Pd/C-MEDIATED ARYLATION FOLLOWED BY I2-CATALYZED HYDRATION STRATEGY: PREPARATION OF FUNCTIONALIZED NOVELINDANONE DERIVATIVES

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GRAPHICAL ABSTRACT

Abstract A simple and inexpensive synthesis of novel 2-(3-oxo-3-arylpropyl)-2,3-dihydro-1H-inden-1-one derivatives has been achieved via Pd/C-mediated arylation followed by I2-mediated regioselective hydration of 2-(prop-2-ynyl)-2,3-dihydro-1H-inden-1-ones. A wide variety of 3-aryl substituted 2-propynyl indanone derivatives were conveniently prepared by using 10% Pd/C-PPh3-CuI as a catalyst system, some of which were used to prepare the corresponding ketones via alkyne hydration in the presence of catalytic I2. In an in vitro study a representative compound showed inhibition of PDE4B (phosphodiesterase type 4B) and binding with this protein in silico.

Keywords Alkyne; hydration; indanone; iodine; Pd/C

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INTRODUCTION

The development of newer and effective strategies for the quicker access to novel compounds of potential pharmacological interest is of great value both in academic and industrial research groups. Accordingly, we devoted our efforts toward the development of a new strategy based on Pd-C-mediated arylation followed by I₂-catalyzed hydration, leading to functionalized indanone derivatives.

Indanone derivatives represent an important class of pharmacologically active molecules. For example, indanocine (A, Fig. 1), a potent cytostatic and cytotoxic indanone, inhibits tubulin polymerization and induces apoptotic cell death in stationary-phase multidrug-resistant cancer cells. Similarly, another indanone analog, donepezil hydrochloride (B, Fig. 1) that acts as AChE (acetylcholinesterase) inhibitor, has been used for the treatment of Alzheimer's disease. Notably, both the molecule A and B contain a 5,6-dimethoxy-2,3-dihydro-1H-inden-1-one ring with a side chain attached at C-2. These observations prompted us to design and synthesize an indanone-based library of novel small molecules represented by C (Fig. 1) in which the 5,6-dimethoxy-2,3-dihydro-1H-inden-1-one ring was retained and new side chains were added at C-2. Because of structural similarity of C with A and B, we anticipated that molecules based on C might show biological activities.

While a number of elegant approaches have been reported for the introduction of a substituent at C-2 of the 5,6-dialkoxy-2,3-dihydro-1H-inden-1-one ring, none of them was applicable for the preparation of our target molecules C. We therefore required a new, straightforward, and practical approach for this purpose and our major focus was to develop a simple and inexpensive methodology. The strategy we adopted for the synthesis of molecules based on C involved (i) an initial introduction of an alkynyl moiety at C-2 of the indanone ring followed by (ii) its functionalization via Pd-mediated reactions and then (iii) hydration of the triple bond. The Pd-catalyzed coupling of terminal alkynes with the (hetero)aryl halide (i.e., the Sonogashira coupling) was the methodology of our choice for this purpose. While a variety of Pd-catalysts [e.g., Pd(PPh₃)₄, (PPh₃)₂PdCl₂, Pd(OAc)₂/PPh₃, etc.] have been explored for the Sonogashira reactions, the use of Pd/CuI–PPh₃ as a less expensive catalyst was found to be attractive in recent times. Because of our continuing interest in Pd/C-mediated alkynylation of aryl and heteroaryl halides, we decided to explore the Pd/C-based methodology as a key step for the synthesis of our target compounds. While the hydration of alkynes leading to various carbonyl derivatives has been studied extensively for more than 100 years, the acid-free alkyne hydration has not been explored until recently. Thus, gold-NHC
(N-heterocyclic carbene) complex/silver hexafluoroantimonate-catalyzed hydration of various alkynes has been reported by Marion et al. in 2009.\[12\] Though several other excellent methodologies have been reported for alkyne hydration,\[13–16\] most of them involved the use of expensive metal catalysts and/or complex ligands. Very recently, we have observed that the use of elemental iodine can be effective for the hydration of 2-propynyl indanone derivatives in the absence of any additional acid catalysts or ligands. Herein we report our preliminary results on Pd\(\text{C}\)-mediated arylation followed by I\(_2\)-mediated hydration of 2-\(\text{C}(\text{prop}-2\text{-ynyl})\)-2,3-dihydro-\(\text{H}\)-inden-1-one derivatives (3 and 4) as shown in Scheme 1. To the best of our knowledge the use of such a strategy based on Pd\(\text{C}\)-mediated coupling followed by I\(_2\)-catalyzed hydration\[17\] is not common in the literature.

