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AgOTf-catalyzed one-pot reaction of 2-alkynylbenzaldehyde, amine, and sodium borohydride

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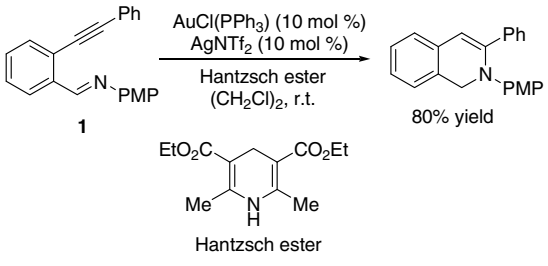
Abstract

One-pot reactions of 2-alkynylbenzaldehydes, amines, and sodium borohydride catalyzed by AgOTf under mild conditions provide a facile protocol for the concise synthesis of 1,2-dihydroisoquinoline derivatives.

Keywords: 2-Alkynylbenzaldehydes; Amine; 1,2-Dihydroisoquinoline; Silver triflate; Sodium borohydride

As a privileged scaffold, 1,2-dihydroisoquinoline is found in many natural products and pharmaceuticals that exhibit remarkable biological activities.[1,2] Significant effort continues to be given to the development of new 1,2-dihydroisoquinoline-based structures and new methods for their construction.[3–6] Recently, metal-catalyzed 6-*endo*-mode cyclization of 2-(1-alkynyl)arylaldimine is reported as a powerful synthetic tool for the synthesis of isoquinolines and 1,2-dihydroisoquinolines.[3,4] Among these, various nucleophiles, such as alkynes, allylstannanes, silyl enol ethers, and active methylene compounds, have been employed in the Lewis acid catalyzed reaction of 2-(1-alkynyl)arylaldimine, leading to 1,2-dihydroisoquinoline derivatives.[3] Takemoto also investigated the cyclization of 2-(1-alkynyl)arylaldimine accompanied by hydride reduction of the iminium intermediate using various reducing agents.[3a] It was found that the use of Et_3SiH was not effective for this purpose in the presence of different Lewis acid catalysts, and the desired cyclic adduct could be obtained in 80% yield by the reaction of 2-(1-alkynyl)arylaldimine **1** with 2 equiv of Hantzsch ester[7] in the presence of $AuCl(PPh_3)/AgNTf_2$ catalyst (10 mol %) (Scheme 1).[8] However, in this reaction, expensive Hantzsch ester and catalyst with high catalytic loading has to be utilized in order to obtain a respectable yield. Moreover, the starting material 2-alkynylarylaldimine **1** should be prepared in advance via condensation of the corresponding aldehyde and amine. Thus, it is highly desired to develop more effective and practical synthetic methodology using reducing agent for 1,2-dihydroisoquinoline formation. Recently, we described that the functionalized 1,2-dihydroisoquinolines could be formed via multi-component reactions of



Scheme 1.

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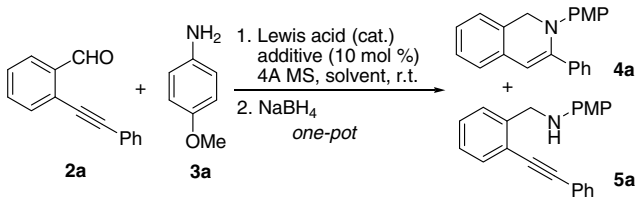
2-(1-alkynyl)benzaldehydes, amines, and diethyl phosphite or organozinc reagents.[9] Prompted by these results, we envisioned that one-pot cyclization of 2-(1-alkynyl)benzaldehydes, in the presence of amines and reducing agent may be possible via hydride reduction, as reported herein.

