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

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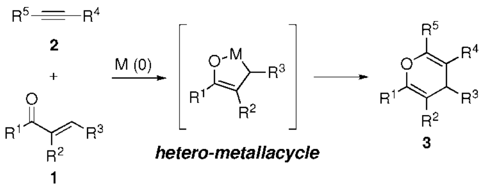
The hetero-Diels−Alder reactions of α,*β*-unsaturated carbonyl compounds (heterodiene) with electron-rich carbon−carbon unsaturated bonds (heterodienophile) are a useful method for the synthesis of six-membered heterocyclic rings and have been widely applied to natural product synthesis.[1,2] However, 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]

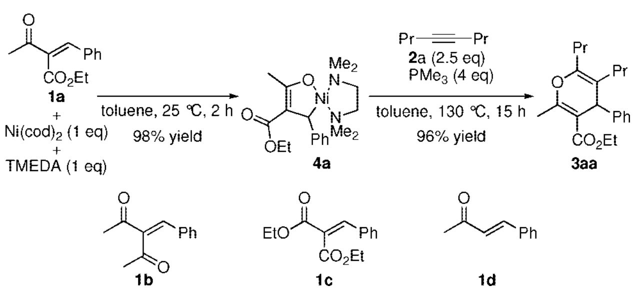
Scheme 1. Transition-Metal-Catalyzed [4 + 2] Cycloaddition



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 $Ni(cod)_2$ 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 benzyliden-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 $Ni(cod)_2$ 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, 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).

Scheme 2. Formation of Oxa-Nickelacycle



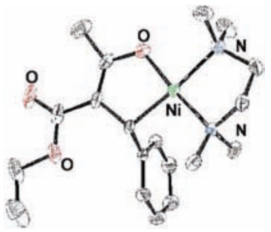
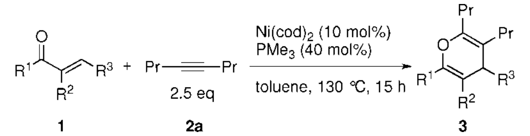


Figure 1. ORTEP Drawing of **4a**.

Table 1. Nickel-Catalyzed Cycloaddition of Enones with 4-Octyne[a]



entry	R^1	R^2	R^3	1	3	yield (%)[b]
1	Me	CO_2Et	Ph	**1a**	**3aa**	99
2	Me	CO_2Et	Pr	**1e**	**3ea**	99
3	Ph	CO_2Et	Ph	**1f**	**3fa**	82
4	Ph	CO_2Et	Pr	**1g**	**3ga**	50
5	Me	C(O)Me	Ph	**1b**	**3ba**	<1
6	EtO	CO_2Et	Ph	**1c**	**3ca**	<1
7	Me	H	Ph	**1d**	**3da**	<1

[a] Reactions were carried out using $Ni(cod)_2$ (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

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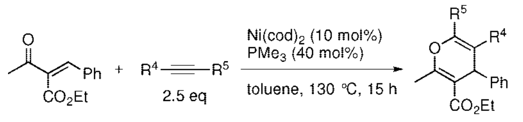
ratio of 7/2 (entry 8). Terminal alkynes failed to participate in the reaction, presumably due to rapid oligomerization of alkynes.

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



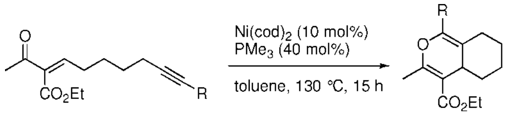
1a **2** **3**

entry	R^4	R^5	2	3	yield (%)
1	Ph	Ph	**2b**	**3ab**	74
2	CH_2OMe	CH_2OMe	**2c**	**3ac**	82
3	CH_2CH_2OMe	Pr	**2d**	**3ad**	74 (1/1)[b]
4	CH_2OMe	Pr	**2e**	**3ae**	88 (3/2)[b]
5	Me	C_5H_{11}	**2f**	**3af**	84 (1/1)[b]
6	Me	*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 %), PMe_3 (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

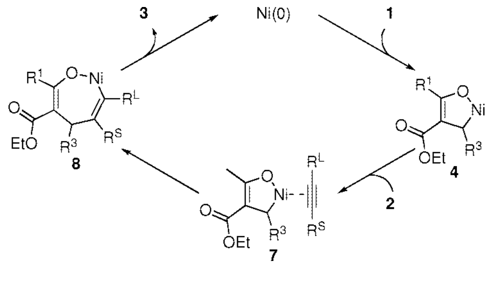


5a (R = Me) **5b** (R = Ph)

6a (R = Me, 92% yield) **6b** (R = Ph, 99% yield)

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 R^3 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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