HETEROCYCLES, Vol. 74, 2007, pp. 649 - 660. © The Japan Institute of Heterocyclic Chemistry
Received, 29th August, 2007, Accepted, 12th October, 2007, Published online, 16th October, 2007. COM-07-S(W)49

A FACILE SYNTHESIS OF 1,2-DIHYDROISOQUINOLINES BY THREE-COMPONENT REACTION

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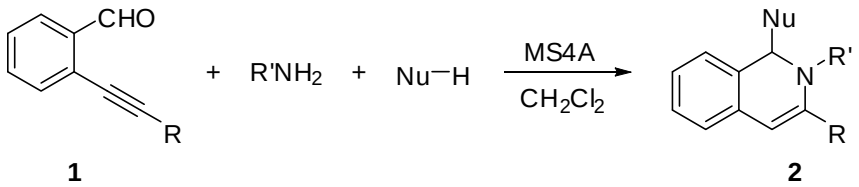
Abstract – 1,2-Dihydroisoquinoline frameworks are constructed efficiently by three-component reactions with ortho-alkynylbenzaldehydes, primary amines, and pronucleophiles under mild conditions.

INTRODUCTION

Isoquinoline and its derivatives constitute an important class of heterocyclic compounds that are 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 reactive reagents or catalysts, such as Brønsted acid. In this paper, we wish to report a novel synthetic method of 1,2-dihydroisoquinoline derivatives **2** via the three component reaction using *ortho*-alkynylbenzaldehydes **1**, primary amines, and pronucleophiles (Nu-H) under catalyst-free conditions (Scheme 1).[3]



Scheme 1. Construction of 1,2-dihydroisoquinolines via three-component reaction

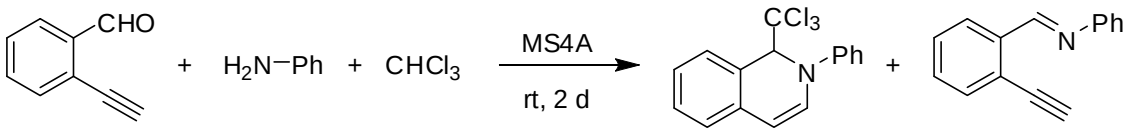
RESULTS AND DISCUSSION

Recently, we developed the AgOTf-catalyzed syntheses of 1,2-dihydroisoquinoline skeletons by the direct addition of pronucleophiles to *ortho*-alkynylarylaldimines.[4,5] On the way to explore the scope of this reaction, we tried to prepare imine compound **3a** from *ortho*-ethynylbenzaldehyde **1a** and aniline, as

This paper is dedicated to Prof. Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

a substrate having a terminal alkynyl group. However, to our surprise, when the reaction was carried out at room temperature in $CHCl_3$ in the presence of MS4A for 1 d, we found that not only the desired imine **3a** but also 1,2-dihydroisoquinoline derivative **2a** were produced. Therefore, we kept monitoring the reaction and finally **3a** disappeared after one more day and we obtained **2a** in 91 % yield as a sole product. These results clearly indicate that (1) **2a** was formed from **3a**; (2) chloroform worked as a pronucleophile; and (3) the 1,2-dihydroisoquinoline framework was constructed without any catalysts, such as AgOTf. Although chloroform is known to work as a useful nucleophile toward various kinds of electrophiles in organic synthesis, relatively strong bases have been employed.[6] These results prompted us to investigate the current three-component reaction under several conditions and results are summarized in Table 1. When chloroform was used as a solvent, **2a** was obtained in 91% yield as mentioned above (entry 1). Even when the reaction was carried out with only 5 equiv of chloroform in CH_2Cl_2, **2a** was obtained as well in 87% yield (entry 2). Interestingly, both reactions needed 2 d for completion and there was no difference in the reaction time (entries 1 and 2). This result suggests that the rate determining step of this reaction has no relationship to the concentration of $CHCl_3$. Reactions with other solvents, such as CH_3CN, THF, and toluene, were sluggish and **3a** was not consumed completely within 2 d (entries 3-5).

