Tetrahedron Letters 53 (2012) 4469–4472

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Solvent-free synthesis of 4-aryl-3,4-dihydrobenzopyran-2-ones via [3+3] cyclocoupling of phenols with cinnamic acid catalyzed by molecular iodine

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ARTICLE INFO

Article history:
Received 10 March 2012
Revised 13 June 2012
Accepted 15 June 2012
Available online 19 June 2012

Keywords:
3,4-Dihydrobenzopyran-2-one
Iodine
Solvent-free
Phenol
Cinnamic acid

ABSTRACT

Molecular iodine was used as a catalyst in the [3+3] cyclocoupling of phenols and cinnamic acids which proceeds via a tandem esterification–hydroarylation process at 120–130 °C under solvent-free conditions. Substituted 4-aryl-3,4-dihydrobenzopyran-2-ones were obtained in good yields.

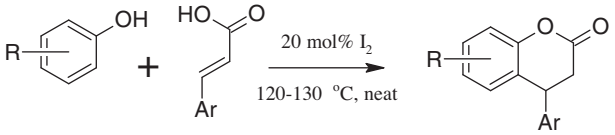
Molecular iodine has received considerable attention in the last few years as an inexpensive, non-toxic, readily available catalyst for various organic transformations.[1] Iodine has high tolerance to air as well as moisture making it an ideal catalyst. It can be easily removed from the reaction mixture by washing with reducing agents. Recently use of iodine as a reagent and catalyst is reviewed[2] for transformation of molecules containing oxygen functional groups. As a continuation of our interest[3] in application of iodine in the synthesis of heterocycles, we herein report the synthesis of 4-aryl-3,4-dihydrobenzopyran-2-ones via the [3+3] cyclocoupling of phenols with cinnamic acids using molecular iodine as a catalyst (Scheme 1).

3,4-Dihydrobenzopyran-2-ones or dihydrocoumarins are well known for fragrance in cosmetics,[4] food flavouring,[5] and perfumery industries.[6] 4-Aryl-3,4-dihydrocoumarins are naturally occurring compounds[7] which exhibit some interesting biological activities such as aldose reductase inhibition,[8] antiherpetic,[9] protein kinases,[10] and are important synthetic intermediates for pharmaceutical compounds. It has been recently reported that 4-aryl-3,4-dihydrocoumarins serve as starting materials for the synthesis of *N*-diaryl (aryl) substituted amides which possess antiarrhythmic properties.[11]

The conventional methods for the synthesis of dihydrocoumarins include, the hydroarylation of cinnamic acids with phenols in strong acidic media,[12] the catalytic hydrogenation of coumarins,[13] Lewis acid promoted reaction of activated phenols with arylonitrile,[14] reaction of Fischer carbene complexes with ketene acetals,[15] *p*-TSA mediated hydroarylation of cinnamic acids with anisoles or phenols,[16] $AlCl_3$ mediated C–C coupling reaction between hydroxyketene ***s,s***-acetals and arenes,[17] [4+2] cycloaddition reaction of *o*-quinone methides with silyl ketene acetals,[18] biotransformation of coumarins by microorganisms,[19] microwave assisted synthesis from phenols and cinnamoyl chloride in the presence of montmorillonite K-10 catalyst,[20] microwave assisted solvent-free synthesis from phenols and cinnamic acid using silica supported Wells-Dawson heteropolyacid as catalyst,[21] and recently the *p*-TSA mediated synthesis from aryl cinnamic esters.[22]

For initial studies β-naphthol and cinnamic acid were chosen as substrates. First the cyclocoupling reactions were studied in different solvents such as ethyl alcohol, methyl alcohol, chloroform, dichloromethane, acetonitrile, dioxane, and water at room temperature using 20 mol % of iodine. Having seen no formation of any products the reaction masses were subjected to reflux conditions (Table 1).

In case of ethyl alcohol only 10% of the desired product was formed after 24 h of refluxing along with a large percentage of ethyl cinnamate. Refluxing the reaction mixture in xylene could



Scheme 1. Reaction of phenol with cinnamic acid.

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http://dx.doi.org/10.1016/j.tetlet.2012.06.069

Table 1
Screening of solvents in refluxing conditions using β-naphthol and cinnamic acid

Solvent	Time (h)	Yield (%)
Methanol	24	30
Chloroform	24	0
Acetonitrile	24	25
1,2-Dichloroethane	24	30
Ethanol	24	10
1,4-Dioxane	24	10
Water	24	10
Toluene	24	20
Acetic acid	24	30
Xylene	5	70
1,2-Dichlorobenzene	5	30

Table 2
Optimization of iodine concentration

Entry	Iodine (mol %)	Time (h)	Yield (%)
1	0	24	0
2	1	24	0
3	5	8	30
4	10	8	50
5	15	3	70
6	20	1	80
7	25	1	78
8	30	1	70

