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Synthesis of Chromones via Palladium-Catalyzed Ligand-Free Cyclocarbonylation of *o*-Iodophenols with Terminal Acetylenes in Phosphonium Salt Ionic Liquids

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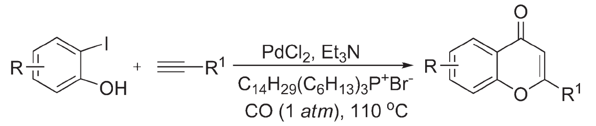
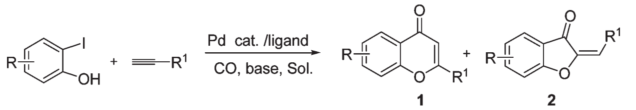


The highly efficient and selective palladium-catalyzed ligand-free cyclocarbonylation reaction of *o*-iodophenols with terminal acetylenes and CO in the phosphonium salt ionic liquid, $C_{14}H_{29}(C_6H_{13})_3P^+Br^-$, affords diversified chromones in good to excellent yields under atmospheric CO pressure. The ionic liquid, as the reaction medium, enhances the efficiency of the cyclocarbonylation reaction.

Flavones, also known as 2-phenylchromones, represent a major class of naturally occurring products, biologically active substances, and drugs.[1] Because of their broad range of significant biological activities,[2] synthetic approaches to this family of products have been extensively investigated.[3] However, most of the methods suffer from harsh reaction conditions, poor substituent tolerance, and low to moderate yields. During the past two decades, the palladium-catalyzed carbonylation of *o*-iodophenols with terminal acetylenes has become an attractive method to synthesize chromones.[4] In some situations, this reaction produces a mixture of six-membered chromones **1** and five-membered aurones **2** (Scheme 1).[5]

SCHEME 1. Pd-Catalyzed Cyclocarbonylation of *o*-Iodophenols and Terminal Acetylenes



Ionic liquids (ILs), because of their low volatility, nonflammability, capability to dissolve various organic and inorganic compounds, and potentially recyclable properties, have attracted considerable attention as environmentally friendly reaction media. Many transition metal-catalyzed reactions in task-specific ionic liquids (TSILs) have established some highly effective and easily separable catalytic systems.[6] Imidazolium-based ionic liquids are most commonly used as these alternative solvents.[7] In recent years, phosphonium salt ionic liquids (PSILs) have been the subject of some

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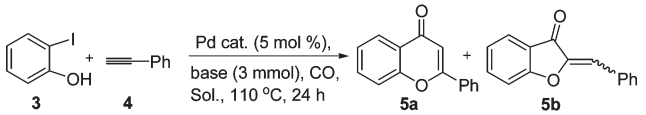
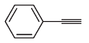
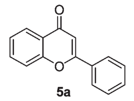
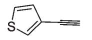
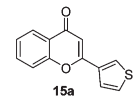
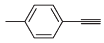
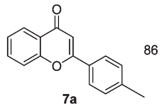
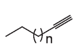
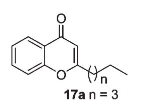
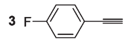
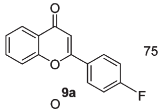
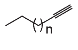
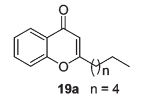
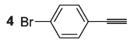
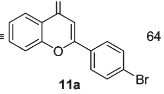
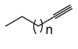
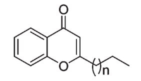
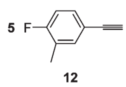
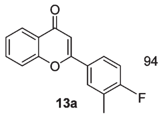
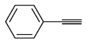
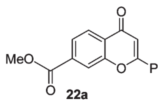
TABLE 1. Palladium-Catalyzed Cyclocarbonylation of *o*-Iodophenol with Phenyl Acetylene[a]