RESULTS AND DISCUSSION

The key starting materials, 2-\((\text{prop}-2\text{-ynyl})\)-2,3-dihydro-\(\text{H}\)-inden-1-one (3 and 4), were synthesized according to a procedure shown in Scheme 2. Thus, 5,6-dimethoxy-2,3-dihydro-\(\text{H}\)-inden-1-one (1) was converted to ethyl-5,6-dimethoxy-1-oxo-2,3-dihydro-\(\text{H}\)-inden-2-carboxylate (2), which was propargylated to give the alkyne 3. The ester hydrolysis followed by decarboxylation of 2 afforded the other alkyne 4. Both the alkynes 3 and 4 were then used for the coupling with a range of iodoarenes in the presence of 10% Pd\(\text{C}\), PPh\(_3\), CuI, and triethylamine in EtOH (Table 1). The reactions proceeded well irrespective of the presence of electron-donating (e.g., Me, MeO, Cl, NH\(_2\) etc) and electron-withdrawing (e.g., NO\(_2\) or F) groups on the iodoarene ring, affording the desired internal alkynes 5 and 6 via a C-C bond-forming reaction. The reaction was also successful when 5-iodoindoline-2,3-dione (entries 11 and 22, Table 1) and ethyl-2-iodo-5,6-dihydro-\(\text{H}\)-cyclopenta[\(b\)]thiophene-3-carboxylate (entry 14, Table 1) were employed as iodoarenes. Altogether, 22 new alkynes were prepared by using this methodology.

### Scheme 1

Synthesis of 2-(3-oxo-3-arylpropyl)-2,3-dihydro-\(\text{H}\)-inden-1-ones (7 and 8) via Pd\(\text{C}\)-mediated coupling followed by I\(_2\)-mediated hydration strategy. Reagents and conditions: (a) \(\text{Pd(CO)}_{3}\text{PPh}_3\text{CuI, Et}_3\text{N, EtOH, reflux, 1.5–24 h.}\) (b) I\(_2\), CH\(_2\)Cl\(_2\)-H\(_2\)O, rt, 24 h.

### Scheme 2

Synthesis of 2-(prop-2-ynyl)-2,3-dihydro-\(\text{H}\)-inden-1-ones (3 and 4). Reagents and conditions: (a) diethyl carbonate, NaH, toluene, reflux, 2 h, yield 85%. (b) Propargyl bromide, K\(_2\)CO\(_3\), dry acetone, rt, 12 h, yield 90%. (c) \(30\%\) NaOH, THF, reflux, 12 h, yield 80%.
in good yields except two cases (entry 9 and 20, Table 1) where the corresponding 1,4-dialkynyl benzene derivative was isolated as a side product. Indeed, an increase in reaction time afforded these side products (i.e., 5l and 6l) as major products (Scheme 3).

Table 1. Pd/C-mediated coupling of 2-(prop-2-ynyl)-2,3-dihydro-1H-inden-1-ones (3 and 4) with iodoarenes

| Entry | Alkynes (3 or 4) | ArI; Ar= | Time (h) | Products (5 or 6) | Yield (%)b |
|-------|------------------|----------|----------|------------------|------------|
| 1     | 3                | Ph       | 2        | 5a               | 63         |
| 2     | 3                | o-MeC6H4 | 3        | 5b               | 75         |
| 3     | 3                | m-MeC6H4 | 3        | 5c               | 63         |
| 4     | 3                | o-MeOC6H4| 3        | 5d               | 92         |
| 5     | 3                | p-MeOC6H4| 3        | 5e               | 89         |
| 6     | 3                | o-NO2C6H4| 1.5      | 5f               | 87         |
| 7     | 3                | m-NO2C6H4| 1.5      | 5g               | 87         |
| 8     | 3                | m-FC6H4  | 1        | 5h               | 92         |
| 9     | 3                | p-IC6H4  | 2        | 5i               | 34c        |
| 10    | 3                | m,p-di-ClC6H5 | 2       | 5j               | 66         |
| 11    | 3                |           | 5        | 5k               | 82         |
| 12    | 4                | Ph       | 24       | 6a               | 76         |
| 13    | 4                | o-MeC6H4 | 24       | 6b               | 58         |
| 14    | 4                |           | 36       | 6c               | 87         |
| 15    | 4                | o-MeOC6H4| 24       | 6d               | 73         |
| 16    | 4                | p-MeOC6H4| 24       | 6e               | 68         |
| 17    | 4                | o-NO2C6H4| 16       | 6f               | 73         |
| 18    | 4                | m-NO2C6H4| 16       | 6g               | 78         |
| 19    | 4                | m-FC6H4  | 12       | 6h               | 72         |
| 20    | 4                | p-IC6H4  | 12       | 6i               | 23c        |
| 21    | 4                | o-NH2(m-ch2)C6H3 | 2       | 6j               | 70         |
| 22    | 4                |           | 5        | 6k               | 65         |

