Nickel-Catalyzed Cross-Couplings of 4-Diethylphosphonooxycoumarins with Organozinc Reagents: An Efficient New Methodology for the Synthesis of 4-Substituted Coumarins

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The palladium-catalyzed and nickel-catalyzed cross-coupling reactions of organic halides and triflates with organometallic reagents are well-known in the literature.[1] Recently, the synthetic community has witnessed significant progress in the nickel-catalyzed cross-coupling reactions, such as the coupling of organostannane with hypervalent iodonium salts or sulfonium salts;[2] the coupling of aryl halides, vinyl phosphates, vinyl triflates, and aryl mesylates with arylboronic acids (Suzuki-type coupling), organozincs (Negishi-type coupling), and Grignards (Kumada-type coupling);[3] and the coupling between polyfunctinal arylzincs and primary alkyl iodides,[4] as well as the coupling of propagylic dithioacetals with Grignard reagents.[5]

In a previous paper, we described the palladium-catalyzed cross-coupling of 4-tosyl coumarin with acetylenes or zinc reagents.[6] These reactions allow us to generate diversified 4-alkynyl coumarins in good yields under mild conditions. In this letter, we report our recent results of using nickel(0) as a catalyst to couple 4-diethylphosphonooxycoumarin with a variety of organozinc reagents in order to synthesize diversified 4-aryl and alkyl coumarins.

Although various methods are known in the literature for the synthesis of 4-substituted coumarin, most of them suffer from harsh reaction conditions (such as the use of stoichiometric amounts of mineral or Lewis acids, or toxic reagents, often under high temperatures), poor substituent tolerance, and low yields.[7]

Recent research has centered on the use of palladium-catalyzed C−C bond formation leading to the 4-substituted coumarins. For example, Larock[8] reported a novel synthetic method for the synthesis of a variety of 3,4-disubstituted coumarins by using the palladium-catalyzed coupling of *o*-iodophenols with internal alkynes and carbon monoxide. Wattanasin[9] and Schio[10] utilized the palladium-catalyzed cross-coupling of 4-trifluoromethylsulfonyloxycoumarins or 4-toluenesulfonyloxycoumarins with organostannanes to generate the corresponding products. Donnelly[11] and Deng[12] employed the palladium-catalyzed Suzuki reaction to synthesize 4-substituted coumarins by coupling arylboronic acids with 4-halogeno- and trifluoromethylsulfonyloxycoumarins.

For the coupling reactions described above, an efficient coupling typically requires heating to ∼80 or over 100 °C for more than 12 h.[8−12] Although the 4-vinyl bromide of coumarins can undergo the Suzuki cross-coupling reaction with arylboronic acids at room temperature,[11] the synthesis of these bromides were conducted by the combination of phosphorus pentabromide with anhydrous formic acid in the absence of a solvent at high temperatures.[13]

In connection with a chemical genetic approach of analyzing biological systems by using interfacing libraries of natural product-like molecules with biological assays,[14] we were interested in synthesizing a coumarin library by using a silyl linker based polystyrene macrobeads.[15]

Therefore, the reactions that proceed at room temperature rather than elevated temperatures will have significant practical advantages, since such a reaction condition will not only allow us to select more diversified substrates for a library construction but can also prevent the polystyrene macrobeads from breakage.

As an alternative to the use of vinyl (or aryl) halides, triflate, and tosylate as electrophilic components for the transition metals catalyzed cross-coupling reactions, vinyl or keten acetal phosphates have been utilized to couple

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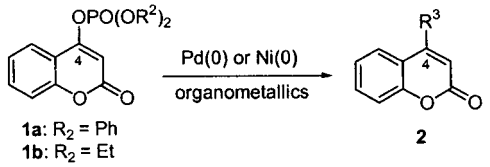
Scheme 1. Syntheses of 4-Substituted Coumarin



with organo-stannanes,[16] -aluminum,[17] -manganeses,[18] -cuprates,[19] -indium,[20] and Grignard reagents,[21] as well as arylboronic acids.[22]

We, therefore, would like to explore the possibility to use the transition metals catalyzed cross-coupling reaction between the vinyl phosphates **1a** and **1b** (Scheme 1) and organometallic reagents to synthesize the 4-substituted coumarin **2**.

