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Rhenium-Catalyzed Regioselective Synthesis of Multisubstituted Pyridines from β-Enamino Ketones and Alkynes via C–C Bond Cleavage

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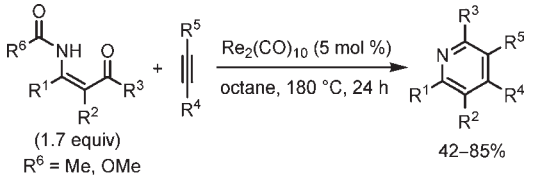
ABSTRACT



A new method is described for the regioselective synthesis of multisubstituted pyridine derivatives. Treatment of *N*-acetyl β-enamino ketones with alkynes in the presence of the rhenium catalyst, $Re_2(CO)_{10}$, gives multisubstituted pyridines regioselectively. In this reaction, the *N*-acetyl moieties are important for the selective formation of the multisubstituted pyridines. This reaction proceeds via insertion of alkynes into a carbon–carbon single bond of β-enamino ketones, intramolecular nucleophilic cyclization, and elimination of acetic acid.

Construction of *N*-heterocycles is one of the most important areas in synthetic organic chemistry. Among them, the synthesis of highly substituted pyridines is of special interest because they are partial structures of many natural products, pharmaceuticals, and organic functional materials.[1,2] From the 19th century, numerous efficient synthetic procedures have been developed for the synthesis of pyridine derivatives.[3,4] One common method involving condensation of amines and carbonyl compounds has been used widely for the synthesis of substituted pyridines, such as the Hantzsch, Knoevenagel, and Chichibabin methods.[5–7] In addition, transition metal catalysts have been used for the synthesis of pyridine derivatives.[8] Recent methods for the synthesis of multisubstituted pyridine derivatives have been accomplished via transition-metal-catalyzed

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C−H bond activation and subsequent C−C bond formation. For example, Ellman−Bergman,[9] Cheng,[10] Chiba,[11] and Rovis[12] have reported the rhodium-catalyzed synthesis of highly substituted pyridines from α,β-unsaturated imines (or oximes) and internal alkynes via insertion of alkynes into an olefinic C−H bond of the α,β-unsaturated imines and successive electrocyclization. In these reactions, nonpolar internal alkynes can be introduced into the pyridine rings. In contrast, only a few examples have been reported for the catalytic synthesis of pyridine derivatives via C−C bond cleavage.[13] These reactions were sometimes limited by regioselectivity and product selectivity. In particular, the use of unsymmetrical alkynes (e.g., 1-phenyl-1-propyne and 1-hexyne) gave a mixture of regioisomers.

The rhenium-catalyzed regioselective insertion of terminal alkynes into a C−C single bond of cyclic and acyclic 1,3-dicarbonyl compounds has already been reported (Figure 1a).[14] In this reaction, a mixture of regio- and stereoisomers was formed. In contrast, only a single product was obtained from β-enamino ketones instead of 1,3-dicarbonyl compounds (Figure 1b). This report describes the first rhenium-catalyzed regioselective synthesis of multisubstituted pyridine derivatives from β-enamino ketones as well as terminal and internal alkynes.[15,16]

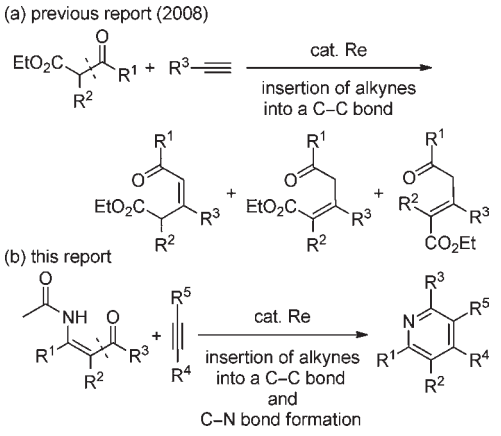
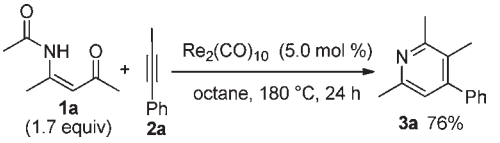


Figure 1. Rhenium-catalyzed insertion of alkynes into a C−C single bond.