aAll the reactions were performed using an appropriate iodoarene (0.33 mmol), 10% Pd/C (0.0022 mmol), PPh3 (0.0086 mmol), CuI (0.022 mmol), alkyne 3 or 4 (0.33 mmol), and Et3N (0.54 mmol) in EtOH (5 mL) at refluxing temperature under nitrogen.

bIsolated yields.

cCorresponding 1,4-dialkynyl benzene derivative was isolated as a side product in this case.
Having prepared a variety of 3-aryl substituted 2-propynyl indanone derivatives (5 and 6) we then performed the I₂-mediated hydration of some of these internal alkynes. These reactions were carried out using alkynes 5 or 6 (0.15 mmol) and a catalytic amount of iodine (0.015 mmol) in dichloromethane-H₂O (4.9 mL of DCM + 0.1 mL of H₂O) at rt for 24 h, and results are summarized in Table 2. Several 2-(3-oxo-3-arylpropyl)-2,3-dihydro-1H-inden-1-one derivatives (7 and 8) were prepared with high regioselectivity by using this method in good yields. The formation of other regioisomers [i.e., 2-(2-oxo-3-arylpropyl)-2,3-dihydro-1H-inden-1-one derivatives] was not observed in any of these cases. Notably, the reaction did not proceed in the absence of I₂ or when performed in dry DCM, indicating the key role played by both catalyst and water.

A plausible reaction mechanism for the I₂-mediated regioselective hydration of 3-aryl-substituted 2-propynyl indanone derivatives (5 and 6) is shown in Scheme 4. The reaction seems to proceed via activation of the triple bond by coordination to

Table 2. Synthesis of ketones 7 and 8 via I₂-mediated hydration of alkynes 5 and 6

| Entry | Alkynes (5 and 6) | Product (7 and 8) | Yield (%)b |
|-------|------------------|------------------|------------|
| 1     | 5a               | 7a               | 87         |
| 2     | 5b               | 7b               | 85         |
| 3     | 5h               | 7c               | 63         |
| 4     | 6a               | 8a               | 84         |
| 5     | 6b               | 8b               | 82         |
| 6     | 6h               | 8c               | 65         |

aAll reactions were carried out by using alkyne 5 or 6 (0.15 mmol) and a catalytic amount of iodine (0.015 mmol) in DCM-H₂O (4.9 mL of DCM + 0.1 mL of H₂O) at rt for 24 h.

bIsolated yields.
I\(^+\) obtained from the molecular iodine. This triggers a nucleophilic attack by the proximal carbonyl group onto the activated triple bond to generate a cyclized vinyl iodide intermediate, E-1 or E-2. However the isolation of product 7 or 8 suggests that the reaction followed a 6-endo-dig process leading to the intermediate E-2. While the generation of E-1 via a 5-exo-dig process is allowed according to Baldwin’s rules,\(^{[18]}\) the intermediate E-1 would afford the corresponding regioisomers [i.e., 2-(2-oxo-3-arylpropyl)-2,3-dihydro-1\(H\)-inden-1-one derivatives instead of the product 7 or 8] that were not isolated. The 5-exo-dig process thus appeared to be a less favored one in the present case, perhaps due to the nonfavorable geometry associated with the 5-5 ring formation rather than the 5-6 ring. Nevertheless, arguably being the predominating intermediate, the vinyl iodide species E-2 undergoes ring opening upon interaction with water to give the intermediate E-3 (via proto-deiodination), which finally undergoes isomerization to give the keto compound 7 or 8. Notably, though the participation of the ester moiety\(^{[16]}\) of 5 in its regioselective alkyne hydration cannot be ruled out completely, the successful hydration of 6 that does not possess an ester group suggests preferential participation of keto group over the ester.