The phosphates **1a** and **1b** were made by treatment of 4-hydroxycoumarin with diethyl- and diphenylchlorophosphates, respectively, and Hünig's base in acetonitrile[23] to give almost quantitative yields of the corresponding phosphates. Both phosphates **1a** and **1b** are stable after heating at 80 °C for 5 h in DMF.

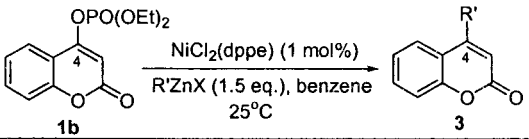
When considering a library construction, we prefer to select the commercially available or syntheticically accessible organometallics, such as organo-stannanes, -cuprates, -zincs, Grignard reagents, and arylboronic acids. However, the sensitive moiety of the α,β-unsaturated lactone in compounds **1a** and **1b** prevents us from using organocuprates and Grignard reagents for the coupling illustrated in Scheme 1. We, therefore, selected organo-stannanes, -zincs, and arylboronic acids as tested substrates in our primary study.

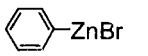
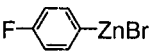
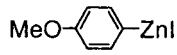
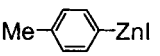
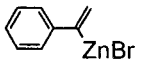
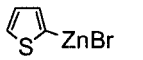
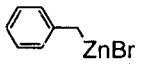
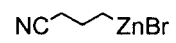
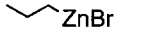
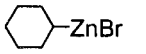
At the beginning of this research, attempts to perform the cross-coupling of vinyl- or phenyl-tributyltin with **1a** and **1b** in the presence of a catalytic amount of $Pd(PPh_3)_4$ or $NiCl_2$(dppe) failed completely, although a verity of solvents and different temperatures (from 25 up to 100 °C) have been tested for these couplings.

We then investigated the Suzuki coupling reactions to synthesize the 4-substituted coumatin **2** by combining the phenylboronic acid with **1a** and **1b** in the presence of catalytic amount of $Pd(Ph_3P)_4$ or $NiCl_2$(dppe) under various conditions. The results were also unsuccessful.

Finally, we transferred our attention to the coupling of the vinyl phosphates **1a** and **1b** (Scheme 1) with organozincs. To the best of our knowledge, utilization of nickel as a catalyst for this type of coupling reaction has not been reported yet. We therefore started to investigate this novel coupling reaction.

Table 1. Nickel-Catalyzed Cross-Coupling Reactions between 4-Diethylphosphonyloxycoumarin 1b and Organozincs



Entry	Zinc Reagent	Time	Product	Yield (%)[a]
1		30 min	**3a**	82
2		1 h	**3b**	78
3		1 h	**3c**	86
4		1 h	**3d**	75
5		1 h	**3e**	84
6		30 min	**3f**	90
7		4 h	**3g**	56
8		8 h	**3h**	58
9		8 h	**3i**	64
10		8 h	**3j**	32

[a] Isolated yields arebased on the phosphate **3b** and refer to a single run.

To this end, phenylzinc bromide was mixed with **1a** or **1b** in the presence of catalytic amount of $Pd(Ph_3P)_4$ in THF at room temperature. To our delight, the desired product 4-phenyl coumarin **2** (Scheme 1) was obtained in 15% and 35% yields, respectively.

After a series of experiments, it was found that among the catalysts tested [$Pd(Ph_3P)_4$, $PdCl_2(Ph_3P)_2$, $NiCl_2$(dppe)], $NiCl_2$(dppe) was proved to be the most efficient; amoung the solvents tested (THF, dioxane, and benzene), benzene was the best choice; between the phosphates **1a** and **1b**, **1b** gave a better result. Taken together, a 82% yield was eventually obtained when $NiCl_2$(pppe) (1.0 mol %) was utilized as a catalyst to promote the coupling reaction between the phosphate **1b** and phenylzinc bromide in benzene *at room temperature.*

Having established a standard set of conditions [$NiCl_2$-(dppe), vinyl phosphate **1b**, benzene, room temperature], several representative couplings between a variety of commercially available oragnozinc reagents and phosphate **1b** were performed. The results are illustrated in Table 1.

