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Efficient Iron-Catalyzed Synthesis of Polysubstituted 1,2-Dihydropyridine Derivatives[1]

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Abstract—A simple ligand-free cyclization of propargylic alcohols with enaminones has been developed by using $FeBr_3$ as catalyst. This reaction provides an easy and convenient method to synthesize polysubstituted 1,2-dihydropyridine derivatives.

Keywords: iron(III) bromide, ligand-free, dihydropyridine, cyclization, catalysis

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1,2-Dihydropyridine and 1,4-dihydropyridine derivatives are important substructures of many biologically active compounds, including natural products and pharmaceuticals [1–6]. Compared to 1,4-dihydropyridine derivatives [7–12], the synthesis of 1,2-dihydropyridines is more difficult [13, 14]. In 2012, Ohmura and Suginome have described an efficient method for dearomatization of pyridines to prepare 1,2-dihydropyridines through rhodium-catalyzed hydroboration [15]. Later, Li and coworkers reported $BF_3{\cdot}Et_2O$-catalyzed reaction of enaminones with propargylic alcohols to synthesize 1,4-dihydropyridines with moderate to good yields [16]. In 2014, Wan and Liu developed tunable three-component reactions of enals, electron deficient alkynes, and primary amines for selective synthesis of 1,2-dihydropyridines [17]. Recently, Tejedor and García-Tellado found a practical metal-free protocol for the synthesis of 1,2-dihydropyridines from propargyl vinyl ethers and primary amines [18].

Although there is some progress in this area [13–19], the above reactions usually require harsh conditions (high temperature) and expensive starting materials and catalyst. Herein, we report a simple ligand-free cyclization of propargylic alcohols with enaminones using $FeBr_3$ as catalyst. This reaction provides an easy and convenient method to synthesize polysubstituted 1,2-dihydropyridine derivatives (Scheme 1).

[1] The text was submitted by the authors in English.

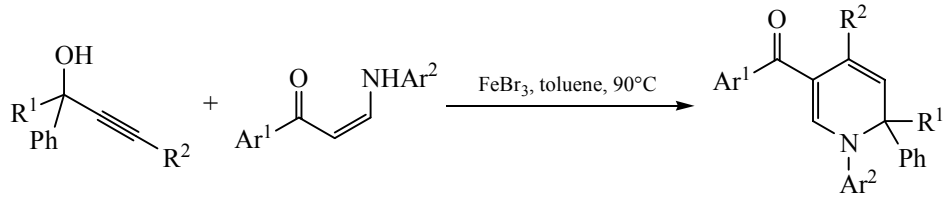
At the beginning, copper(I) iodide was selected to catalyze the reaction between propargyl alcohol (**1a**) and (*Z*)-1-phenyl-3-(phenylamino)prop-2-en-1-one (**2a**). However, no reaction occurred. When $Cu(OAc)_2$

Table 1. Synthesis of phenyl(1,4,6,6-tetraphenyl-1,6-dihydropyridin-3-yl)methanone (**3a**) from 1,1,3-triphenylprop2-yn-1-ol (**1a**) and 1-phenyl-3-(phenylamino)prop-2-en-1-one (**2a**) in different solvents in the presence of different catalysts[a]

Run no.	Catalyst	Solvent	Yield of **3a**,[b] %
1	CuI	Toluene	<5
2	CuCl	Toluene	8
3	$Cu(OAc)_2$	Toluene	12
4	$FeCl_2$	Toluene	62
5	$FeCl_3$	Toluene	68
6	$FeBr_3$	Toluene	78
7	$FeBr_3$	Benzene	67
8	$FeBr_3$	DCE	73
9	$FeBr_3$	THF	41
10	$FeBr_3$	DMF	<5
11	–	Toluene	<5

[a] Conditions: **1a**, 0.5 mmol; **2a**, 0.55 mmol; catalyst, 10 mol %; solvent, 2 mL; 90°C. 6 h.
[b] Isolated yield based on **1a**.

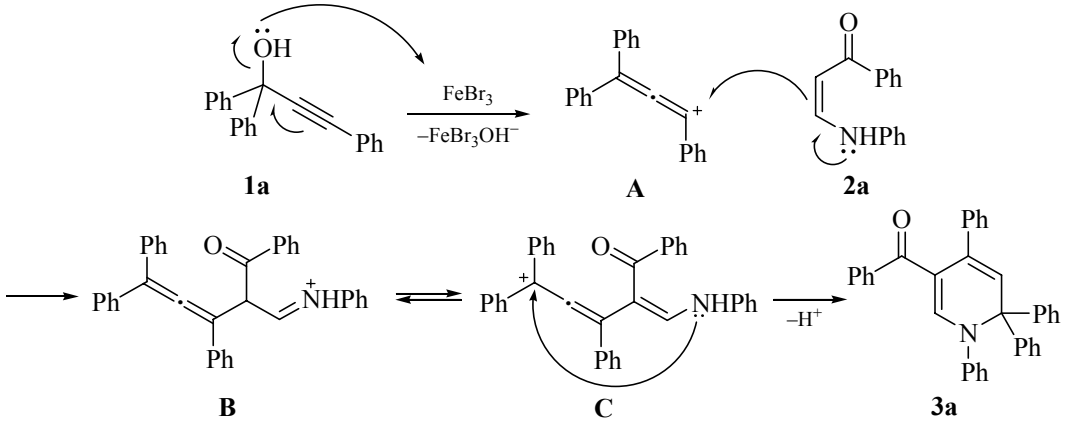
Scheme 1.



