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Synthesis of 1,2-Dihydroisoquinolines via Rhenium-Catalyzed Tandem Cyclization and Nucleophilic Addition of 2-(1-Alkynyl)arylaldimines

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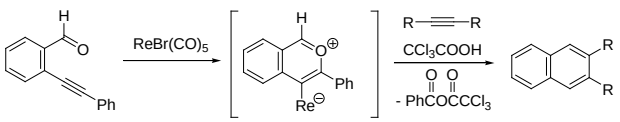
The synthetic method of 1,2-dihydroisoquinolines via the 6-endo-dig cyclization of 2-alkynylaldimines and the nucleophilic addition has been developed. When the 2-alkynylaldimines were reacted with various nucleophiles such as nitromethane, dimethyl malonate, phenylacetylene, hydrosilane, allylstannane, and ketene silyl acetal in the presence of a rhenium catalyst, the corresponding 1,2-dihydroisoquinolines were obtained in moderate to good yields.

Keywords: Rhenium, 2-Alkynylaldimines, 1,2-Dihydroisoquinolines

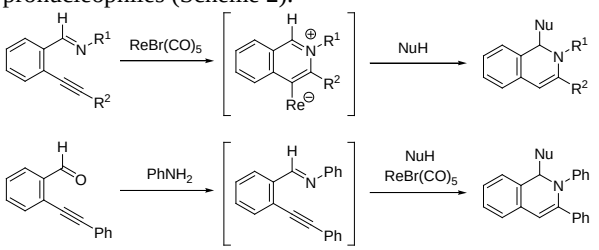
The 1,2-dihydroisoquinoline ring system is well known and used as the core nucleus in a wide variety of biologically active pharmacophores.[1] A number of approaches to the synthesis of 1,2-dihydroisoquinilines has been reported.[2] Among the various methods, functionalization of the isoquinolines core, which was generated by the 6-endo-dig ring closure reaction of 2-(1-alkynyl)arylaldimines, with carbon pronucleophiles was recently discovered as a powerful synthetic tool of the 1,2-dihydroisoquinolines; however, there are some drawbacks on these methods; (i) limitation of the substrates and (ii) instability under a moist or air conditions.[3]

Recently, we have found that the rhenium complex show a novel catalytic ability for the benzannnulation reaction of 2-(phenylethynyl)benzaldehyde and alkynes in the presence of trichloroacetic acid giving the corresponding 2,3-disubstituted naphthalenes (Scheme 1).[4] For the reaction, it was proposed the reaction path including the intermolecular nucleophilic attack of the oxygen of the formyl function on the carbon-carbon triple bond of the 2-(1-alkynyl)benzaldehydes.



Scheme 1.

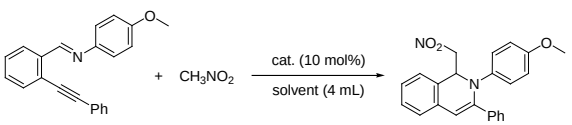
We have become interested in the application of the rhenium catalytic system for the efficient construction of the 1,2-dihydroisoquinolines core by the intermolecular nucleophilic attack of the nitrogen of the imino group on the carbon-carbon triple bond of the 2-(1-alkynyl)arylaldimines. Now, the synthesis of 1,2-dihydroisoquinolines by the rhenium-catalyzed reaction of 2-(1-alkynyl)arylaldimines and pronucleophiles was examined. We describe the results of the reaction of the 2-(1-alkynyl)arylaldimines and pronucleophiles, such as nitroalkanes, active methylene compounds, terminal alkyne, hydrosilane, allylstannane, and ketene silyl acetal, and the three-component coupling reaction of 2-(phenylethynyl)benzaldehyde, aniline and pronucleophiles (Scheme 2).[5]



Scheme 2.