It is noteworthy that the selected arylzinc halides (entries 1−6) give good to excellent yields of the corresponding products **3a**−**f** after coupling with the vinyl phosphate **1b**, and all these reactions went to completion *within 0.5−1 h at room temperature.*

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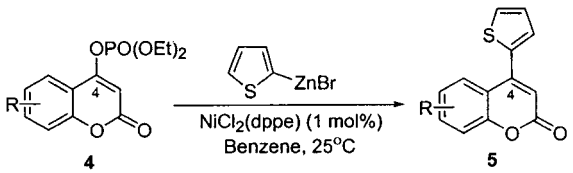
Table 2. Cross-Coupling Reactions between 2-Thienylzinc Bromide with Different Vinyl Phosphates



4
4a: R = 6-Me
4b: R = 6-Cl
4c: R = 7-OMe

5
5a: R = 6-Me
5b: R = 6-Cl
5c: R = 7-OMe

entry	phosphate	time	product	yield (%)[a]
1	**1b**	30 min	**3f**	90
2	**4a**	4 h	**5a**	84
3	**4b**	4 h	**5b**	88
4	**4c**	5 h	**5c**	91

[a] Isolated yields based on the phosphate and refer to a single run.

Under reaction conditions similar to those used for the cross-coupling of arylzinc halides, alkylzincs bromides (entries 7−10) gave lower yields of products **3i** and **3j**, even when the amount of organozinc reagents were increased to 2.0 equiv in relation to the vinyl phosphate **1b**. The results for the alkylzinc couplings are in significant contrast with those of Grignard reagents couplings under similar conditions.[24] The reasons for the low yields are not clear. Since β-elimination is always competing with reductive elimination, it seems to be that after transmetalation of the alkylzinc reagents to nickel, the rate of β-elimination is faster than that of *trans-cis* isomerization and reductive elimination; as a result, β-elimination predominates over the coupling reactions. We suspected that by changing nickel catalysts with different ligands might alter the rates of β-elimination, *trans-cis* isomerization, and reductive elimination, and improved results could be obtained.

We also investigated the possibility of using the diversified 4-diethylphosphonooxycoumarins **4** (entries 2−4) in coupling with 2-thienylzinc (Table 2).

As expected, the substitutions on the phenyl rings (entries 2−4) did not effect the coupling results, and excellent yields were obtained.

Further study, which is related to the effect of substitution groups at the C-3 position of coumarin, is currently underway in our laboratory.

The goal of this research has been to develop an efficient method for the combinatorial synthesis of a coumarin library under mild conditions in order to utilize silyl linker based macrobeads as solid supports. We have addressed the issue of whether reactions could be carried out at room temperature to prevent the large beads from breakage. We have found that the nickel-catalyzed cross-coupling reactions of 4-diethylphosphonooxycoumarins with organozinc reagents proceed at room temperature to give satisfactory yields. It is important to notice that the benzylic zinc reagents and some alkylzinc bromides can also couple with 4-diethylphosphonooxycoumarins under such mild conditions.

In conclusion, the chemistry described above demonstrates the usefulness of 4-diethylphosphonooxycoumarins as stable and easily accessible substrates that can undergo nickel-catalyzed cross-coupling with a variety of organozinc bromides to give 4-substituted coumarins at room temperature. Application of this chemistry to construct a combinatorial library of coumarin is currently under way in our laboratory.

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Experimental Section

General Procedure for Synthesis of 4-Substituted Coumarins. A round-bottom flask (25 mL) was flame-dried under high vacuum. Upon cooling, 4-diethylphosphonyloxycoumarin (0.5 mmol), $NiCl_2$(dppe) (2.6 mg, 1 mol %), benzene (4 mL), and zinc reagent (0.75 mmol) were added. The reaction mixture was stirred at room temperature. Following completion of the reaction as monitored by TLC, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a short silica gel bed. The filtrate was concentrated to a residue that was purified by flash chromatography to give the corresponding product.