1a–1c **2a–2g** **3a–3j**

1, $R^1 = R^2 =$ Ph (**a**), $R^1 =$ Me, $R^2 =$ Ph (**b**), $R^1 =$ Ph, $R^2 =$ H (**c**); **2**, $Ar^1 = Ar^2 =$ Ph (**a**), $Ar^1 =$ Ph, $Ar^2 = 4\text{-MeOC}_6H_4$ (**b**), $Ar^1 =$ Ph, $Ar^2 = 4\text{-ClC}_6H_4$ (**c**), $Ar^1 =$ Ph, $Ar^2 = 3\text{-ClC}_6H_4$ (**d**), $Ar^1 = 4\text{-ClC}_6H_4$, $Ar^2 =$ Ph (**e**), $Ar^1 = Ar^2 = 4\text{-ClC}_6H_4$ (**f**), $Ar^1 =$ Ph, $Ar^2 = 4\text{-BrC}_6H_4$ (**g**); for R^1, R^2, Ar^1, Ar^2 in **3**, see Table 2.

Scheme 2.



was used as catalyst, the desired product was obtained in 12% yield (Table 1, run no. 3). The yield of **3a** was improved to 62% when the catalyst was changed to $FeCl_2$ (Table 1, run no. 4). Encouraged by this result, different catalysts were tested in this reaction. The results revealed that $FeBr_3$ was the best catalyst (Table 1, run no. 6). Next, the effect of the solvent was also checked for get higher yield of the product. Solvent experiments showed that toluene was superior to other solvents. Thus, the best reaction conditions were found (Table 1, run no. 6). It should be noted that the reaction could not happen without iron catalyst (Table 1, run no. 11).

With the optimal conditions in hands, the scope of iron-catalyzed cyclization of propargylic alcohols with enaminones was also examined. Generally, this reactions work well, and the desired products were isolated in moderate to good yields. Electron-donating group in the aromatic ring gave a higher yield than electron-withdrawing group (Table 2; run nos. 3, 4). The best result (yield 82%) was achieved with enaminone **IIb** having a 4-methoxyphenyl group on the nitrogen.

In addition, a possible reaction mechanism for the iron-catalyzed cyclization of propargylic alcohols with enaminones was proposed based on the earlier work [16]. Initially, propargylic alcohol **1a** reacts with $FeBr_3$ to form intermediate **A** which takes up enaminone **2a** to produce intermediate **B**. Isomerization of the latter gives intermediate **C** which undergoes intramolecular cyclization to final product **3a** (Scheme 2).

In summary, a simple and convenient ligand-free procedure has been developed for the synthesis of polysubstituted 1,2-dihydropyridine derivatives via cyclization of propargylic alcohols with enaminones in the presence of $FeBr_3$ as catalyst. A probable reaction mechanism has also been proposed. Further investigation on the scope of this reaction is now in progress.

EXPERIMENTAL

All solvents were dried and purified by known procedures and were distilled under nitrogen over appropriate drying agents prior to use. The products were isolated by column chromatography on silica gel

Table 2. Synthesis of dihydropyridines **3a**–**3j** from propargylic alcohols **1a**–**1c** and enaminones **2a**–**2g** in the presence of $FeBr_3$[a]

Run no.	Initial reactants	R^1	R^2	Ar^1	Ar^2	Product	Yield,[b] %
1	**1a**, **2a**	Ph	Ph	Ph	Ph	**3a**	78
2	**1b**, **2a**	Me	Ph	Ph	Ph	**3b**	76
3	**1b**, **2b**	Me	Ph	Ph	4-$MeOC_6H_4$	**3c**	82
4	**1b**, **2c**	Me	Ph	Ph	4-ClC_6H_4	**3d**	77
5	**1b**, **2d**	Me	Ph	Ph	3-ClC_6H_4	**3e**	75
6	**1b**, **2e**	Me	Ph	4-ClC_6H_4	Ph	**3f**	68
7	**1b**, **2f**	Me	Ph	4-ClC_6H_4	4-ClC_6H_4	**3g**	71
8	**1b**, **2g**	Me	Ph	Ph	4-BrC_6H_4	**3h**	73
9	**1a**, **2c**	Ph	Ph	Ph	4-ClC_6H_4	**3i**	69
10	**1c**, **2d**	Ph	H	Ph	3-ClC_6H_4	**3j**	<5

[a] Conditions: **1a**, 0.5 mmol; **2a**, 0.55 mmol; $FeBr_3$, 10 mol %; toluene, 2 mL; 90°C. 6 h.
[b] Isolated yield based on **1**.