entry	cat.	base	CO	temp (°C)	sol.	yield[b] of **5a**
1	$Pd(PPh_3)_2Cl_2$	Et_3N	200 psi	110	PSIL102	95
2[c]	$Pd(PPh_3)_4$	K_2CO3	200 psi	110	PSIL102	ND
3	$Pd(PPh_3)_2Cl_2$	Et_3N	1 atm	110	PSIL102	74
4	$Pd(PPh_3)_2Cl_2$	Et_3N	1 atm	rt	PSIL102	trace
5	$Pd(OAc)_2$	Et_3N	1 atm	110	PSIL102	91
6	$PdCl_2$	Et_3N	1 atm	110	PSIL102	95
7	$PdCl_2$	Et_2NH	1 atm	110	PSIL102	58
8[d]	$PdCl_2$	Et_3N	1 atm	110	PSIL101	50
9[e]	$PdCl_2$	Et_3N	1 atm	110	PSIL110	41[h]
10[f]	$PdCl_2$	Et_3N	1 atm	110	PSIL109	43[i]
11	$PdCl_2$	Et_3N	1 atm	110	[BMIM]NTf_2	35[j]
12[g]	$PdCl_2$	Et_3N	1 atm	110	Et_3N	28[k]

[a] Reaction conditions: *o*-iodophenol (1 mmol), phenyl acetylene (2 mmol), Pd cat. (5 mol %), Et_3N or Et_2NH (3 mmol) or K_2CO_3 (4 mmol), PSIL or [BMIM]NTf_2 (1.5 g). [b] Isolated yield. [c] Neither product **5a** nor **5b** was detected. The only detected product was 2-(2-phenylethynyl)-phenol. [d] PSIL101: $C_{14}H_{29}(C_6H_{13})_3P^+Cl^-$. [e] PSIL110: $C_{14}H_{29}P^+\ PF_6^-$. [f] PSIL109: $C_{14}H_{29}(C_6H_{13})_3P^+NTf_2^-$. [g] Reaction was run in 3 mL of Et_3N. [h] 15% **5b** was obtained. [i] 28% **5b** was obtained. [j] 23% **5b** was obtained. [k] 35% **5b** was obtained.

TABLE 2. Palladium-Catalyzed Cyclocarbonylation of *o*-Iodophenols with Terminal Acetylenes[a]

Entry	Alkyne	Product	Yield(%)[b]	Entry	Alkyne	Product	Yield(%)[b]
1	 **4**	 **5a**	95	6	 **14**	 **15a**	92
2	 **6**	 **7a**	86	7	 **16** n = 3	 **17a** n = 3	86
3	 **8**	 **9a**	75	8[c]	 **18** n = 4	 **19a** n = 4	96
4	 **10**	 **11a**	64	9	 **20** n = 2	 **21a** n =2	68
5	 **12**	 **13a**	94	10[d]	 **4**	 **22a**	79

[a] Reaction conditions: *o*-iodophenols (1 mmol), terminal acetylenes (2 mmol), $PdCl_2$ (5 mol %), Et_3N (3 mmol), $C_{14}H_{29}(C_6H_{13})_3P^+Br^-$ (1.5 g), 110 °C, 24 h. [b] Isolated yield. [c] Use of [BMIM]NTf_2 as reaction medium under identical reaction conditions afforded 41% of **19a** and 26% of 2-heptylidenebenzofuran-3(2*H*)-one. [d] Methyl 3-hydroxy-4-iodobenzoate was used as the substrate.

publications. They have higher thermal stability than the nitrogen-based analogues. McNulty and co-workers, as well as several other groups, described several different reactions in PSILs affording products in good to excellent yields.[8] Recently, we reported several palladium-catalyzed reactions in PSILs.[9]

Kalini and Torii et al. reported the syntheses of chromones via palladium-catalyzed cyclocarbonylation of *o*-iodophenols with terminal acetylenes, the yields of the products were based on rather unreliable TLC and UV spectroscopy yields. Several of the chromones were isolated in quite low yields (45−63%).[4f,h] These results encouraged us to investigate the utility of PSILs for the cyclocarbonylation of *o*-iodophenols with terminal acetylenes to give 2-substituted chromones.