4-Phenylcoumarin (3a):[6] 82% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.41 (s, 1H), 7.20−7.30 (m, 2H), 7.40−7.60 (m, 7H); ^{13}C NMR (125.7 MHz) δ (ppm) 161.0, 155.9, 154.5, 135.5, 132.2, 129.9, 129.1, 128.7, 127.3, 124.4, 119.3, 117.6, 115.5; MS (APCI) [$C_{15}H_{10}O_2$], *m*/*z* ($M^+ + 1$) calcd 223, found 223.

4-(4-Fluorophenyl)coumarin (3b): 78% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.38 (s, 1H), 7.24−7.30 (m, 3H), 7.43−7.50 (m, 4H), 7.58 (t, J = 8.0 Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 160.8, 154.8, 154.4, 146.7, 132.3, 130.7, 130.6, 127.0, 124.5, 119.1, 117.7, 116.4, 116.3, 115.6; MS (APCI) [$C_{15}H_9FO_2$], *m*/*z* ($M^+ + 1$) calcd 241, found 241.

4-(4-Methoxyphenyl)coumarin (3c): 86% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.92 (s, 3H), 6.38 (s, 1H), 7.07 (d, J = 8.5 Hz, 2H), 7.25−7.30 (m, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.54−7.62 (m, 2H); ^{13}C NMR (125.7 MHz) δ (ppm) 161.2, 161.1, 155.6, 154.5, 132.0, 130.2, 127.7, 127.3, 124.3, 119.4, 117.6, 114.9, 114.6, 55.7; MS (APCI) [$C_{16}H_{12}O_3$], *m*/*z* ($M^+ + 1$) calcd 253, found 253.

4-(4-Methylphenyl)coumarin (3d): 75% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.48 (s, 3H), 6.39 (s, 1H), 7.25−7.60 (m, 8H); ^{13}C NMR (125.7 MHz) δ (ppm) 161.1, 156.0, 154.5, 140.2, 132.6, 132.1, 129.8, 128.7, 127.3, 124.3, 119.4, 117.6, 115.2, 21.6; MS (APCI) [$C_{16}H_{12}O_2$], *m*/*z* ($M^+ + 1$) calcd 237, found 237.

4-(2-Phenylvinyl)coumarin (3e): 84% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.50 (s, 1H), 5.95 (s, 1H), 6.45 (s, 1H), 7.06−7.14 (m, 1H), 7.24−7.52 (m, 8H); ^{13}C NMR (125.7 MHz) δ (ppm) 161.1, 156.1, 154.2, 144.5, 138.1, 132.0, 129.2, 129.0, 127.4, 126.6, 124.4, 119.1, 117.9, 117.4, 116.2; MS (APCI) [$C_{17}H_{12}O_2$], *m*/*z* ($M^+ + 1$) calcd 249, found 249.

2-(4′-Coumarin)thiophene (3f):[6] 90% yield as a yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.53 (s, 1H), 7.25−7.34 (m, 2H), 7.42−7.45 (m, 2H), 7.58−7.61 (m, 2H), 7.94 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 160.7, 154.4, 148.2, 136.2, 132.4, 129.6, 128.8, 128.4, 126.9, 124.6, 118.6, 117.7, 115.4; MS (APCI) [$C_{13}H_8O_2S$], *m*/*z* ($M^+ + 1$) calcd 229, found 229.

4-(Phenylmethyl)coumarin (3g):[6] 56% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.14 (s, 2H), 6.16 (s, 1H), 7.25−7.38 (m, 7H), 7.50−7.58 (m, 1H), 7.68 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 161.1, 154.8, 154.0, 136.2, 132.0, 129.3, 129.2, 127.5, 124.9, 124.5, 119.5, 117.5, 116.0, 38.3; MS (APCI) [$C_{16}H_{12}O_2$], *m*/*z* ($M^+ + 1$) calcd 237, found 237.

