Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 114–116

Catalytic synthesis of 1,4-dihydropyridine derivatives using scandium(III) triflate

Satoshi Kikuchi, Masahiro Iwai, Hiroyuki Murayama and Shin-ichi Fukuzawa*

Department of Applied Chemistry, Institute of Science and Engineering, Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo, Japan

Received 6 September 2007; revised 29 October 2007; accepted 1 November 2007
Available online 4 November 2007

Abstract—Scandium(III) triflate smoothly catalyzed the reaction of imines with ethyl propiolate (2.5 equiv) to produce the corresponding N-substituted 1,4-dihydropyridines in good yields in toluene or BTF under reflux conditions. It also catalyzed the reaction of aniline and ethyl propiolate (3.2 equiv) to give another 1,4-dihydropyridine bearing three ester groups in moderate yield under the same conditions.

Recently, we reported that $RE(OTf)_3$[1] catalyzed the reaction of aromatic amines, aldehydes, and ethyl propiolate in EtOH under reflux conditions to give the several substituted quinolines.[2] When we have optimized the reaction conditions, we found that, when we used imines as substrates and toluene as a solvent instead of EtOH, N-substituted 1,4-dihydropyridine was obtained predominantly.[3]

1,4-Dihydropyridines are versatile compounds because their derivatives play important roles in medicinal chemistry; for example, nifedipine, amlodipine and other antihypertensive agents.[4] Among the numerous methods developed for the synthesis of 1,4-dihydropyridines, Hantzsch reaction is one of the most well-accepted methods and much effort has been made to modify this reaction.[5] However, these classical methods were not enough to make pyridine libraries.

In 2001, Balalaie and Kowsari reported that microwave irradiation promoted the three-component reaction of an aromatic amine, an aromatic aldehyde, and ethyl propiolate to give N-substituted 1,4-dihydropyridine in a high yield.[6] This method may be useful for easily preparing 1,4-dihydropyridine but required expensive microwave apparatus and severe reaction conditions.[7]

We herein report an expeditious and useful method for the synthesis of N-substituted 1,4-dihydropyridines in the presence of a catalytic amount of $Sc(OTf)_3$.

We examined the effect of the RE triflates (RE = Sc, Y, La, Ce, Pr, Nd, Sm, Yb) and other Lewis acids on the yield of product in the reaction of imine **1a** with ethyl propiolate **2** in toluene (Table 1). Table 1 shows that $Sc(OTf)_3$ is the most appropriate Lewis acid for this reaction (entry 1).[8] When we used the trifluoromethanesulfonic acid as a typical Brønsted acid, the reaction hardly proceeded (entry 12).

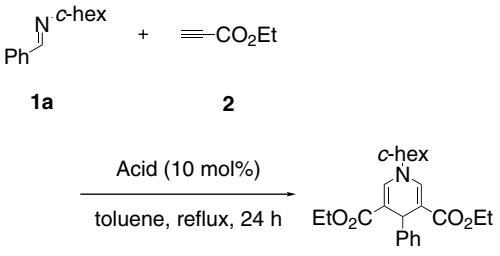
We next investigated solvents in the reaction using $Sc(OTf)_3$ (10 mol %) and the results are summarized in Table 2. Product **3a** was hardly obtained in benzene and THF (entries 1 and 5). When EtOH and 1, 2-dicholoroethane were used as solvents, the reaction could proceed but the yields of **3a** were lower than that in toluene (entries 4 and 6). The best results were obtained in toluene and benzotrifluoride (BTF) (entries 1 and 3).

We usually carried out the reaction of imines **1a**–**m** with **2** in toluene at reflux and the results are shown in Table 3.[9] We performed the reaction of the imines, which were prepared from benzaldehyde and aliphatic amines or substituted anilines (entries 1–8). When we used imines **1a**–**d** with N-alkyl groups, the yields of the 1,4-dihydropyridines **3a**–**d** were low (entries 1–4). The reaction of imine **1e** gave 1,4-dihydropyridine **3e** in moderate yield (45% yield). In the reaction of imines **1f** and **1g**, the reaction smoothly proceeded to give 1,4-dihydropyridines **3f**

* Corresponding author. Tel.: +81 338171916; fax: +81 338171985; e-mail: fukuzawa@chem.chuo-u.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.003

Table 1. Lewis acids catalyzed reaction of imine **1a** with ethyl propiolate **2**[a]