We now report that the ionic liquid, PSIL102, $C_{14}H_{29}(C_6H_{13})_3P^+Br^-$, can be employed as a very efficient reaction medium for the selective synthesis of chromones by palladium-catalyzed cyclocarbonylation of *o*-iodophenols with terminal acetylenes. The reaction affords high yields of the desired products.

Initially, the cyclocarbonylation of *o*-iodophenol with phenyl acetylene was chosen as the model reaction. The results are presented in Table 1.

The results in Table 1 show that cyclocarbonylation of *o*-iodophenol with phenyl acetylene can be performed in PSIL102, $C_{14}H_{29}(C_6H_{13})_3P^+Br^-$, affording **5a** in 95% isolated yield when $Pd(PPh_3)_2Cl_2$ was used as the catalyst and Et_3N as the base under 200 psi of CO pressure and 110 °C (Table 1, entry 1). In contrast, when $Pd(PPh_3)_4$ was used as the catalyst and K_2CO_3 as the base, neither **5a** nor **5b** was formed (Table 1, entry 2). So $Pd(PPh_3)_2Cl_2$ was used for further investigations. When the CO pressure was reduced from 200 psi to 1 atm, the yield decreased from 95% to 74% (Table 1, entry 3). Running the reaction at room temperature instead of 110 °C afforded trace quantities of the product (Table 1, entry 4). To our surprise, without any phosphine ligand, both $Pd(OAc)_2$ and $PdCl_2$ catalyzed the reaction very efficiently with PSIL102 as the reaction medium and **5a** was obtained in 91% and 95% yields, respectively (Table 1, entries 5 and 6). A reaction carried out under similar conditions but with conventional solvent did not give any of the desired product.[4f] When the reaction was carried out with Et_2NH as the base instead of Et_3N, the isolated yield was reduced from 95% to 58% (Table 1, entry 7). From the above results, $PdCl_2$ was chosen as the optimal catalyst and Et_3N as the base. Other ionic liquids were also investigated for the cyclocarbonylation reaction (Table 1). When the reaction was carried out in PSIL101, $C_{14}H_{29}(C_6H_{13})_3P^+Cl^-$, the isolated yield of **5a** was only 50% (Table 1, entry 8). Running the reaction in other ionic liquids gave the expected product and its isomer in low selectivity (Table 1, entries 9, 10, and 11). With Et_3N as the base and solvent, two isomers were isolated in 63% total yield (Table 1, entry 12). Hence, a pronounced counteranion effect was observed showing the increase in selectivity and yield of **5a** when moving from bistriflamide to bromide: $Br^- > Cl^- > NTf_2^-$.

The optimal reaction conditions for the cyclocarbonylation reaction in PSIL102 were then applied to a variety of aromatic and aliphatic terminal acetylenes. The results are summarized in Table 2.

The results in Table 2 show that by the use of simple $PdCl_2$ as catalyst, Et_3N as base, and PSIL102 as the ionic liquid, the cyclocarbonylation of *o*-iodophenol with both aromatic and aliphatic terminal acetylenes proceeded well, affording products in good to excellent yields. Acetylenes containing methyl or electron-withdrawing substituents on the aromatic

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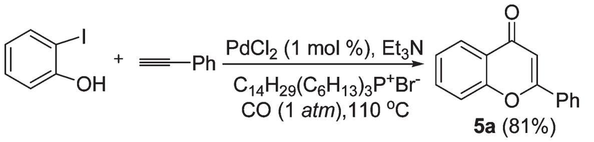
(9) (a) Cao, H.; McNamee, L.; Alper, H. *Org. Lett.* **2008**, *10*, 5281. (b) Yang, Q.; Robertson, A.; Alper, H. *Org. Lett.* **2008**, *10*, 5079. (c) Cao, H.; McNamee, L.; Alper, H. *J. Org. Chem.* **2008**, *73*, 3530.

