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An Environmentally Friendly Synthetic Method of 1,2-Dihydroisoquinoline Frameworks via Three-Component Reaction with *o*-Alkynylbenzaldehydes, Primary Amines, and Pronucleophiles

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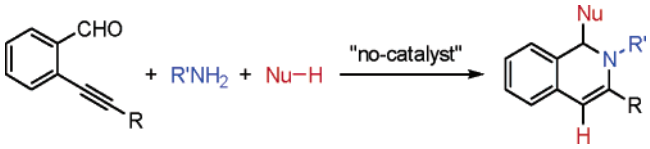
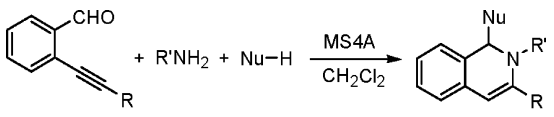
ABSTRACT



Three-component reactions with *ortho*-alkynylbenzaldehydes, primary amines, and pronucleophiles (Nu-H), such as $CHCl_3$, proceeded to give 1,2-dihydroisoquinoline derivatives in good to high yields in the absence of any catalysts under mild reaction conditions.

The multicomponent reaction is one of the most efficient synthetic methods for organic molecules.[1] The strategy offers significant advantages over classical step-by-step approaches allowing the formation of several bonds and the construction of complex molecular architectures from simple precursors in a single synthetic operation without the need for isolation of intermediates. In this paper, we wish to report a novel synthetic method of 1,2-dihydroisoquinoline derivatives **2** via the three-component reaction using *o*-alkynylbenzaldehydes **1**, primary amines, and pronucleophiles (Nu-H) under mild reaction conditions *without any catalysts* (Scheme 1).

Scheme 1



1 **2**

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

(1) For reviews, see: (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602−1634. (c) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekenth, A. R.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899−907. (d) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471−1499. (e) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101−4111. (f) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (g) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, 3321−3329. (h) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366−374.

(2) Asao, N.; Yudha S., S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526−5528.

(3) For other synthetic methods of 1,2-dihydroisoquinolines from *o*-alkynylarylaldimines, see: (a) Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339−7341. (b) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3822−3825.

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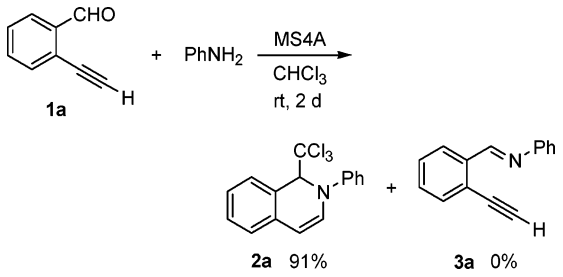
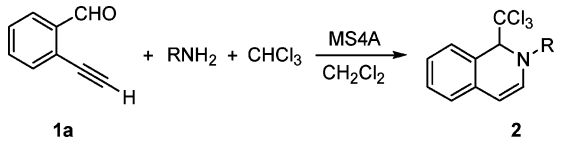
Scheme 2



sole product (Scheme 2). This result clearly indicated that (1) **2a** was formed from **3a**, (2) chloroform worked as a pronucleophile unexpectedly, 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.[4] Therefore, this result prompted us to investigate this 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 shown in Scheme 2 (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 the $CHCl_3$. Therefore, we decided to use CH_2Cl_2 as a solvent for diminishing the amount of pronucleophile (i.e. $CHCl_3$). To know the generality of this reaction, we next examined the reactions using various kinds of amines instead of aniline. When *p*-anisidine was used, the reaction proceeded smoothly and the corresponding product **2b** was obtained in 91% yield (entry 3). Although *p*-trifluoromethylphenylamine can be used for the present reaction, the reaction was sluggish and 6 d were needed for completion (entry 4). It was found that the reactions with aliphatic amines proceeded faster than those with aromatic amines (entries 5−7). The reaction proceeded well even with sterically bulky *tert*-butylamine (entry 8).[5] To know whether MS4A is essential or not, we conducted the reaction in the absence of MS4A. Although the reaction needed longer time for completion, the desired product **2g** was obtained in high yield even without MS4A (entry 9). This result suggests that MS4A promotes the imine formation from aldehyde **1a** and amines as a dehydrating agent, but it is not essential for the construction of dihydroisoquinoline frameworks.

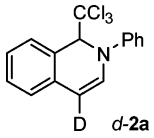
Table 1. Three-Component Reactions with **1a**, Amines, and Chloroform[a]



entry	R	reaction time (d)	**2**	yield (%)[b]
1[c]	Ph	2	**2a**	91
2	Ph	2	**2a**	87
3	*p*-$MeOC_6H_4$	1.5	**2b**	91
4	*p*-$CF_3C_6H_4$	6	**2c**	76
5	$PhCH_2$	0.8	**2d**	72
6	CH_2=$CHCH_2$	0.4	**2e**	89
7	C_4H_9	0.3	**2f**	77
8	*t*-C_4H_9	0.5	**2g**	96
9[d]	*t*-C_4H_9	1.2	**2g**	93

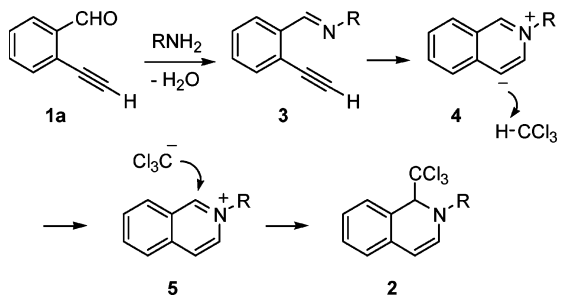
[a] Reactions were carried out with **1a** (1 equiv), amine (1 equiv), and $CHCl_3$ (5 equiv) in the presence of MS4A in CH_2Cl_2 at room temperature unless otherwise mentioned. [b] Isolated yields. [c] Reaction was conducted in $CHCl_3$ as a solvent instead of CH_2Cl_2. [d] Reaction was performed without MS4A.