Table 1. Solvent effects on the three-component reaction[a]



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

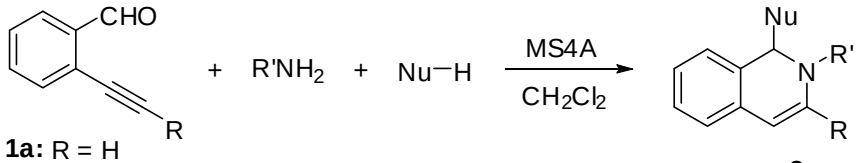
Entry	Solvent	Yield of **2a**[b]	Yield of **3a**[b]
1	$CHCl_3$	91%[c]	
2	CH_2Cl_2	87%[c]	
3	MeCN	54%	7%[d]
4	THF	46%	43%
5	toluene	54%	27%

[a] Reactions were carried out using **1a** (1 equiv), aniline (1 equiv), and $CHCl_3$ (5 equiv) in the presence of MS4A at room temperature for 2 d. [b] Determined by ^1H NMR spectra of the reaction products using CH_2Br_2 as an internal standard. [c] Isolated yields. [d] The compound **1a** was recovered in 14% yield.

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 1). In contrast, when *p*-trifluoromethylphenylamine was used as an electron poor aryl amine, the reaction was sluggish and the constructed imine from **1a** and *p*-trifluoromethylphenylamine was not consumed completely even after 6 d (entry 2). The reactions using aliphatic amines proceeded faster than

those using aromatic amines (entries 3-6). The reaction proceeded well even with sterically bulky *tert*-butyl amine (entry 6).[7] Even when the reaction was conducted in the absence of MS4A, the corresponding product was obtained in high yield although the reaction needed longer time for completion (entry 7). This result suggests that MS4A promotes the imine formation from aldehyde and amine as a dehydrating agent, but it is not essential for the construction of dihydroisoquinoline frameworks. Not only chloroform but also other pronucleophiles, such as nitromethane, dimethyl malonate, and phenylacetylene, worked well and the corresponding products were obtained, respectively (entries 8-10). 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 at room temperature. However, the reaction proceeded in $(CH_2Cl)_2$ at 70 ºC and the corresponding products were obtained in high yields (entries 11-12).

Table 2. Preparation of 1,2-dihydroisoquinolines via the three-component reaction[a]



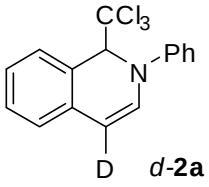
1a: R = H
1b: R = *n*-Bu
1c: R = Ph

Entry	R	R'NH_2	Nu-H	condition		Yield [b]
1	H	*p*-$MeOC_6H_4NH_2$	$CHCl_3$	rt, 1.5 d	**2b**	91%
2	H	*p*-$CF_3C_6H_4NH_2$	$CHCl_3$	rt, 6 d	**2c**	76%
3	H	$PhCH_2NH_2$	$CHCl_3$	rt, 0.8 d	**2d**	72%
4	H	CH_2=$CHCH_2NH_2$	$CHCl_3$	rt, 0.4 d	**2e**	89%
5	H	*n*-$BuNH_2$	$CHCl_3$	rt, 0.3 d	**2f**	77%
6	H	*t*-$BuNH_2$	$CHCl_3$	rt, 0.5 d	**2g**	96%
7[c]	H	*t*-$BuNH_2$	$CHCl_3$	rt, 1.2 d	**2g**	93%
8	H	*p*-$MeOC_6H_4NH_2$	$MeNO_2$	rt, 2 d	**2h**	78%
9	H	$PhNH_2$	$CH_2(CO_2Me)_2$	rt, 2 d	**2i**	59%
10	H	*p*-$MeOC_6H_4NH_2$	PhC≡CH	rt, 2 d	**2j**	72%
11[d]	*n*-Bu	CH_2=$CHCH_2NH_2$	$CHCl_3$	70 ºC, 0.9 d	**2k**	83%
12[d]	Ph	CH_2=$CHCH_2NH_2$	$CHCl_3$	70 ºC, 0.8 d	**2l**	89%

[a] Reaction was carried out using **1** (1 equiv), amine (1 equiv), and pronucleophile (5 equiv) in the presence of MS4A in CH_2Cl_2 unless otherwise mentioned. [b] Isolated yields. [c] Reaction was performed in the absence of MS4A. [d] Reaction was conducted in $(CH_2Cl)_2$ as a solvent.

