JOC Note

Dramatic Effects of Ionic Liquids on the Palladium-Catalyzed Cyclocarbonylation of Enynols with Thiols

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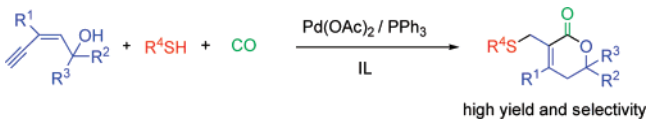
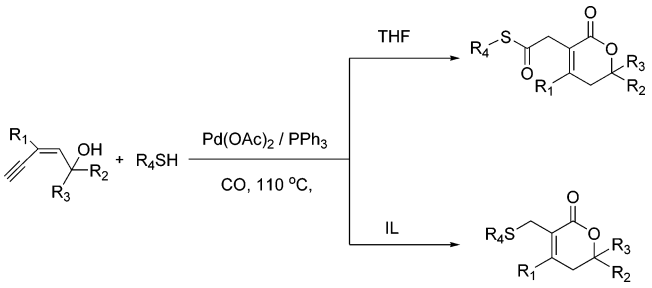


Palladium-catalyzed carbonylation reactions of enynols with thiols in ionic liquids afford monocarbonylated 6-membered-ring lactones in high yields and good selectivity. These results are significantly different from those obtained when conducting the reaction in THF. The recyclability of the catalytic system was also investigated.

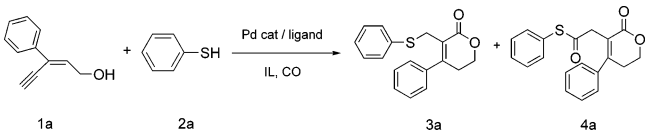
Recently, ionic liquids (IL) have attracted considerable attention as efficient and environmentally friendly reaction media.[1] The important advantages of ionic liquids include high thermal stability, negligible vapor pressure, the capacity to dissolve various organic and inorganic compounds and organometallic catalysts, as well as the potential for recycling.[2] These properties result in enhanced rates, higher yields, and higher selectivities in chemical processes when compared to conventional solvents. Thus, ionic liquids have been used instead of volatile organic solvents for a variety of reactions such as Diels–Alder reactions,[3] Heck reactions,[4] hydroformylations,[5] and cyclocarbonylation reactions.[6]

We have recently reported a novel palladium-catalyzed cyclocarbonylation and thiocarbonylation reaction of enynols with thiols, which affords double carbonylated products, usually as thioester-containing 6-membered-ring lactones using THF as the solvent.[7] Herein we report the dramatic effects of ionic liquids on this palladium-catalyzed cyclocarbonylation of enynols with thiols, which not only provided high yields of reactions, but also changed the chemoselectivity, forming the monocarbonylated compound, the thioether-substituted 6-membered-ring lactone, as the main product (Scheme 1). Unsaturated lactones and lactones containing a thioester or a thioether group are valuable building blocks and useful subunits in natural and unnatural products possessing interesting biological activities.[8]

SCHEME 1



SCHEME 2



Results and Discussion. Initially, we chose the cyclocarbonylation of 3-phenyl-2-penten-4-yn-1-ol (**1a**) with thiophenol (**2a**) as the model reaction (Scheme 2). The catalytic system $Pd(OAc)_2/PPh_3$, previously used for the double carbonylation of enynols and thiols, and the ionic liquid BMIM·PF_6 were used for the present reaction.

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(1) Recent reviews: (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772. (c) Sheldon, R. *Chem. Commun.* **2001**, 2399. (d) Wilkes, J. S. *Green Chem.* **2002**, *4*, 73. (e) Welton, T. *Coord. Chem. Rev.* **2004**, *248*, 2459. (f) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015.

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TABLE 1. Cyclocarbonylation Reaction of 3-Phenyl-2-penten-4-yn-1-ol and Thiolphenol under Different Conditions[a]