Treatment of **1a** with 1-phenyl-1-propyne (**2a**) in the presence of a catalytic amount of $Re_2(CO)_{10}$ in octane at 180 °C for 24 h gave multisubstituted pyridine **3a** in 76% yield as a single regioisomer (Scheme 1).[17−20] In this reaction, the *N*-acetyl moiety was important for formation of pyridine derivatives. Using β-enamino ketones with other functional groups, such as *N*-isopropylcarbonyl, benzoyl, pentafluorobenzoyl, trichloroacetyl, trifluoroacetyl, and pentafluoroethylcarbonyl, produced multisubstituted pyridine **3a** in low yields.

Scheme 1. Rhenium-Catalyzed Synthesis of Pyridine **3a** from *N*-Acetyl β-Enamino Ketone **1a** and Alkyne **2a**



Next, several β-enamino ketones (Table 1) were examined. These reactions produced the corresponding pyridines as a single product. Regioselective synthesis of pyridines **3b** and **3c** also can be accomplished using β-enamino ketones, **1b** and **1c**, which have a phenyl group at the R^1 or R^3 position, respectively, of the β-enamino ketones (entries 1 and 2). These results indicate that a C−C single bond was cleaved between the carbonyl and α-carbons of the β-enamino ketones. The β-enamino ketone with phenyl groups at the R^1 and R^3 positions, **1d**, provided the corresponding pyridine **3d** in 60% yield (entry 3). Moreover, treatment of **2a** with *N*-acetyl β-enamino ketone **1e** with a methyl group at the α-position gave the desired pyridine **3e** in 57% yield (entry 4). The reaction of cyclic β-enamino ketone **1f** produced tetrahydroquinoline derivative **3f** in 69% yield (entry 5).[21]

The scope and limitations of several internal alkynes were also investigated (Table 2).[22] The use of the aryl alkyne with an electron-donating group at the *para*-position, **2b**,

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(17) A side reaction occurred when using phenyl acetylene, which is described in Table 2, entry 9.

(18) This reaction did not proceed when using $MnBr(CO)_5$, $ReBr(CO)_5$, $[ReBr(CO)_3(thf)]_2$, $[ReH(CO_4)]_n$, $W(CO)_6$, $Mn_2(CO)_{10}$, $Fe_3(CO)_{12}$, $Ru_3(CO)_{12}$, $Ir_4(CO)_{12}$, and $Rh_4(CO)_{12}$. Dimerization of β-enamino ketone occurred upon using $Rh_4(CO)_{12}$.

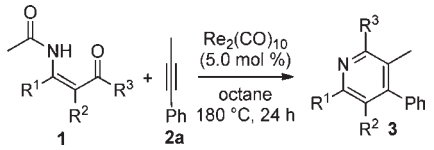
(19) Investigation of several solvents: Toluene 73%, MeCN 47%, DMF 0%, 1,2-dichloroethane 0%, neat 15%.

(20) In this reaction, small amounts of several products by hydrolysis of **1a** (for example, 1,3-diketone and acetic acid) were detected by GCMS. In addition, polymerization of internal alkyne **2a** also occurred.

(21) *o*-Acetylacetanilide and five-membered cyclic β-enamino ketone bearing an *N*-acetyl group at an external ring position did not promote the formation of pyridine derivatives.

(22) The reaction of *N*-acetyl enamino ketone **1a** with *cis*-stylbene (or *trans*-4-octene) did not proceed except for the decomposition of **1a**.

