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Ytterbium-catalyzed synthesis of dihydropyridines

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ABSTRACT

The reaction of anilines, benzaldehydes, and ethyl 3,3-diethoxypropionate in the presence of $Yb(OTf)_3$ proceeded under mild reaction conditions to give dihydropyridines (DHPs). We have found that the reaction depended on the solvent and the DHPs were obtained selectively in 1,4-dioxane as a solvent. Various 2,6-unsubstituted DHPs were synthesized in one pot in satisfactory yields.

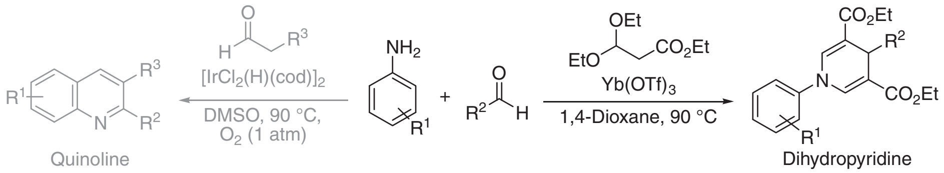
Introduction

Dihydropyridines (DHPs) are important nitrogen-containing heterocycles, and have some interesting biological activities,[1] such as widely used calcium channel blockers.[2] In 1998, Hilgeroth et al. reported that several DHP dimers showed the inhibition of HIV-1 protease.[1d–f] DHPs are also useful as synthetic intermediates.[3] So far various DHP syntheses[4] have been reported, and among them Hantzsch method[4a] using 1,3-dicarbonyl compounds is one of the most useful general synthetic methods for DHPs, which gives 2,6-disubstituted DHP known as the Hantzsch ester. Although normal Hantzsch esters do not show any fluorescence, 2,6-unsubstituted DHPs are known to show strong blue fluorescence.[5] However, photo-electronic property of DHPs is not studied much despite potential usefulness since synthesis of 2,6-unsubstituted DHPs[6] having various functional groups is not easy by Hantzsch method. Eisner method[6a] using highly reactive propargyl esters instead of 2-formylacetates is one of the few methods for 2,6-unsubstituted DHPs. Recently, the Eisner method has been improved by the use of imines or enamines as sources of amines and aldehydes. Fukuzawa and co-workers succeeded the synthesis of 2,6-unsubstituted DHPs from propargyl esters and imines using Sc catalyst.[6b] Li and co-workers also reported DHP synthesis using enaminone and aldehyde.[6c] However, development of simple chemistry for various 2,6-unsubstituted DHPs starting with amines, aldehydes, and esters directly is expected in view of the practical science.

Previously, we reported the Yb- or Ir-catalyzed multi-substituted quinoline syntheses.[7] In the course of our studies to develop various heterocycles, we have found that the reaction with anilines, ethyl glyoxylate and ethyl 3,3-diethoxypropionate proceeded unexpectedly to yield DHPs (Scheme 1). Herein, we describe the novel and versatile 2,6-unsubstituted DHP synthesis catalyzed by Lewis acids using ethyl 3,3-diethoxypropionate, which is stable enough to be handled easily and is a readily available useful starting material for organic synthesis.[8]

Results and discussions

At first the reactions with *p*-anisidine (**1a**), ethyl glyoxylate (**2a**) and ethyl 3,3-diethoxypropionate (**3a**) were carried out using



Scheme 1. Ir- or Yb-catalyzed one-pot synthesis of quinolines and dihydropyridines.

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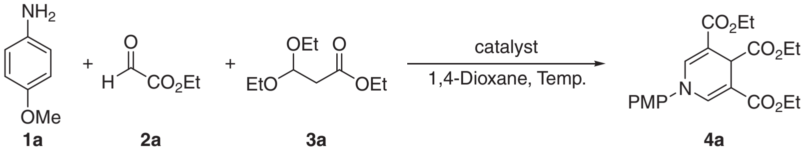
Table 1
One-pot synthesis of DHPs under various reaction conditions