(200–300 or 100–200 mesh) using ethyl acetate and petroleum ether as eluents. The progress of reactions and the purity of products were routinely monitored by TLC using SiO_2 plates, and spots were visualized under UV light. The ^{1}H NMR spectra were recorded on a Bruker Avance III 600 (600 MHz) spectrometer using $CDCl_3$ as a solvent and tetramethylsilane as reference.

Phenyl(1,4,6,6-tetraphenyl-1,6-dihydropyridin-3-yl)methanone (3a). Iron(III) bromide (10 mol %) was added at room temperature to a mixture of propargylic alcohol **1a** (0.50 mmol) and enaminone **2a** (0.55 mmol) in toluene (2 mL), and the mixture was stirred for 6 h at 90°C. When the reaction was complete, the solvent was distilled off, and the residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 10, by volume) as eluent. ^{1}H NMR spectrum, δ, ppm: 7.67 s (1H), 7.47–7.38 m (5H), 7.34–6.90 m (20H), 5.63 s (1H).

(6-Methyl-1,4,6-triphenyl-1,6-dihydropyridin-3-yl)(phenyl)methanone (3b). ^{1}H NMR spectrum, δ, ppm: 7.68 d (2H, *J* = 5.4 Hz), 7.54 d (2H, *J* = 6.0 Hz), 7.43–7.10 m (15H), 6.94–6.80 m (2H), 5.19 s (1H), 1.82 s (3H).

[1-(4-Methoxyphenyl)-6-methyl-4,6-diphenyl-1,6-dihydropyridin-3-yl](phenyl)methanone (3c). ^{1}H NMR spectrum, δ, ppm: 7.66 d (2H, *J* = 6.6 Hz), 7.54 d (2H, *J* = 7.2 Hz), 7.42–7.12 m (12H), 6.81–6.62 m (4H), 5.17 s (1H), 3.73 s (3H), 1.78 s (3H).

[1-(4-Chlorophenyl)-6-methyl-4,6-diphenyl-1,6-dihydropyridin-3-yl](phenyl)methanone (3d). ^{1}H NMR spectrum, δ, ppm: 7.67 d (2H, *J* = 4.8 Hz), 7.53 d (2H, *J* = 6.6 Hz), 7.42–7.25 m (7H), 7.24–7.06 m (7H), 6.79 d (2H, *J* = 7.8 Hz), 5.19 s (1H), 1.82 s (3H).

[1-(2-Chlorophenyl)-6-methyl-4,6-diphenyl-1,6-dihydropyridin-3-yl](phenyl)methanone (3e). ^{1}H NMR spectrum, δ, ppm: 7.68 d (2H, *J* = 7.8 Hz), 7.54 d (2H, *J* = 6.0 Hz), 7.43–7.28 m (7H), 7.24–7.06 m (7H), 6.90 s (1H), 6.75 d (1H, *J* = 6.6 Hz), 5.21 s (1H), 1.84 s (3H).

(4-Chlorophenyl)(6-methyl-1,4,6-triphenyl-1,6-dihydropyridin-3-yl)methanone (3f). ^{1}H NMR spectrum, δ, ppm: 7.58 d (2H, *J* = 8.4 Hz), 7.54 d (2H, *J* = 7.2 Hz), 7.44–7.13 m (14H), 6.92–6.83 m (2H), 5.19 s (1H), 1.82 s (3H).

(4-Chlorophenyl)[1-(4-chlorophenyl)-6-methyl-4,6-diphenyl-1,6-dihydropyridin-3-yl]methanone (3g). ^{1}H NMR spectrum, δ, ppm: 7.70–7.45 m (4H), 7.44–6.98 m (13H), 6.88–6.71 m (2H), 5.19 s (1H), 1.82 s (3H).

[6-Methyl-1-(4-methylphenyl)-4,6-diphenyl-1,6-dihydropyridin-3-yl](phenyl)methanone (3h). ^{1}H NMR spectrum, δ, ppm: 7.67 d (2H, *J* = 7.8 Hz), 7.54 d (2H, *J* = 7.2 Hz), 7.43 t (2H, *J* = 7.2 Hz), 7.38–7.30

m (6H), 7.24–7.20 m (3H), 7.11 s (1H), 6.97 d (2H, J = 8.4 Hz), 6.74 d (2H, J = 7.2 Hz), 5.18 s (1H), 2.26 s (3H), 1.80 s (3H).

[1-(4-Chlorophenyl)-4,6,6-triphenyl-1,6-dihydropyridin-3-yl](phenyl)methanone (IIIi). ^{1}H NMR spectrum, δ, ppm: 7.59 s (1H), 7.48–7.06 m (20H), 7.00 d (2H, J = 8.4 Hz), 6.91 d (2H, J = 8.4 Hz), 5.65 s (1H).

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