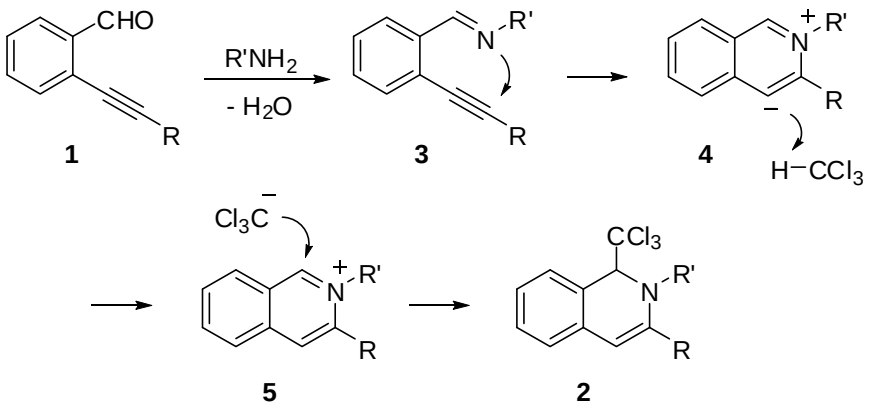
When the reaction of **1a** was examined with use of $CDCl_3$ instead of $CHCl_3$, the deuterated product *d*-**2a** was obtained in 89% yield in which D content was 98% by NMR analysis and no deuterium was found in other carbons of the product. On the basis of this result, we proposed the reaction mechanism as shown in Scheme 2. At the beginning, the imine **3** would be formed from **1** and amine. Nucleophilic attack of the

imine nitrogen to the alkyne would form the zwitterionic salt **4**, which would be stabilized by the resonance effect. Abstraction of a proton from chloroform by the anionic part of **4** would occur to generate the intermediate **5**. The subsequent attack of Cl_3C^- to **5** would produce **2**.[8] One might think of another possibility that amine might promote the reaction by abstraction of a proton from chloroform and the resulting counteranion (Cl_3C^-) would work as a nucleophile. To know such abstraction proceeds smoothly or not, we prepared a 0.2 molar solution of aniline in $CDCl_3$ in the presence of MS4A and monitored it by NMR spectroscopy. Even after 2 d, however, any significant changes of the integration value of the aminoprotons were not detected. Additionally, if the reaction proceeds along this mechanism in the deuteration experiment, **2a** should be produced predominantly over *d*-**2a** because **6** has proton and deuterium on the nitrogen atom in 2:1 ratio as shown in Scheme 3. The kinetic isotope effect would also promote the formation of **2a** than *d*-**2a**. Since the deuteration experiment was carried out with 1 equiv of aniline against **1a**, it might be possible to consider that most of the aniline would react with **1a** to form imine **3a** and only the remaining small amount of aniline might work as a catalyst. In that case, due to the formation of the deuterated aniline ($PhND_2$), which might be formed by repeating the abstraction of deuterium from $CDCl_3$, selective formation of *d*-**2a** would be possible. To check whether this mechanism is acceptable or not, we examined the deuteration experiment using 2 equiv of aniline. Although D content was slightly decreased to 95%, *d*-**2a** was obtained selectively in 81% yield and these results support the proposed mechanism as shown in Scheme 2.

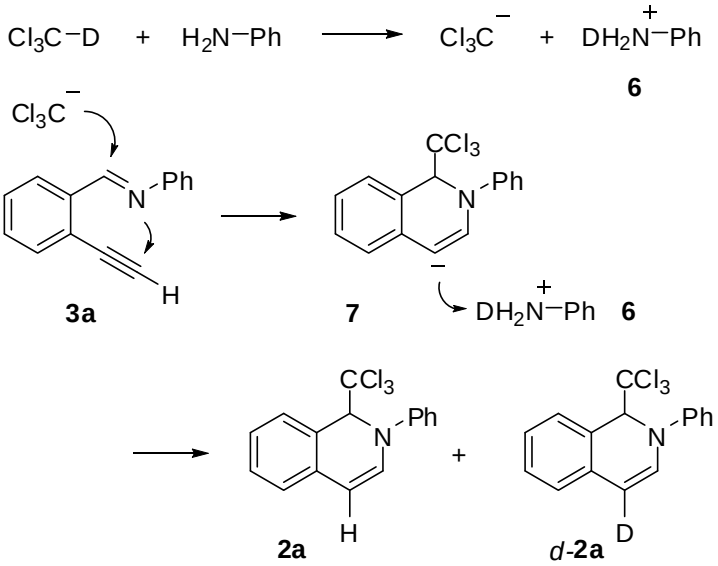


d-**2a**

Figure 1.

