

Nickel-catalyzed Decarbonylative Cycloaddition of Phthalic Anhydrides with 1,3-Dienes

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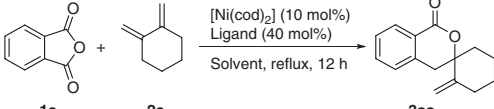
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An intermolecular nickel-catalyzed decarbonylative [4 + 2] cycloaddition has been developed where phthalic anhydrides react with 1,3-dienes to afford substituted 3-vinyldihydroisocoumarins.

Dihydroisocoumarins are a class of naturally occurring heterocyclic compounds; their biological and physiological effects are also of interest.¹ A representative synthetic method is intramolecular cyclization of homophthalic acid derivatives.² Meanwhile, transition-metal-catalyzed diversity oriented intermolecular hetero-annulation to afford dihydroisocoumarins is an attractive synthetic method, nevertheless, few reactions of 2-iodobenzoic acid with carbon-carbon double bonds are reported.³ Thus, the development of alternative methodologies, which would allow for straightforward access to structurally diverse dihydroisocoumarins, remains an important research topic. Herein, we would like to report our results of an unprecedented decarbonylative cycloaddition of phthalic anhydrides with 1,3-dienes, which may open the way for a facile divergent synthesis of dihydroisocoumarins.⁴⁻⁶

We first examined the ligand effects in the decarbonylative cycloaddition of phthalic anhydride (**1a**) with 1,2-dimethylenecyclohexane (**2a**) using [Ni(cod)₂] as a Ni(0) precursor. The reaction was performed in refluxing MeCN for 12 h, and the results are summarized in Table 1. Among the ligands examined, PMe₃ gave the best result (90% yield, Entry 1). Trace or lower amounts of **3aa** were obtained in the cases using PMe₂Ph, PMePh₂, PPh₃, PCy₃, and IMes in place of PMe₃ (Entries 2–6). In other solvents such as 1,4-dioxane, tetrahydrofuran (THF), and pyridine, yields were even lower (Entries 7–9). On addition of ZnCl₂ (20 mol %),^{4a} the yield of **3aa** was decreased to 36% (Entry 10).

Table 1. Nickel-catalyzed [4 + 2] cycloaddition of phthalic anhydride **1a** with 1,3-diene **2a**^a

				
Entry	Ligand	Solvent	Additive	Yield/% ^b
1	PMe ₃	MeCN	—	90
2	PMe ₂ Ph	MeCN	—	51
3	PMePh ₂	MeCN	—	41
4	PPh ₃	MeCN	—	25
5	PCy ₃	MeCN	—	44
6	IMes ^c	MeCN	—	<1
7	PMe ₃	1,4-Dioxane	—	50
8	PMe ₃	THF	—	<1
9	PMe ₃	Pyridine	—	<1
10	PMe ₃	MeCN	ZnCl ₂ ^d	36

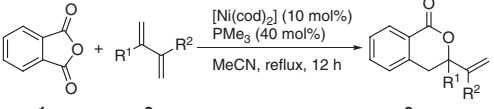
^aReactions were carried out using [Ni(cod)₂] (10 mol %), ligand (40 mol %), **1** (0.5 mmol), and **2** (3 mmol) in 20 mL of refluxing solvent for 12 h. ^bIsolated yields. ^c1,3-Bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene. ^d20 mol %.

With the optimized reaction conditions, the scope of the reaction with other 1,3-dienes was examined (Table 2). The cycloaddition of **1a** with 2,3-dimethyl-1,3-butadiene (**2b**) gave the product **3ab** in 64% yield (Entry 1). The reaction of **1a** with unsymmetrical 1,3-dienes was also examined. 2-Alkyl-substituted 1,3-diene **2c** reacted with **1a** to give correspondingly substituted cycloadduct **3ac** in 74% yield (Entry 2). Myrcene (**2d**) also reacted with **1a** as 1,3-diene to afford cycloadduct **3ad** in 73% yield (Entry 3). The reaction of bulky silyl group-substituted 1,3-diene and phenyl-substituted 1,3-diene with **1a** provided cycloadducts **3ae** and **3af** in 23% and 35% yield, respectively (Entries 4 and 5).

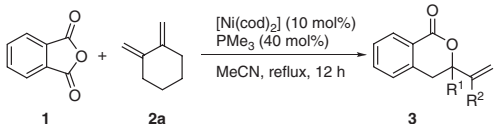
However, 1,1-disubstituted 1,3-dienes, 1,4-disubstituted 1,3-dienes, and 1-monosubstituted 1,3-dienes, failed to participate in the reaction.

