



A novel organozinc reagent 4-coumarinylzinc bromide; preparation and application in the synthesis of 4-substituted coumarin derivatives

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ABSTRACT

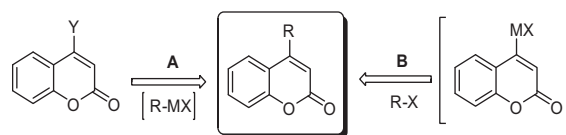
A novel organozinc reagent, 4-coumarinylzinc bromide, was prepared by the direct oxidative addition of active zinc to 4-bromocoumarin. The resulting organozinc bromide underwent the palladium-catalyzed cross-coupling reactions with a variety of aryl halides and acid chlorides affording the corresponding coupling products in good yields under mild conditions.

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Due to the particular interest in the coumarin moiety in natural products¹ as well as in material chemistry,² numerous studies have focused on the development of a versatile synthetic methodology for the preparation of coumarin derivatives. Among the well-known procedures, palladium-catalyzed cross-coupling reactions of organometallic reagents with coumarin derivatives are one of the predominant approaches, especially for the preparation of 4-substituted coumarins (route **A** in Scheme 1). Scheme 1 illustrates the schematic diagram of the convenient synthetic routes utilizing organometallic reagents for the 4-substituted coumarin derivatives.

Although various methods were reported for the synthesis of 4-substituted coumarin, inconvenient reaction conditions were utilized in most of the previously reported reactions.³ As mentioned before, route **A** in Scheme 1 is the most widely used in the synthesis of the title compound. For example, Yang described the preparation of 4-substituted coumarin using palladium-catalyzed cross-coupling reaction of 4-tosylcoumarins^{4a} and nickel-catalyzed cross-coupling reaction of 4-diethylphosphonoxycoumarins with organozinc.^{4b} A similar approach using palladium-catalyzed cross-coupling reaction of 4-trifluoromethylsulfonyloxycoumarins or 4-toluenesulfonyloxycoumarins with organostannes was also reported by Wattanasin and Schio, respectively.⁵ The Suzuki-type coupling reaction with 4-halocoumarin was employed to generate the 4-substituted coumarins.⁶

Even though the route **A** could provide a variety of 4-substituted coumarins, a drawback to this procedure is that some of the organometallic reagents are not readily available. Therefore, in spite of the present methodologies, there is still a need to explore a versatile synthetic methodology for the construction of a chemical library of 4-substituted coumarin derivatives. We considered the alternative route to the synthesis of 4-substituted coumarins,



Scheme 1. Synthetic routes for 4-substituted coumarin.

Table 1
Coupling reaction with benzoyl chloride

Entry	Acid chloride	Product ^a (%)
1	X = H (1a)	(90)
2	X = 3-Br (1b)	(86)
3	X = 4-F (1c)	(88)
4	X = 4-CF ₃ (1d)	(91)
5	X = 4-OMe (1e)	(92)
6	X = 3-CH ₂ Cl (1f)	(79)

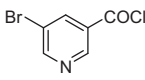
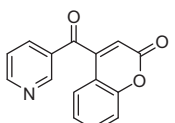
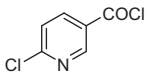
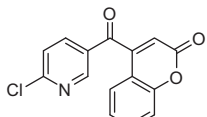

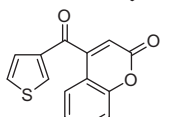
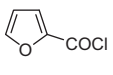
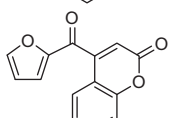
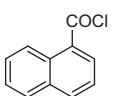
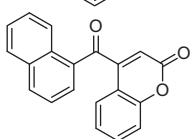
^a Isolated yield (based on acid chloride).

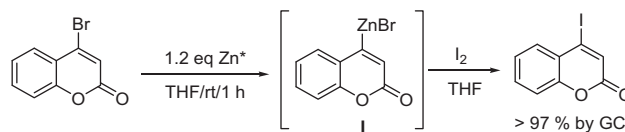
depicted route **B** in Scheme 1. We assumed that this route could provide a versatile way of introducing a variety of different substituents at the 4-position of coumarin. The direct preparation and application of 4-coumarinylzinc bromide represents a novel and versatile approach to many new substituted coumarins.

