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Synthesis of Coumarins via Palladium-Catalyzed Carbonylative Annulation of Internal Alkynes by *o*-Iodophenols

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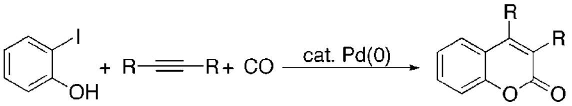
ABSTRACT



A variety of substituted coumarins have been prepared in good yields by the palladium-catalyzed coupling of *o*-iodophenols with internal alkynes and 1 atm of carbon monoxide. Unlike most of the previous work on the palladium-catalyzed carbonylation of alkynes, the insertion of the internal alkyne occurs in preference to the insertion of CO.

The propensity of unsaturated compounds, such as alkenes, alkynes, and carbon monoxide, to undergo insertion into a carbon−metal bond makes them some of the most versatile substrates for transition metal-catalyzed organic transformations. It is, therefore, not surprising that many such transformations have been developed over the past two decades. For example, the palladium-catalyzed annulation of dienes and internal alkynes has been developed in our laboratories for the synthesis of various carbo- and heterocyclic molecules, such as indoles,[1] benzofurans,[2] isocoumarins,[3] indenones,[4] isoquinolines,[5] α-pyrones,[3,6] naphthalenes,[7] and phenanthrenes.[8]

The ability to achieve controlled insertion of two unsaturated molecules into a carbon−metal bond possesses significant advantages for organic synthesis since it should allow rapid, efficient, and selective construction of complex molecular structures. Palladium-catalyzed reactions involving insertion of an unsaturated hydrocarbon and carbon monoxide into an aryl−metal bond have attracted significant attention in the past decade. Negishi and co-workers have studied intramolecular versions of these reactions in which a carbon−carbon double or triple bond is tethered to the aryl halide.[9] Only a few examples of palladium-catalyzed three-component processes have been reported.[10] Norbornene,[11] norbornadiene,[12] or allenes[13] react with *o*-iodophenol in the presence of carbon monoxide and a palladium catalyst to

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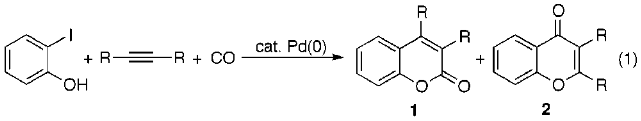
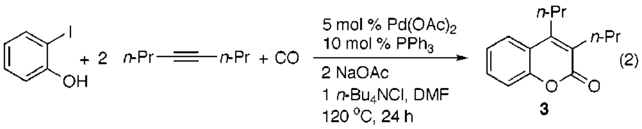
afford coumaranone or chromone derivatives. Palladium-catalyzed reactions of internal alkynes with aryl halides and carbon monoxide are reported to produce furans[14] or 2(1*H*)-furanones[15] depending on the structure of the alkyne employed.

Our continuing interest in the palladium-catalyzed annulation of internal alkynes prompted us to examine the annulation of internal alkynes with *o*-iodophenols in the presence of carbon monoxide. We envisioned that such annulation would result in the formation of either coumarins (**1**) or chromones (**2**) depending on the sequence of insertion of the internal alkyne and carbon monoxide into the carbon–palladium bond (eq 1).



Naturally occurring coumarins possess interesting biological activity, including anticancer and HIV-1-specific reverse transcriptase inhibitor properties.[16] However, classic methods for the synthesis of coumarins, such as the Perkin[17] and Pechman reactions[18] and their variations,[19] suffer major shortcomings such as the use of stoichiometric amounts of mineral or Lewis acids, or toxic reagents, often under high temperatures. The scope of these processes is therefore somewhat limited. Only a few applications of transition-metal catalyzed reactions for the synthesis of coumarins have been reported, and most of these are of limited scope.[12,20] Herein, we report that the palladium-catalyzed coupling of *o*-iodophenols, internal alkynes, and carbon monoxide allows efficient synthesis of 3,4-disubstituted coumarins bearing a variety of functional groups.

The reaction of *o*-iodophenol and 4-octyne in the presence of 1 atm of carbon monoxide under reaction conditions similar to those of our previous annulation conditions (eq 2) resulted in the exclusive formation of 3,4-di-*n*-propylcoumarin (**3**). The isomeric 2,3-di-*n*-propylchromone was not detected. However, the yield of the desired coumarin was low. To find the optimal reaction conditions, we studied the effect of various reaction parameters (base, phosphine, chloride source, stoichiometry, temperature, etc.) on the outcome of the reaction. The optimal reaction conditions thus far achieved utilize 1 equiv of *o*-iodophenol, 5 equiv of alkyne, 1 atm of CO, 5 mol % of $Pd(OAc)_2$, 2 equiv of pyridine, and 1 equiv of *n*-Bu_4NCl in DMF at 120 °C. The use of pyridine as a base is crucial for the success of the reaction. Only low yields of coumarin **3** have been obtained when inorganic bases or tertiary alkylamines were employed as the base. One atmosphere of carbon monoxide is sufficient for the reaction. Indeed, the use of higher pressures of carbon monoxide resulted in the formation of a large number of unidentified products.



Next, using the optimal reaction conditions, the annulation of various internal alkynes has been investigated. The results are summarized in Table 1. Both dialkyl (entry 1) and diaryl acetylenes (entry 2) are readily annulated, although a longer reaction time is required in the latter case to drive the reaction to completion. Unsymmetrical alkyl aryl alkynes also afford the desired products in good yields (entries 3 and 4). However, the insertion of these alkynes into the aryl–palladium bond proceeds with only modest regioselectivity, and mixtures of regioisomers are isolated in both cases. The regioselectivity is governed by steric factors with the larger substituent on the triple bond ending up at the 3-position of the coumarin. This regioselectivity is consistent with regioselectivity observed in our other palladium-catalyzed annulations of internal alkynes. However, this reaction is considerably more sensitive to steric hindrance around the triple bond. Alkynes with bulky substituents, such as 4,4-dimethyl-2-pentyne (entry 5), produce only very low yields of coumarins.

