SYNTHESIS OF 3-SUBSTITUTED ISOCOUMARINS THROUGH ACYLOXYPALLADATION OF *o*-ALKENYLBENZOIC ACIDS

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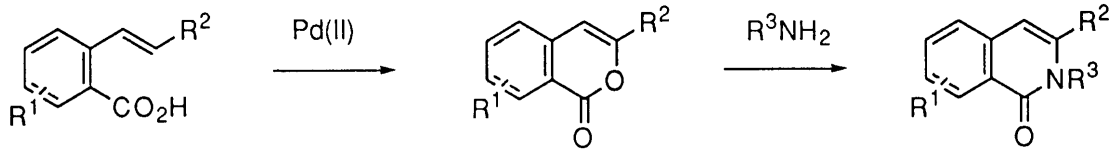
Cyclization of *o*-alkenylbenzoic acids in the presence of Pd catalyst and benzoquinone led to 3-substituted isocoumarins in high yield. The isocoumarins obtained were converted to isoquinolones by treatment with primary amines.

KEYWORDS isocoumarin; acyloxypalladation; *o*-alkenylbenzoic acid; palladium(II); benzoquinone; isoquinolone

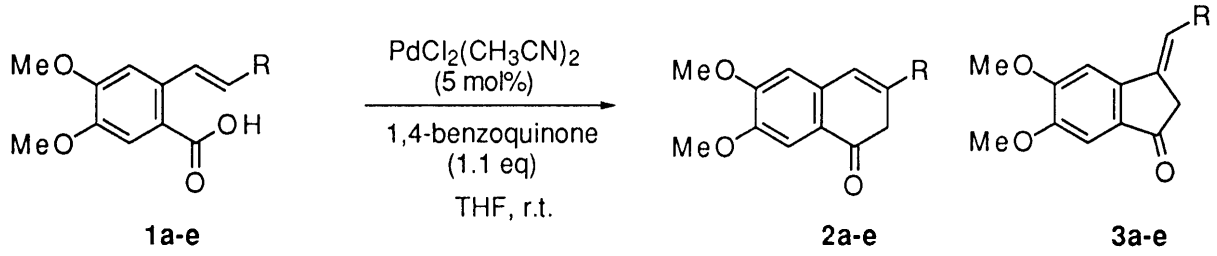
A wide variety of isocoumarins occur naturally, and the isocoumarin ring system also plays an important role as an intermediate for a synthesis of several natural products.[1] Recently, several biologically interesting 3-substituted isocoumarins — for example, achlisocoumarin I[2] and thunberginol A[3] — were isolated. Various methods are known for the synthesis of isocoumarin-containing structures.[4] Palladium-catalyzed intramolecular addition of a carboxylic acid to an alkene becomes an efficient route toward lactones.[5] Although this method has been applied to a synthesis of 3-substituted isocoumarins from *o*-alkenylbenzoic acids,[6] the catalytic use of palladium reagent and the use of more highly functionalized benzoic acid derivatives have not yet been described. We wish to report in this paper Pd-catalyzed cyclization of *o*-alkenylbenzoic acid derivatives and a further synthesis of isoquinolone from the isocoumarine obtained.



Treatment of 4,5-dimethoxy-2-styrylbenzoic acid (**1a**)[7, 8] with 1 eq of $PdCl_2(CH_3CN)_2$ in the presence of triethylamine provided 3-phenylisocoumarin **2a** and benzylidenephthalide **3a** in 80% yield (**2a** : **3a** = 96 : 4). In order to improve this reaction to a catalytic one, the Pd(0) generated should be reverted back to Pd(II) by the addition of an oxidant. The reactions were carried out with 5 mol% of palladium reagent and an oxidant such as Cu(II) and O_2 at room temperature in THF for 12 h, giving **2a** and **3a**. However, neither the yield nor the cyclization selectivity were satisfied. Benzoquinone was found to be the best oxidant. The reaction with benzoquinone (1.1 eq) for 2 h

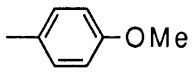
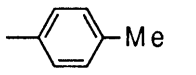
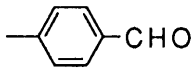
gave the isocoumarin **2a** in quantitative yield with high cyclization selectivity (Table I, entry 1).