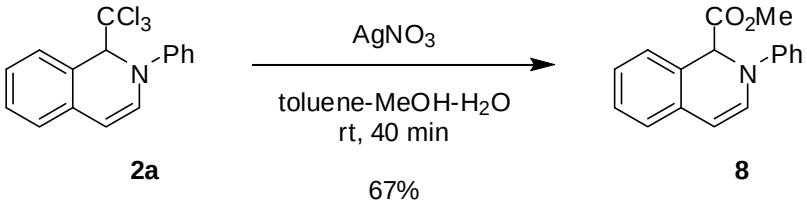


Scheme 2. Reaction mechanism of the three-component reaction

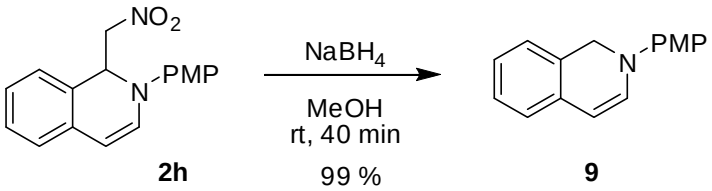


Scheme 3

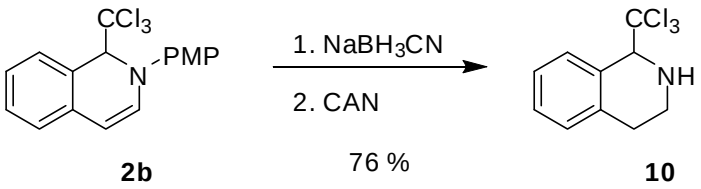
The obtained products would be useful as building blocks for synthesis of isoquinoline alkaloids.[1] For instance, since the trichloromethyl group can be used as a masked acid chloride, **2a** was converted to the ester **8** easily by treatment with silver nitrate in 67% yield (Scheme 4).[9] Interestingly, treatment of **2h** with $NaBH_4$ in MeOH resulted in the formation of **9** (Scheme 5). Probably, the reaction proceeds through the elimination of nitromethane, followed by the hydride attack from $NaBH_4$ to the resulting iminium salt. It is noteworthy that **9** was not obtained directly by the reaction of **1a** with *p*-anisidine in the presence of $NaBH_4$. Reduction of **2b** with sodium cyanoborohydride to tetrahydroisoquinoline and the subsequent oxidative cleavage of *p*-methoxyphenyl (PMP) group with cerium ammonium nitrate[10] also proceeded smoothly to afford tetrahydroisoquinoline **10** in 76% yield in two steps (Scheme 6).



Scheme 4



Scheme 5



2b **10**

Scheme 6

An efficient and atom economical synthetic method of 1,2-dihydroisoquinoline derivatives **2** has been developed through the three-component process, i.e., *ortho*-alkynylbenzaldehydes **1**, primary aliphatic or aromatic amines, and pronucleophiles, which involves an interesting mechanistic aspect. It is obvious that the present reaction is a simple and environmentally benign preparation method because neither catalysts nor any highly reactive reagents are needed. In particular, the noncatalyzed self-construction of **2** 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. Further studies to elucidate the mechanism of this reaction and to extend the scope of synthetic utility are in progress in our laboratory.

EXPERIMENTAL

General. All reagents were used as supplied unless otherwise stated. Molecular Seives 4A beads (abt 2 mm) was purchased from nacalai tesque. Before use, it was dried under 140 °C for 2 h in oven. Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated plates. Column chromatography was performed using 100-210 μm Silica Gel 60N (Kanto Chemical Co., Inc.), 40-50 μm Silica Gel 60N (Kanto Chemical Co., Inc.), and basic Chromatorex-NH 200-350 mesh (Fuji Silysia LTD.). NMR spectra were measured at 400 MHz for ^{1}H and 100 MHz for ^{13}C on a JEOL JNM-AL 400 (400 MHz). 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 $CDCl_3$. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; Mass spectra were recorded on HITACHI M-2500S (EI, HRMS), Bruker APEX III (ESI-TOF MS, HRMS), PerSeptive BioSystems Mariner™ (ESI-TOF MS, LRMS), and PerSeptive BioSystems Voyager DE STR (MALDI-TOF MS, LRMS). Melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Elemental analyses were performed with a Yanaco CHN corder MT-6.

General Procedure for the Synthesis of 1,2-dihydroisoquinolines 2. The preparation of **2a** is representative. To a mixture of **1a** (130 mg, 1 mmol) and MS4A (1 g) in CH_2Cl_2 (5 mL) were added

aniline (90 μL, 1 mmol) and $CHCl_3$ (400 μL, 5 mmol) at rt. After the mixture was stirred at 25 °C for 2 d, the mixture was filtered through a pad of celite for removal of MS4A. The solvent was evaporated 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 2-phenyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (**2a**) (282 mg, 0.87 mmol) in 87% yield. White needle; IR (KBr) 3037, 1624, 1595, 1560, 1502, 1257, 1225, 1132, 945, 922, 862, 773, 752, 727, 692, 638 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.21 – 7.29 (m, 4H), 7.05 (tt, *J* = 7.3, 1.2 Hz, 1H), 6.79 (dd, *J* = 7.3, 1.5 Hz, 1H), 6.13 (d, *J* = 7.3 Hz, 1H), 5.81 (d, *J* = 1.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) 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) Calcd. For $C_{16}H_{12}Cl_3N$ ($[M + H]^+$) 324.0108. Found 324.0108; mp 132 °C.

