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Palladium-catalyzed synthesis of aurone from salicyloyl chloride and phenylacetylene

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Abstract

Salicyloyl chloride has been found to react with phenylacetylene under the catalytic action of a palladium(0) complex with trioctylamine as ligand to give *o*-hydroxyphenyl phenylalkynyl ketone as the main product. The ketone undergoes selective cyclization to aurone in the presence of a palladium(0)-triphenylphosphine catalyst.

We previously reported [1] that the reaction of iodophenol with carbon monoxide and phenylacetylene in the presence of $Pd(PPh_3)_4$ gives aurone in ca. 80% yield. We now have found that it is possible to obtain the same product in the absence of carbon monoxide in a two step palladium(0)-catalyzed reaction, starting from salicyloyl chloride and phenylacetylene, which allows the isolation of an intermediate hydroxyalkynyl ketone (eq. 1).

$$(o\text{-OH})C_6H_4COCl + PhC{\equiv}CH \rightarrow \underset{\text{(I)}}{(o\text{-OH})C_6H_4COC{\equiv}CPh} \qquad (1)$$

Trialkylamines that are not too strongly coordinating because of their bulkiness turn out to be the best ligands. Their nature and their ratio to palladium and to salicyloyl chloride are critical, because they may also catalyze the formation of salicylides from salicyloyl chloride. Thus reaction involving trioctylamine at 50 °C for six hours led to a total yield of 89% (56% of ketone I, 19% of aurone (II) and 14% of flavone (III)), whereas with tributylamine or cyclohexyldiethylamine the yield dropped to $< 50\%$. Even lower yields were obtained with triethylamine (ca. 28%) and *N*-ethylmorpholine (ca. 18%). Quinoline, *p*-dimethylaminopyridine, tetramethylethylenediamine, and tetramethylguanidine did not give the desired products. A delicate balance of coordinating power, steric effects and basicity has thus to be reached to obtain satisfactory results.

The type of solvent also is important. Anisole proved to be effective and was extensively used. In general aprotic solvents of low polarity appear to be suitable.

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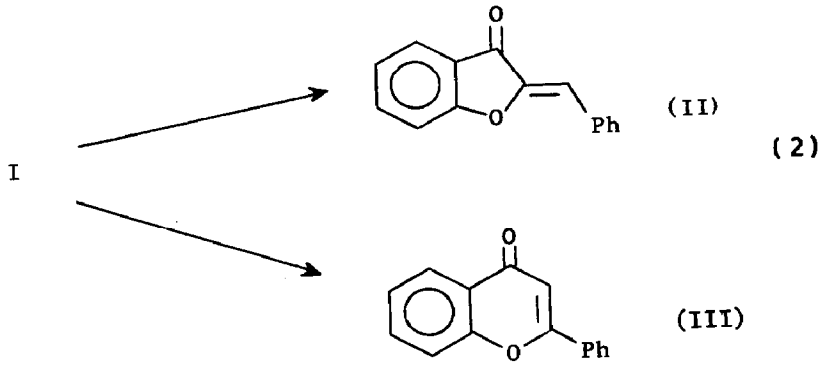
The temperature is critical, the yield being lower at temperatures above or below 50 °C.

Reaction 1 must involve oxidative addition of salicyloyl chloride to palladium, followed by replacement of chloride with the phenylalkynyl group and coupling of the latter with the aroyl group.

From the synthetic point of view it is noteworthy that although a palladium–copper-catalyzed synthesis of alkynyl ketones in amine solvents has been reported [2], it did not work in the case of salicyloyl chloride, and so the present method provides a useful route to ketone I.

The ketone can undergo two cyclization processes, leading to flavone or aurone (eq. 2).



(2)

While formation of these products can be brought about non-selectively by heating or by adding a base or acid, in known procedures [3], cyclization exclusively to II is catalyzed by palladium(0) complexes with triarylphosphines as ligands.

The pathway leading to II involves an oxidative addition of the OH group to palladium [4], followed by intramolecular triple bond insertion and reductive elimination. It should be noted that, although formation of two stereoisomers is possible, a *cis* addition of the phenoxy and hydrido groups to the triple bond must lead to *E* aurone. Formation of the more stable *Z* is isomer is thus to be attributed to a fast isomerization of the initially formed *E* isomer.

The reason why the synthesis of aurone from salicyloyl chloride requires two steps to obtain the best selectivity is that the palladium(0)-tertiary phosphine-catalyzed reaction is in competition with the reaction of salicyloyl chloride with itself, and to favour the former with respect to the latter, a more efficient ligand (a tertiary amine) has to be used. Under these conditions the reaction gives compound I as the main product. The latter cyclizes to II selectively in the presence of less basic ligands (triphenylphosphine). By contrast ketone I can be formed and cyclized directly to II, starting from iodophenol and carbon monoxide, because the competition mentioned above does not operate and the tertiary phosphine ligand can be used.

In conclusion the use of salicyloyl chloride in palladium-catalyzed acylation of alkynes has been shown to lead to an interesting precursor for the synthesis of aurone or flavone. Although the new procedure was aimed at the synthesis of aurone, it can be expected to be useful for analogous selective cyclizations.

Experimental

Preparation of ketone I

A solution of trioctylamine (708 mg, 2.00 mmol) in 1 ml of amisole was added to Pd(dibenzylideneacetone)$_2$ (15 mg, 0.026 mmol) and the mixture was stirred under nitrogen. A solution of salicyloyl chloride (188 mg, 1.20 mmol) and phenylacetylene (122 mg, 1.20 mmol) in 2 ml of anisole was then added. The solution was stirred at 50 °C for 6 h under nitrogen, cooled to room temperature, and diluted with methylene chloride (10 ml). The solution was shaken with dilute sulfuric acid, neutralized with sodium bicarbonate, and washed with water. The products were analyzed by GLC (silicone) and separated by TLC on silica, using dichloromethane : hexane 70 : 30 as the eluent. Ketone I, 56%, aurone, 19%, and flavone, 14%, were obtained in an overall yield of 89% on salicyloyl chloride.

Preparation of aurone II

A solution of compound I (76 mg, 0.34 mmol) in 2 ml of anisole was added to a mixture of Pd(dibenzylideneacetone)$_2$ (10 mg, 0.017 mmol) and triphenylphosphine (9 mg, 0.034 mmol) under nitrogen and the mixture was stirred at 80 °C for 6 h. After extraction with methylene chloride (5 ml) and separation by TLC on silica as above, aurone was obtained in 80% yield.

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