When the reaction was examined with use of $CDCl_3$ under the same reaction conditions, the deuterated product *d*-**2a**



was obtained in 89% yield in which D content was 98% 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 3. At the beginning, the imine **3** would be formed from **1a** and amine. Nucleophilic attack of the imine nitrogen to the alkyne would form the twitterionic 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**.[6] One might think of another possibility that amine might promote the reaction by abstraction of a proton from

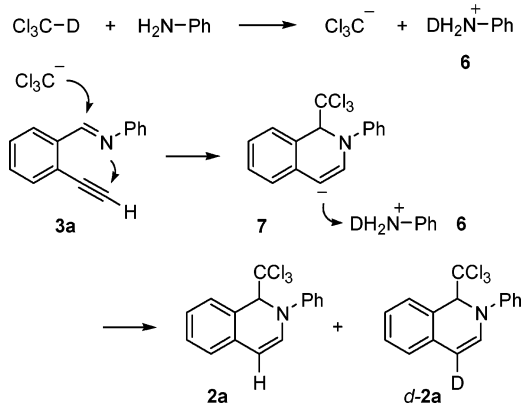
Scheme 3



(4) For recent examples with $CHCl_3$ as a nucleophile, see: (a) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329−16332. (b) Habay, S. A.; Schafmeister, C. E. *Org. Lett.* **2004**, *6*, 3369−3371. (c) Aggarwal, V. K.; Mereu, A. *J. Org. Chem.* **2000**, *65*, 7211−7212 and references therein.

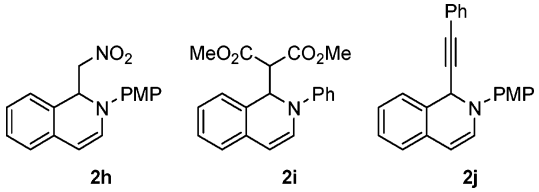
chloroform and the resulting counteranion (Cl_3C^-) would work as a nucleophile. However, if the reaction proceeds along this mechanism in the deuteration experiment, **2a** should be produced predominantly over *d*-**2a** because **6** has proton and deuterium on the nitrogen atom in a 2:1 ratio as shown in Scheme 4. Since the deuteration experiment was

Scheme 4



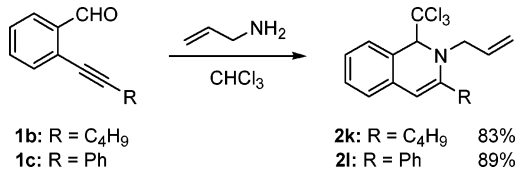
carried out with 1 equiv of aniline against **1a**, it might be possible to consider that most of the aniline would react with **1a** to form imine **3a** and only the remaining small amount of aniline might work as a catalyst. In that case, due to the formation of the deuterated aniline ($PhND_2$), which would be formed by repeating the abstraction of deuterium from $CDCl_3$, selective formation of *d*-**2a** might 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 our proposed mechanism as shown in Scheme 3.

To explore the scope of the present reaction, we examined reactions using other pronucleophiles instead of $CHCl_3$, such as nitromethane, dimethyl malonate, and phenylacetylene. All of reactions using these pronucleophiles completed within 2 d at room temperature and the corresponding products, **2h**−**j**, were obtained in 78%, 59%, and 72% yields, respectively.



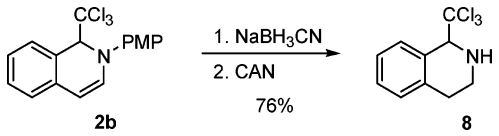
We next examined the three-component reaction using substrates having substituents at the terminus of the alkyne part. When the reaction of **1b**, having a butyl group, was carried out with allylamine and chloroform in CH_2Cl_2 at room temperature, the reaction was very sluggish and only a trace amount of product was obtained. However, the reaction proceeded in $(CH_2Cl)_2$ at 70 °C for 0.9 d and the corresponding product **2k** was obtained in 83% yield. The reaction of **1c**, having a phenyl group, also gave **2***l* in 89% yield under similar conditions (70 °C for 0.8 d) (Scheme 5).

Scheme 5



The obtained products would be useful as precursors of tetrahydroisoquinoline alkaloids.[7] For instance, **2b** was converted to **8** in 76% yield in two steps (Scheme 6).

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., *o*-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.

Supporting Information Available: Spectroscopic and analytical data for **2a**−***l*** and **8**, and the procedure for the synthesis of **2** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Larock and co-workers have reported the palladium-catalyzed synthetic methods of isoquinolines using *o*-alkynylarylaldimines, having a *tert*-butyl group on the nitrogen atom, see: (a) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980−988. (b) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920−928. (c) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042−7047. (d) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437−3444. (e) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86−94. (f) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042−8051. (g) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553−556.

(6) Addition of chloroform to quaternary protoberberine alkaloids was reported, see: Marek, R.; Sečkářová, P.; Hulová, D.; Marek, J.; Dostál, J.; Sklenář, V. *J. Nat. Prod.* **2003**, *66*, 481−486.

(7) For reviews, see: (a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341−3370. (b) Bentley, K. W. *Nat. Prod. Rep.* **2004**, *21*, 395−424. (c) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669−1730.