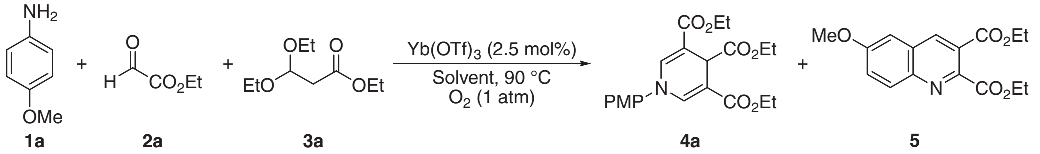
Entry	Catalyst (mol %)	Temp. (°C)	Yield[a] (%)
1	Blank	90	Trace
2	Yb(OTf)^3 (2.5)	50	N.R.
3		90	73
4		120	42
5	$[IrCl_2(H)(cod)]_2$ (2.5)	90	28[b]
6	$[IrCl(cod)]_2$ (2.5)	90	Trace
7	$Ir(acac)_3$ (2.5)	90	Trace
8	$[RhCl(cod)]_2$ (2.5)	90	Trace
9	$Ru(acac)_3$ (2.5)	90	Trace
10	$Fe(acac)_3$ (2.5)	90	Trace
11	$ZnCl_2$ (2.5)	90	21
12	$TiCl_4$ (2.5)	90	61
13	$Sc(OTf)_3$ (2.5)	90	57
14	$La(OTf)_3$ (2.5)	90	53
15	$Sm(OTf)_3$ (2.5)	90	62
16	$Eu(OTf)_3$ (2.5)	90	64
17	$Pr(OTf)_3$ (2.5)	90	51
18	PTSA monohydrate (2.5)	90	31
19	DOWEX® (2.5)	90	48
20	4 M HCl in 1,4-dioxane (5.0)	90	67
21	TfOH (7.5)	90	50

[a] Isolated yields based on *p*-anisidine (**1a**).
[b] DMSO was used as a solvent.

various Brønsted and Lewis acids and the results are summarized in Table 1. When the reaction was carried out without catalyst at 90 °C, the DHP **4a** was scarcely obtained (entry 1). In the reaction at 50 °C in the presence of $Yb(OTf)_3$ as a catalyst, the reaction did not proceed, but the reaction at 90 °C gave **4a** in 73% yield (entries 2 and 3). However in the reaction at 120 °C, the yield of **4a** was decreased to 42% (entry 4). Transition metal salts and complexes were less effective or inactive (entries 5–10). The reaction with the Lewis acids, $ZnCl_2$ and $TiCl_4$, gave **4a** in 21% and 61% yields (entries 11 and 12). $Sc(OTf)_3$ was not so effective in this reaction system as the synthesis from imines and propargyl ester as Fukuzawa et al. reported (entry 13). Other lanthanoid triflates, $La(OTf)_3$, $Sm(OTf)_3$, $Eu(OTf)_3$ and $Pr(OTf)_3$, gave similar activities as $Sc(OTf)_3$ in this reaction (entries 14–17). When Brønsted acids, such as PTSA monohydrate and DOWEX®, were used, **4a** was obtained in low yields (entries 18 and 19). However, when a catalytic amount of 4 M HCl in 1,4-dioxane or TfOH was used, the reaction proceeded to give **4a** in moderate yields, 67% and 57%, respectively (entries 20 and 21). As above $Yb(OTf)_3$ was the best catalyst for the synthesis of the DHP **4a** and used for further studies of DHP synthesis.

Various solvents in this reaction under oxygen were studied, and the results are shown in Table 2. The selectivity of the DHP **4a** and the quinaldate **5** depends upon the solvents. The reaction of *p*-anisidine (**1a**), ethyl glyoxylate (**2a**) and ethyl 3,3-diethoxy-

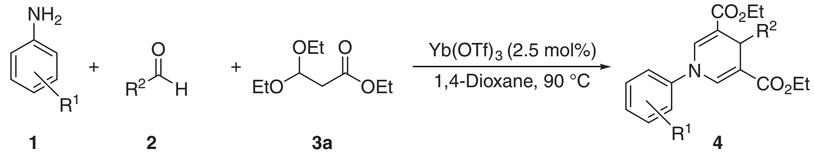
Table 2
One-pot synthesis of DHPs under various solvents