Table 3
Reaction of various phenols with cinnamic acids under optimized reaction conditions[23]

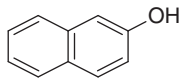
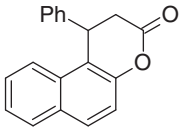
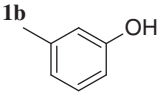
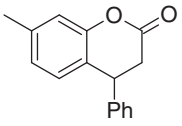
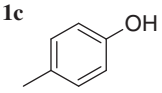
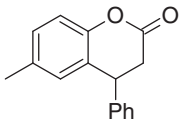
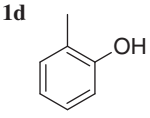
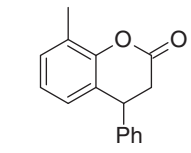
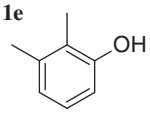
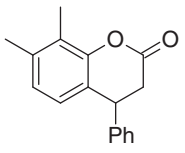
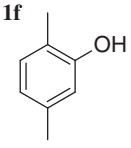
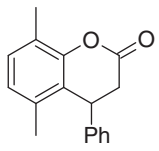
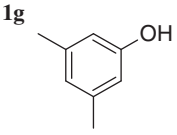
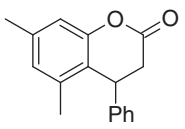
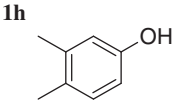
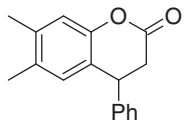
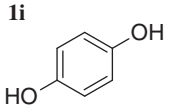
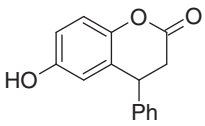
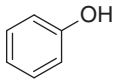
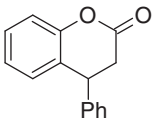
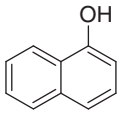
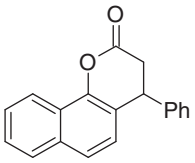
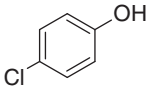
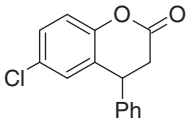
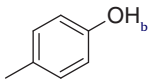
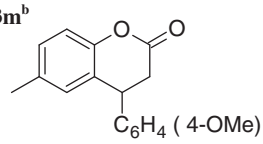
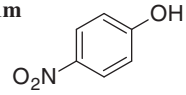
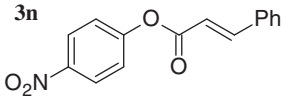
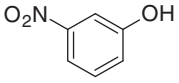
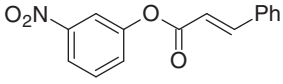
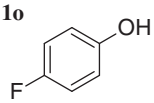
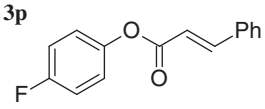
Entry	Substituted	Product	Time (h)	Yield[a] (%)
1	**1a** 	**3a** 	1	80
2	**1b** 	**3b** 	1.5	78
3	**1c** 	**3c** 	1	83
4	**1d** 	**3d** 	3	60
5	**1e** 	**3e** 	4	83
6	**1f** 	**3f** 	5	65
7	**1g** 	**3g** 	2	85
8	**1h** 	**3h** 	2	85

Table 3 (*continued*)

Entry	Substituted	Product	Time (h)	Yield[a] (%)
9	**1i** 	**3i** 	2	77
10	**1j** 	**3j** 	4	60
11	**1k** 	**3k** 	4	65
12	**1l** 	**3l** 	3	70
13	**1c** 	**3m**[b] 	1.5	78
14	**1m** 	**3n** 	24	20
15	**1n** 	**3o** 	24	30
16	**1o** 	**3p** 	24	50

[a] Isolated % yield after column chromatography.
[b] In this case *p*-methoxy cinnamic acid was used.

account for 70% of the product formation in 5 h. However the reaction in refluxing 1,2-dichlorobenzene resulted only in 30% formation of the product in 5 h.

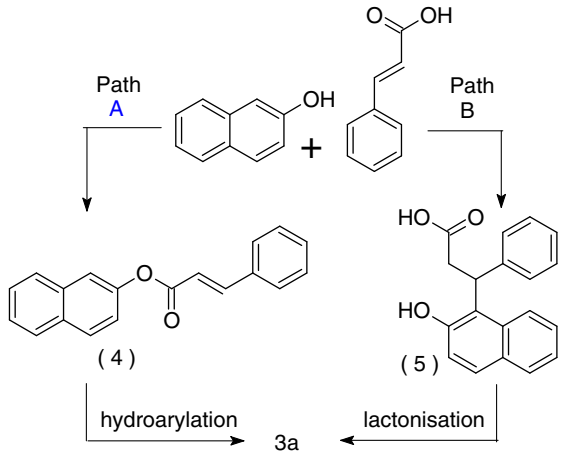
Encouraged by these results, we thought of carrying out the reaction under solvent-free conditions. The reactions were studied at different temperature conditions. Formation of the product was observed in the range of 80–130 °C. As the reaction was complete within one hour without solvent at 120–130 °C, this condition was selected for further studies. Lower temperatures (80–100 °C) prolonged the reaction time. For standardizing the catalyst amount we used different catalyst loadings (Table 2). Higher catalyst loading could not enhance the reaction rates or increase the yields evidently.

