



An efficient route to 4-substituted coumarins, 2(5H)-furanones, and pyrones via palladium-catalyzed couplings of alkenyl tosylates with organoindium reagents

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ABSTRACT

Highly efficient palladium-catalyzed couplings of alkenyl tosylates with organoindium reagents under mild conditions are described, which give rise to 4-substituted coumarins, 2(5H)-furanones, and pyrones in good to excellent yields.

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It is well known that transition-metal catalyzed cross-coupling reactions are regarded as one of the most powerful methods for carbon–carbon bond formation, which have been extensively employed in a wide range of areas of organic chemistry.¹ Among the organometallic reagents (B, Zn, Mg, Sn, Si, etc.) utilized in the coupling reactions, organoindium compound has attracted much attention recently due to its versatile chemistry and stability in aqueous/protic conditions.² Meanwhile, for the electrophile employed, arenesulfonate or mesylate is regarded as an important alternative^{3–9} since they are very stable and easily accessible.

In our continuous efforts toward accessing privileged scaffolds,¹⁰ we became interested in exploring efficient coupling reactions to facilitate the generation of natural product-like compounds. It is well known that coumarin, pyrone, and 2(5H)-furanone are important structural units in naturally occurring products, therapeutics, and synthetic analogues with interesting biological activities^{11–14} (Fig. 1). For example, Rofecoxib is an anti-inflammatory drug launched by Merck and approved by FDA.^{12k} Rubrolides A–F are potent antibiotics.^{12g} Prompted by the advantages of organoindium compounds and arenesulfonates in cross-coupling reactions, we started to investigate the coupling reactions of the corresponding

alkenyl tosylates with organoindium reagents, with an expectation to provide an efficient route for the synthesis of these compounds.

Initial studies were performed for the reaction of 4-tosyloxycoumarin **1a** with tri(4-methoxyphenyl)indium **2a** (Scheme 1). The tosylate could be easily synthesized via the reaction of 4-hydroxycoumarin with *p*-toluenesulfonyl chloride. To identify suitable conditions for this transformation, at the outset the reaction was carried out in the presence of PdCl₂(PPh₃)₂ (5 mol %) as a catalyst in toluene at room temperature. To our delight, we observed the formation of the desired product **3a** although the reaction could not go to completion after 24 h. A similar result was displayed when Pd(OAc)₂ was used as a replacement. Further screening of solvents revealed that THF was the best choice. Under this condition, the reaction catalyzed by Pd(OAc)₂ (5 mol %) was highly efficient which was completed in 1 min with almost quantitative yield (98%). Blank experiment showed that no reaction

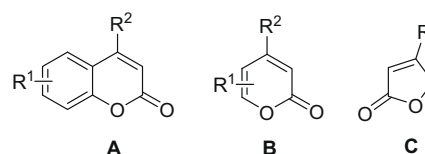
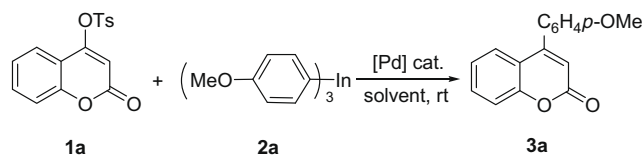


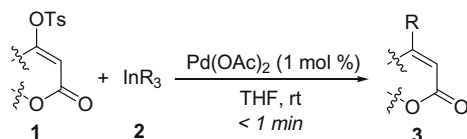
Figure 1. Structures of coumarin A, pyrone B, and 2(5H)-furanone C.

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Scheme 1. Initial studies for the reaction of 4-tosyloxycoumarin **1a** with tri(4-methoxyphenyl)indium **2a**.

Table 1
Palladium-catalyzed reactions of alkenyl tosylates with organoindium reagents^{a,15}



Entry	Substrate 1	R	Yield ^b (%)
1		4-MeOC ₆ H ₄ (2a)	98 (3a)
2	1a	C ₆ H ₅ (2b)	98 (3b)
3	1a	4-FC ₆ H ₄ (2c)	95 (3c)
4	1a	ⁿ Bu (2d)	81 (3d)
5		4-MeOC ₆ H ₄ (2a)	98 (3e)
6	1b	C ₆ H ₅ (2b)	70 (3f)
7	1b	4-FC ₆ H ₄ (2c)	97 (3g)
8	1b	ⁿ Bu (2d)	93 (3h)
9		4-MeOC ₆ H ₄ (2a)	95 (3i)
10		4-MeOC ₆ H ₄ (2a)	96 (3j)
11	1d	C ₆ H ₅ (2b)	97 (3k)
12	1d	4-FC ₆ H ₄ (2c)	96 (3l)
13	1d	ⁿ Bu (2d)	81 (3m)
14		4-MeOC ₆ H ₄ (2a)	97 (3n)
15	1e	C ₆ H ₅ (2b)	96 (3o)
16	1e	ⁿ Bu (2d)	89 (3p)
17		4-MeOC ₆ H ₄ (2a)	97 (3q)
18	1f	C ₆ H ₅ (2b)	83 (3r)
19	1f	4-FC ₆ H ₄ (2c)	94 (3s)
20		4-MeOC ₆ H ₄ (2a)	89 (3t)
21	1g	C ₆ H ₅ (2b)	82 (3u)
22	1g	4-FC ₆ H ₄ (2c)	94 (3v)

^a Reaction conditions: alkenyl tosylate **1** (0.5 mmol), organoindium reagent **2** (0.5 mmol), Pd(OAc)₂ (1 mol %), THF (3.0 mL), room temperature.