2-Phenyl-1-(trichloromethyl)-1,2-dihydroisoquinoline-*d* (d-2a)

White needle; IR (KBr) 3065, 3042, 1611, 1595, 1562, 1258, 1450, 1225, 1115, 961, 895, 868, 812, 777, 733, 692 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.21 – 7.29 (m, 4H), 7.05 (td, *J* = 7.3, 1.2 Hz, 1H), 6.79 (s, 1H), 5.82 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 146.7, 133.1, 130.0, 129.2, 129.1, 125.7, 124.1, 123.4, 122.5, 118.6, 108.4 (1*J* (C,D) = 26 Hz), 104.8, 74.7 (one carbon sp2 missing due to overlapping); HRMS (ESI) Calcd. for $C_{16}H_{11}DCl_3N$ ($[M + H]^+$) 325.0171. Found 325.0171; mp 134 °C.

2-(4-Methoxyphenyl)-1-(trichloromethyl)-1,2-dihydroisoquinoline (2b)

Light yellow solid; IR (KBr) 3065, 3013, 2963, 2932, 2837, 1618, 1580, 1562, 1512, 1454, 1323, 1290. 1182, 1040, 949, 822, 797 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, *J* = 7.6 Hz, 1H), 7.38 (td, *J* = 7.6, 1.2 Hz, 1H), 7.29 – 7.21 (m, 4H), 6.92 – 6.88 (m, 2H), 6.71 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.04 (d, *J* = 7.3 Hz, 1H), 5.73 (d, *J* = 1.2 Hz, 1H), 3.81 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 155.7, 141.0, 133.4, 130.8, 130.1, 129.0, 125.4, 123.9, 122.6, 121.4, 114.5, 107.0, 105.0, 75.8, 55.6; HRMS (ESI) Calcd. for $C_{17}H_{14}Cl_3NO$ ($[M + H]^+$) 354.0214. Found 354.0214; mp 95 °C.

1-(Trichloromethyl)-2-(4-(trifluoromethyl)phenyl)-1,2-dihydroisoquinoline (2c)

Yellow oil; IR (neat) 3069, 1614, 1568, 1520, 1456, 1326, 1296, 1259, 1229, 1167, 1119, 1074, 827, 781, 733, 646 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H), 7.36 – 7.29 (m, 4H), 6.81 (dd, *J* = 7.3, 1.4 Hz, 1H), 6.29 (d, *J* = 7.3 Hz, 1H), 5.87 (d, *J* = 1 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.7, 132.6, 129.9, 129.4, 127.3 (3*J* (C, F) = 4 Hz), 126.4, 124.6, 124.3, 124.2 (1*J* (C, F) = 270 Hz), 124.0, 123.8 (2*J* (C, F) = 33 Hz), 117.1, 111.1, 104.1, 73.7; HRMS (ESI) Calcd. for $C_{17}H_{11}Cl_3F_3N$ ($[M + H]^+$) 391.9982. Found 391.9982.

2-Benzyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (2d)

White solid; IR (KBr) 3028, 2916, 1622, 1450, 1418, 1367, 1325, 1221, 1210, 826, 781, 768, 719, 644, 613 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.37 – 7.33 (m, 2H), 7.28 – 7.14 (m, 5H), 7.09 – 7.07 (m, 2H), 6.39 (d, *J* = 7.1 Hz, 1H), 5.72 (d, *J* = 7.1 Hz, 1H), 5.21 (d, *J* = 1.2 Hz, 1H), 4.93 (d, *J* = 16 Hz, 1H), 4.76 (d, *J* = 16 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 138.1, 134.7, 134.4, 130.3, 128.8, 128.6, 127.4, 126.7, 124.7, 123.6, 121.1, 106.1, 102.2, 75.7, 61.3; HRMS (ESI) Calcd for $C_{17}H_{14}Cl_3N$ ($[M + H]^+$) 338.0265. Found 338.0265; mp 85 °C.

