doi:10.1246/cl.2011.322

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

Kyohei Fujiwara, Takuya Kurahashi,* and Seijiro Matsubara*
Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510

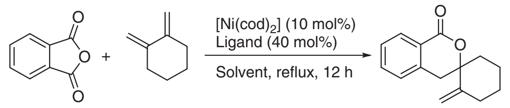
(Received January 13, 2011; CL-110034; E-mail: tkuraha@orgrxn.mbox.media.kyoto-u.ac.jp, matsubar@orgrxn.mbox.media.kyoto-u.ac.jp)

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, PMe$_3$ gave the best result (90% yield, Entry 1). Trace or lower amounts of **3aa** were obtained in the cases using PMe$_2$Ph, PMePh$_2$, PPh$_3$, PCy$_3$, and IMes in place of PMe$_3$ (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 ZnCl$_2$ (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]



1a **2a** **3aa**

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

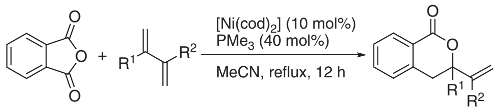
[a]Reactions were carried out using [Ni(cod)$_2$] (10 mol %), ligand (40 mol %), **1** (0.5 mmol), and **2** (3 mmol) in 20 mL of refluxing solvent for 12 h. [b]Isolated yields. [c]1,3-Bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene. [d]20 mol %.

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 bulkyl 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).

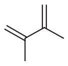
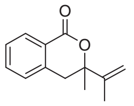
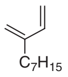
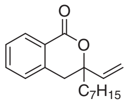
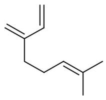
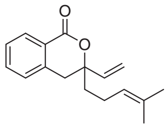
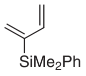
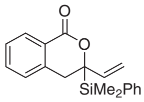
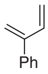
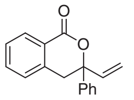
However, 1,1-disubstituted 1,3-dienes, 1,4-disubstituted 1,3-dienes, and 1-monosubstituted 1,3-dienes, failed to participate in the reaction.

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]

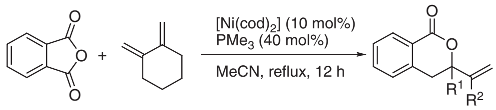


1a **2** **3**

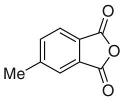
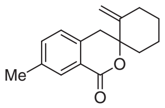
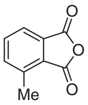
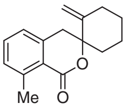
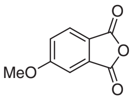
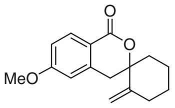
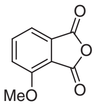
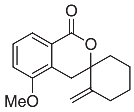
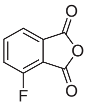
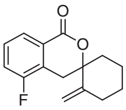
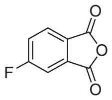
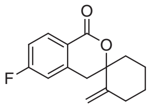
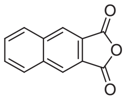
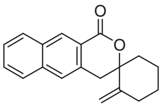
Entry	2	Diene	3	Product	Yield/%[b]
1	**2b**		**3ab**		64
2	**2c**		**3ac**		74
3	**2d**		**3ad**		73
4	**2e**		**3ae**		23 (72 h)
5	**2f**		**3af**		35

[a]Reactions were carried out using [Ni(cod)$_2$] (10 mol %), PMe$_3$ (40 mol %), **1a** (0.5 mmol), and **2** (3 mmol) in 20 mL of refluxing MeCN for 12 h. [b]Isolated yields.

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



1 **2a** **3**

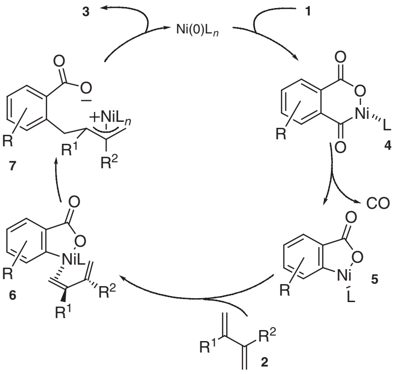
Entry	1	Phthalic anhydride	3	Product	Yield/%[b]
1	**1b**		**3ba**		73 (1/1)[c,d]
2	**1c**		**3ca**		74[d,e]
3	**1d**		**3da**		57 (7/3)[c,d]
4	**1e**		**3ea**		80[d,e]
5	**1f**		**3fa**		99 (7/3)[c]
6	**1g**		**3ga**		75 (1/1)[c]
7	**1h**		**3ha**		67

[a] Reactions were carried out using [Ni(cod)$_2$] (10 mol %), PMe$_3$ (40 mol %), **1** (0.5 mmol), and **2a** (3 mmol) in 20 mL of refluxing MeCN for 12 h. [b] Isolated yields. [c] Ratio of regioisomers. [d] Reaction time; 36 h. [e] Single 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 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.