We next examined the scope of the substituents on phthalic anhydrides, and results are summarized in Table 3. The reaction of 4-methylphthalic anhydride (**1b**) with **2a** gave cycloadduct **3ba** in 73% yield as a 1/1 mixture of regioisomers, while the reaction of 3-methylphthalic anhydride (**1c**) with **2a** afforded **3ca** with complete regio control (Entries 1 and 2). These results may suggest that the sterically less hindered carbonyl moiety of **1c** reacted with Ni(0) catalyst to afford **3ca** regioselectively. Meanwhile, it is

Table 2. Nickel-catalyzed [4 + 2] cycloaddition of phthalic anhydride **1a** with 1,3-dienes **2**^a

				
Entry	2	Diene	3	Yield/% ^b
1	2b		3ab	64
2	2c		3ac	74
3	2d		3ad	73
4	2e		3ae	23 (72 h)
5	2f		3af	35

^aReactions were carried out using [Ni(cod)₂] (10 mol %), PMe₃ (40 mol %), **1a** (0.5 mmol), and **2** (3 mmol) in 20 mL of refluxing MeCN for 12 h. ^bIsolated yields.

Table 3. The scope of nickel-catalyzed [4 + 2] cycloaddition of phthalic anhydrides **1** with 1,3-diene **2a**^a


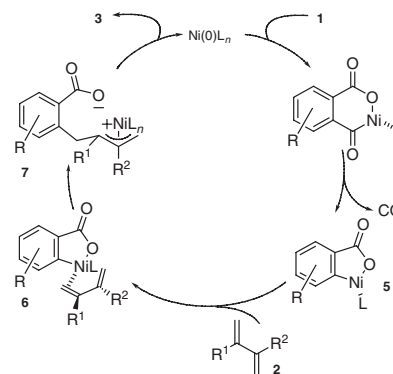
Entry	1	Phthalic anhydride	3	Product	Yield/% ^b
1	1b		3ba		73 (1/1) ^{c,d}
2	1c		3ca		74 ^{d,e}
3	1d		3da		57 (7/3) ^{c,d}
4	1e		3ea		80 ^{d,e}
5	1f		3fa		99 (7/3) ^c
6	1g		3ga		75 (1/1) ^c
7	1h		3ha		67

^aReactions were carried out using [Ni(cod)₂] (10 mol %), PMe₃ (40 mol %), **1** (0.5 mmol), and **2a** (3 mmol) in 20 mL of refluxing MeCN for 12 h. ^bIsolated yields. ^cRatio of regioisomers. ^dReaction time; 36 h. ^eSingle regioisomer.

noteworthy that 3-methoxyphthalic anhydride (**1e**) also reacted with **2a** to afford **3ea** regioselectively in 80% yield (Entry 4). The effects of 3-methoxy substituents are not clear at the moment, however we assumed that the selectivity is ascribed to coordination of oxygen to the nickel center through oxidative addition. The cycloaddition of 3-fluoro-substituted phthalic anhydride **1f** with **2a** gave **3fa** in 99% yield with a regioselectivity ratio of 7/3 (Entry 5). The reaction of 2,3-naphthalenedicarboxylic anhydride (**1h**) with **2a** also provides cycloadduct **3ha** in 67% yield (Entry 7).

We propose a plausible mechanism involving oxidative addition of the more electron-deficient carbonyl moiety of **1** to Ni(0) bearing electron-rich phosphine ligands, giving the nickelacycle **4** (Scheme 1).^{7,8} Subsequent decarbonylation provides oxanickelacycle **5**. Insertion of **2** through the more electron-rich carbon–carbon double bond to C–Ni bond leads to the more stable acyclic π -allylnickel intermediate **7**, which undergoes nucleophilic addition of oxygen to π -allylnickel at the more substituted carbon to give **3** and regenerates the starting Ni(0) complex.^{4e}

In summary, we have developed a new nickel-catalyzed decarbonylative [4 + 2] cycloaddition of phthalic anhydrides with

**Scheme 1.** Plausible reaction pathway.

1,3-dienes to provide dihydroisocoumarins. The reaction may realize a facile divergent synthesis of dihydroisocoumarins, which are widely distributed in nature. Their biological and physiological effects are also of interest.

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