ORGANIC LETTERS

2000
Vol. 2, No. 12
1765−1768

Regiospecific Carbonylative Annulation of Iodophenol Acetates and Acetylenes To Construct the Flavones by a New Catalyst of Palladium–Thiourea–dppp Complex

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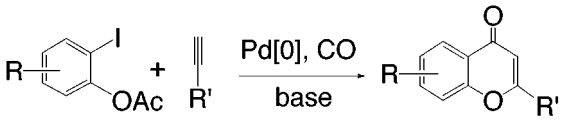
Received April 14, 2000

ABSTRACT



Regiospecific carbonylative annulation of *o*-iodophenol acetates and acetylenes mediated by palladium–thiourea–dppp complex in the presence of base at 40 °C under a balloon pressure of CO generates diversified flavones in high yields. This newly developed synthetic technology provides a highly efficient method for potential application to the combinatorial synthesis of those heterocycles on the solid support.

Natural products are the richest known sources of small molecules that bind proteins with high specificity, thanks to millions of years of evolution and selection. Flavones, also known as 2-phenylchromones, constitute one of the major classes of naturally occurring products. Because of their broad range of significant biological activities,[1] this family of molecules has been extensively investigated and more than 4000 chemically unique flavonoids have been isolated from plants.[2]

In connection with our development of a chemical genetic approach to analyzing biological systems by using interfacing libraries of small molecules with creative biological assays,[3] we were interested in developing improved methods for the combinatorial synthesis of a flavonoid library.

Although several approaches for the synthesis of flavones have been developed, most of the methods suffer from harsh reaction conditions, poor substituent tolerance, and low yields.[4]

The use of palladium as a catalyst for the syntheses of heterocyclic molecules has been a fertile area of research for the past two decades.[5] Recent advances in palladium-catalyzed carbonylation of *o*-iodophenols with acetylenes to synthesize the scaffold of flavones have shown this methodology to be particularly attractive.[6] However, this reaction

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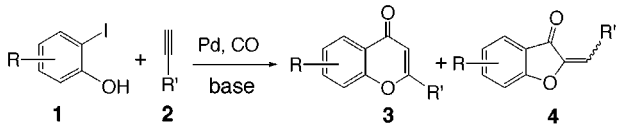
10.1021/ol000087t CCC: $19.00
Published on Web 05/11/2000

is known to produce a mixture of six-membered flavones **3** and five-membered aurones **4** (Scheme 1).

Scheme 1. Palladium-Catalyzed Carbonylative Cyclization of *o*-Iodophenols and Acetylenes



Mechanistically, the formations of six-membered flavones **3** and five-membered aurones **4** presumably result from the different processes [6b,c,7,8] shown in Figure 1.

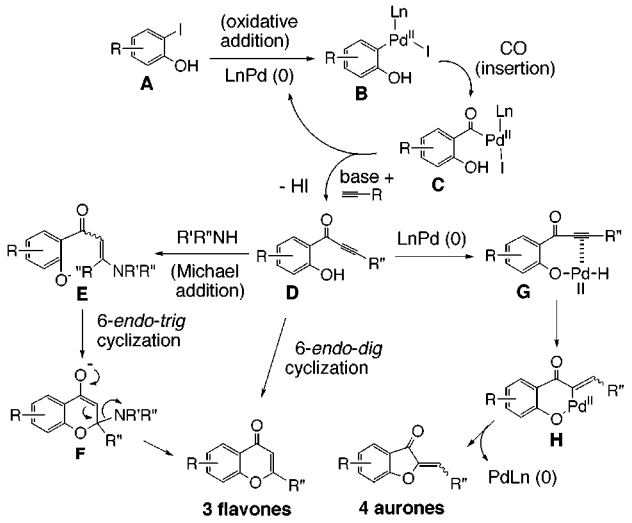


Figure 1. Mechanistic interpretation for the formation of flavone **3** and aurone **4**.

In this catalytic cycle, **D** would be a critical intermediate in the formation of **3** and **4**. The intermediate **D** might form a complex **G** with palladium(0), followed by rearrangement and reductive elimination to afford aurones **4**. On the other hand, the same intermediate **D** could either undergo a direct 6-*endo-dig* cyclization or proceed through **E** and **F** stages to form flavones **3** (see Figure 1).

Torii and Kalinin have nicely resolved this regioselective problem by using a large excess of diethylamine to competitively generate the intermediate **E** from **D** in order to form the six-membered scaffold of flavone **3** (Figure 1). However, the employed conditions are rather drastic (120 °C, 20 kg/cm^2).[6c]

Recently, Brueggemeier[7] developed a different approach to the synthesis of flavonoid molecules. Although his method has resolved the regioselectivity problem for the synthesis of flavones, multiple steps had to be added to achieve this.

Our need for a mild and convergent method to be used in the combinatorial synthesis of a flavonoid library promoted us to reinvestigate the synthetic approach illustrated in Scheme 1.