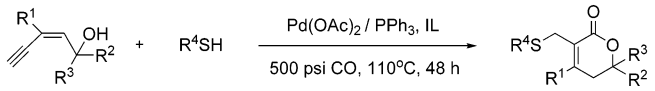
	catalyst	IL	temp (°C)	CO (psi)	time (h)	isolated yield(%) **3a**	isolated yield(%) **4a**
1	$Pd(OAc)_2/PPh_3$	$[BMIM][PF_6]$	110	500	48	91	
2	$Pd(OAc)_2$	$[BMIM][PF_6]$	110	500	48	NA	
3	$Pd(OAc)_2/PPh_3$	$[BMIM][PF_6]$	110	500	24	70	
4	$Pd(OAc)_2/PPh_3$	$[BMIM][PF_6]$	80	500	48	75	
5	$Pd(OAc)_2/PPh_3$	$[BMIM][PF_6]$	110	300	48	87	
6	$Pd(OAc)_2/PPh_3$	$[BMIM][PF_6]$	110	700	48	96	
7	$Pd(OAc)_2$/dppb	$[BMIM][PF_6]$	110	500	48	31	
8	$Pd(OAc)_2$/dppp	$[BMIM][PF_6]$	110	500	48	50	27
9	$Pd(OAc)_2/PPh_3$	$[BMIM][NTf_2]$	110	500	48	88	
10	$Pd(OAc)_2$/dppb	$[BMIM][NTf_2]$	110	500	48	48	26
11	$Pd(OAc)_2$/dppp	$[BMIM][NTf_2]$	110	500	48	82	13
12	$Pd(OAc)_2/PPh_3$	$[BMIM][BF_4]$	110	500	48	65	24

[a] 3-Phenyl-2-penten-4-yn-1-ol (1.0 mmol), thiophenol (1.0 mmol), $Pd(OAc)_2$ (0.02 mmol), PPh_3 (0.08 mmol) or dppb, dppp (0.04 mmol), ionic liquid (2.5 g).

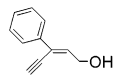
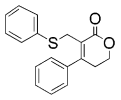
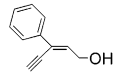
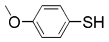
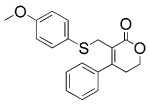
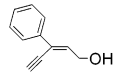
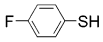
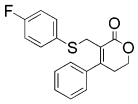
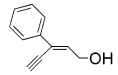
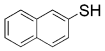
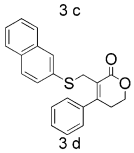
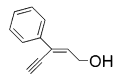
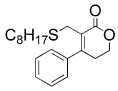
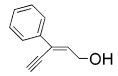
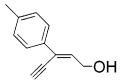
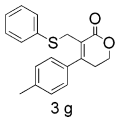
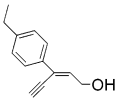
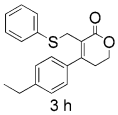
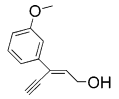
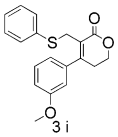
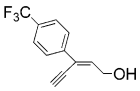
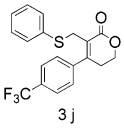
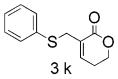
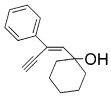
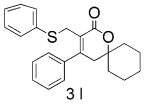
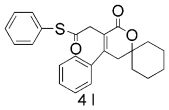
Treatment of 3-phenyl-2-penten-4-yn-1-ol (1 mmol) and thiophenol (1 mmol) with 400 psi of carbon monoxide in the presence of a catalytic amount of $Pd(OAc)_2$ (2 mol %) and PPh_3 (8 mol %) in BMIM·PF_6 at 110 °C for 48 h resulted in the formation of the monocarbonylated product **3a** in 91% yield (Table 1, entry 1). At lower temperature, lower CO pressure, or shorter reaction time, the reaction gave **3a** in reduced yield (Table 1, entries 3, 4, and 5), while higher CO pressure could raise the yield of **3a** to 96% (Table 1, entry 6). Without ligand or with bidentate phosphines such as 1,4-bis(diphenylphosphino)butane (dppb), the reaction did not occur or gave inferior results (Table 1, entries 2 and 7). With 1,3-bis(diphenylphosphino)propane (dppp), the reaction provided the monocarbonylated product **3a** in 50% yield, together with 27% of the double-carbonylated product **4a** (Table 1, entry 8). Table 1 also shows the results of the reaction with other kinds of ionic liquids. The system of $Pd(OAc)_2/PPh_3$/BMIM·NTf_2 gave **3a** as a sole product in 88% yield, while using dppb or dppp, or $Pd(OAc)_2/PPh_3$/BMIM·BF_4 provided the mixture of **3a** and **4a** (Table 1, entries 9, 10, 11, and 12).

The optimized conditions (Table 1, entries 1 and 9) were applied to other enynols with a variety of thiols, and the results are reported in Table 2.