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Table 2
Coupling reaction with heteroaryl acid chloride

I + Acid chloride		1 % Pd(PPh ₃) ₄		product	2a - 2e
1.0 eq	0.8 eq	THF/ rt/ 30 min			
Entry	Acid chloride	Product ^a (%)			Yield ^a (%)
1			2a	75	
2			2b	70	
3			2c	85	
4			2d	79	
5			2e	81	


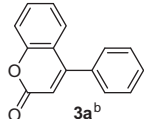

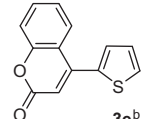
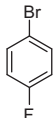
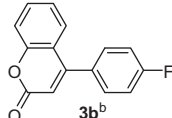
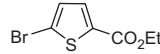
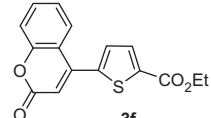
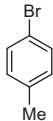
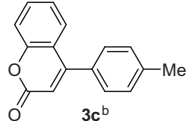
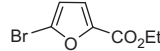
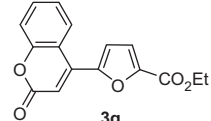
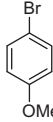
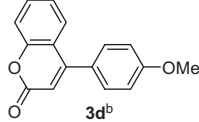

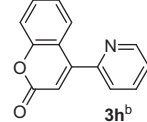
^a Isolated yield (based on acid chloride).**Scheme 2.** Preparation of 4-coumarinylzinc bromide (1).

In our continuing effort to develop a new class of organozinc reagents, we found that 4-coumarinylzinc bromide (**1**) was easily prepared by the direct insertion of active zinc to 4-bromocoumarin under mild conditions.⁷ Herein, we would like to report our preliminary results obtained from the cross-coupling reaction of the 4-coumarinylzinc bromide with a wide range of electrophiles (**Scheme 2**).

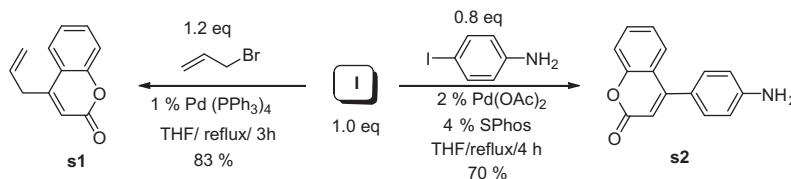
Prior to the study of this reagent in the coupling reactions, an aliquot of the solution was treated with iodine and analyzed by GC and GC–MS to confirm the formation of the corresponding organozinc reagent. Both analyses clearly showed the formation of 4-iodocoumarin. In addition, ¹H NMR spectroscopic investigation was completed with the isolated product of the reaction aliquot after acidic quenching.⁸ From these results, it could be concluded that the corresponding organozinc reagent (**1**) was successfully obtained.

As described in aforementioned reports,^{4–6} introducing aryl and alkyl substituents directly to the C4-position of coumarin has been primarily carried out via palladium-catalyzed cross-coupling reactions with the corresponding organometallic reagents (route **A** in **Scheme 1**). We have taken a different approach which allows the introduction of a carbonyl group in the C4-position. **Table 1** shows the results observed from Pd-catalyzed cross-coupling reactions with a variety of aryl acid chlorides. These reactions yields a carbonyl group directly bonded to C4-position of coumarin. All of the coupling reactions were completed in 30 min at room temper-

Table 3
Coupling reaction with arylhalide

		I	+	aryl halide	$\xrightarrow[THF/rt/6\ h]{1\ \% Pd(PPh_3)_4}$	product		
		1.0 eq		0.7 eq		3a - 3h		
Entry	Halide	Product	Yield ^a (%)	Entry	Halide	Product	Yield ^a (%)	
1		 3a ^b	83	5		 3e ^b	81	
2		 3b ^b	75	6		 3f	84	
3		 3c ^b	77	7		 3g	88	
4		 3d ^b	76	8		 3h ^b	79	

^a Isolated yield (based on aryl halide).^b All the spectroscopic data are consistent with literature value (Ref. 4).



Scheme 3. Expansion of coupling reaction.

ature in THF in the presence of 1 mol % Pd(PPh₃)₄. Not only a simple acid chloride but halogenated benzoyl chlorides were successfully coupled with **1** under very mild conditions affording the corresponding products (**1a**, **1b**, and **1c**, Table 1) in excellent yields. Both coupling reactions with benzoyl chlorides possessing electron-withdrawing group (CF₃) and electron-donating group (OCH₃) gave rise to the products (**1d** and **1e**, Table 1) in 91% and 92% isolated yield, respectively. A benzoyl chloride possessing a benzylic halide reacted under the conditions used in this study to give the product **1f** in good yields (entry 6, Table 1). Unfortunately, the desired coupling product was not obtained from the coupling reactions with alkyl carbonyl chlorides under the same reaction conditions.