4-(3-Cyanopropyl)coumarin (3h):[6] 58% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.05−2.18 (m, 2H), 2.55 (t, J = 7.0, 6.5 Hz, 2H), 2.99 (t, J = 8.0, 7.5 Hz, 2H), 6.33 (s, 1H), 7.33−7.39 (m, 2H), 7.58 (t, J = 8.5, 7.5 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 160.7, 154.1, 153.8, 132.4, 124.8, 124.2, 118.9, 118.8, 117.8, 114.8, 30.5, 24.1, 17.2; MS (APCI) [$C_{13}H_{11}NO_2$], *m*/*z* ($M^+ + 1$) calcd 214, found 214.

4-Propylcoumarin (3i): 64% yield as a colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.10 (t, J = 7.4 Hz, 3H), 1.68−1.84 (m, 2H), 2.76 (dt, J = 7.6, 1.0 Hz, 2H), 6.29 (s, 1H), 7.26−7.37 (m, 2H), 7.49−7.67 (m, 2H); ^{13}C NMR (125.7 MHz) δ (ppm) 161.3, 156.3, 154.0, 131.8, 124.6, 124.4, 119.6, 117.6, 114.2, 33.9, 21.6, 14.2; MS (APCI) [$C_{12}H_{12}O_2$], *m*/*z* ($M^+ + 1$) calcd 189, found 189.

4-Cyclohexylcoumarin (3j):[6] 32% yield as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.32−1.52 (m, 5H), 1.85−2.02 (m, 5H), 2.90−2.95 (m, 1H), 6.32 (s, 1H), 7.31−7.38 (m, 2H),

7.52 (t, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 161.8, 161.0, 154.1, 131.6, 124.3, 124.2, 119.0, 117.8, 111.9, 39.2, 32.7, 26.8, 26.3; MS (APCI) [$C_{15}H_{16}O_2$], *m*/*z* ($M^+ + 1$) calcd 229, found 229.

2-(4′-(6′-Methylcoumarin))thiophene (5a): 84% yield as a yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.42 (s, 3H), 6.50 (s, 1H), 7.25−7.30 (m, 1H), 7.31 (d, $J = 8.5$ Hz, 1H), 7.40 (d, $J = 8.5$ Hz, 1H), 7.44 (d, $J = 3.5$ Hz, 1H), 7.58 (d, $J = 5.0$ Hz, 1H), 7.71 (s, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 160.9, 152.6, 148.2, 136.3, 134.3, 133.3, 129.5, 128.6, 128.4, 126.6, 118.2, 117.5, 115.4, 21.3; MS (APCI) [$C_{14}H_{10}O_2S$], *m*/*z* ($M^+ + 1$) calcd 243, found 243.

2-(4′-(6′-Chlorocoumarin))thiophene (5b): 88% yield as a yellowish oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 6.54 (s, 1H), 7.24−7.61 (m, 5H), 7.88 (d, $J = 2.2$ Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 160.0, 152.8, 147.2, 135.5, 132.3, 130.1, 129.8, 129.1, 128.6, 126.3, 119.7, 119.2, 116.2; MS (APCI) [$C_{13}H_7ClO_2S$], *m*/*z* ($M^+ + 1$) calcd 263, found 263.

2-(4′-(7′-Methoxycoumarin))thiophene (5c): 91% yield as a yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.92 (s, 3H), 6.37 (s, 1H), 6.87−6.92 (m, 2H), 7.23−7.25 (m, 1H), 7.41−7.44 (m, 1H), 7.56 (dd, $J = 5.5$, 1.5 Hz, 1H), 7.84 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 163.2, 161.1, 156.3, 148.3, 129.4, 128.6, 128.3, 127.9, 112.7, 112.1, 112.0, 101.5, 56.1; MS (APCI) [$C_{14}H_{10}O_3S$], *m*/*z* ($M^+ + 1$) calcd 259, found 259.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR and mass spectra for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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