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Double Carbonylation Reactions of Enynols and Thiols to Form Thioester Substituted 6-Membered Ring Lactones

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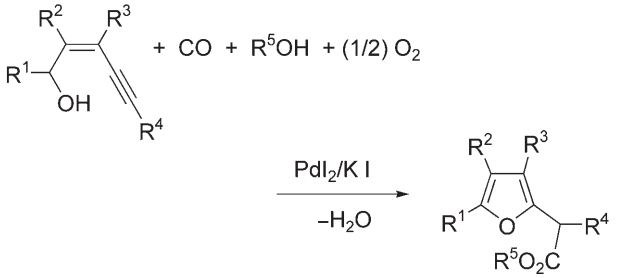
Abstract: The double carbonylation reaction of enynols with thiols affords functionalized 6-membered ring lactones. Two kinds of 6-membered ring lactones were obtained by the use of different palladium complexes with added phosphine ligands.

Keywords: double carbonylation; enynols; homogeneous catalysis; 6-membered ring lactones; palladium; thiols



Scheme 1.

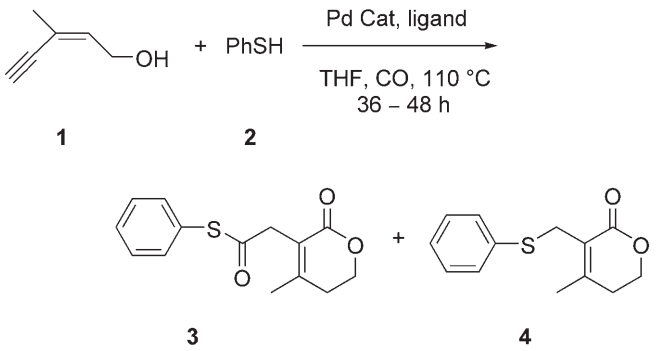
Transition metal-catalyzed carbonylation is recognized as one of the most important carbonyl-forming reactions in organic synthesis.[1] Cyclocarbonylation is especially useful for the synthesis of cyclic compounds possessing a carbonyl moiety.[2] Unsaturated lactones are useful subunits in an impressive number of natural and unnatural products possessing interesting biological activities,[3] and they are also valuable chiral building blocks, such as for example the Prelog–Djerassi lactone.[4] Cyclocarbonylation has been extensively investigated to develop methods for the construction of lactones from alkenols, alkynols, enynes and dienynes, as well as from other substrates.[5]

The chemistry of enynols has attracted considerable attention in recent years. As multifunctional molecules, enynols can be used for the synthesis of furan derivatives by cycloisomerization catalyzed by complexes of transition metal catalysts such as ruthenium, palladium, gold, copper and silver.[6] There are few reports of the carbonylation of enynols.[7] One example is the synthesis of furan-2-acetic esters from *(Z)*-2-en-4-yn-1-ols where carbonylation is accompanied by ring closure with side chain CO incorporation (Scheme 1).

We previously demonstrated that palladium complexes can catalyze thiocarbonylation reactions of unsaturated species.[8] We now report a novel palladium-catalyzed cyclocarbonylation and thiocarbonylation reaction of enynols with thiols to give thioester substituted α,β-unsaturated 6-membered ring lactones. This is the first example of cyclocarbonylation to form multifunctional α,β-unsaturated 6-membered ring lactones from enynols. Furthermore, together with other findings,[9] it has corrected the widely accepted concept that "sulfur compounds are poisons to transition metal catalysts".

Reaction of 3-methyl-2-penten-4-yn-1-ol (**1**) with thiophenol (**2**), carbon monoxide, and catalytic quantities of a variety of palladium complexes in THF at 110 °C for 36–48 h resulted in the formation of the dicarbonylated lactone **3**, with the monocarbonylated product **4** as the by-product (Scheme 2).

To explore this novel reaction, we first screened several palladium catalysts (Table 1). Initial catalyst screening indicated that the use of different palladium(0) or palladium(II) complexes with added phosphine ligands displayed different catalytic activities with respect to the formation of the two kinds of lactones. The use of 5 mol% palladium acetate (relative to thiol) with 4 equivs. of triphenylphosphine or Pd(PPh_3)$_4$ gave the highest selectivity for the dicarbonylated lactone, with 62% yield of the lactone **3**



Scheme 2.

