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Simultaneous exploration of TBAF·3H$_2$O as a base as well as a solvating agent for the palladium catalyzed Suzuki cross-coupling of 4-methyl-7-nonafluorobutylsulfonyloxy coumarins under microwave irradiation

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ABSTRACT

A concise, efficient and facile protocol for the synthesis of a variety of 4-methyl-7-aryl/heteroaryl coumarins has been developed by utilizing the palladium catalyzed Suzuki cross-coupling reaction of 4-methyl-7-nonafluorobutylsulfonyloxy coumarin with a wide range of electronically diverse boronic acids under microwave irradiation. In the presence of a suitable catalyst, ligand and base, the coupling reaction proceeded smoothly to give the biaryls in satisfactory to exceptional yields. The dual role of TBAF·3H$_2$O as a base as well as a solvating agent and the utilization of dppp as a ligand with moderate bite angle (91°) were found to be instrumental for the success of the reaction. Prominent features of this optimization conditions include: shorter reaction times, good to excellent yield and exceptional tolerance to a wide variety of functional groups.

1. Introduction

The Suzuki–Miyaura cross-coupling reaction between organoboranes and organic halides or pseudohalides has emerged as one of the foremost methods for the creation of carbon–carbon bonds under mild conditions [1]. The reaction provides an efficient pathway to a range of pharmaceuticals, herbicides, natural products, polymers and liquid crystalline materials and hence has significantly extended its scope in recent years [2]. Salient features of these reactions are the availability, stability and non-toxicity of a variety of boronic acids, extensive functional group tolerance and easy access for product isolation [3]. These features evidently reveal its significance in synthetic chemistry and hence this reaction has found widespread use in pharmaceutical industries. The microwave assisted organic synthesis (MAOS) has gained remarkable importance in drug discovery laboratories these days mostly due to their superior reaction rates, selectivity and product yields as compared to standard thermal conditions [4]. Transition metal catalyzed cross-coupling reactions usually take hours or days for completion by conventional heating whereas the use of microwave irradiation will complete those reactions in minutes with excellent reproducibility and lesser side-reactions [5].

Coumarins are an important class of benzopyrones that are essentially found in green plants either in free or combined state [6]. They represent one of the most active classes of compounds and possess a wide spectrum of biological activity [7]. Coumarin derivatives have numerous therapeutic applications including photo chemotherapy, anti-tumor therapy, anti-HIV therapy [8], and are also active as anti-bacterial [9], anti-inflammatory [10] and anti-coagulating agents [11]. In addition, coumarins are known to be lipid lowering agents with moderate triglyceride lowering activity [12] whereas hydroxycoumarins are powerful chain breaking anti-oxidants and can prevent free radical injury [13,14]. The coumarin core is present within the chemical structure of several pharmaceutical drugs such as warfarin, acenocoumarol, carbochromen etc. and in antibiotics such as novobiocin, clorobiocin and coumermycin A1 [15]. In view of these varied applications, the investigation of facile and efficient methods for

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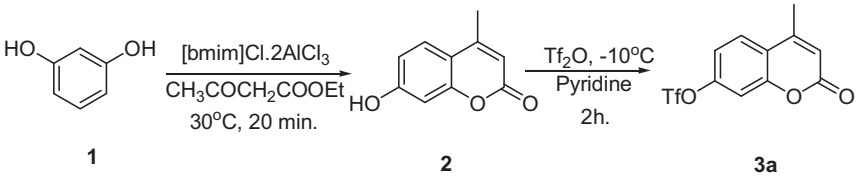


Scheme 1. Synthesis of 4-methyl-7-trifluoromethylsulfonyloxy coumarin intermediate.

the synthesis of diversely substituted coumarin derivatives has been the aim of many researchers for the past 20 years [16].

The diverse applications of coumarins in various fields of chemistry have been extensively reported in the literature. Furthermore, the structure activity relationship (SAR) studies of various aryl/heteroaryl coumarins have revealed the fact that the presence of substituted heteroaryl/aryl groups in the coumarin moiety is an indispensable characteristic for their pharmacological action [17]. Coumarin derivatives with substitution at 7th position are known to possess various bioactive applications [18]. 4-Methyl-7-substituted coumarins are reported to have diverse applications in the field of medicinal chemistry such as Monoamine Oxidase Inhibitory Potency and DNA binding capacity [19]. Even though the synthesis of various 3,4,6,7 and 8 substituted coumarins have been extensively reported in the literature [20], the synthesis of 7-substituted coumarins require the conversion of its triflate to corresponding boronic ester which took 17 h for completion and the further biaryl coupling was quite unclear [21]. Furthermore, the methodology for the synthesis of 7-arylcoumarins was reported to be time consuming over night reactions with relatively lower yields [22]. Moreover, the instability (lactone ring cleavage) of the coumarin scaffold in basic as well as under prolonged heating conditions was broadly reported in literatures [17,23]. These observations prompted us to utilize the microwave irradiation for the synthesis of coumarin derivatives by considering the fact that the reactions could reach to completion within minutes as compared to conventional heating methodologies.