We then assessed the potential biological activities of all these compounds (i.e., 5–8) synthesized. Because of our longstanding interest in the identification of novel PDE4/TNF-\(\alpha\) inhibitors,\(^{[19–22]}\) all these compounds were tested for their PDE4 inhibitory properties in vitro using PDE4B enzyme assay.\(^{[23]}\) Because the PDE4B subtype among the four subtypes of PDE4 (e.g., A, B, C, and D) has been indicated to have key role in inflammatory cell regulation,\(^{[24]}\) inhibition of the PDE4B was thought to be beneficial for the potential treatment of diseases such as COPD and asthma without causing adverse effects.\(^{[25]}\) Among all the compounds tested, 5a showed >30% inhibition of PDE4B when tested at 30\(\mu\)M using a known inhibitor rolipram\(^{[26]}\) as a reference compound. To understand its preferred binding modes with the PDE4B protein, molecular modeling studies were performed using co-crystal structural coordinates of PDE4B from the protein data. Because 5a can exist in two optical isomers [e.g., (R)- and (S)], both forms were used for the docking studies. Based on docking results, no significant binding variations were observed between (R) and (S) forms of 5a. The C-5 methoxy group of 5a was found to interact

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**Scheme 4.** Proposed reaction mechanism for the I\(_2\)-mediated hydration of 3-aryl substituted 2-propynyl indanone derivatives (5 and 6).
with the His-278 residue of PDE4B protein via an H-bond (Fig. 2). The overall interaction of 5a with the PDE4B protein was indicated by the glide score obtained for 5a (−5.93 for R and −5.48 for S isomer; see supporting information, Table S-1).

CONCLUSIONS

In conclusion, we have disclosed a new, simple, and inexpensive strategy for the synthesis of novel indanone derivatives of potential pharmacological interest. These compounds were prepared first time via (i) an initial introduction of an alkynyl moiety at C-2 of the indanone ring followed by (ii) its arylation via Pd/C-mediated reactions and then (iii) I2-mediated hydration of the triple bond. A wide variety of 3-aryl substituted 2-propynyl indanone derivatives were conveniently prepared by using 10% Pd/C-PPh₃-CuI as a catalyst system in the presence of triethylamine in EtOH.
Some of them were converted to the corresponding ketones in the presence of I$_2$ without using any additional acid catalysts or ligands. A representative compound 5a showed inhibition of PDE4B when tested in vitro. Docking studies indicated that one of the methoxy groups of this molecule played key roles in the interactions with the PDE4B protein. Overall, the synthetic methodology presented here could be useful in constructing a library of molecules related to indanone that have potential medicinal value.

**EXPERIMENTAL**

**General Procedure for the Pd/C-Mediated Coupling of 2-(Prop-2-ynyl)-2,3-dihydro-1$^H$-inden-1-ones (3 and 4) with Iodoarenes**

A mixture of iodo compound (0.33 mmol), 10% Pd/C (0.0022 mmol), PPh$_3$ (0.0086 mmol), CuI (0.022 mmol), and triethylamine (0.54 mmol) in EtOH (5 mL) was stirred for 30 min under a nitrogen atmosphere. To this mixture was added alkyne 3 or 4 (0.33 mmol) slowly, and the mixture was refluxed. The reaction was monitored by thin-layer chromatography (TLC). The mixture was then cooled to room temperature and filtered through celite; EtOH was removed under reduced pressure. The residue was diluted with water (50 mL) and extracted with EtOAc (3 × 25 mL). The organic layers were collected, combined, washed with water (2 × 25 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue thus obtained was purified by column chromatography to afford the title compounds.

**Synthesis of Ketones 7 and 8 via I$_2$-Mediated Hydration of Alkynes 5 and 6**

To a solution of alkyne 5 or 6 (0.15 mmol) dissolved in DCM-H$_2$O (4.9 mL of DCM + 0.1 mL of H$_2$O) was added a catalytic amount of iodine (0.015 mmol), and the mixture was stirred at rt. After completion of the reaction (monitored by TLC), the mixture was then diluted with dichloromethane (25 mL) and washed with saturated aqueous solution of Na$_2$S$_2$O$_3$ (25 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product obtained was purified by column chromatography.

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**SUPPLEMENTAL MATERIAL**

Supplemental data for this article can be accessed on the publisher’s website.

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