Palladium-based catalysts are renowned for their great tunability by combining with different ligands. In comparison with homopalladium catalysts, palladium−thiourea complexes have the advantage of catalyzing a facile carbonylation reactions.[9]

We previously demonstrated that palladium−thiourea is an effective cocatalyst for the syntheses of 2,3-disubstituted benzo[*b*]furans by carbonylative annulation under very mild conditions (at 45 °C *under a balloon pressure of CO*).[10] We reported here our recent results for the use the $PdCl_2(Ph_3P)_2$−thiourea−dppp (1:1:1) complex as a powerful catalyst for the syntheses of flavonoid molecules.

Initially, four pairs of iodophenols and acetylenes were selected as substrates to test this carbonylative annulation because they are either commercially available or easily accessible. To our delight, the six-membered flavones (**5a**−**8a**) were obtained in acceptable yields (50−70%) by using the complex of $PdCl_2(Ph_3P)_2$−thiourea as a catalyst in the

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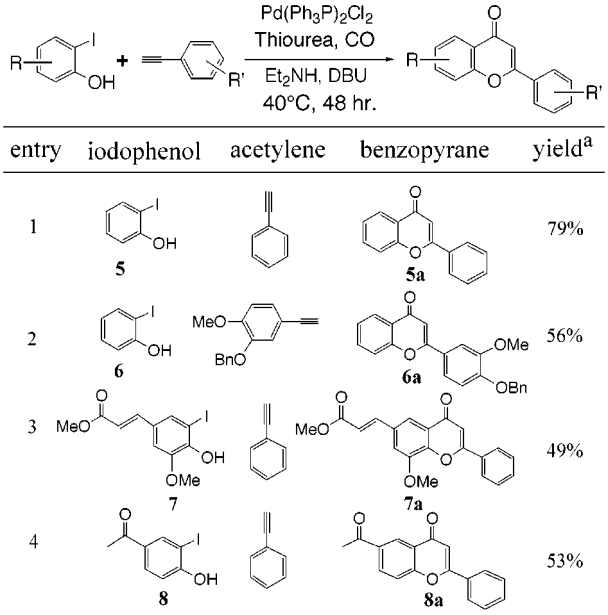
presence of diethylamine at 40 °C *under a balloon pressure of CO* (see Table 1).

Table 1. Palladium−Thiourea-Catalyzed Carbonyaltive Annulation of Iodophenols and Acetylenes



entry	iodophenol	acetylene	benzopyrane	yield[a]
1	**5**		**5a**	79%
2	**6**		**6a**	56%
3	**7**		**7a**	49%
4	**8**		**8a**	53%

a: pure products after flash chromatography

However, there were some problems associated with this reaction. First, a significant amount of aurone **3** were observed in all cases (10−20%); second, even though the reaction proceeded for more than 2 days, about 10−20% of iodophenols still remained. Efforts to overcome these problems by changing the catalysts, using different bases or solvents, and even increasing the reaction temperature (which leads to decomposition) were unsuccessful. We speculated that these problems could be resolved by changing a hydroxyl group to an acetoxy in the substrate of iodophenol.

We reasoned that the following advantages accompany the use of an acetoxy as a latent hydroxyl group. (1) As an electron-withdrawing group (cf. hydroxyl group), acetoxy can reduce the electron density of the aromatic ring in substrate **A** (see Figure 2); therefore the reaction rate of oxidative addition of **A** to Pd(0) will be increased and the problem associated with the conversion of starting material to product might be resolved. (2) Since the hydroxyl group was converted to the acetoxy, the intermediate **D** could only undergo Michael addition to form **E**, so complex **H** cannot be formed. (3) Due to the instability of the phenolic acetoxy in the intermediate **E**, it will eventually undergo displacement

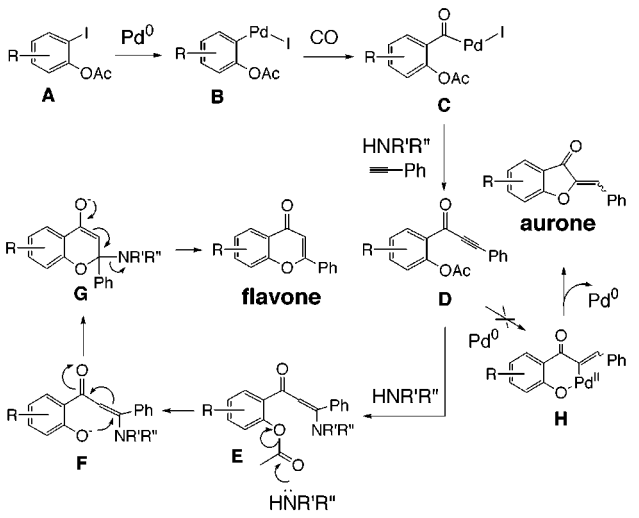
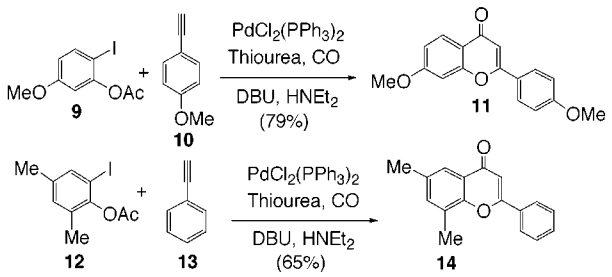


Figure 2. Mechanistic interpretation of regio-specific formation of flavone.

by an amine to afford the corresponding *o*-hydroxyl-α,*β*-unsaturated ketone **F**, which would finally lead to 6-*endo-trig* cyclization to give **G** and then eliminate the amine to flavone.