Table 1. Reactions between Several β-Enamino Ketones **1** and 1-Phenyl-1-propyne (**2a**)[a]



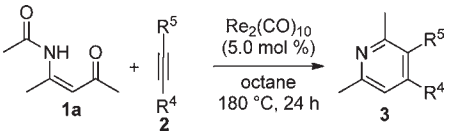
entry	R^1	R^2	R^3	product	yield / %[b]
1	Ph	H	Me	**1b**	**3b** 58 (61)
2	Me	H	Ph	**1c**	**3c** 65 (73)
3	Ph	H	Ph	**1d**	**3d** 60 (60)
4	Me	Me	Me	**1e**	**3e** 57 (63)
5[c]				**1f**	**3f** 69 (70)

[a] **1** (1.7 equiv). [b] Isolated yield. Yield determined by ^{1}H NMR is reported in parentheses. [c] **1f** (1.0 equiv), $Re_2(CO)_{10}$ (10 mol %).

produced only one regioisomer **3g** in 85% yield (entry 1). Regioselectivity was not affected by the steric hindrance at the *ortho*-position of alkyne **2c**, and the corresponding pyridine derivative **3h** was produced in 60% yield (entry 2). However, an aryl alkyne with an electron-withdrawing group at the *para*-position, **2d**, led to a decrease in reactivity and regioselectivity (entry 3). The reaction of enyne **2e** with **1a** provided a mixture of **3j** and **3j′** in 47% yield (**3j** and **3j′** = 97:3, entry 4). Internal alkynes with two alkyl or aromatic groups **2f**−**2i** were transformed to the corresponding multisubstituted pyridines **3k**−**3n** in 59−72% yields (entries 5−8). Use of phenylacetylene (**2j**) produced the desired pyridine **3o** and unexpected acetylpyridine **5a** in 42% and 18% yields, respectively (entry 9).[23]

Changing the *N*-acetyl moiety of β-enamino ketone **1a** to a methoxycarbonyl group yielded multisubstituted pyridine **3o** in 43% yield without side products (Scheme 2). Addition of 1.0 equiv of methyl carbamate increased the yield of **3o** to 56%. The reaction also proceeded with an

Table 2. Reactions between *N*-Acetyl β-Enamino Ketone **1a** and Several Alkynes **2**[a]



entry	R^4	R^5	product	yield (%)[b]
1	R = 4-MeO	**2b**	**3g**	85 (87)
2	2-Me	**2c**	**3h**	60 (66)
3[c]	4-Cl	**2d**	**3i** + **3i′**	46 (60) [85:15]
4	Me	**2e**	**3j** + **3j′**	47 (60) [97:3]
5[d]	^{n}C$_5$H$_{11}$	**2f**	**3k**	65 (70)
6	Ph	**2g**	**3l**	59 (62)
7	4-MeOC$_6$H$_4$	**2h**	**3m**	68 (72)
8		**2i**	**3n**	72 (76)
9[e]	H	Ph	**2j**	**3o** 42 + **5a** 18

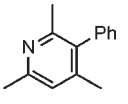
[a] **1a** (1.7 equiv). [b] Isolated yield. Yield determined by ^{1}H NMR is reported in parentheses. [c] The regioselectivity was determined by ^{1}H NMR. [d] **1a** (1.0 equiv), $Re_2(CO)_{10}$ (10 mol %). [e] **1a** (1.0 equiv), **2j** (2.0 equiv), toluene, 180 °C, 24 h.

aliphatic alkyne; treatment of enamino ketone **4** with 1-dodecyne (**2k**) gave the corresponding pyridine (**3p**) in 41% yield. In contrast, the reaction of *N*-acetyl β-enanino ester **6** with phenylactylene (**2j**) gave multisubstituted ethoxycarbonylpyridine **5b** in 29% yield as a single product (Scheme 2).[24]

The structures of the pyridine derivatives **3** demonstrated that the alkynes **2** insert between the carbonyl and α-carbons of β-enamino ketones **1**. The proposed mechanism for the formation of the pyridine derivatives is shown in

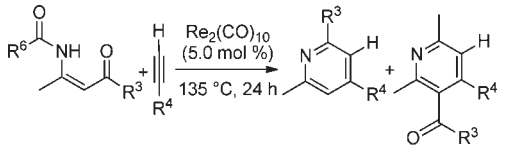
(23) Multisubstituted acetylpyridine **5a** is generated via rhenium-catalyzed nucleophilic addition of β-enamino ketone **1a** to alkyne **2j** and successive cyclization. For examples of rhenium-catalyzed addition of active methylene compounds to terminal alkynes (or β-enamino esters to allenes), see: (a) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823. (b) Kuninobu, Y.; Yamashita, A.; Yamamoto, S.-i.; Yudha, S. S.; Takai, K. *Synlett* **2009**, *20*, 3027.