(Table 1, entries 1 and 2). Use of different solvents (toluene, dichloromethane), or lower or higher pressures of carbon monoxide, gave inferior results (Table 1, entries 3–6). Bidentate phosphines such as 1,3-bis(diphenylphosphino)propane(dppp) gave the monocarbonylated product **4** in 37% yield, with 39% of **3** (Table 1, entry 7). The Pd(0) catalyst $Pd_2(dba)_3$ and PPh_3 afford **3** in 56% yield (Table 1, entry 9).

The conditions developed in Table 1, entry 1, were applied to the reaction of **1** and other enynols with a variety of thiophenols and the results are reported in Table 2. Thiophenol affords a substantially higher yield of the thioester substituted lactone **3** than *p*-bromothiophenol (62% *vs.* 40%), while *p*-methoxythiophenol afforded the thioester lactone in lower yield (Table 2, entries 1–3). Although 2-naphthalenethiol also reacts with **1**, the yield is a little lower than using *p*-bromothiophenol as the reactant (Table 2, entry 4). The aliphatic thiol, isopropyl thiol, reacts in a similar manner (Table 2, entry 5). Other enynols **1** with R^1 = H, C_2H_5, Ph, R^2 = H, CH_3, react with thiophenols affording products in 23–81% yield (Table 2, entries 6–13). Enynols with an internal alkyne moiety are unreactive under the usual conditions. This may be due to the substitution on the alkyne group retarding the addition of thiols. We also found that thiophenol provided the best isolated yield of the double carbonylation product. Aliphatic thiols and thiols bearing electron-donating groups on the aromatic ring can also be effectively employed for these reactions.

We propose the following two pathways as possible mechanisms for this reaction (Scheme 3). Path **a)** involves oxidative addition of PdLn to the OH bond of **1** and coordination of the triple bond to Pd to give **5**, followed by carbonyl insertion into the Pd–O bond to form **6**. Intramolecular hydropalladation of **6** may afford **7**, and reductive elimination of the latter results in the formation of **8**. 1,4-Addition of PhSPdHLn to **8** would give **9** , and subsequent CO insertion (to **10)** and reductive elimination of $Pd(^0)$ results in the formation of the thioester substituted α,β-unsaturated 6-membered ring lactone **3**. The reaction

Table 1. Effect of palladium catalysts, solvent and pressure on the double carbonylation and cyclization of 3-methyl-2-penten-4-yn-1-ol (**1**) with PhSH (**2**).[a]

Entry	Catalyst	Solvent	Time [h]	CO [psi]	Yield [%][b] **3**	**4**
1	$Pd(OAc)_2$/dppp	THF	36	500	39	37
2	$Pd(OAc)_2$/dppb	THF	36	500	51	18
3	$Pd_2(dba)_3$/4 PPh_3	THF	36	500	56	14
4	$Pd(OAc)_2$/4 PPh_3	THF	36	500	62	--
5	$Pd(PPh_3)_4$	THF	36	500	62	--
6	$Pd(OAc)_2$/4 PPh_3	Toluene	36	500	27	--
7	$Pd(OAc)_2$/4 PPh_3	CH_2Cl_2	36	500	35	--
8	$Pd(OAc)_2$/4 PPh_3	THF	36	200	48	--
9	$Pd(OAc)_2$/4 PPh_3	THF	36	800	43	--

[a] *Reaction conditions:* **1** (3 mmol), **2** (1.0 mmol), Pd catalyst (0.05 mmol), PPh_3 (0.2 mmol) or dppb or dppp (0.1 mmol), solvent (15 mL) , CO 500 psi, 110 °C.
[b] Yields were calculated based on the limited reagent **2.**

may alternatively proceed *via* path **b**), i.e., formation of RSPdLnH and coordination to the triple bond of **1** would give **11**, followed by cyclization to form **12**. Carbonyl insertion of the latter to **13**, followed by reductive elimination of RSPdH would afford **8**, which then is converted to **3** as already described.

A crystal structure of **3** ($R^1 = C_2H_5$, $R^2 = CH_3$, $R^3 =$ Ph) was determined, and is illustrated in Figure 1.

