

Nickel-Catalyzed [4 + 2] Cycloaddition of Enones with Alkynes

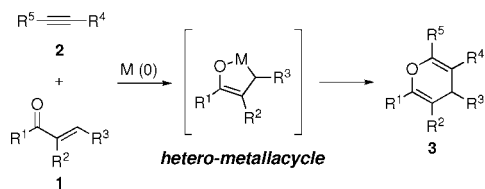
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The hetero-Diels–Alder reactions of α,β -unsaturated carbonyl compounds (heterodiene) with electron-rich carbon–carbon unsaturated bonds (heterodienophile) are a useful method for the synthesis of six-membered heterocyclic rings and have been widely applied to natural product synthesis.^{1,2} However, the low reactivity of alkynes as heterodienophiles has limited their use in the reaction, and only ynamides were available as heterodienophiles.³ While transition metal-catalyzed [4 + 2] cycloadditions of α,β -unsaturated carbonyl compounds with alkynes would be a solution for the problem, such reactions have not been studied well so far.⁴ We postulated that such cycloaddition would proceed via heterometallacycle intermediates,^{5,6} which are formed by oxidative cyclization of low valent transition metals to α,β -unsaturated carbonyl compounds, and subsequent insertion of alkynes (Scheme 1). Thus, we attempted the addition of enone **1** and alkyne **2** using nickel(0) catalyst to form polysubstituted pyranes **3**.⁷

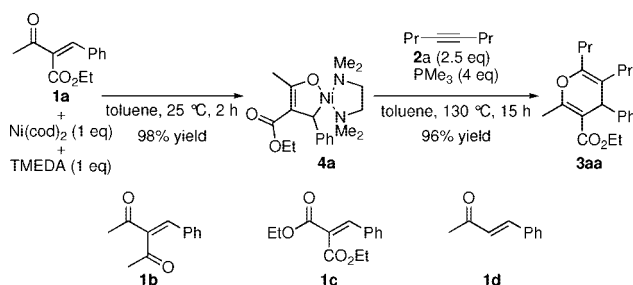
Scheme 1. Transition-Metal-Catalyzed [4 + 2] Cycloaddition



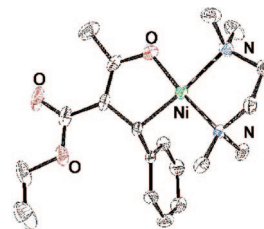
The formation of oxa-nickelacycle was investigated first by a stoichiometric reaction of an enone and a nickel(0) complex. The reaction of ethyl benzylidene acetoacetate (**1a**) with $\text{Ni}(\text{cod})_2$ and TMEDA at 25 °C gave an oxa-nickelacycle (**4**) quantitatively (Scheme 2).⁸ The molecular structure of **4** was unambiguously confirmed by the X-ray crystal structure analysis, which showed that the nickel(II) complex has square planar molecular geometry (Figure 1). Treatment of oxanickelacycle **4** with 4-octyne (**2a**) in the presence of PMe_3 afforded the pyran **3aa** in 96% isolated yield. Neither benzylidene-substituted pentane-2,4-dione **1b** nor diethyl malonate **1c** was converted into the corresponding oxanickelacycle even for prolonged reaction times. Considering that **1d** was also inert to oxidative cyclization of nickel(0), we found α -ester-substituted α,β -unsaturated ketone to be a suitable substrate for oxa-nickelacycle formation.

The obtained results expanded the possibilities of the catalytic reactions of **1a** with alkynes. Indeed, the reaction of ethyl benzylidene acetoacetate (**1a**) with 4-octyne (**2a**) in the presence of 10 mol % of $\text{Ni}(\text{cod})_2$ and 40 mol % of PMe_3 in toluene at 130 °C afforded the pyran **3aa** in 99% yield (Table 1, entry 1). Not even trace amounts of **3aa** were obtained in the absence of nickel catalyst. The extension of this result was examined for the reactions of various enones with **2a**; results are summarized in Table 1. The cycloaddition of **1e** with **2a** gave the product **3ea** in 90% yield (entry 2). Enones **1f** and **1g** also reacted with **2a** to furnish pyrans in 82% and 50% yields, respectively (entries 3 and 4). Predictably,

Scheme 2. Formation of Oxa-Nickelacycle



enones such as **1b**, **1c**, and **1d** failed to participate in the reaction due to difficulties in formation of oxa-nickelacycle intermediates and were recovered quantitatively (entries 5–7).

