Efficient Route to 4-Substituted-2(5*H*)-furanones, 2(1*H*)-quinolones, and pyrones by Nickel-catalyzed Cross-coupling of Arenesulfonates with Organozinc Reagents

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Nickel(II)-catalyzed cross-coupling reactions of 4-tosyl-2(1*H*)-quinolone, pyrone, and 2(5*H*)-furanone with various organozinc reagents provide an efficient and practical method for the high-yielding synthesis of 4-substituted 2(1*H*)-quinolones, pyrones, and 2(5*H*)-furanones.

2(1*H*)-quinolones **A**, pyrones **B**, and 2(5*H*)-furanones **C** are important structural units in naturally occurring products, therapeutics, and synthetic analogues with interesting biological activities.[1–3] (Figure 1) For example, Rofecoxib is an anti-inflammatory drug launched by Merck and approved by FDA.[2k] Rubrolides A–F are potent antibiotics.[2g]

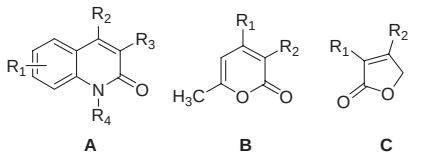
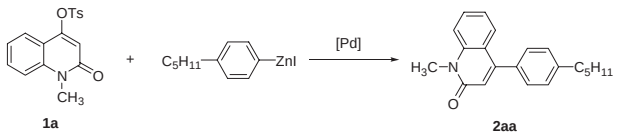


Figure 1.

Recently, we have witnessed the important progress of using arenesulfonates as electrophiles for the cross-coupling reactions since arenesulfonates are more easily handled and considerably less expensive than the corresponding triflates.[4–9] In this field, we also reported the applications of 4-hydroxycoumarin-derived 4-tosyloxycoumarin as a unique replacement for its corresponding triflate in palladium-catalyzed cross-coupling reactions with acetylenes,[5b] organozinc reagents,[5b] and arylboronic acids,[4h,4i] respectively, in the synthesis of various 4-substituted coumarins. The structural similarity of 4-hydroxycoumarin and 4-hydroxy-2(1*H*)-quinolone, 4-hydroxy-pyrone, and 4-hydroxy-2(5*H*)-furanone led us to envisage that these tosylates also could be employed in transition metal-catalyzed cross-coupling reactions as an ideal alternative compared with triflate in terms of their stability, as well as cost and commercial availability of reagents. Herein, we would like to report a novel and efficient route to 4-subsituted-2(5*H*)-furanones, 2(1*H*)-quinolones, and pyrones via nickel-catalyzed cross-coupling of 4-tosylates with organozinc reagents.

These tosylates were prepared simply from the corresponding 4-hydroxy species with *p*-toluenesulphonyl chloride in the presence of triethylamine. At the outset of our research, 4-tosyloxy-1-methyl-2(1*H*)-quinolone **1a** was selected for model studies. Due to their easy handling and long shelf life, arylboronic acid derivatives would be the starting materials of choice. However, when 4-tosyloxy-1-methyl-2(1*H*)-quinolone **1a** was employed in the palladium-catalyzed Suzuki-type cross-coupling reactions under several conditions, no product was detected at all. We, therefore, investigated the possibility of utilizing zinc reagent as substrate under palladium-catalyzed cross-coupling conditions. (Scheme 1)



Scheme 1.

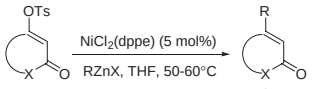
Initial studies were performed by using different palladium catalyst ($Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(MeCN)_2$, $PdCl_2(PhCN)_2$, and $Pd_2(dba)_3$) in the reaction of compound **1a** with 4-pentylphenylzinc iodide. To our delight, we observed the formation of the corresponding product **2a**, albeit in low yield (10–30%). However, addition of ligand or changing solvents or temperature did not improve the reaction yield. Since C–O bond would undergo oxidative addition during the reaction process, we thus shifted our focus to other transition-metal catalyst, such as nickel, which in most cases, is more active than palladium.