ring react quite efficiently with *o*-iodophenol to form the corresponding chromones in 64–94% yields (Table 2, entries 2–5). The heteroaromatic substituted acetylene **14** could also give 2-thiophene-substituted chromone in 92% yield (Table 2, entry 6). All three aliphatic acetylenes reacted with *o*-iodophenol affording 2-alkyl-substituted chromones in good yields (Table 2, entries 7–9). Note that for entry 8, use of an *N*-based ionic liquid affords significantly reduced yield of **19a** (41%), as well as the formation of a substantial amount of 2-heptylidenebenzofuran-3(2*H*)-one (26%). When methyl 3-hydroxy-4-iodobenzoate was used as the substrate for the reaction with phenyl acetylene, the anticipated product was obtained in 79% yield (Table 2, entry 10). Thus, our method can be considered as a valuable alternative to the existing methods,[4a,c] as it affords better yields for some of the 2-alkyl-substituted chromones,[4c] and hetero-aryl-substituted chromones **5a**, **7a**, and **15a**.[4a] In addition, our method does not require the use of phosphine ligand.

We have also briefly investigated if the catalyst loading can be reduced to further improve the efficiency of the reaction. Thus, exposure of *o*-iodophenol and phenyl acetylene to our optimized cyclocarbonylation conditions using 1 mol % $PdCl_2$ as catalyst led to the desired product **5a** in 81% isolated yield (eq 1). Therefore, the product is isolated in good yield using this reduced loading of the catalyst.



5a (81%)

(1)

The recyclability of the reaction mixture containing active catalyst and PSIL102 in the cyclocarbonylation reaction of *o*-iodophenol with 1-octyne (Table 2, entry 8) was also investigated, and 78% isolated yield of **19a** was obtained in the second run (see experimental details in the Supporting Information).

In conclusion, PSIL102, $C_{14}H_{29}(C_6H_{13})_3P^+Br^-$, is a highly effective reaction medium for the palladium-catalyzed cyclocarbonylation of *o*-iodophenols with terminal acetylenes. By using PSIL102 as the ionic liquid, the reaction proceeds in a highly efficient and selective way to give various chromones in good to excellent yields under atmospheric CO pressure and no phosphine ligand is required.

Experimental Section

General Procedure for the Cyclocarbonylation of *o*-Iodophenols with Terminal Acetylenes. A mixture of *o*-iodophenol (1.0 mmol), terminal acetylene (2 mmol), $PdCl_2$ (0.05 or 0.01 mmol), Et_3N (3 mmol), and PSIL102 [trihexyl(tetradecyl)phosphonium bromide] (1.5 g) was added to the autoclave with magnetic stirring. The autoclave was closed, purged three times with CO, and pressurized with CO at room temperature at 15 psi, and then the autoclave was immersed in an oil bath preheated at 110 °C for 24 h. Excess CO was discharged at room temperature. The reaction mixture was purified by flash chromatography on silica gel with hexane/EtOAc (v/v, 10:1) as the eluant to give the corresponding chromones in 64–96% yields.

2-Phenyl-4*H*-chromen-4-one (5a). The title compound was prepared from the cyclocarbonylation of *o*-iodophenol with phenyl acetylene according to the general procedure, and the desired product was obtained in 95% yield after flash chromatography on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, 1H, J = 8.0 and 1.6 Hz), 7.76 (d, 1H, J = 1.6 Hz), 7.74 (d, 1H, J = 2.0 Hz), 7.56–7.52 (m, 1H), 7.41–7.34 (m, 4H), 7.28–7.24 (m, 1H), 6.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 162.9, 155.8, 133.4, 131.3, 128.7, 125.9, 125.2, 124.8, 123.6, 117.8, 107.1; HRMS (EI) m/z calcd for $C_{15}H_{10}O_2$ (M^+) 222.0681, found 222.0679.

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Supporting Information Available: Detailed experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.