Figure 1. ORTEP Drawing of **4a**.Table 1. Nickel-Catalyzed Cycloaddition of Enones with 4-Octyne^a

Reaction scheme showing the synthesis of compound **3** from compound **1** and alkyne **2a** under the following conditions: $\text{Ni}(\text{cod})_2$ (10 mol %), PMe_3 (40 mol %), toluene, 130 °C, 15 h.

entry	R ¹	R ²	R ³	1	3	yield (%) ^b
1	Me	CO ₂ Et	Ph	1a	3aa	99
2	Me	CO ₂ Et	Pr	1e	3ea	99
3	Ph	CO ₂ Et	Ph	1f	3fa	82
4	Ph	CO ₂ Et	Pr	1g	3ga	50
5	Me	C(O)Me	Ph	1b	3ba	<1
6	EtO	CO ₂ Et	Ph	1c	3ca	<1
7	Me	H	Ph	1d	3da	<1

^a Reactions were carried out using $\text{Ni}(\text{cod})_2$ (10 mol %), PMe_3 (40 mol %), **1** (0.5 mmol), and 4-octyne (1.25 mmol) in 5 mL of toluene (130 °C). ^b Isolated yields.

The scope of the cycloaddition of **1a** with various alkynes is summarized in Table 2. The reaction of **2b** and **2c** with **1a** gave the cycloadducts in 74% and 82% yields, respectively (entries 1 and 2). The addition of unsymmetrical alkynes **2d–2g** gave the pyrans consisting of regioisomers in a range of 1/1 to 3/1 ratio (entries 3–6), whereas the reaction of **2h** gave the pyran **3ah** as a single isomer (entry 7). Cyclopropyl-substituted alkyne **2i** also reacted with **1a** to furnish **3ai** in 68% yield with regioisomers in a

ratio of 7/2 (entry 8). Terminal alkynes failed to participate in the reaction, presumably due to rapid oligomerization of alkynes.

Table 2. Nickel-Catalyzed Cycloaddition of **1a** with Alkynes^a

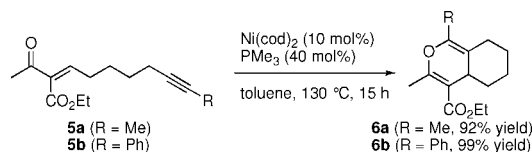
entry	R ⁴	R ⁵	2	3	yield (%)
1	Ph	Ph	2b	3ab	74
2	CH ₂ OMe	CH ₂ OMe	2c	3ac	82
3	CH ₂ CH ₂ OMe	Pr	2d	3ad	74 (1/1) ^b
4	CH ₂ OMe	Pr	2e	3ae	88 (3/2) ^b
5	Me	C ₅ H ₁₁	2f	3af	84 (1/1) ^b
6	Me	<i>i</i> Pr	2g	3ag	73 (3/1) ^b
7	Me	Ph	2h	3ah	79
8	cyclopropyl	Ph	2i	3ai	68 (7/2) ^b

^a Reactions were carried out using Ni(cod)₂ (10 mol %), PMe₃ (40 mol %), **1** (0.5 mmol), and **2** (1.25 mmol) in 5 mL of toluene (130 °C).

^b Ratio of regioisomers.

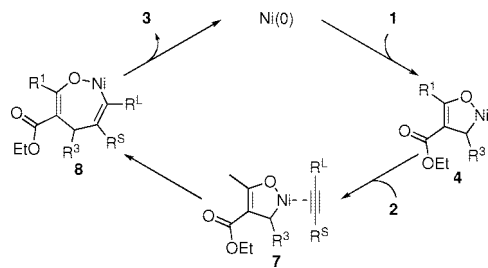
The intramolecular [4 + 2] cycloaddition was also investigated. The reaction of **5** proceeded under optimized conditions to give **6** in 92% and 99% yields, respectively (Scheme 3).

Scheme 3. Nickel-Catalyzed Intramolecular [4 + 2] Cycloaddition



The formation of polysubstituted pyranes **3** can be rationalized as arising from oxidative cyclization of nickel(0) to an enone **1** to form oxa-nickelacycle **4** (Scheme 4). Subsequent coordination of alkyne takes place to give intermediate **7**; here, the steric repulsive interaction is minimal between bulkier R^L and R³ of the oxanickelacycle. Insertion of an alkyne into C–Ni bond leads to the seven-membered oxa-nickelacycle **8**, which undergoes reductive elimination to give **3** and regenerates the starting nickel(0) complex.⁹

Scheme 4. Plausible Reaction Mechanism for Nickel-Catalyzed [4 + 2] Cycloaddition of Enones with Alkynes



In summary, we have developed a new nickel-catalyzed [4 + 2] cycloaddition reaction of enones with alkynes to provide polysubstituted pyrans. We demonstrated for the first time that enones are susceptible to oxidative cyclization of nickel(0); such reactions allow inter- or intramolecular cycloaddition with alkynes.

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Supporting Information Available: Experimental procedures including spectroscopic and analytical data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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