2-Allyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (2e)

Colorless oil; IR (neat) 3067, 2910, 1622, 1487, 1460, 1111, 824, 770, 737, 646, 613 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, *J* = 7.6 Hz, 1H), 7.35 (dd, *J* = 7.6, 6.8 Hz, 1H), 7.21 (dd, *J* = 7.6, 6.8 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.34 (d, *J* = 7.1, 1H), 5.81 – 5.71 (m, 1H), 5.70 (d, *J* = 7.1 Hz, 1H), 5.14 (s, 1H), 5.12 – 5.04 (m, 2H), 4.25 (dd, *J* = 16, 6.3 Hz, 1H), 4.12 – 4.07 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 134.4, 134.2, 133.9, 130.3, 128.8, 124.7, 123.6, 121.0, 117.2, 106.0, 102.1, 75.3, 60.2; HRMS (ESI) Calcd. for $C_{13}H_{12}Cl_3N$ ($[M + H]^+$) 288.0108. Found 288.0107.

2-Butyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (2f)

Yellow oil; IR (neat) 3061, 2959, 2930, 2871, 1622, 1487, 1466, 1163, 1113, 823, 783, 768, 737 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.38 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.31 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.16 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.09 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.31 (dd, *J* = 7.3, 1.2 Hz, 1H), 5.64 (d, *J* = 7.3 Hz, 1H), 5.10 (d, *J* = 1.2 Hz, 1H) 3.60 – 3.45 (m, 2H), 1.52 – 1.43 (m, 2H), 1.21 (sextet, *J* = 7.3 Hz, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 134.6, 134.1, 130.2, 128.8, 124.5, 123.5, 121.1, 106.1, 101.8, 76.2, 57.6, 32.4, 19.9, 13.9; HRMS (ESI) Calcd. for $C_{14}H_{16}Cl_3N$ ($[M + H]^+$) 304.0421. Found 304.0421.

2-*tert*-Butyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (2g)

Light yellow oil; IR (neat) 3065, 2974, 1618, 1564, 1489, 1454, 1302, 1188, 947, 824, 773, 617 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 6.8, 7.3 Hz, 1H), 7.22 (dd, *J* = 7.3, 6.8 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.55 (dd, *J* = 7.3, 1.0 Hz, 1H), 5.99 (d, *J* = 7.3 Hz, 1H), 5.33 (s, 1H), 1.32 (s, 9H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 133.9, 131.3, 129.9, 128.6, 125.1, 123.4, 123.3, 108.4, 105.7, 70.9, 58.2, 28.8; HRMS (ESI) Calcd. for $C_{14}H_{16}Cl_3N$ ($[M + H]^+$) 304.0421. Found 304.0421.

2-(4-Methoxyphenyl)-1-(nitromethyl)-1,2-dihydroisoquinoline (2h)

Orange solid; IR (KBr) 3065, 2961, 2837, 1618, 1583, 1564, 1531, 1456, 1379, 1275, 1184, 1036, 815,

772 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.28 (td, *J* = 7.3, 1.0 Hz, 1H), 7.15 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.07 (d, *J* = 7.3 Hz, 1H), 7.01 (ddd, *J* = 8.8, 3.7, 2.0 Hz, 2H), 6.89 (ddd, 8.8, 3.7, 2.2 Hz, 2H), 6.54 (dd, *J* = 7.3, 1.5 Hz, 1H), 5.97 (d, *J* = 7.3 Hz, 1H), 5.75 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 1H), 4.67 (dd, *J* = 11, 7.3 Hz, 1H), 4.49 (dd, *J* = 11, 7.3 Hz, 1H), 3.79 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 155.4, 138.3, 131.2, 129.2, 128.7, 126.3, 125.9, 124.8, 123.8, 119.0, 114.8, 105.1, 75.3, 60.2, 55.6; HRMS (EI) Calcd. for $C_{17}H_{16}N_2O_3$ (M^+) 296.1161. Found 296.1160; mp 94 °C.

2-(2-Phenyl-1,2-dihydro-isoquinolin-1-yl)malonic acid dimethyl ester (2i)

Yellow powder; IR (KBr) 3067, 2952, 1730, 1595, 1296, 1228, 773, 750, 694 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.31 – 7.26 (m, 3H), 7.16 – 7.11 (m, 5H), 6.96 (t, *J* = 7.32 Hz, 1H), 6.61 (d, *J* = 7.08 Hz, 1H), 6.14 (d, *J* = 7.36 Hz, 1H), 5,93 (d, *J* = 9.76 Hz, 1H), 4.06 (d, *J* = 9.76 Hz, 1H), 3.55 (s, 3H), 3.54 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 167.7, 167.4, 144.3, 131.2, 129.2, 128.6, 128.0, 127.1, 126.5, 125.9, 123.7, 121.6, 117.1, 107.8, 59.7, 53.7, 52.7, 52.5; HRMS (EI) Calcd. for $C_{20}H_{19}NO_4$ (M^+) 337.1314. Found 337.1312; mp 122 °C.