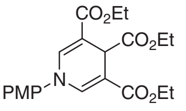
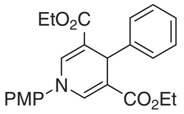
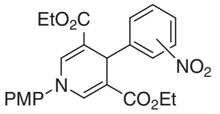
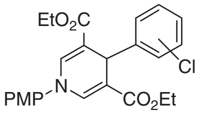
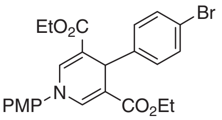
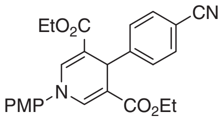
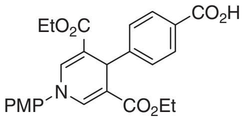
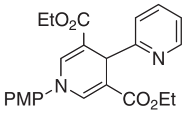
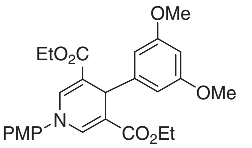
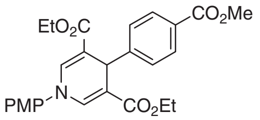
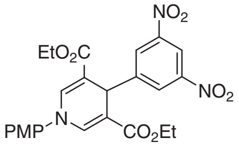
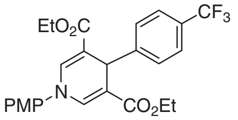
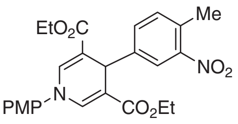
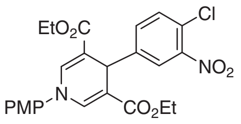
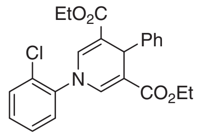
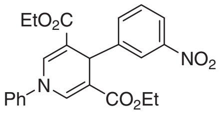
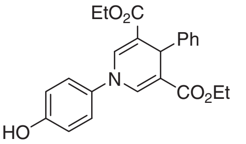
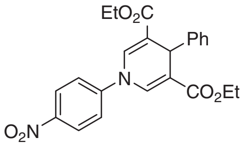
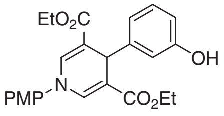
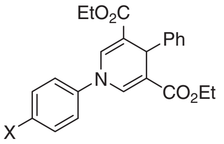


Entry	Solvent	Yield[a] (%)	
		4a	**5**
1	DMSO	51	20
2	CH_3CN	58	Trace
3	DMF	72	14
4	1,4-Dioxane	74	Trace
5	Toluene	58	21
6	THF	20	16
7	Benzene	18	16
8	CH_2Cl_2	3	11
9	Ethanol	0	0
10	NMP	Trace	Trace

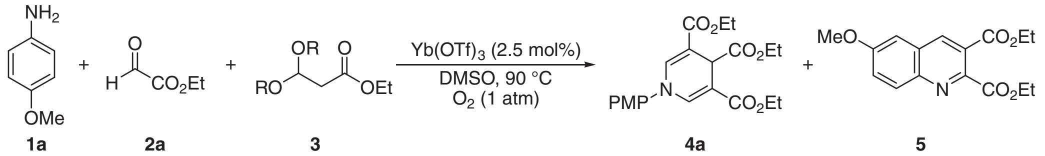
[a] Isolated yields based on *p*-anisidine (**1a**).

Table 3
Yb-catalyzed one-pot synthesis of various DHPs



Product (yield[a])			
 **4a** (73 %)	 **4b** (31 %)	 **4c** (*o*-, 32 %) **4d** (*m*-, 71 %) **4e** (*p*-, 73 %)	 **4f** (*o*-, 55 %) **4g** (*m*-, 60 %) **4h** (*p*-, 50 %)
 **4i** (57 %)	 **4i** (65 %)	 **4k** (82 %)	 **4l** (21 %)
 **4m** (57 %)	 **4n** (69 %)	 **4o** (62 %)	 **4p** (66 %)
 **4q** (62 %)	 **4r** (67 %)	 **4s**(49 %)	 **4t** (66 %)
 **4u** (63 %)	 **4v** (29 %)	 **4w** (27 %)	 **4x** (X = F, 53 %) **4y** (X = Br, 32 %) **4z** (X = I, 51 %)

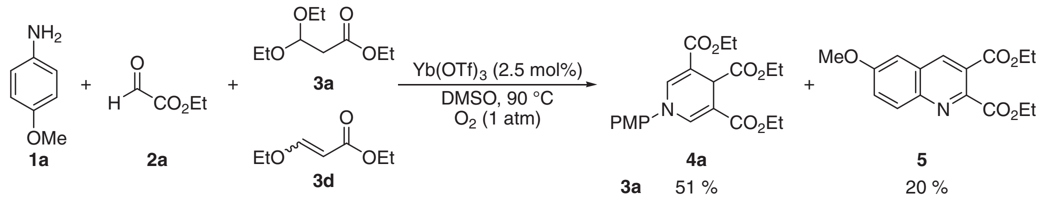
[a] Isolated yields based on arylamine **1**.