When *N*-[2-(phenylethynyl)benzylidene]-4-methoxybenzenamine (**1a**) was treated with one equivalent amount of nitromethane (**2a**) in the presence of the $ReBr(CO)_5$ (10 mol%) catalyst in dichloroethane solvent at 80 °C for 15 h, 1-nitromethyl-3-phenyl-2-(4-methpxyphenyl)-1,2-dihydroisoquinoline (**3a**) was obtained in 20% yield without the formation of 5-exo-dig cyclized product (Entry 1 in Table 1). The yield of the **3a** was improved by increasing the amount of nitromethane, extending the reaction time and increasing the reaction temperature to 100 °C (Entries 1-5). $ReCl(CO)_5$ showed almost the same catalytic ability as $ReBr(CO)_5$, **3a** was obtained in 40% yield (Entries 3 and 6). In the case of other rhenium complexes, such as $Re_2(CO)_{10}$ and CH_3ReO_3, the yield of **3a** slightly decreased (Entries 7 and 8). When toluene was used as the solvent, the reaction smoothly proceeded to give **3a** in 87% yield (Entry 9). Even when acetonitrile and THF were used as the solvent, the reaction occurred to give **3a** in 21 and 58% yields, respectively, but in the case of hexane, **3a** was not obtained at all (Entries 10-12).

Table 1. Various Reaction Conditions



1a (0.2 mmol) **2a** **3a**

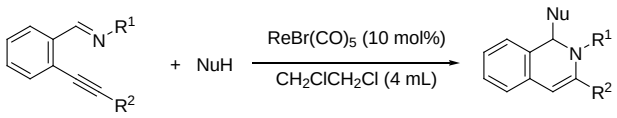
Entry	Catalyst	Solvent	**2a** (eq.)	Temp., °C	Time, h	Yield, %[a]
1	$ReBr(CO)_5$	$(CH_2Cl)_2$	1	80	15	20
2	$ReBr(CO)_5$	$(CH_2Cl)_2$	2	80	15	39
3	$ReBr(CO)_5$	$(CH_2Cl)_2$	4	80	15	41
4	$ReBr(CO)_5$	$(CH_2Cl)_2$	4	80	48	75
5	$ReBr(CO)_5$	$(CH_2Cl)_2$	4	100	15	90(82)
6	$ReCl(CO)_5$	$(CH_2Cl)_2$	4	80	15	40
7	$Re_2(CO)_{10}$	$(CH_2Cl)_2$	4	80	15	24

8	CH_3ReO_3	$(CH_2Cl)_2$	4	80	15	25
9	$ReBr(CO)_5$	toluene	4	80	15	87
10	$ReBr(CO)_5$	hexane	4	80	15	0
11	$ReBr(CO)_5$	CH_3CN	4	80	15	21
12	$ReBr(CO)_5$	THF	4	80	15	58

[a] ^{1}H-NMR yield. The number in parenthesis shows the isolated yield.

To determine the applications of the reaction, we first examined the reaction of various 2-(1-alkynyl)arylaldimines and nitromethane (**2a**) (Table 2). For the reaction of *N*-[2-(2-phenylethynyl)benzylidene]benzeneamine **1b** and *N*-[2-(2-phenylethynyl)benzylidene]-4-methylbenzenamine **1c**, the corresponding 1,2-dihydroisoquinolines, **3b** and **3c**, were formed in 75 and 78% yields, with the formation of small amount of complicated by-products (Entries 2 and 3). In the case of the *N*-benzyl aldimine, the yield of 1,2-dihydroisoquinoline **3d** decreased due to the formation of various complicated by-products (Entry 4). The 3-alkyl substituted 1,2-dihydroisoquinoline **3e** was also synthesized by the rhenium catalytic system (Entry 5) In contrast to aldimines, in the case of ketimine, the corresponding 1,2-dihydroisoquinoline was not obtained at all. When **1a** was treated with nitroethane under the same reaction conditions as that of entry 3 in Table 1, the yield of the product **3f** was low; however, the yield of **3f** was improved by the addition of benzoic acid and the corresponding 1,2-dihydroisoquinoline was obtained in 73% yield with a mixture of diastereoisomers (Entry 6). The use of active methylene compounds instead of nitromethane as a pronucleophile was next investigated. When **1b** was treated with dimethyl malonate, the 6-endo-dig cyclization of **1b** and the tandem nucleophilic addition efficiently proceeded to give the corresponding 1,2,3-trisubstituted 1,2-dihydroisoquinoline **3g** in 84% yield (Entry 7). For the reaction of malonitrile, the desired product **3h** was not obtained (Entry 8). The terminal alkyne, such as phenylacetylene, proved to be a prenucleophile for this tandem cyclization (Entry 9).