In conclusion, we have discovered the novel palladium-catalyzed double carbonylation and cyclization reaction of enynols with thiols to form thioester-containing 6-membered ring lactones in excellent selectivity and in moderate to good yields. This interesting transformation will likely provide an opportunity to access a wide variety of compounds of potential interest to the pharmaceutical industry.

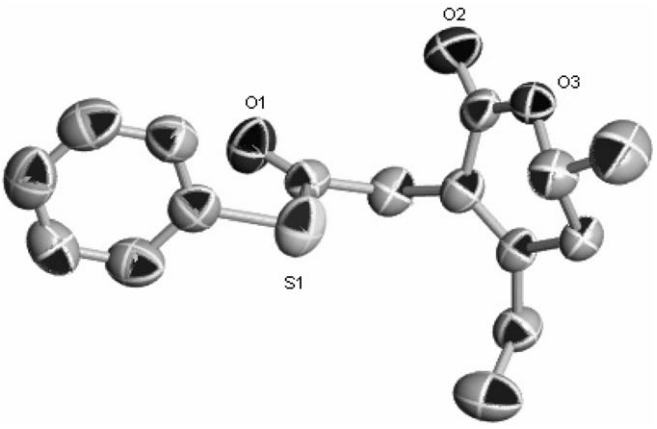
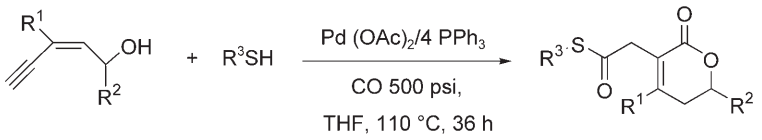


Figure 1. Crystal structure of **3** ($R^1 = C_2H_5$, $R^2 = CH_3$, $R^3 =$ Ph).

Table 2. Scope of the regioselective double carbonylation and cyclization reaction of enynols and thiols.[a]



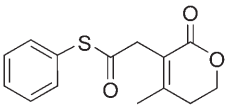
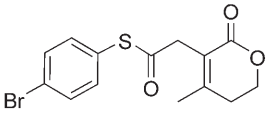
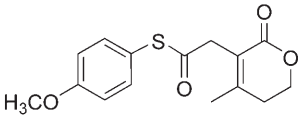
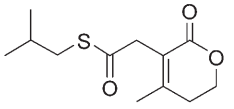
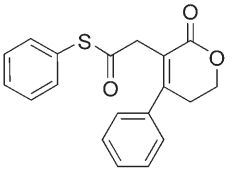
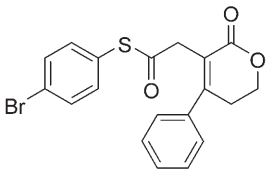
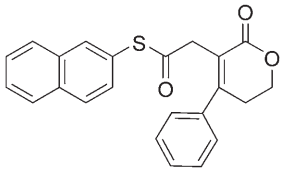
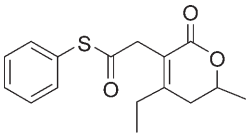
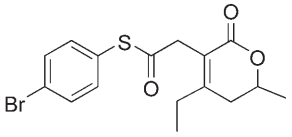
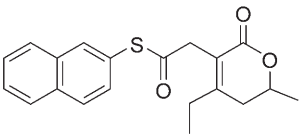
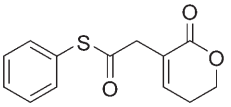
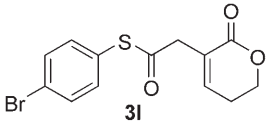
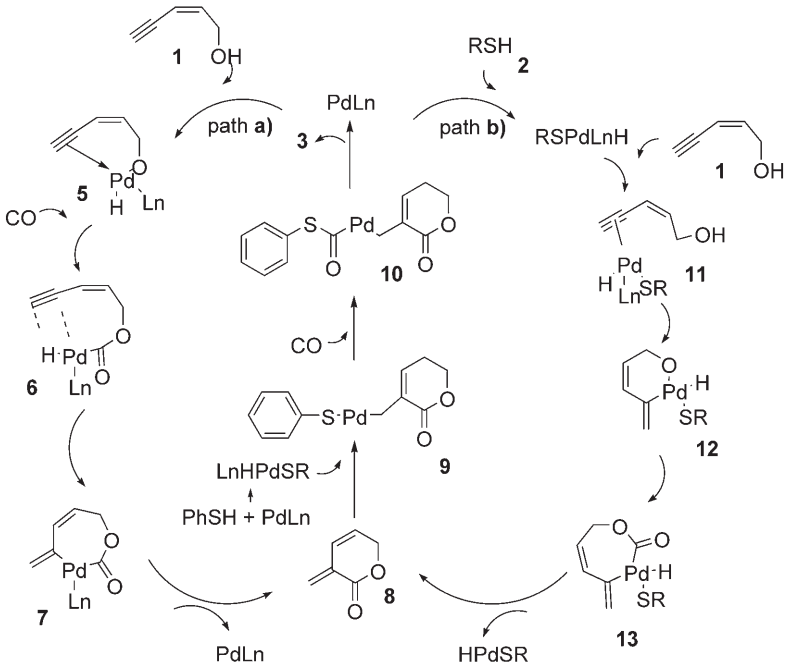
Entry	R^1	R^2	R^3	Product	Yield [%]
1	CH_3	H	C_6H_5	 **3a**	62
2	--	--	4-BrC_6H_4	 **3b**	40
3	--	--	4-$CH_3OC_6H_4$	 **3c**	30
4	--	--	$(CH_3)_2CHCH_2$	 **3d**	33
5	C_6H_5	--	C_6H_5	 **3e**	81