We have also investigated the annulation of alkynes bearing various functional groups. Propargylic alcohols failed to react cleanly in this process. However, an appropriately protected propargylic alcohol (entry 6) yielded the desired product in 65% yield, a yield similar to that of the annulation of 4-octyne. Again, however, a mixture regioisomers has been obtained. Better regioselectivity has been observed in the reactions of silyl acetylenes. The annulation of 1-trimethylsilyl-1-propyne afforded exclusively coumarin **12** in 43% yield (entry 7). The bulky trimethylsilyl group improves the regioselectivity but simultaneously lowers the yield over other simple alkyl or aryl groups. Note, however, the substantial increase in yield over that obtained using 4,4-dimethyl-2-pentyne (entry 5). Very good regioselectivity was also observed in the annulation of an alkynone (entry 8).

Coumarins bearing substituents in the 6- or 7-positions have also been synthesized in good yields. Either an electron-withdrawing (entry 9) or an electron-donating substituent (entry 10) can be introduced into position 6 of the coumarin by using the appropriate phenol. The substituents do not affect the yields of the process, although the reaction is faster

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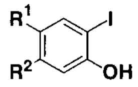
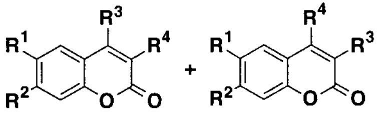
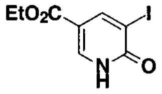
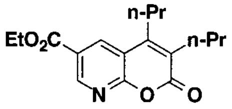
Table 1. Synthesis of Coumarins via Carbonylative Annulation of Internal Alkynes with *o*-Iodophenols[a]

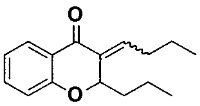
entry	phenol		alkyne		time, h	product(s)		% isolated yield (ratio)
			$R^3{\equiv}R^4$					
	R^1	R^2	R^3	R^4				
1	H	H	*n*-Pr	*n*-Pr	24	**3**		63
2			Ph	Ph	48	**4**		59
3			Me	Ph	24	**5**	**6**	72 (79:21)[b]
4			Et	Ph	24	**7**	**8**	78 (72:28)[b]
5			Me	*t*-Bu	24	**9**		9
6			CH$_2$OBn	Ph	24	**10**	**11**	65 (75:25)[b]
7			Me	SiMe$_3$	24	**12**		43
8			Et	CH$_3$CO	24	**13**	**14**	61 (90:10)[c]
9	CO$_2$Et	H	*n*-Pr	*n*-Pr	24	**15**		59
10	OMe	H			12	**16**		66
11	H	CO$_2$Me			6	**17**		62
12	 **18**				24	 **19**		70

[a] Representative experimental procedure: iodophenol (0.5 mmol), alkyne (2.5 mmol), pyridine (1.0 mmol), *n*-Bu$_4$NCl (0.5 mmol), and palladium acetate (0.025 mmol, 5 mol %) in DMF (5 mL) have been stirred under a balloon pressure of carbon monoxide at 120 °C for the indicated amount of time. [b] The regioisomers have been separated by column chromatography. [c] An inseparable mixture of isomers has been obtained.

when 2-iodo-4-methoxyphenol is employed. An electron-withdrawing substituent has also been introduced into the 7-position of the coumarin (entry 11). This reaction is significantly faster than the others, reaching completion within 6 h. The use of an analogous phenol bearing an electron-donating substituent, 2-iodo-5-methoxyphenol, failed to afford the anticipated coumarin under the standard reaction conditions. The only product isolated from the reaction is 3-methoxyphenol arising from deiodination of the starting phenol.

Finally, heterocyclic analogues of *o*-iodophenol are also effective in the carbonylative annulation of internal alkynes. Thus, 3-iodo-2-pyridone **18** affords the azacoumarin **19** in 70% yield.

We propose a mechanism for this carbonylative annulation involving (1) reduction of Pd(OAc)$_2$ to the actual Pd(0) catalyst, (2) oxidative addition of *o*-iodophenol to Pd(0), (3) insertion of the internal alkyne, (4) insertion of carbon monoxide, and (5) attack of the phenolic oxygen on the resulting acyl−palladium complex leading to formation of the coumarin and regeneration of the Pd(0) catalyst. It is remarkable that the insertion of an alkyne occurs in preference to the insertion of CO. While it has been reported that the insertion of an alkyne tethered to an aryl halide is competitive with insertion of CO,[9c] to the best of our knowledge, this is the first example of such selectivity in an intermolecular reaction. Moreover, this selectivity appears to be restricted to internal alkynes. For example, the annulation of 4,5-nonadiene under our standard conditions resulted in the formation of 3-*n*-butylene-2-*n*-propyl-2,3-dihydro-4*H*-1-benzopyran-4-one (**20**), in analogy with the results reported by Alper.[13]



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In conclusion, we have developed an efficient, palladium-catalyzed synthesis of 3,4-disubstituted coumarins from readily available starting materials. The synthesis employs mild conditions and can accommodate a wide variety of functional groups both on the alkyne and the phenol.

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Supporting Information Available: General experimental procedure and ^{1}H and ^{13}C NMR spectra and characterization data for compounds **3**, **4**, **7**−**17**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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