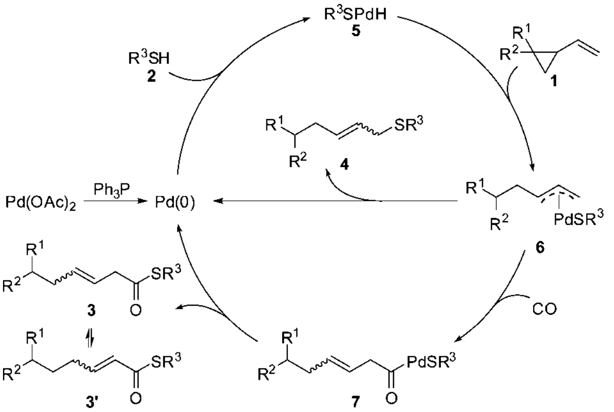
SCHEME 1. Proposed Reaction Pathway



(Table 2, entry 2). Reactions with arylthiols, such as 2-naphthalenethiol (**2e**), afford a mixture of the ring-opening carbonylated products **3e** and **3′e** (71% yield, **3e**/**3′e** = 20:1) and ring-opening product **4e** (7% yield) (Table 2, entry 5). When 1-octanethiol was employed as the substrate, no products were obtained at all.

Several VCPs were thiocarbonylated by Pd(OAc)$_2$/PPh$_3$ to give the corresponding unsaturated thioesters in moderate to excellent yields (Table 2, entries 1 and 8−14). The reactivity of the VCPs was sensitive to the nature of the substituted functional group. An electron-withdrawing group of the VCPs such as methoxycarbonyl and acetyl activate the VCPs for this reaction. High CO pressure is necessary for improving the yield when bulky VCPs are used for the reaction (Table 2, entries 9−11). The presence of the acetyl group could decrease the selectivity between the β,γ-unsaturated thioester **3** and the α,β-unsaturated isomer **3′** (Table 2, entries 8 and 12). 1,1-Dibenzenesulfonyl 2-vinylcyclopropane only gave the thiocarbonylated product in 36% yield, with the corresponding thioether formed in 34% yield under the optimized conditions (Table 2, entry 13). 1,1-Diphenyl-2-vinylcyclopropane only gave quite low conversions due to low activity even at 150 °C under 400 psi of CO.

While a precise reaction mechanism awaits further study, a possible catalytic cycle for the palladium-catalyzed thiocarbonylation of **1** with thiol **2** is outlined in Scheme 1. Pd(0) is readily formed in situ by the reduction of Pd(OAc)$_2$ in the presence of a phosphine ligand.[13] Oxidative addition of Pd(0) to **2** can give the thiopalladium complex **5**,[14] which can coordinate with the VCPs, affording the η^3-allylpalladium complex **6** by intramolecular hydropalladation and ring opening.[15] Reductive elimination of **6** would afford the thioester **4**, with regeneration of the palladium catalyst. Insertion of CO into the Pd−C bond of the σ-allyl analogue of **6**, followed by intramolecular transfer, would afford the acylpalladium complex **7**.[16] Reductive elimination of **7** can form the thioester **3**, with regeneration of the palladium catalyst. Further isomerization of the β,γ-unsaturated thioester **3** would give the α,β-unsaturated isomer **3′**.[17]

In summary, an effective catalytic system [Pd(OAc)$_2$/PPh$_3$] was developed for the ring-opening thiocarbonylation of VCPs, thiols, and carbon monoxide to form the corresponding unsaturated thioesters in moderate to excellent yields. This reaction provides a general method for the ring-opening thiocarbonylation of VCPs. It further demonstrates the utility of transition metal catalysts for the synthesis of sulfur compounds. Further investigation on the mechanism of the reaction as well as a catalytic asymmetric variant is ongoing.

Experimental Section

General Procedure for the Palladium-Catalyzed Thiocarbonylation of VCPs with Thiols and Carbon Monoxide. An autoclave, its glass liner, and a magnetic stirring bar were dried in an oven and cooled in a drybox. The liner was charged with Pd(OAc)$_2$ (0.05 mmol) and PPh$_3$ (0.225 mmol). The vinylcyclopropanes (2 mmol), thiol (1 mmol), and 5 mL of CH$_2$Cl$_2$ were then added to the liner. The gauge and gauge block assembly were attached. The CO line was flushed three times with CO, and the system was also pressurized and flushed three times with CO, gradually increasing the pressure to 400 psi. The autoclave was then placed in the center of an oil bath on a heater stirrer preset to 100 °C for 48−120 h. The autoclave was removed from the oil bath and allowed to cool to room temperature. The excess gas was discharged and the system disassembled. The reaction mixture was filtered through Celite and washed with diethyl ether. The solvent was removed by rotary evaporation under reduced pressure. The residue was separated by flash chromatography on silica gel.

Dimethyl 2-(5-oxo-5-(phenylthio)pent-2-enyl)malonate (3a) (Table 2, entry 1): Colorless oil; yield 77%; MW = 322.38; IR (cm^{-1}, C=O) 1701, 1732; ^{1}H (300 MHz, CDCl$_3$) δ (ppm) 7.42 (s, 5H), 5.59−5.78 (m, 2H), 3.76 (s, 6H), 3.50 (t, J = 7.5 Hz, 1.4H), 3.34 (d, J = 2.9 Hz, 1.6H), 2.70 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 195.8, 168.7, 134.9, 131.9, 130.0, 129.8, 129.6, 128.0, 125.0, 124.0, 53.1, 53.0, 51.8, 51.6, 47.4, 42.4, 32.2, 27.4; MS (EI, 70 eV) *m/z* 322.1 (M$^+$); HRMS (EI,70 eV) calcd for C$_{16}$H$_{18}$O$_5$S, 322.0875; found 322.0867.

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Supporting Information Available: Full experimental details, characterization for all new compounds, copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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