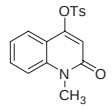
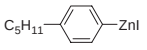
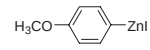
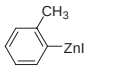
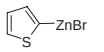
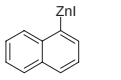
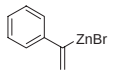
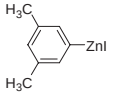
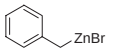
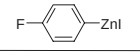
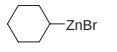
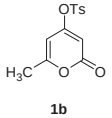
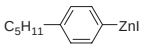
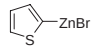
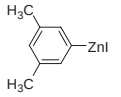
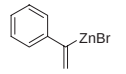
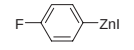
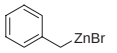
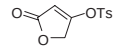
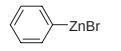
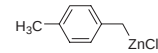
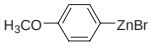
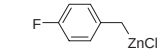
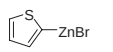
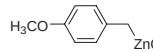
As expected, in the reaction of compound **1a** with 4-pentylphenylzinc iodide using $NiCl_2(dppp)$ (5 mol %) as the catalyst, 71% yield of the desired product **2a** was afforded in 12 hours at 50 °C. After further survey of different nickel catalysts, solvents, and temperature, $NiCl_2(dppe)$ was identified to be the best catalyst and 84% yield of **2a** was obtained after 12 hours when the reaction was performed in THF at about 50–60 °C. Although we routinely conduct these cross-coupling at 50 °C, they can in fact be accomplished at room temperature, although a long reaction time is needed.

To demonstrate the generality of this method, we next investigated the scope of this reaction and the results are summarized in Table 1. The operation is simple: Organozinc reagent (2.0 equiv.) was added to a solution of substrate **1** (0.25 mmol) and $NiCl_2(dppe)$ (5 mol %) in THF (2.0 mL) under argon atmosphere. The reaction mixture was stirred overnight at about 50–60 °C. After the reaction was completed and monitored by TLC, the mixture was separated directly by flash column chromatography (silica gel) to afford the corresponding product.

These conditions have proved to be useful for coupling a range of tosylates with an array of organozinc reagents (Table 1). For compound **1a**, various organozinc reagents are suitable substrates. Both electron-rich and electron-poor arylzinc reagents gave similar yields. The reactions were very clean and the desired products were afforded in good yields. It is noteworthy that not only aryl- or vinylzinc reagents but also alkylzinc reagents were suitable for this reaction. For example, when cyclohexylzinc bromide was employed in the reaction, 68% yield of the corresponding product **2j** was obtained. When 4-tosyloxy-6-methyl-pyrone **1b** and 4-tosyloxy-2(5*H*)-furanones **1c** were

Table 1. Nickel-catalyzed cross-coupling reactions of compound **1** with various organozinc reagents



Substrate	RZnX	Product	RZnX	Product
 **1a**		**2a (84%)**		**2f (80%)**
		**2b (82%)**		**2g (88%)**
		**2c (82%)**		**2h (85%)**
		**2d (89%)**		**2i (83%)**
		**2e (75%)**		**2j (68%)**
 **1b**		**2k (78%)**		**2n (86%)**
		**2l (81%)**		**2o (78%)**
		**2m (70%)**		**2p (71%)**
 **1c**		**2q (75%)**		**2t (77%)**
		**2r (71%)**		**2u (69%)**
		**2s (82%)**		**2v (72%)**

employed as substrates, organozinc reagents were again suitable partners in this process. It is noteworthy that the products **2t**, **2u**, and **2v**, which were synthesized from the reactions of **1c** with benzylzinc chloride in one step, were the intermediates for the synthesis of biologically active lignan analogues. However, the previously reported method for these compounds was from tin reagents in multi-steps.[10]

In summary, the nickel(II)-catalyzed cross-coupling reactions of 4-tosyloxy-2(1*H*)-quinolone, pyrone, and 2(5*H*)-furanone with various organozinc reagents disclosed herein represent a simple, efficient, practical synthesis of 4-substituted 2(1*H*)-quinolones, pyrones, and 2(5*H*)-furanones. The advantages of this method include good substrate generality, the use of air-stable, inexpensive tosylate under extremely mild conditions, and experimental ease. Combinatorial synthesis of these natural product-like compounds on solid support is under investigation in our research group.

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