However when less than 20 mol % of iodine was used prolonged reaction time was needed. No product was formed in the absence of catalyst.

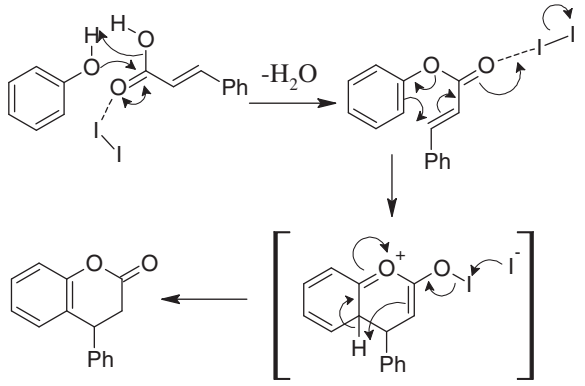
After optimization of reaction conditions the reaction was explored for substrate scope (Table 3).[23] Several phenols having electron donating groups were rapidly converted into dihydrocoumarins with good yields. The ortho substituted methyl phenols also gave the dihydrocoumarins in moderate to good yields (**3d**–**3f**). Parent phenol gave 60% yield of product (**3j**) in 4 h, while α-naphthol gave product (**3k**) in 65% yield. Phenol with electron withdrawing chloro group at *para* position gave the product (**3l**) in good yield (70%). Strong electron withdrawing nitro groups at *para* and *meta* positions did not yield the dihydrocoumarins but resulted in the formation of the corresponding nitro phenyl cinnamates after 24 h in low yields.

Similarly *p*-fluorophenol resulted in the formation of ester **3p** in 50% yield. The reaction was also performed with *p*-methoxy substituted cinnamic acid, which on reaction with *p*-cresol gave the corresponding dihydrocoumarin (**3m**).

The formation of dihydrocoumarins has been accounted for in two different pathways (Scheme 2), either via transesterification followed by hydroarylation (path A, Scheme 2) or via hydroarylation followed by lactonization (path B, Scheme 2). In the case of reaction of phenols with cinnamic acid using *p*-toluenesulfonic acid,[16] dihydrocoumarin formation occurs via transesterification followed by intramolecular hydroarylation (path A, Scheme 2), while phenols react with benzylidine malonates in the presence



Scheme 2. Possible pathways leading to the formation of dihydrocoumarin (**3a**).



Scheme 3. The probable mechanism.

of a catalytic amount of $TiCl_4$[12c] to give dihydrocoumarin via hydroarylation followed by lactonization. (path B, Scheme 2).

To study the mechanism in the present case, (E)-2-naphthyl cinnamate **(4)** was subjected to the standardized reaction condition. The dihydrocoumarin (**3a**) was obtained along with trace amounts of cinnamic acid and β-naphthol. Similarly, methyl ether of β-naphthol was heated with cinnamic acid in the presence of 20 mol % of iodine at 120–160 °C for 3 h to evaluate the possibility of direct hydroarylation. However, we did not observe any change in the reaction mass. Thus, in the present case most likely, transesterification takes place first followed by hydroarylation (path A, Scheme 2). The probable mechanism of iodine catalyzed cyclocoupling is depicted in Scheme 3.

In conclusion, we have developed a simple, convenient, metal and solvent-free process for the one pot synthesis of 4-aryl-3,4-dihydrocoumarins by using inexpensive and readily available starting materials, in good yields. The main feature of the present method is that it provides an efficient, cost-effective, easy to handle, and environmentally benign route, with the use of iodine as a mild and safer catalyst. The reaction is important from the green chemistry point of view also because hydroarylation exhibits perfect atom economy.

Acknowledgment

D.P.K is thankful to UGC for the award of Junior Research Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012. 06.069.

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23. *General procedure for the synthesis of dihydrocoumarins:* Iodine (0.13 mmol) was added into a mixture of phenol (0.69 mmol) and cinnamic acid (0.69 mmol) under an air atmosphere and the mixture was neat heated at 120–130 °C for a period of time (1–4 h). Following completion of the reaction as monitored by TLC, the reaction mixture was cooled, diluted with ethyl acetate, washed with aqueous sodium thiosulphate solution and dried over anhydrous sodium sulphate. The solvent was removed under vacuum to provide the crude products. Further purification was done by column chromatography on silica gel with hexanes/ethyl acetate (4:1) as an eluent.