Since the heterocyclic moiety found in many natural compounds plays a critical role for biological activity, our next attempt was to couple **1** with several heteroaryl acid chlorides. Table 2 illustrates the reaction conditions and the results. Once again, it should be emphasized that all the coupling reactions were carried out under mild conditions. 5-Bromonicotinoyl chloride and 6-chloronicotinoyl chloride were efficiently employed for the coupling reaction giving rise to the products (**2a** and **2b**) in moderate yields (entries 1 and 2, Table 2). 3-Thiophenecarbonyl chloride and 2-furoyl chloride were also coupled with **1** under the same conditions and the coupling products (**2c** and **2d**, Table 2) were obtained in 85% and 79% yields, respectively.

In an effort to evaluate the overall feasibility of the organozinc **1**, coupling reactions with arylhalides were performed. The aforementioned route **A** can also provide the 4-aryl-substituted coumarins. However, as illustrated in Scheme 1, our strategy (route **B**) is to use a totally new organometallic reagent instead of known organometallic reagents. Palladium-catalyzed coupling reaction of **1** with iodobenzene (entry 1, Table 3) and bromobenzenes (entries 2, 3, and 4, Table 3) proceeded smoothly resulting in the formation of 4-arylsubstituted coumarins (**3a**, **3b**, **3c**, and **3d**, Table 3) in good yields. Heteroaryl halides also proceeded smoothly to yield 4-heteroaryl-substituted coumarins in good yields. Interestingly, the reaction conditions used before worked well for the coupling reaction with heteroaryl compounds. 2-Bromothiophene reacted with **1** to afford **3e** in 85% yield (entry 1, Table 3). Good results were obtained from the coupling reactions using bromothiophene and bromofuran bearing a functional group (entries 6 and 7, Table 3). The coupling reaction with 2-bromopyridine also proceeded well to generate **3h** in good yield (entry 8, Table 3).

In order to demonstrate the exceptional versatility of this reaction, two other very different types of halides were reacted with an excellent reagent. A S_N2'-type reaction was performed with allyl bromide resulting in the formation of 4-allylcoumarin (**s1**) in 83% yield (Scheme 3). Consequently, we then investigated the coupling reaction with a haloaromatic amine. As illustrated in Scheme 3, the coupling reaction was easily accomplished with 4-iodoaniline using 2 mol % Pd(OAc)₂ and 4 mol % SPhos in THF at

refluxing temperature affording 4-(4'-aminophenyl)coumarin (**s2**) in moderate yield.⁹

In conclusion, a novel synthetic route for the preparation of 4-substituted coumarin derivatives has been demonstrated. It has been accomplished by utilizing a simple coupling reaction of a readily available 4-coumarinylzinc bromide (**1**), which was prepared via the direct insertion of active zinc to 4-bromocoumarin. The subsequent coupling reactions with a variety of different electrophiles have been carried out under mild conditions providing a new class of 4-substituted coumarins. Development of the analogues of our organozinc reagent and their applications are currently under way.

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- Representative procedures:** (a) Preparation of 4-coumarinylzinc bromide (**1**): In an oven-dried 50 mL round-bottomed flask equipped with a stir bar was added 1.40 g of active zinc (Zn⁰, 22.0 mmol). 4-Bromocoumarin (4.50 g, 20.0 mmol) dissolved in 20 mL of THF was then cannulated neat into the flask at room temperature. The resulting mixture was stirred for 1 h at room temperature. The whole mixture was settled down and then the supernatant was used for the subsequent coupling reactions; (b) Representative Pd-catalyzed cross-coupling reaction procedure: into a 25 mL round-bottomed flask were added Pd(PPh₃)₄ (0.025 g, 1 mol %) and 4.0 mL of 4-coumarinylzinc bromide (**1**) (0.5 M in THF, 2.0 mmol) was added into the flask under an argon atmosphere. Next, 4-methoxybenzoyl chloride (0.27 g, 1.60 mmol) was slowly added via a syringe while being stirred at room temperature. The resulting mixture was stirred at room temperature for 30 min. Quenched with 3 M HCl solution, it was then extracted with ethyl ether (10 mL × 3). Washed with saturated NaHCO₃, Na₂S₂O₃ solution and brine, it was then dried over anhydrous MgSO₄. Purification by column chromatography on silica gel (20% ethyl acetate/80% heptane) afforded 0.39 g of **1e** in 92% isolated yield as white solid (mp 107–108 °C). MS (EI) *m/z* (relative intensity): 280 (M⁺, 80), 252 (25), 135 (100).
- All chemical shifts of the reduced product (coumarin) were consistent with the literature values; The Aldrich Library of ¹³C and ¹H FT NMR Spectra.
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