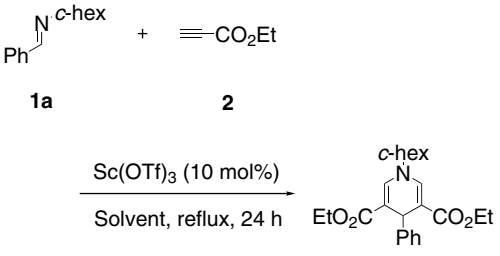
1a **2** **3a**

c-hex=cyclohexyl

Entry	Acid	Yield[b] (%)
1	$Sc(OTf)_3$	22
2	$Y(OTf)_3$	9
3	$La(OTf)_3$	Trace
4	$Ce(OTf)_3$	2
5	$Pr(OTf)_3$	4
6	$Nd(OTf)_3$	3
7	$Sm(OTf)_3$	Trace
8	$Yb(OTf)_3$	5
9	$InCl_3$	12
10	$AlCl_3$	6
11	$TiCl_2(O^iPr)_2$	2
12	TfOH	7

[a] **1a** (0.5 mmol), **2** (1.2 mmol), acid (0.05 mmol) under toluene (5 mL) reflux conditions for 24 h.
[b] GC yield.

Table 2. $Sc(OTf)_3$ catalyzed reaction of imine **1a** with ethyl propiolate **2**[a]



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

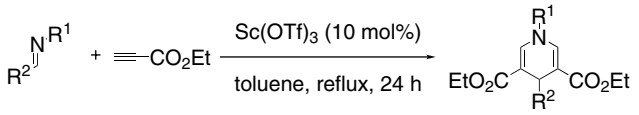
c-hex=cyclohexyl

Entry	Solvent	Yield[b] (%)
1	Toluene	22
2	Benzene	5
3	BTF	29
4	EtOH	14
5	THF	Trace
6	$ClCH_2CH_2Cl$	16

[a] **1a** (0.5 mmol), **2** (1.2 mmol), $Sc(OTf)_3$ (0.05 mmol) under solvent (5 mL) reflux conditions for 24 h.
[b] GC yield.

and **3g** in good yields (75% and 62%, respectively) (entries 6 and 7). When imine **1h** was used, the corresponding **3h** was obtained in 77% yield (entry 8). We next carried out the reaction of the imines derived from the *para*-substituted benzaldehyde and *p*-anisidine to investigate the substituent effect of the 4-position of R^2 on the reaction (entries 9–12). These reactions smoothly proceeded to give the corresponding **3** in good and moderate yields. In the case of the methyl group (electron-donating group), the yield of **3** become high (78%), and when the imine had an electron-withdrawing group (Cl, F, NO_2), the yields were moderate (34–54%). The reaction with **1c**, **1g**, and **1h** yielded **3c**, **3g**, and **3h** in higher yields in BTF than those in toluene (entries 3, 7 and 8).[10] The reaction of imine **1m** derived from 3-phenylpropanal was performed in the same conditions, however, the corresponding pyridine was not obtained (entry 13).

Table 3. The reaction of imines **1a–m** with **2**[a]

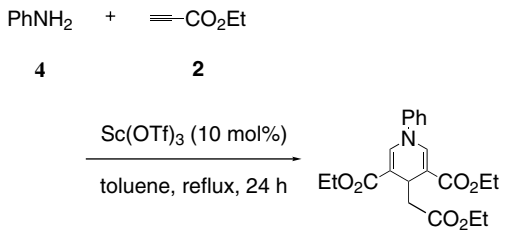


1a-m **2** **3a-m**

Entry	Imine	R^1	R^2	Product **3**	Yield[b] (%)
1	**1a**	*c*-Hex	Ph	**3a**	22[c]
2	**1b**	*t*-Bu	Ph	**3b**	18
3[d]	**1c**	Bn	Ph	**3c**	28
4	**1d**	$CHPh_2$	Ph	**3d**	35
5	**1e**	Ph	Ph	**3e**	45[c]
6	**1f**	*p*-$MeOC_6H_4$	Ph	**3f**	75[c]
7[d]	**1g**	*p*-MeC_6H_4	Ph	**3g**	62[c]
8[d]	**1h**	2,6-MeC_6H_4	Ph	**3h**	77
9	**1i**	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	**3i**	78
10	**1j**	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	**3j**	54
11	**1k**	*p*-$MeOC_6H_4$	*p*-FC_6H_4	**3k**	47
12	**1l**	*p*-$MeOC_6H_4$	*p*-$NO_2C_6H_4$	**3l**	34
13	**1m**	*p*-$MeOC_6H_4$	$PhCH_2CH_2$	**3m**	0

[a] **1** (0.5 mmol), **2** (1.25 mmol), $Sc(OTf)_3$ (0.05 mmol) in toluene (5 mL) at reflux for 24 h.
[b] Isolated yield.
[c] GC yield.
[d] BTF was used as a solvent instead of toluene.

During our study, we also found that the 1,4-dihydropyridine bearing a carboethoxy methyl group at the 4-position **5**[11] was obtained in 42% GC yield from the reaction of aniline **4** with ethyl propiolate **2** in toluene under reflux conditions (Scheme 1).