Table 2. (Continued)

Entry	R^1	R^2	R^3	Product	Yield [%]
6	C_6H_5	--	4-BrC_6H_4	 **3f**	32
7	C_6H_5	--	2-$C_{10}H_7$	 **3g**	45
8	C_2H_5	CH_3	C_6H_5	 **3h**	51
9	C_2H_5	CH_3	4-BrC_6H_4	 **3i**	63
10	C_2H_5	CH_3	2-$C_{10}H_7$	 **3j**	35
11	H	H	C_6H_5	 **3k**	23
12	H	H	4-BrC_6H_4	 **3l**	31

[a] *Reaction conditions:* enynols (3 mmol), thiol (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol) and THF (15 mL) , CO 500 psi, 110 °C, 36 h.



Scheme 3. Possible mechanisms.

Experimental Section

General Procedure for the Thiocarbonylation Reactions

A mixture of **1** (3.0 mmol), thiol (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol) and THF (15 mL) was reacted in an autoclave at 500 psi of carbon monoxide for 36 h at 110 °C. The reaction mixture was cooled to room temperature and the excess CO was released. The mixture was filtered through Celite or silica gel, and concentrated by rotary evaporation. The separation and the purification of products were achieved by preparative TLC on silica gel using *n*-hexane-ethyl acetate (1:1) as the eluet.

***S*-Phenyl 2-(4-Methyl-2-oxo-5,6-dihydro-2*H*-pyran-3-yl)-ethanethioate (3a):** IR: $\nu = 1701\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.03$ (s, 3H), 2.50 (t, $J = 6.0$ Hz, 2H), 3.78 (s, 2H), 4.37 (t, $J = 6.0$ Hz, 2H), 7.41 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$, 31.1, 41.4, 65.5, 120.7, 127.9, 129.6, 129.9, 135.0, 155.3, 165.2, 195.0; anal. calcd.: C 64.10, H 5.38; found: C 64.21, H 5.23.

***S*-4-Bromophenyl 2-(4-Methyl-2-oxo-5,6-dihydro-2*H*-pyran3-yl)ethanethioate (3b):** IR: $\nu = 1701\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.02$ (s, 3H), 2.55 (t, $J = 6.0$ Hz, 2H), 3.75 (s, 2H), 4.37 (t, $J = 6.0$ Hz, 2H), 7.24–7.53 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$, 31.1, 41.5, 65.5, 120.5, 124.5, 127.0, 132.8, 136.4, 155.6, 165.2, 194.4; Anal. calcd.: C 49.28, H 3.84; found: C 49.51, H 3.84.

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