2-(4-Methoxyphenyl)-1-(2-phenylethynyl)-1,2-dihydroisoquinoline (2j)

White thin needle; IR (KBr) 3061, 2997, 2833, 1616, 1564, 1510, 1489, 1456, 1350, 1294, 1178, 1128, 1040, 829, 768 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.36 – 7.33 (m, 2H), 7.26 – 7.10 (m, 9H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.57 (d, *J* = 7.3, 1H), 5.90 (s, 1H), 5.86 (d, *J* = 7.3 Hz, 1H), 3.82 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 155.0, 139.2, 131.7, 131.3, 130.7, 128.1, 128.0, 127.5, 125.8, 125.7, 123.6, 122.7, 118.6, 114.6, 103.1, 87.9, 84.9, 55.6, 52.2 (one carbon sp^2 missing due to overlapping); HRMS (ESI) Calcd. for $C_{24}H_{19}NO$ ($[M + Na]^+$) 360.1359. Found 360.1359; mp 154 °C.

2-Allyl-3-Butyl-1-trichloromethyl-1,2-dihydroisoquinoline (2k)

Yellow oil; IR (neat) 2956, 2933, 1625, 1488, 1172, 777, 736, 613 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, *J* = 7.60 Hz, 1H), 7.30 (dt, *J* = 7.56, 1.24 Hz, 1H), 7.15 (dt, *J*= 7.32, 1.20 Hz, 1H), 7.05 (d, *J* = 7.56 Hz, 1H), 5.66 (s, 1H), 5.66 – 5.58 (m, 1H), 4.98 (s, 1H), 4.97 (ddd, *J* = 17.36, 2.92, 1.48 Hz, 1H), 4.85 (ddd, *J* = 17.32, 2.92, 1.48 Hz, 1H), 4.36 (dddd, *J* = 17.60, 4.40, 4.40, 1.68 Hz, 1H), 3.92 (ddt, *J* = 17.80, 5.36, 1.48 Hz, 1H), 2.46 (ddd, *J* = 14.04, 9.00, 5.36 Hz, 1H), 2.18 (ddd, *J* = 16.20, 9.28, 7.08 Hz, 1H), 1.72 – 1.60 (m, 2H), 1.53 – 1.37 (m, 2H), 0.97 (t, *J* = 7.32 Hz, 3 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 144.5, 135.0, 134.2, 129.7, 128.7, 124.2, 123.2, 121.9, 115.9, 106.2, 103.9, 76.6, 56.1, 33.2, 30.1, 22.6, 13.9; HRMS (ESI) Calcd. for $C_{17}H_{20}Cl_3N$ ($[M + H]^+$) 364.0426. Found 364.0421.

2-Allyl-3-phenyl-1-trichloromethyl-1,2-dihydroisoquinoline (2l)

Yellow oil; IR (neat) 3389, 3064, 3026, 2922, 1493, 1460, 1205, 843, 797, 752 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.72 – 7.68 (m, 2H), 7.46 – 7.39 (m, 5H), 7.29 – 7.22 (m, 2H), 6.14 (s, 1H), 5.54 (m, 1H), 5.10 z(s, 1H), 4.97 (dd, *J* = 1.96, 0.72 Hz, 1H), 4.93 (dd, *J* = 1.96 , 0.72 Hz, 1H), 4.09 (ddt, *J* = 16.08, 4.88, 1.78Hz, 1H), 3.81 (ddd, *J* = 16.12, 7.08, 1.90 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 145.2, 137.4, 134.6, 133.9, 130.2, 128.9, 128.5, 127.9, 125.5, 124.4, 123.2, 117.2, 108.7, 108.6, 105.6, 74.6, 58.1; HRMS (ESI) Calcd. for $C_{19}H_{16}Cl_3N$ ($[M + H]^+$) 344.0739, Found 344.0734.