Table 2. Synthesis of Various 1,2-Dihydroisoquinolines[a]

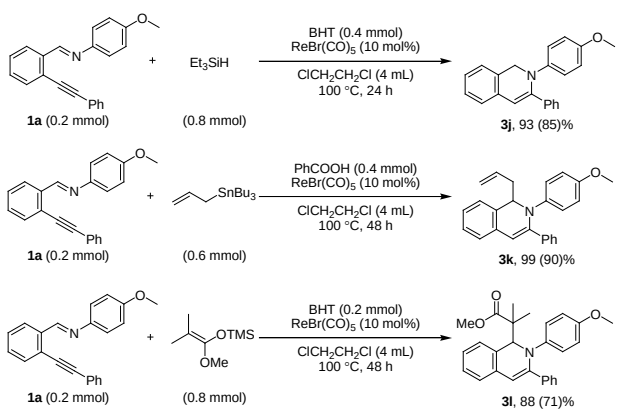


1 (0.2 mmol) (0.8 mmol) **3**

Entry	R^1	R^2	NuH	Yield, %[b]
1[c]	4-$CH_3OC_6H_4$	Ph **1a**	CH_3NO_2	**3a**, 90 (82)
2[d]	Ph	Ph **1b**	CH_3NO_2	**3b**, 75 (66)
3[d]	4-$CH_3C_6H_4$	Ph **1c**	CH_3NO_2	**3c**, 78 (76)
4	$PhCH_2$	Ph **1d**	CH_3NO_2	**3d**, 47 (40)
5	Ph	C_4H_9 **1e**	CH_3NO_2	**3e**, 73 (48)
6[e]	Ph	Ph **1b**	$C_2H_5NO_2$	**3f**, 73 (44) *d.r.* = 5 : 1
7[f]	Ph	Ph **1b**	$CH_2(COOCH_3)_2$	**3g**, 84 (68)
8[f]	Ph	Ph **1b**	$CH_2(CN)_2$	**3h**, 0
9[g]	4-$CH_3OC_6H_4$	Ph **1a**	Ph—≡	**3i**, (86)

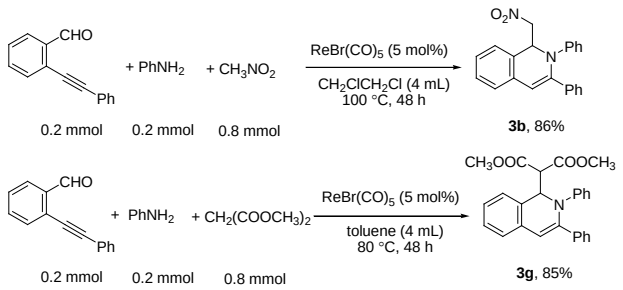
[a] Reaction conditions: **1** (0.2 mmol), NuH (0.8 mmol) $ReBr(CO)_5$ (10 mol%), CH_2ClCH_2Cl (4 mL) at 80 °C for 15 h.
[b] ^{1}H-NMR yield. The number in parenthesis shows the isolated yield.
[c] At 100 °C. [d] For 96 h. [e] Benzoic acid (0.2 mmol) was added.
[f] Reaction conditions: $ReBr(CO)_5$ (5 mol%) at 100 °C for 24 h.
[g] At 100 °C for 48 h.