The reaction was initially studied with 2-alkynylbenzaldehydes **2a**, which was selected as suitable substrate for reaction development. We found that, in the presence of silver triflate as catalyst and sodium borohydride as the hydride source, the reaction of 2-alkynylbenzaldehydes **2a** with *p*-anisidine **3a** in EtOH afforded the desired product **4a** in 56% yield (Table 1, entry 1). Following an extensive investigation, we observed that the result could be dramatically improved in the presence of proline as additive (88% yield, Table 1, entry 2). Inferior results were displayed when other Lewis acids were employed in the reaction. For instance, only 34% yield of product **4a** accompanied with 48% of product **5a** was obtained when CuI was used as the catalyst (Table 1, entry 3). Similar results were generated while other Lewis acids such as $Cu(OTf)_2$, $Zn(OTf)_2$, $In(OTf)_3$, $Dy(OTf)_3$, and $FeCl_3$ were utilized in the reaction (Table 1, entries 4–8). These results indicated that AgOTf is the most efficient catalyst for this kind of transformation and only product **4a** was detected in the reaction. Further screening revealed that ethanol is the solvent of choice. Other solvents such as dichlorometahne, DCE, and MeCN gave unsatisfactory results (Table 1, entries 9–11). Lower yield was obtained when pyrrolidine or acetic acid was used as additive instead of proline (Table 1, entries 12 and 13). Similar yield was observed when the catalytic amount of AgOTf was reduced to 2–5 mol % (Table 1, entries 14 and 15). However, the reaction was retarded when 0.1 mol % of AgOTf was employed in the reaction (data not shown in Table 1). AgOTf is demonstrated crucial for the reaction. Without AgOTf, only 13% yield of product **4a** was obtained in the presence of proline (Table 1, entry 16), while product **5a** was generated in the absence of proline (62% yield, Table 1, entry 17). Increasing amount of proline could not improve the result (76% yield, Table 1, entry 18). Slightly lower yield of desired **4a** was observed without the addition of molecular sieves (78% yield, Table 1, entry 19).

To explore the scope of the reaction, a set of substrates were subjected to the reaction under optimized conditions (AgOTf (2–5 mol %), proline (10 mol %), 4 Å MS, ethanol, room temperature), and the results are summarized in Table 2. Complete conversion and moderate to good isolated yields were observed for most of cases utilized. For the reactions of 2-alkynylbenzaldehydes **2a** with anilines, better results were obtained when anilines with electron-donating groups attached on the aromatic ring were employed. For example, 2-alkynylbenzaldehyde **2a** reacted with 2-methoxybenzeneamine **3c** leading to the corresponding product **4c** in 80% yield (Table 2, entry 3), while 56% yield of product **4f** was afforded when 4-chlorobenzeneamine **3f** was used in the reaction (Table 2, entry 6).

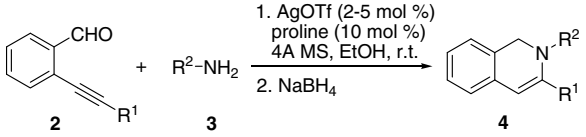
Table 1
Screening conditions for the reaction of alkynylbenzaldehydes **2a**, *p*-anisidine **3a** with sodium borohydride



Entry	Lewis acid	Additive	Solvent	Yield[a] (%)	
				4a	**5a**
1	AgOTf (10 mol %)	—	EtOH	56	—
2	AgOTf (10 mol %)	Proline	EtOH	88	—
3	CuI (10 mol %)	Proline	EtOH	34	48
4	$Cu(OTf)_2$ (10 mol %)	Proline	EtOH	36	16
5	$Zn(OTf)_2$ (10 mol %)	Proline	EtOH	18	42
6	$In(OTf)_3$ (10 mol %)	Proline	EtOH	11	16
7	$Dy(OTf)_3$ (10 mol %)	Proline	EtOH	23	37
8	$FeCl_3$ (10 mol %)	Proline	EtOH	18	42
9	AgOTf (10 mol %)	Proline	CH_2Cl_2	43	—
10	AgOTf (10 mol %)	Proline	$(CH_2Cl)_2$	47	—
11	AgOTf (10 mol %)	Proline	MeCN	59	—
12	AgOTf (10 mol %)	Pyrrolidine	EtOH	56	—
13	AgOTf (10 mol %)	AcOH	EtOH	62	—
14	AgOTf (5 mol %)	Proline	EtOH	88	—
15	AgOTf (2 mol %)	Proline	EtOH	87	—
16	—	Proline	EtOH	13	—
17	—	—	EtOH	—	62
18[b]	AgOTf (10 mol %)	Proline	EtOH	76	—
19[c]	AgOTf (10 mol %)	Proline	EtOH	78	—

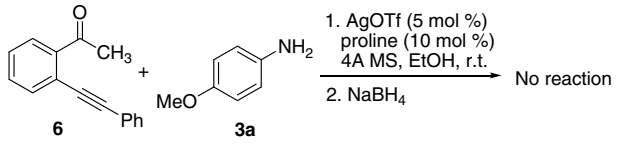
[a] Isolated yield based on 2-alkynylbenzaldehydes **2a**.
[b] In the presence of 30 mol % of proline.
[c] Without molecular sieves.