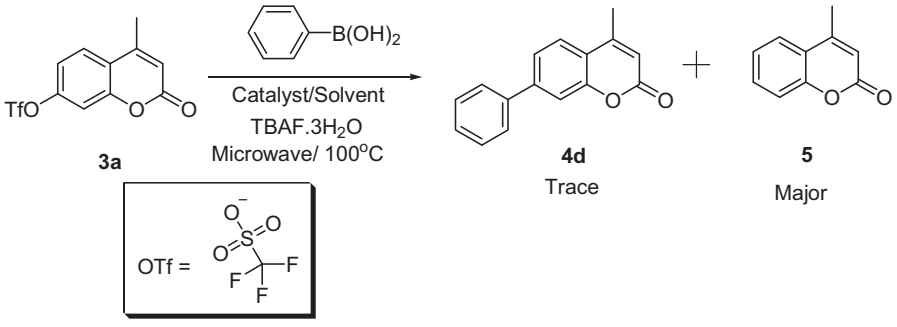
As a continuation of our ongoing research program in the synthesis of biologically active molecules [24], we were interested in synthesizing some 7-substituted coumarins which may possess considerable pharmacological activities. On continuation of our ongoing research on palladium catalyzed cross-coupling reactions [25], it has been planned to apply the Suzuki coupling reaction for the synthesis of various coumarin analogues under microwave irradiation. Among the pseudohalides, the stability and reactivity of nonaflates over corresponding triflates in the palladium catalyzed cross-coupling reactions has been recently reported from our laboratory [26]. In this letter, we report a facile and reliable protocol for the synthesis of a variety of 4-methyl-7-aryl/heteroaryl coumarins by utilizing the Suzuki cross-coupling reaction of 4-methyl-7-nonafluorobutylsulfonyloxy coumarin with various aryl/heteroaryl boronic acids under microwave irradiation. To the best of our knowledge, the exploration of the 7th position of coumarins for direct arylation by Suzuki coupling under microwave irradiation is few.

2. Results and discussion

The parent 4-methyl-7-hydroxycoumarin molecule **2** was prepared by the modified Pechmann cyclization of resorcinol **1** with ethyl acetoacetate in 1-butyl-3-methylimidazolium chloroaluminate at 30 °C for 20 min [27] (Scheme 1). The obtained hydroxy coumarin **2** was then converted to corresponding triflate **3a** by treating it with trifluoromethanesulfonic anhydride in dichloromethane (DCM) and pyridine at −10 °C for 2 h. The intermediate thus obtained was then subjected to Suzuki coupling with the intention of synthesizing an array of novel 4-methyl-7-aryl/heteroaryl coumarins of considerable pharmacological relevance (Scheme 2).

As a model reaction, we selected the triflate **3a** and phenylboronic acid in various solvents under microwave irradiation for optimizing the reaction conditions. We decided to optimize the reaction by employing TBAF·3H_2O as a base as it has been reported to have significant effect in suppressing the hydrolysis of pseudohalides by increasing its solvation in the reaction medium [26,28]. To our disappointment, we obtained the detriflated product **5** as the major product in all the explored conditions (Table 1). The triflate proved to be highly unstable in the reaction conditions which could be presumably due to the unstable nature of the intermediate Pd(II) complex that is expected to form during its preliminary oxidative addition to Pd(0).

Our subsequent efforts were to optimize the reaction conditions by changing the substrate to corresponding nonaflates. The hydroxycoumarin intermediate **2** was converted to the corresponding nonaflate by treating it with 1.5 equivalent of nonafluorobutanesulfonic anhydride at −10 °C in dichloromethane (DCM) and pyridine as base for 2 h. The obtained nonaflate intermediate **3b** was found to be highly stable than the corresponding triflates and did not decompose even after storing for a longer period of time. The intermediate **3b** was then subjected to Suzuki coupling with various boronic acids with the objective of synthesizing a variety of novel 4-methyl-7-substituted coumarins (Scheme 3).



Scheme 2. Suzuki coupling of 4-methyl-7-trifluoromethylsulfonyloxy coumarin intermediate with phenylboronic acid.