(24) Treatment of (*Z*)-methyl (4-oxo-2-penten-2-yl)carbamate (*N*-methoxycarbonyl β-enamino ketone, **4**) with 1-phenyl-1-propyne (**2a**) at 150 °C for 24 h produced a mixture of pyridines **3a** and **3a′** in 55% yield (**3a**:**3a′** = 72:28).



3a′

Scheme 2. Selective Synthesis of Multisubstituted Pyridines with Terminal Alkynes



R^6 = OMe, R^3 = Me (**4**), R^4 = Ph (**2j**)[a]	43% (**3o**)	0%
	56% (**3o**)[b]	0%
R^6 = OMe, R^3 = Me (**4**), R^4 = ^{n}C$_{10}$H$_{21}$ (**2k**)[c]	41% (**3p**)	0%
R^6 = Me, R^3 = OEt (**6**), R^4 = Ph (**2j**)[d]	0%	29% (**5b**)

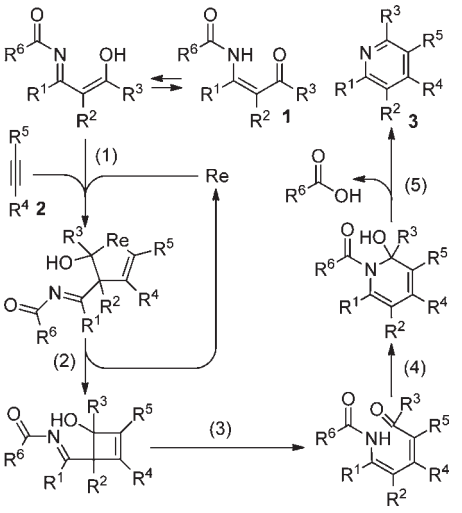
[a] **1g** (1.0 equiv), **2j** (2.0 equiv), dioxane. [b] Methyl carbamate (1.0 equiv) was added as an additive. [c] **1g** (1.0 equiv), **2k** (2.0 equiv), methyl carbamate (1.0 equiv), dioxane. [d] **6** (2.0 equiv), **2j** (1.0 equiv), toluene.

Scheme 3: (1) oxidative cycloaddition of an enol form of β-enamino ketone **1**, alkyne **2**, and the rhenium catalyst; (2) reductive elimination to give a cyclobutene intermediate and regenerate the rhenium catalyst;[25] (3) C−C bond cleavage by the *retro*-aldol-type reaction (*N*-acyl group works as an electron acceptor); (4) intramolecular nucleophilic cyclization; (5) elimination of acetic acid to give pyridine derivative **3**. In this reaction, the direction of insertion of the alkyne is similar to rhenium-catalyzed insertion of alkynes into a C−C bond of a β-keto ester.[14]

In summary, the rhenium-catalyzed regioselective synthesis of multisubstituted pyridines was accomplished successfully by the reaction of an *N*-acetyl β-enamino ketone with an internal alkyne. This reaction proceeded via regioselective insertion of alkynes into a C−C single bond of β-enamino ketones. As a result, two substituents from the alkynes were introduced at the 3- and 4-positions of the pyridine derivatives regioselectively. For reactions between *N*-acetyl β-enamino ketones and a terminal alkyne, two pyridines were generated. In contrast, the selectivity of the product improved and only one pyridine was formed when using an *N*-methoxycarbonyl β-enamino ketone. This reaction may become a useful method for synthesizing multisubstituted pyridines regioselectively.

(25) The reason for the regioselectivity is not clear; however, the steric hindrance between the substituents of alkynes and ligands of the rhenium catalyst may be responsible for the regioselectivity.

Scheme 3. Proposed Mechanism for the Formation of Multisubstituted Pyridines



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Supporting Information Available. General experimental procedures and characterization data for pyridine derivatives **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.