TABLE 2. Cyclocarbonylation Reaction of Enynols and Thiols[a]



1 a-g 2 a-f 3 a-l

Entry	Enynols	Thiols	Products	Isolated yield(%) [BMIM][PF6]	Isolated yield(%) [BMIM][NTf2]
1			 3 a	91	88
2			 3 b	44	65
3			 3 c	68	73
4			 3 d	82	82
5		$C_8H_{17}SH$	 3 e	87	89
6			3 f	91	89
7			 3 g	86	90
8			 3 h	78	83
9			 3 i	79	86
10			 3 j	53	75
11			 3 k	70	87
12			 3 l	33	56
			 4 l	17	34

[a] Enynols (1.0 mmol), thiol (1.0 mmol), $Pd(OAc)_2$ (0.02 mmol), PPh_3 (0.08 mmol), ionic liquid (2.5 g).

The results show that both BMIM·PF_6 and BMIM·NTf_2 were excellent ionic liquids for most substrates. Thiophenol affords a higher yield of the lactone **3** than *p*-fluorothiophenol and *p*-methoxythiophenol (Table 2, entries 1−3). 2-Naphthalenethiol also reacts with **1**, and the yield is a little lower than that with thiophenol (Table 2, entry 4). The aliphatic thiols, isopropylthiol and 1-octanethiol, also provided **3** in high yields (Table 2, entries 5 and 6). Other enynols (**1**, with R^1 = H, Ar, R^2, R^3 = H) react with thiophenol affording **3** in good yields (entries 7−11). Enynols with $R^3 = C_5H_{10}$ provide both the monocarbonylated **3*l*** and the double carbonylated lactones **4*l*** (Table 2, entry 12). Use of enynol with a methyl group at R^1 also provided a mixture of **3** and **4**. According to the mechanism we proposed in previous work,[7] this may be due to these substitutions retarding the addition of thiols even after the second CO insertion reaction.

In conclusion, the ionic liquids, BMIM·PF_6 or BMIM·NTf_2, are excellent reaction media for the palladium-cataylzed cyclocarbonylation reaction of enynols and thiols. The reaction formed monocarbonylated 6-membered-ring lactones in good selectivity and high yields. The remarkable difference in chemoselectivity for ionic liquids versus conventional solvents was demonstrated, although the rationale for the different behavior needs additional experimentation.

Experiment Section

General Procedure for the Cyclocarbonylation Reactions of Enynols with Thiols. A mixture of enynol (1.0 mmol), thiol (1.0 mmol), $Pd(OAc)_2$ (0.02 mmol), PPh_3 (0.08 mmol) ,and [BMIM]-[NTf_2] (2.5 g) was added to the autoclave. The autoclave was closed, purged three times with carbon monooxide, pressurized with 500 psi of CO, and then heated at 110 °C for 36−48 h. Excess CO was discharged at room temperature. The resulting solution was extracted with ether (6 × 5 mL). The combined ether phase was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient from hexane to hexane/EtOAc 5:1) to give **3** (56−91%). For recovery and reuse of the ionic liquid containing the palladium catalyst, fresh enynol and thiol were added to the remaining ionic liquid for the next run.

4-Phenyl-3-(phenylthiomethyl)-5,6-dihydro-2*H*-pyran-2-one (Table 2, entry 1), 3a: IR 1705 cm^{-1} (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (t, J = 6.0 Hz, 2H), 3.90 (s, 2H), 4.1 (t, J = 6.0 Hz, 2H), 7.10−7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 32.7, 65.8, 125.2, 127.4, 127.7, 129.0, 129.2, 129.4, 132.1, 135.7, 138.0, 153.5, 165.3; MS (EI) *m/z* 296 (M^+, 29); HRMS (EI) *m/z* calcd for $C_{18}H_{16}O_2S$ (M^+) 296.0871, found 296.0859.

4-Phenyl-3-(phenylthiomethyl)-1-oxaspiro[5,5]undec-3-en-2-one (Table 2, entry 12), 3*l*: IR 1701 cm^{-1} (C═O); ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.27−1.97 (m, 10H), 2.67 (s, 2H), 3.93 (s, 2H), 7.14−7.39 (m, 10H); ^{13}C (75 MHz, $CDCl_3$) 22.1, 25.8, 32.1, 36.3, 41.9, 80.1, 124.6, 126.9, 127.7, 129.1, 129.2, 129.2, 131.2, 136.1, 138.8, 150.3, 165.1; MS (EI) *m/z* 364 (M^+, 32); HRMS (EI) *m/z* calcd for $C_{23}H_{24}O_2S$ (M^+) 364.1497, found 364.1520.

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Supporting Information Available: Full experiment details, characterization for all new compounds, copies of NMR spectra, and the details of X-ray crystal structure analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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