Scheme 1. Plausible reaction pathway.

This work was supported by Grants-in-Aid from MEXT, Japan. T.K. also acknowledges the Asahi Glass Foundation, Kansai Research Foundation, and Mizuho Foundation for the Promotion of Sciences.

References

1 a) X. Jiang, J. García-Fortanet, J. K. De Brabander, *J. Am. Chem. Soc.* **2005**, *127*, 11254. b) M. Altemöller, J. Podlech, D. Fenske, *Eur. J. Org. Chem.* **2006**, 1678. c) K. Umehara, M. Matsumoto, M. Nakamura, T. Miyase, M. Kuroyanagi, H. Noguchi, *Chem. Pharm. Bull.* **2000**, *48*, 566. d) P. Kongsaeree, S. Prabpai, N. Sriubolmas, C. Vongvein, S. Wiyakrutta, *J. Nat. Prod.* **2003**, *66*, 709. e) P. Jiao, J. B. Gloer, J. Campbell, C. A. Shearer, *J. Nat. Prod.* **2006**, *69*, 612.

2 a) R. Wenger, W. Frank, *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 1279. b) A. Bhati, *J. Org. Chem.* **1962**, *27*, 1183. c) R. D. Barry, R. A. Balding, *J. Heterocycl. Chem.* **1972**, *9*, 1255.

3 a) S. E. Denmark, W. Pan, *Org. Lett.* **2003**, *5*, 1119. b) M. Chakravarty, K. C. Kumara Swamy, *J. Org. Chem.* **2006**, *71*, 9128.

4 a) Y. Kajita, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2008**, *130*, 17226. b) Y. Kajita, S. Matsubara, T. Kurahashi, *J. Am. Chem. Soc.* **2008**, *130*, 6058. c) Y. Yoshino, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2009**, *131*, 7494. d) A. Ooguri, K. Nakai, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2009**, *131*, 13194. e) K. Fujiwara, T. Kurahashi, S. Matsubara, *Org. Lett.* **2010**, *12*, 4548.

5 a) T. Miura, M. Yamauchi, M. Murakami, *Org. Lett.* **2008**, *10*, 3085. b) T. Miura, M. Yamauchi, M. Murakami, *Chem. Commun.* **2009**, 1470. c) M. Yamauchi, M. Morimoto, T. Miura, M. Murakami, *J. Am. Chem. Soc.* **2010**, *132*, 54. d) T. Miura, M. Yamauchi, A. Kosaka, M. Murakami, *Angew. Chem., Int. Ed.* **2010**, *49*, 4955. e) T. Miura, M. Morimoto, M. Yamauchi, M. Murakami, *J. Org. Chem.* **2010**, *75*, 5359.

6 For related Pd-catalyzed cycloadditions via elimination of CO$_2$, see: a) R. Shintani, M. Murakami, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 12356. b) C. Wang, J. A. Tunge, *J. Am. Chem. Soc.* **2008**, *130*, 8118. c) R. Shintani, T. Tsuji, S. Park, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 7508.

7 a) E. M. O'Brien, E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2003**, *125*, 10498. b) J. B. Johnson, E. A. Bercot, J. M. Rowley, G. W. Coates, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 2718.

8 a) B. M. Trost, F. Chen, *Tetrahedron Lett.* **1971**, *12*, 2603. b) K. Sano, T. Yamamoto, A. Yamamoto, *Chem. Lett.* **1984**, 941. c) K. Sano, T. Yamamoto, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2741. d) T. Yamamoto, K. Sano, A. Yamamoto, *J. Am. Chem. Soc.* **1987**, *109*, 1092. e) R. Fischer, D. Walther, R. Kempe, J. Sieler, B. Schönecker, *J. Organomet. Chem.* **1993**, *447*, 131.