Preparation of methyl 2-phenyl-1,2-dihydroisoquinoline-1-carboxylate (8)

To a solution of **2a** (66 mg, 0.2 mmol) in toluene (2.0 mL) were added MeOH (10 mL) and a solution of $AgNO_3$ (207 mg, 1.22 mmol) in deionized water (1.0 mL), successively, under Ar atmosphere. The resulting mixture was stirred at rt for 24 h, then a saturated aqueous $NaHCO_3$ was added. The mixture was extracted with Et_2O three times. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to leave the crude product, which was purified by flash silica gel column chromatography using hexane and EtOAc (4:1) as an eluent to give **8** in 67 % yield. Colorless solid; IR (film) 3064, 2930, 2830, 1692, 1491, 1254, 1127, 1001, 908 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.71 – 7.61 (m, 1H), 7.52 – 7.44 (m, 1H), 7.43 – 7.33 (m, 4H), 7.32 – 7.22 (m, 3H), 6.59 (brd, *J* = 9.0 Hz, 1H), 6.41 (brd, *J* = 9.0 Hz, 1H), 4.63 (br, 1H), 3.67 (br, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz, 333 K) δ 166.1, 140.8, 133.8, 131.0, 128.82, 128.77, 127.3, 127.2, 126.9, 126.6 (two carbons), 124.6, 116.8, 81.5, 58.0; *Anal.* Calcd for $C_{17}H_{15}NO_2$, C: 76.96, H: 5.70, N: 5.28, Found C:76.71, H: 5.75, N: 5.26; LRMS (MALDI) Calcd. for $C_{17}H_{15}NNaO_2$ ($[M + Na]^+$) 288.0995. Found 288.1129.

Preparation of 2-(4-methoxyphenyl)-1,2-dihydroisoquinoline (9)

To a solution of **2h** (296 mg, 1.0 mmol) in MeOH (10 mL) was added $NaBH_4$ (37.8 mg, 1.0 mmol) at 0 ºC. After the mixture was stirred for 40 min under rt, a saturated aqueous NH_4Cl was added and the mixture was extracted with Et_2O three times. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to leave the crude product, which was purified by basic silica gel column chromatography using hexane and EtOAc (10:1) as an eluent to give **9** (235 mg, 0.99 mmol) in 99 % yield. Colorless solid; IR (film) 3070, 2950, 2834, 1625, 1509, 1284, 1254, 1036 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.24 – 7.13 (m, 1H), 7.10 – 7.03 (m, 1H), 7.02 – 6.94 (m, 4H), 6.93 – 6.87 (m, 2H), 6.57 (d, *J* = 7.6 Hz, 1H), 5.61 (d, *J* = 7.6 Hz, 1H), 4.80 (s, 2H), 3.80 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 154.4, 139.8, 132.9, 132.7, 127.5, 127.3, 125.5, 125.3, 122.9, 117.2, 114.5, 101.8, 55.6, 50.3; HRMS (ESI) Calcd. for $C_{16}H_{14}NO$ ($[M - H]^+$) 236.1070. Found 236.1069.

Preparation of 1-(Trichloromethyl)-1,2,3,4-tetrahydroisoquinoline (10)

To a solution of **2b** (514 mg, 1.45 mmol) in THF (100 mL) were added hydrogen chloride (5.8 mL, 2M solution of Et_2O, 11.6 mmol) and sodium cyanoborohydride (911 mg, 14.5 mmol) at 0 °C. After the mixture was stirred for 3 h at rt, a saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with Et_2O three times. The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated to leave the crude product, which was passed through a short pad of basic silica gel using Et_2O as an eluent to give 2-phenyl-1-trichloromethyl-1,2,3,4-tetrahydro-isoquinoline. Without further purification, it was dissolved in MeCN (18 mL) and a solution of CAN (1.83 g, 3.34 mmol) in water (18 mL) was slowly added at -48 °C. The mixture was allowed to warm to ambient temperature over a period of 30 min and saturated aqueous sodium sulfite was added. The mixture was extracted with Et_2O three times. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was transferred to basic silica gel column chromatography using a mixture of hexane and Et_2O (4:1) as an eluent to give **10** (277 mg, 1.11 mmol) in 76% yield as an overall yield from **2b**. Yellow oil; IR (neat) 3389, 3064, 3026, 2922, 1493, 1460, 1205, 843, 797, 752 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1H), 7.20 (m, 2H), 4.83 (s, 1H), 3.57 (quintet, *J* = 5.4 Hz, 1H), 3.11 (m, 1H), 2.99 (m, 1H), 2.81 (dt, *J* = 15, 5.1 Hz, 1H), 2.77 (br, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 138.5, 130.7, 130.3, 128.7, 128.2, 125.1, 107.1, 71.0, 40.5, 29.8; HRMS (ESI) Calcd. for $C_{10}H_{10}Cl_3N$ ($[M + H]^+$) 249.9952. Found 249.9952.

ACKNOWLEDGEMENTS

This work was supported in part by a Grant-in-Aid from the Sumitomo Foundation.

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