Preparation of 1,2-Dihydroisoquinolines by a Three-Component Reaction under Catalyst-Free Conditions

Kentaro Iso,[a] S. Salprima Yudha,[a] Naoki Asao*[a,b]

[a] Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

[b] Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan
Fax +81(22)7953899; E-mail: asao@mail.tains.tohoku.ac.jp

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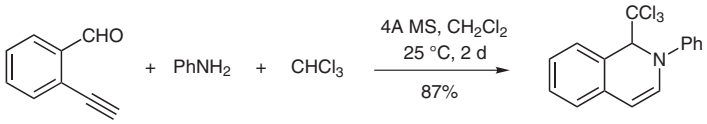
Abstract: A variety of 1,2-dihydroisoquinoline derivatives have been efficiently prepared by a three-component reaction using *ortho*-alkynylbenzaldehydes, primary amines, and pronucleophiles under mild catalyst-free conditions.

Key words: catalyst-free conditions, 1,2-dihydroisoquinoline, direct addition, multicomponent reaction, pronucleophile



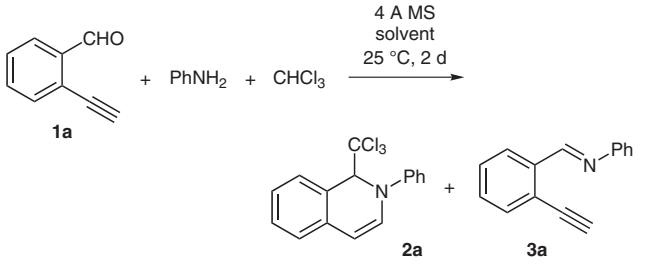
Scheme 1

Introduction

1,2-Dihydroisoquinolines constitute an important class of heterocyclic compounds of pharmacological significance and represent useful building blocks for natural products synthesis.[1,2] Consequently, many efforts have been made to develop synthetic methods of these useful compounds. However, known procedures generally need highly reactive reagents or catalysts, such as Brønsted acid. Recently, we reported the AgOTf-catalyzed synthesis of 1,2-dihydroisoquinoline skeletons by the direct addition of pronucleophiles to *ortho*-alkynylaryl aldimines, which were prepared from *ortho*-alkynylaldehydes and proper amines.[3,4] Interestingly, when the reactions were conducted using *ortho*-ethynylbenzaldehyde, having no substituents at the terminus of the alkynyl part, we noticed that the products were constructed even in the absence of the silver catalyst. Herein, ***we describe an environmentally benign three-component one-pot procedure*** using *ortho*-alkynylbenzaldehydes, amines, and pronucleophiles under catalyst-free conditions (Scheme 1).[5]

When *ortho*-ethynylbenzaldehyde (**1a**) was treated with aniline in chloroform in the presence of molecular sieves (4A MS) at room temperature, chloroform behaved as a pronucleophile and the trichloromethyl-substituted 1,2-dihydroisoquinoline **2a** was obtained in 91% yield.[6] Optimization experiments revealed that **2a** was obtained in high yield even when the reaction was conducted with five equivalents of $CHCl_3$ in CH_2Cl_2 as a solvent (Table 1). Solvents like MeCN, THF, or toluene did not lead to completion of the reaction; the formation of intermediate aldimine **3a** could be detected by ^1H NMR spectroscopy (entries 3–5).

Table 1 Three-Component Reaction with **1a**, Aniline, and $CHCl_3$[a]



Entry	Solvent	Yield of **2a** (%)[b]	Yield of **3a** (%)[c]
1	$CHCl_3$	91	0
2	CH_2Cl_2	87	0
3	MeCN	54	7
4	THF	46	43
5	toluene	54	27

[a] Reaction conditions: Aldehyde **1a** (1 equiv), aniline (1 equiv), $CHCl_3$ (5 equiv), 4A MS, 25 °C, 2 d.
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopy.

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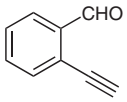
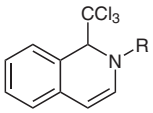
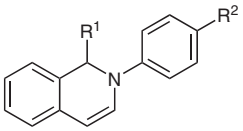
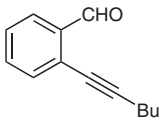
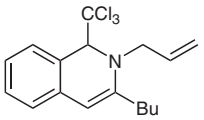
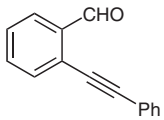
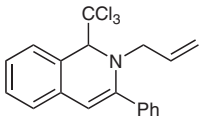
Scope and Limitations

The optimized reaction conditions described above provided a variety of 1,2-dihydroisoquinoline derivatives (Table 2). Electron rich aryl amine, such as *p*-anisidine, gave the desired product in high yield (entry 2). In contrast, when the electron poor aryl amine was used, such as *p*-trifluoromethylphenylamine, the reaction was sluggish (entry 3). The reactions using aliphatic amines proceeded faster than those using aromatic amines (entries 4–7). The reaction proceeded well even with sterically bulky *tert*-butylamine (entry 7). Even when the reaction was conducted in the absence of molecular sieves, the corresponding product was obtained in high yield although the reaction needed longer time for completion (entry 8). This result suggests that the presence of molecular sieves promotes the imine formation from aldehyde and amine as a dehydrating agent, but it is not essential for the construction of dihydroisoquinoline framework. Not only chloroform but also other pronucleophiles, such as nitromethane, dimethyl malonate, and phenylacetylene, worked well and the corresponding products were obtained, respectively (entries 9–11). Unfortunately, the reactions of aldehydes having substituents at the terminus of the alkynyl part, such as **1b** and **1c**, did not provide the desired products under the standard reaction conditions. However, the reaction proceeded in DCE at 70 °C and the