This idea works so well that when both substituted *o*-acetoxyiodobenzenes **9** and **12** were reacted with acetylenes **10** and **13**, respectively, under a condition listed in Scheme 2, the corresponding flavones **11** and **14** were obtained in

Scheme 2. Syntheses of Flavones **11** and **14**



79% and 65% yields and only trace amount of aurones **3** were observed in these reactions. This is truly an impressive improvement since only 0−10% of flavones was obtained when Ortar utilized the corresponding *o*-hydroxyliodobenzenes as the substrates in his flavone syntheses.[6b]

To assess the generality of such a method to construct the scaffold of flavones, eight pairs of *o*-acetoxyiodobenzenes and arylacetylenes were utilized for this purpose. Thus, the *o*-acetoxyiodobenzenes (**15**−**20**) (see Table 2) were synthesized by treatment of the corresponding *o*-hydroxyliodobenzenes with acetyl chloride in the presence of triethylamine in THF at room temperature in high yields. The corresponding *o*-hydroxyliodobenzenes (related to the compounds of **16**−**20**) and the arylacetylene (entries 2 and 4) were

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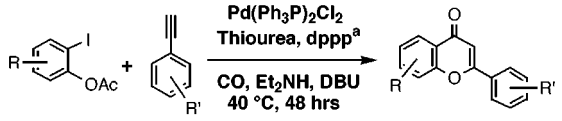
Table 2. $PdCl_2(PPh_3)_2$−Thiourea−dppp (1:1:1) Complex Catalyzed Carbonylative Annulation of *o*-Acetoxyiodobenzenes with Arylacetylenes



entry	iodophenol	acetylene	flavone	yield[b]
1	**15**		**15a**	92%
2	**15**		**15b**	88%
3	**16**		**16a**	83%
4	**16**		**16b**	76%
5	**17**		**17a**	85%
6	**18**		**18a**	70%
7	**19**		**19a**	68%
8	**20**		**20a**	78%

a: dppp = 1,3-bis(diphenylphosphino)propane
b: pure products after flash chromatography

constructed using the known procedure,[11] and the rest of iodophenols and phenylacetylenes are commercially available.

After considerable experimentation, it was found that the complex of $PdCl_2(PPh_3)_2$−thiourea−dppp (1:1:1) is the best catalyst for this carbonylative annulation, and the results are summarized in Table 2. The detailed experimental information is provided in the Supporting Information.

From the results, we can make the following observations. (1) Unsubstituted *o*-acetoxyiodobenzenes give high yields of flavones (entries 1 and 2). (2) Electron-donating groups on the aromatic ring of arylacetylenes (entries 3 and 4) give slightly lower yields of flavones than the corresponding unsubstituted arylacetylenes (entries 1 and 3). (3) Both electron-rich (entries 3 and 4) and electron-deficient (entries 5 and 6), as well as multiply substituted *o*-acetoxyiodobenzenes (entries 7 and 8), give satisfactory yields of the corresponding flavones.

Therefore, by using an acetoxy as a latent hydroxyl group, we have essentially prevented the five-membered aurone's formation and resolved the problem of converting the starting material to the product.

In summary, we have developed a highly efficient synthetic technology for carbonylative cyclization of *o*-acetoxyiodobenzens with arylacetylenes to construct the corresponding flavones. This extended carbonylative annulation provides a general method for the syntheses of flavonoid compounds. Such an efficient manipulation of multiple steps (one carbon−heteroatom bond and two carbon−carbon bonds) in this particular catalytic cycle will make this method a powerful tool for a combinatorial synthesis of this type of molecules on solid support.

The newly developed synthetic technology provides a highly efficient method for potential application to the combinatorial synthesis of those heterocycles on solid support, and a combinatorial synthesis of flavonoid library is currently under investigation in our laboratory.

Acknowledgment. We thank Professors Stuart L. Schreiber and Timothy J. Mitchison and Rebecca Ward for their invaluable advice during the course of this research. Financial support from the NIH (Grant 1PO1 CA78048), Merck & Co. (Grant MCI97MITC804), and Merck KGaA is gratefully acknowledged.

Supporting Information Available: Experimental procedures and ^1H and C^{13} NMR spectra for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000087T