The latter method was applied to cyclization of several *o*-aklenylbenzoic acids. The results are shown in Table I.[9] In the case of styryl compounds, the substituent on aromatic ring (R) affected cyclization selectivity. In the order of MeO > Me > CHO, the selectivity decreased according to electron-withdrawing ability (entry 2-4). On the other hand, *o*-hexenylbenzoic acid **1e** gave exclusively 3-butylisocoumarin **2e** in good yield (entry 5).



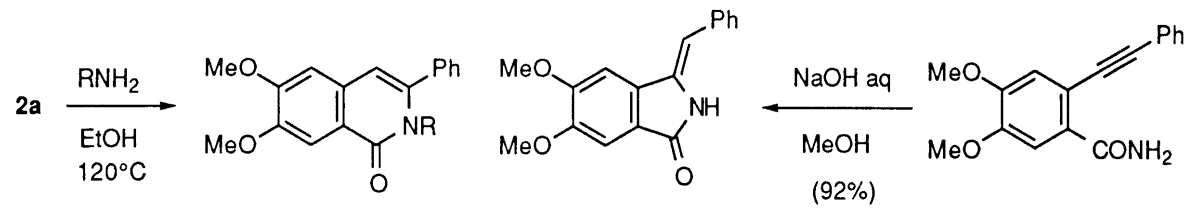
1a-e **2a-e** **3a-e**

Table I. $PdCl_2(CH_3CN)_2$ Catalyzed Cyclization of **1** in the Presence of Benzoquinone

Entry	1	R	Reaction time (h)	2 : 3	Yield (%)
1	**1a**	Ph	2	99 : 1	98
2	**1b**		2	93 : 7	90
3	**1c**		2	86 : 14	73
4	**1d**		2	74 : 26	82
5	**1e**	*n*-Bu	6	100 : 0	83

The reaction proceeded through acyloxypalladation followed by β-hydride elimination. Although the precise mechanism of 6-*endo* and 5-*exo* selectivity has not been clarified, the selectivity would be affected by the electron demand of carbon-carbon double bond.[10]

The isocoumarins obtained were easily converted to the corresponding isoquinolones by treatment with primary amins. For example, treatment of **2a** with ammonia or methylamine in EtOH gave the isoquinolone **4** or **5**. This process will be very useful because direct cyclization of *o*-alkynylbenzamide **6** in basic medium gave only the benzylidenephthalimide **7**.[11]



4 : R = H; **5** : R = Me
(72 %) (88 %)

7 **6**

Thus, we have identified a successful palladium-catalyzed cyclization method for the synthesis of isocoumarins.[12] The present method is easy to carry under mild conditions. This process is also applicable to the synthesis of isoquinolones, synthetic intermediates for benzo[c]phenanthridine alkaloids.[13]

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7) The compounds **1a**-**1d** were prepared from methyl 2-iodo-4,5-dimethoxybenzoate and styrene derivatives by Heck reaction($Pd(OAc)_2$, $(n\text{-}Bu)_4NCl$, DMF, 100°C / 12 h), followed by hydrolysis.
8) We chose 4,5-dimethoxy derivatives **1** because our final synthetic targets are benzo[c]-phenanthridine alkaloids,[13] most of which possess the same oxygenation pattern on one aromatic ring as **1**.
9) All new compounds were satisfied by elemental analysis and spectral data.
10) In order to clarify the mechanism, the reactions with various types of substituted 2-styryl-benzoic acids are in progress.
11) N. Nishiwaki, M. Komatsu, Y. Ohshiro, *Synthesis*, 41 (1991); N Nishiwaki, S. Minakata, M. Komatsu, Y. Ohshiro, *Synlett*, 273 (1990).
12) Recently, $Pd(OAc)_2$-catalyzed cyclization of alkenoic acid was reported. R. C. Larock, T. R. Hightower, *J. Org. Chem.*, **58**, 5298 (1993). In this paper, *o*-propenylbenzoic acid was treated with 5 mol % of $Pd(OAc)_2$ and NaOAc in DMSO under O_2 atmosphere at 80°C to give 3-methylisocoumarin in 80% yield. This condition was applied to cyclization of **1a**, giving **2a** and **3a** in a ratio of 99 : 1 (52% yield).
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