^b Isolated yield based on alkenyl tosylate **1**.

occurred in the absence of palladium catalyst. Reducing the amount of palladium catalyst to 1 mol % did not diminish the reactivity of this transformation (1 min, 98% yield).

Subsequently, we started to investigate the scope of this reaction. Thus, various 4-tosyloxycoumarins **1** were employed in the reactions of organoindium compounds under the palladium-catalyzed conditions [Pd(OAc)₂ (1 mol %), THF, room temperature] (Table 1). It was noteworthy that all reactions went to completion in 1 min under the mild condition with good yields. This Pd-catalyzed 4-substituted coumarin formation was found to be workable with triarylindium reagents as well as trialkylindium compounds. For example, the reaction of 4-tosyloxycoumarin **1a** with triphenylindium **2b** gave rise to the desired product **3b** in 98% yield (Table 1, entry 2). When tri(4-fluorophenyl)indium **2c** was employed in the above-mentioned reaction, the product **3c** with a similar yield was isolated (Table 1, entry 3). Interestingly, tri(*n*-butyl)indium **2d** was a suitable substrate as well in the reaction, which afforded the corresponding product **3d** in 81% yield (Table 1, entry 4). Usually, the β-hydrogen elimination would occur when other alkyl metal reagents (such as Zn and Sn) were utilized in the above-mentioned cross-coupling reactions. Thus, the method using organoindium compounds as coupling partners provided an efficient route to 4-alkylcoumarins. This condition was also workable for other 4-tosyloxycoumarins **1b–e** bearing chloro, fluoro, and methyl functionality on the aromatic backbone. For instance, 6-chloro-4-tosyloxycoumarin **1b** reacted with tri(4-methoxyphenyl)indium **2a** leading to the desired coumarin **3e** in 98% yield (Table 1, entry 5). Reactions of indium reagent **2b** or **2c** with 6-chloro-4-tosyloxycoumarin **1b** proceeded well to generate the desired product **3f** or **3g** in 70% or 97% yield, respectively (Table 1, entries 6 and 7). Again, tri(*n*-butyl)indium **2d** reacted with 6-chloro-4-tosyloxycoumarin **1b**, giving rise to the 4-butyl-6-chlorocoumarin **3h** in 93% yield (Table 1, entry 8). During these transformations, the chloro group attached on the aromatic ring was retained. It means that the alkenyl tosylate is more reactive than aryl chloride. Reactions of 6-fluoro-4-tosyloxycoumarin **1c**, 6-methyl-4-tosyloxycoumarin **1d**, and 6,7-dimethyl-4-tosyloxycoumarin **1e** with organoindium compounds **2** also proceeded smoothly to generate the desired products in good to excellent yields (Table 1, entries 9–16). 4-Tosyloxypyrone **1f** and 4-tosyloxy 2(5*H*)-furanone **1g** were examined as well. As expected, all reactions worked well to generate the corresponding products in high yields (Table 1, entries 17–22).

In summary, we have described an efficient and facile route for the synthesis of 4-substituted coumarins, 2(5*H*)-furanones, and pyrones via palladium-catalyzed cross-coupling reactions of alkenyl tosylates with organoindium compounds. The transformation is highly efficient and the reactions usually complete in 1 min under extremely mild conditions with high yields. Exploring application of organoindium reagents in other coupling reactions is under investigation in our laboratory, and the results will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.096.

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- General procedure for the Pd(OAc)₂-catalyzed reaction of alkenyl tosylates with organoindium reagents: organoindium reagent 2 (0.5 mmol) in THF (1.0 mL) was added to a mixture of Pd(OAc)₂ (1 mol %) and alkenyl tosylate 1 (0.5 mmol) in THF (2.0 mL) at room temperature. After completion of the reaction as indicated by TLC (less than 1 min), the solvent was evaporated. The residue was then diluted with EtOAc (10 mL), washed with H₂O (10 mL), dried by anhydrous MgSO₄. Evaporation of the solvent followed by purification on silica gel provided the corresponding product 3. Data of selected example: 4-(4-methoxyphenyl)coumarin (**3a**)^{4d}. Yield: 98%; ¹H NMR (400 MHz, CDCl₃): 3.89 (s, 3H), 6.35 (s, 1H), 7.05 (d, J = 8.7 Hz, 2H), 7.22–7.26 (m, 1H), 7.40–7.42 (m, 3H), 7.54–7.57 (m, 2H). m/z (ESI): 253 (M⁺+H) (for details, please see Supplementary data).