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Pd-Catalyzed direct arylation approach to the 6*H*-dibenzo[*c*,*h*]chromenes : Total synthesis of arnottin I†

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Abstract : An efficient synthesis of 6*H*-dibenzo[*c*,*h*]chromenes has been achieved from 2-bromobenzyl-α-naphthyl ethers via a Pd-catalyzed intramolecular direct-arylation using easily available $Pd(PPh_3)_4$ or $Pd(OAc)_2/PPh_3$ at elevated temperature. The reaction affords biaryl-coupling products in good to excellent yields in 6–9 h (up to 94% yields). A tentative mechanism has been proposed to understand the reaction pathway. Applying the methodology, a straightforward and concise total synthesis of arnottin I has been demonstrated by converting the biaryl-coupling products to the 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one using pyridinium chlorochromate (PCC) mediated oxidation.

Keywords : Direct biaryl-coupling, Pd-catalyzed, 6*H*-dibenzo[*c*,*h*]chromenes, oxidation, 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one, arnottin I.

Introduction

In recent years, strategies for the synthesis of natural products that rely on transition metal-catalyzed cross-coupling reactions predominate in the literature over other approaches[1]. In this regard, intramolecular transition-metal-catalyzed arene C–H bond functionalization reactions have emerged as versatile tools for the atom- and step-economical assembly of aromatic compounds and has been utilized in the total synthesis of various natural products[2]. These reactions substitute one of the preactivated arenes with a simple arene (Scheme 1) which ultimately leads to the discovery of 'ideal synthesis'[3]. Despite the associated advantages, several important challenges still remain to be overcome. For example, the predominant of direct arylation reactions employ aryl iodides as coupling partners[4]. For more reactive aryl iodides, moderately electron-rich monodentate phosphines such as PPh_3 are typically used. In case of aryl bromides and chlorides, more sterically bulky and electron-rich trialkylphosphine or Buchwald's biphenylphosphines are required[5,2c-e].

The impetus for the synthesis of biaryl compounds lies in their exhaustive use as building blocks of many alkaloids and carbocyclic natural products[6]. Especially, those having 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton constitute the basic skeleton of wide range of biologically active metabolites of certain *Streptomyces* species[7–11]. Gilvocarcins (**1b-c**)[7] and other related compounds, such as ravidomycin (**1d**)[8] and chrysomycins (**1e-f**)[9], are metabolites of certain *Streptomyces* species and belong to a class of aryl *C*-glycoside antibiotics[10] (Fig. 1). The coumarin-based natural product arnottin I (**1a**), having a 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton is found in gilvocarcin-type antibiotics[11]. Arnottin I (**1a**) is a non-alkaloidal minor component isolated from the bark of *Xanthoxylum arnottianum* Maxim, which belongs to the family *Rutaceae*[11a]. These natural products sharing a common tetracyclic aromatic nucleus, 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one with the C-4 position attached with a sugar moiety have greatly attracted the synthetic chemists. Defucogilvocarcins[12] having a similar chromophore have also been extensively studied (Fig. 1). In this regard, mainly the regioselective synthesis of highly substituted 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one comes up as a major challenge.

†**In honour of Professor Sunil Kumar Talapatra on the occasion of his 80th birthday.**