4 **2** **5**; 42%

Scheme 1.

In conclusion, we developed a useful method for the synthesis of 1,4-dihydropyridine derivatives from imines using catalytic amount of scandium(III) triflate. We could apply this method to the reaction of aniline **4** with ethyl propiolate **2** and found that the novel 1,4-dihydropyridine was obtained in good yield. Further examination for the reaction mechanism is in progress.

Acknowledgment

This work was financially supported by Chuo University Joint Research Grant.

References and notes

1. Reviews, see: (a) Kobayashi, S. *Synlett* **1994**, 689; (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227.
2. Kikuchi, S.; Iwai, M.; Fukuzawa, S. *Synlett* **2007**, 2639.
3. The reviewer comments that our work is an extension of our previous quinoline synthesis. However, we think that this is the point of interest of the present work. We could synthesize quinolines or dihydropyridines preferentially from the same starting materials by just changing a solvent.
4. (a) Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 762; (b) Goldmann, S.; Stoltefuss, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1559; (c) Nakayama, H.; Kasoaka, Y. *Heterocycles* **1996**, *42*, 901.
5. Recent examples, see: (a) Chari, M. A.; Syamasundar, K. *Catal. Commun.* **2005**, *6*, 624; (b) Wang, L.-M.; Sheng, J.; Zhang, L.; Han, J.-W.; Fan, Z.-Y.; Tian, H.; Qian, C.-T. *Tetrahedron* **2005**, *61*, 1539; (c) Lee, J. H. *Tetrahedron Lett.* **2005**, *46*, 7329; (d) Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 5771; (e) Vohra, R. K.; Bruneau, C.; Renaud, J.-L. *Adv. Synth. Catal.* **2006**, *384*, 2571; (f) Wang, G.-W.; Xia, J.-J.; Miao, C.-B.; Wu, X.-L. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 454.
6. Balalaie, S.; Kowsari, E. *Monatsh. Chem.* **2001**, *132*, 1551.
7. A kitchen microwave, which is typically used as the microwave, is dangerous for the organic syntheses due to the difficulty in controlling the reaction temperature.
8. When the three-component coupling reaction of cyclohexylamine, benzaldehyde and ethylpropiolate was carried out in the same conditions, pyridine **3a** was obtained in 14% yield.
9. *Typical procedures*: To a toluene or BTF solution (5 mL) of $Sc(OTf)_3$ (24.6 mg, 0.05 mmol) and imine (0.5 mmol) in a round-bottom flask containing a stirring bar was added the ethyl propiolate (130 μL, 1.28 mmol) using a microsyringe. This mixture was heated at reflux for 24 h. After cooling to rt, the reaction was quenched with brine and extracted three times with ethyl acetate. This combined organic layer was dried over Na_2SO_4. This organic layer was filtered and evaporated under reduced pressure. The residue was purified by preparative TLC (SiO_2, hexane/ethyl acetate = 4/1) and/or preparative HPLC (GPC column, $CHCl_3$ as eluent) to give the desired products.[12]
10. When we used toluene as a solvent, the yields of **3c**, **3g**, and **3h** were 19%, 35%, and 27%, respectively.
11. CCDC 655306 contains the supplementary crystallographic data for compound **5**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
12. *Data for selected compounds*:
Compound **3b**: ^{1}H NMR (300 MHz, $CDCl_3$): $d = 1.19$ (t, $J = 4.2$ Hz, 3H), 3.84 (s, 3H), 4.09 (m, 4H), 4.95 (s, 1H), 6.95 (d, $J = 12.3$ Hz, 2H), 7.19 (m, 5H), 7.37 (d, $J = 8.8$ Hz, 2H), 7.55 (s, 2H). ^{13}C NMR ($CDCl_3$): $d = 14.2$, 37.5, 55.6, 60.2, 110.2, 114.9, 122.8, 126.5, 128.0, 128.3, 136.3, 146.3, 158.2, 166.9.
Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$): $d = 1.18$ (t, $J = 4.2$ Hz, 3H), 1.31 (t, $J = 4.2$ Hz, 6H), 2.60 (d, $J = 2.7$ Hz, 2H), 4.03 (q, $J = 4.2$ Hz, 2H), 4.25 (m, 5H), 7.23 (d, $J = 4.2$ Hz, 2H), 7.27 (t, $J = 4.5$ Hz, 1H), 7.42 (t, $J = 4.5$ Hz, 2H), 7.58 (s, 2H). ^{13}C NMR ($CDCl_3$): $d = 14.1$, 14.3, 29.5, 40.4, 59.9, 60.2, 108.1, 120.7, 126.2, 129.7, 137.5, 142.9, 166.6, 171.3.