Table 2
AgOTf-Catalyzed one-pot reactions of 2-alkynylbenzaldehydes **2**, amines **3**, and sodium borohydride[10]



Entry	R^1	R^2	Product	Yield[a] (%)
1	C_6H_5 (**2a**)	4-$MeOC_6H_4$ (**3a**)	**4a**	88
2	C_6H_5 (**2a**)	3-$MeOC_6H_4$ (**3b**)	**4b**	75
3	C_6H_5 (**2a**)	2-$MeOC_6H_4$ (**3c**)	**4c**	80
4	C_6H_5 (**2a**)	4-MeC_6H_4 (**3d**)	**4d**	80
5	C_6H_5 (**2a**)	C_6H_5 (**3e**)	**4e**	96
6	C_6H_5 (**2a**)	4-ClC_6H_4 (**3f**)	**4f**	56
7	C_6H_5 (**2a**)	4-FC_6H_4 (**3g**)	**4g**	60
8	C_6H_5 (**2a**)	3-$NO_2C_6H_4$ (**3h**)	**4h**	73
9	C_6H_5 (**2a**)	3-$CF_3C_6H_4$ (**3i**)	**4i**	67
10	C_6H_5 (**2a**)	$C_6H_5CH_2$ (**3j**)	**4j**	Trace
11	C_6H_5 (**2a**)	*n*-Hexyl (**3k**)	**4k**	Trace
12	4-$MeOC_6H_4$ (**2b**)	4-$MeOC_6H_4$ (**3a**)	**4l**	90
13	4-$MeOC_6H_4$ (**2b**)	C_6H_5 (**3e**)	**4m**	73
14	4-$MeOC_6H_4$ (**2b**)	4-FC_6H_4 (**3g**)	**4n**	94
15	Cyclopropyl (**2c**)	4-$MeOC_6H_4$ (**3a**)	**4o**	Trace

[a] Isolated yield based on 2-alkynylbenzaldehydes **2**.



Scheme 2.

Although anilines worked well in this reaction, only a trace amount of product was observed when aliphatic amines, such as benzylamine and *n*-hexylamine, were utilized in the reactions of 2-alkynylbenzaldehyde **2a** (Table 2, entries 10 and 11). The R^1 attached on the alkynyl group is also important in this kind of transformation. When 4-methoxyphenyl group was used as the replacement of phenyl group in substrate **2**, good yields were generated despite *p*-anisidine **3a** or 4-fluorobenzeneamine **3g** was employed in the reaction (Table 2, entries 12 and 14). However, to our surprise, only a trace amount of product was detected when R^1 was changed to cyclopropyl group due to the stability of the product (Table 2, entry 15). Formyl group in substrate **2** is crucial in this reaction. When formyl group was replaced by acetyl group (Scheme 2), no reaction occurred at all which was presumably due to the instability of formed imine in situ.

In summary, we have described AgOTf-catalyzed one-pot reactions of 2-alkynylbenzaldehydes, amines, and sodium borohydride under mild conditions, which provide a facile and efficient protocol to facilitate the concise synthesis of 1,2-dihydroisoquinoline derivatives. We believe that this method provides an excellent complement to the 1,2-dihydroisoquinoline synthesis. The advantages of this method include the use of inexpensive reagent and catalyst under mild conditions, and experimentally operational ease.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.143.

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10. *General procedure*: A solution of 2-alkynyl benzaldehyde **2** (0.30 mmol, 1.0 equiv), amine **3** (0.30 mmol, 1.0 equiv), AgOTf (2–5 mol %), proline (10 mol %), 4A MS (30 mg) in C_2H_5OH (3.0 mL) was stirred at room temperature under N_2 for 8 h, then $NaBH_4$ (2.0 equiv) was added and the reaction mixture was stirred for another 5 min. The reaction solvent was evaporated and the residue was purified on silica gel to afford the corresponding product **4**. Selected example: 2-(4-Methoxyphenyl)-3-phenyl-1,2-dihydroisoquinoline (**4a**), colorless liquid, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 4.86 (s, 2H), 6.49 (s, 1H), 6.61 (d, $J = 8.8$ Hz, 2H), 6.79 (d, $J = 8.8$ Hz, 2H), 6.97 (d, $J = 7.3$ Hz, 1H), 7.10 (dt, $J = 2.0$, 7.3 Hz, 1H), 7.16–7.23 (m, 5H), 7.49 (d, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 56.0, 110.6, 113.8, 123.4, 123.9, 124.8, 126.1, 127.2, 127.8, 127.9, 128.1, 128.5, 133.7, 137.2, 140.5, 144.2, 154.6. IR (film): 3047, 2924, 1601, 1508, 1452, 1383, 1244, 1035, 763 cm^{-1}; HRMS calcd for $C_{22}H_{19}NO$: 313.1467; found, 313.1475.