Table 2 Preparation of 1,2-Dihydroisoquinolines by the Three-Component Reaction[a]

Entry	1	Amine	Pronucleophile	Time (d)	Product	Yield (%)[b]
						
	1a					
1	**1a**	$PhNH_2$	$CHCl_3$	2	R = Ph	87
2	**1a**	4-$MeOC_6H_4NH_2$	$CHCl_3$	1.5	R = 4-$MeOC_6H_4$	91
3	**1a**	4-$CF_3C_6H_4NH_2$	$CHCl_3$	6	R = 4-$CF_3C_6H_4$	76
4	**1a**	$BnNH_2$	$CHCl_3$	0.8	R = $PhCH_2$	72
5	**1a**	CH_2=$CHCH_2NH_2$	$CHCl_3$	0.4	R = CH_2=$CHCH_2$	89
6	**1a**	$BuNH_2$	$CHCl_3$	0.3	R = Bu	77
7	**1a**	*t*-$BuNH_2$	$CHCl_3$	0.5	R = *t*-Bu	96
8[c]	**1a**	*t*-$BuNH_2$	$CHCl_3$	1.2	R = *t*-Bu	93
						
9	**1a**	4-$MeOC_6H_4NH_2$	$MeNO_2$	2	R^1 = CH_2NO_2, R^2 = MeO	78
10	**1a**	$PhNH_2$	$CH_2(CO_2Me)_2$	2	R^1 = $CH(CO_2Me)_2$, R^2 = H	59
11	**1a**	4-$MeOC_6H_4NH_2$	PhC≡CH	2	R^1 = PhC≡C, R^2 = MeO	72
12[d]		CH_2=$CHCH_2NH_2$	$CHCl_3$	0.9		83
	1b					
13[d]		CH_2=$CHCH_2NH_2$	$CHCl_3$	0.8		89
	1c					

[a] Reaction was conducted using **1** (1 equiv), amine (1 equiv), and pronucleophile (5 equiv) in the presence of 4A MS in CH_2Cl_2 at 25 °C unless otherwise mentioned.
[b] Isolated yield.
[c] Reaction was conducted in the absence of 4A MS.
[d] Reaction was conducted in DCE at 70 °C.

corresponding products were obtained in high yields (entries 12, 13).

In conclusion, we have reported an efficient and atom economical synthetic method of 1,2-dihydroisoquinoline derivatives from readily available starting materials. It is obvious that the present reaction is simple and environmentally benign preparation method because neither catalysts nor any highly reactive reagents are needed. In particular, the noncatalyzed self-construction was observed in the reactions using **1a** by just mixing three components at room temperature. The obtained products are known to be versatile intermediates for various kinds of bioactive compounds, such as tetrahydroisoquinoline alkaloids.

All reagents were used as supplied unless otherwise stated. Molecular sieve beads (4A MS; ca. 2 mm) were purchased from Nacalai Tesque, and were dried before use in an oven (140 °C) for 2 h. Analytical thin-layer chromatography (TLC) was performed using NH TLC plates (Fuji Silysia Chemical LTD.). Column chromatography was performed using 100–210 mm Silica Gel 60N (Kanto Chemical Co., Inc.), 40–50 mm Silica Gel 60N (Kanto Chemical Co., Inc.), and basic Chromatorex-NH 200–350 mesh (Fuji Silysia Chemical LTD.). NMR spectra were measured at 400 MHz for ^{1}H and 100 MHz for ^{13}C on a JEOL JNM-AL 400 spectrometer. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane with reference to internal residual $CHCl_3$ (δ = 7.26) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ = 77.0) in $CDCl_3$. Mass spectra were recorded on HITACHI M-2500S (EI, HRMS) or Bruker APEX III (ESI-TOF MS, HRMS). Melting points were measured on a Yanaco MP-S3 micro melting point apparatus.

2-Phenyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (2a); Typical Procedure

To a mixture of 2-ethynylbenzaldehyde (**1a**; 130 mg, 1 mmol, 1.00 equiv) and 4A MS (1 g) in CH_2Cl_2 (5 mL) were added aniline (90 μL, 1 mmol, 1.00 equiv) and $CHCl_3$ (400 μL, 5 mmol, 5.00 equiv) at 25 °C under argon. After stirring for 2 days at 25 °C, the resulting dark brown mixture was filtered through a pad of Celite for removal of 4A MS. The solvent was evaporated under reduced pressure to leave the crude product, which was purified by basic silica gel column chromatography using a mixture of hexane and Et_2O as an eluent to give **2a**; yield: 282 mg (87%); white needles; mp 132 °C.

IR (KBr): 3037, 1624, 1595, 1560, 1502, 1257, 1225, 1132, 945, 922, 862, 773, 752, 727, 692, 638 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 7.6 Hz, 1 H), 7.40–7.33 (m, 3 H), 7.21–7.29 (m, 4 H), 7.05 (m, 1 H), 6.79 (dd, J = 7.3, 1.5 Hz, 1 H), 6.13 (d, J = 7.3 Hz, 1 H), 5.81 (d, J = 1.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 133.1, 129.9, 129.2, 129.1, 129.0, 125.7, 124.1, 123.4, 122.5, 118.5, 108.7, 104.8, 74.6.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{12}Cl_3N$: 324.0108; found: 324.0108.

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