We examined the tandem reaction of (2-phenylethynyl)benzylidene]benzeneamine **1a** with hydrosilane, allylstannane or ketene silyl acetal (Scheme 3). When **1a** was treated with triethylhydrosilane in the presence of $ReBr(CO)_5$ catalyst, the corresponding 2,3-disubstituted 1,2-dihydroisoquinoline **3j** was formed in 39% yield. The yield of product **3j** was improved by the addition of proton source, such as di-*tert*-butyl-*p*-cresol, and **3j** was formed in 93% yield. In the case of allylsilane, dihydroisoquinoline was not obtained at all. In contrast to allylsilane, when allylstannane was used as allylation agent, the corresponding 1,2,3-trisubstituted 1,2-dihydroisoquinoline **3k** was formed in 99% yield. The reaction of ketene silyl acetal proceeded smoothly in the presence of 2,6-di-*tert*-butyl-*p*-cresol to give the corresponding 1,2,3-trisubstituted dihydroisoquinoline **3l** in 88% yield.



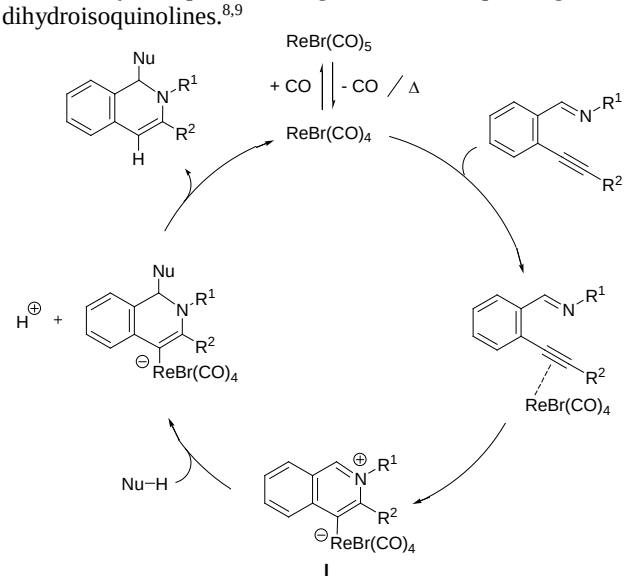
The number in parenthesis shows the isolated yield.
Scheme 3.

We were next interested in the rhenium-catalyzed one-pot synthesis of 1,2,3-trisubstituted 1,2-dihydroisoquinolines by the three-component coupling of 2-alkynylbenzaldehyde, amine and pronucleophile (Scheme 4). When 2-(phenylethynyl)benzaldehyde was treated with aniline and nitromethane in the presence of a catalytic amount of $ReBr(CO)_5$ at 100 °C for 48h, the three-component coupling reaction efficiently proceeded to give the corresponding 1,2,3-trisubstituted 1,2-dihydroisoquinoline **3b** in 86% yield. Even when dimethyl malonate instead of nitromethane was used as the pronucleophile, the desired product **3g** was obtained in 85% yield.



Scheme 4.

A plausible reaction pathway for the rhenium-catalyzed reaction is shown in Scheme 5. First, the decarbonylation of $ReBr(CO)_5$ to form $ReBr(CO)_4$, which is the coordinative unsaturated 16-electron complex, is the first step of the catalytic reaction.[7] The intermolecular nucleophilic attack of the nitrogen of the imino group on the carbon-carbon triple bond, which is activated by the coordination with the rhenium complex, formed the corresponding **I**. The nucleophilic addition of nitroalkanes, active methylene compounds and the terminal alkyne to **I**, followed by the protonation gave the corresponding 1,2-dihydroisoquinolines.[8,9]



Scheme 5.

In summary, we showed that the rhenium complex acts as the catalyst for the reaction of 2-(1-alkynyl)arylaldimines and pronucleophiles, such as nitroalkanes, active methylene compounds, terminal alkyne, hydrosilane, allylstannane, and ketene silyl acetal, and the three-component coupling reaction of 2-(phenylethynyl)benzaldehyde, aniline and pronucleophiles giving the corresponding 1,2-dihydroisoquinolines. The application of the reaction and determining the reaction pathway are now in progress.

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9 When **1a** was treated with ketene silyl acetal in the presence of D_2O, the deuterium atom was introduced at the 4-position of 1,2,3-trisubstituted 1,2-dihydroisoquinoline **3l**.