	4a	**5**
3a (R = Et)	51 %	20 %
3b (R = Pr)	40 %	35 %
3c (R = -CH_2CH_2-)	0 %	0 %

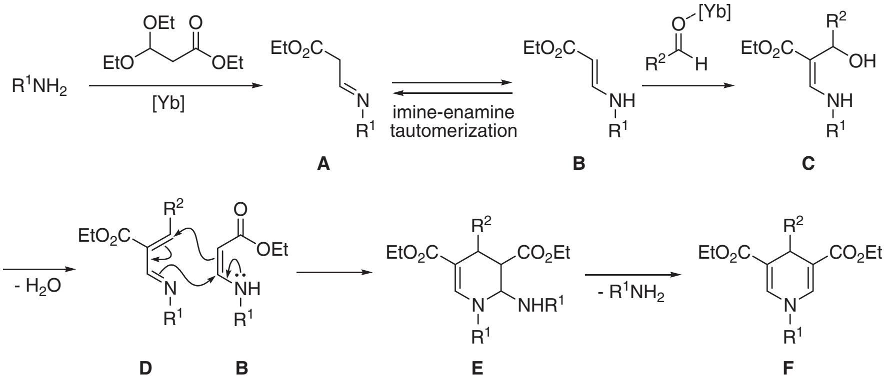
Scheme 2. The effect of acetal moiety for Yb-catalyzed one-pot DHP synthesis.

propionate (**3a**) with Yb catalyst in DMSO at 90 °C, **4a** and **5** were obtained in 51% and 20% yields, respectively (entry 1). The reaction in acetonitrile gave **4a** in 58% yield, but formation of **5** was scarcely observed by TLC analysis (entry 2). Although DMF as an aprotic polar solvent was used, the yield of **4a** increased (72%) and the undesired **5** was also obtained in 14% yield (entry 3). The most satisfactory result was obtained when the reaction in 1,4-dioxane was carried out and **4a** was obtained in a good yield (74%) without formation of **5** even under oxygen atmosphere (entry 4). The reaction in aprotic non-polar solvent, such as toluene gave **4a** and **5** in 58% and 21% yields (entry 5). In this reaction, THF, benzene, CH_2Cl_2, ethanol and NMP were less effective or inactive (entries 6–10).



	4a	5
3a	51 %	20 %
3d	19 %	72 %
trans- **3d**	6 %	41 %
cis- **3d**	17 %	44 %

Scheme 3. The comparison of acetal and vinyl ether in Yb-catalyzed one-pot DHP synthesis.



Scheme 4. The plausible reaction mechanism of Yb-catalyzed one-pot DHP synthesis.

These solvents have lower boiling points, indicating that the higher temperature is necessary for this reaction. This is in accordance with the results of entry 2 in Table 1.

From these results, $Yb(OTf)_3$ and 1,4-dioxane were chosen as a suitable catalysis system and applied to synthesis of various DHPs **4**. Thus, the reactions of anilines **1**, aldehyde **2** and ethyl 3,3-diethoxypropionate (**3a**) in the presence of $Yb(OTf)_3$ at 90 °C were carried out to synthesize the corresponding *N*-aryl-3,5-diethoxycarbonyl-DHPs **4**. As shown in Table 3, the reactions with various electron deficient aldehydes gave the corresponding DHPs in good yields (**4d**–**4j** and **4k**–**4r**). On the other hand, DHPs such as **4m** and **4w** bearing electron donating group in 4-aryl moiety were obtained in moderate yields. The DHP **4c**, which was obtained from reaction with *o*-nitrobenzaldehyde, was obtained in 32% yield because of the steric hindrance of the *o*-nitro substituent in aryl moiety at 4-position of DHP. The reaction with various functionalized anilines also gave DHPs in good yields.

When ethyl 3,3-dipropylpropionate (**3b**) was used instead of **3a**, **4a** and **5** were obtained in 40% and 35% yields. The reaction with cyclic acetal **3c** did not proceed to give any **4a** and **5** (Scheme 2).

The ethyl vinyl ether **3d** was considered as an intermediate for the reaction and used for the synthesis of **4a**, however the selectivity of the reaction was very different from that with the reaction of ethyl 3,3-diethoxypropionate (**3a**). Thus the reaction with the ethyl vinyl ether **3d** (*cis*- and *trans*-isomers mixture) gave **4a** and **5** in 19% and 72% yields. Although *cis*- or *trans*-isomer of **3d** was used separately, the quinaldate **5** was obtained as a major product in each reaction (Scheme 3).

The above result indicates that **3d** is not intermediate for **4a**. The plausible reaction mechanism of DHP synthesis is considered as shown in Scheme 4. At first, in the presence of Yb catalyst, amine and activated ethyl 3,3-diethoxypropionate formed imine **A**. This imine intermediate **A** can easily tautomerize enamine intermediate **B**, and reacts with Yb-activated aldehyde to form enaminoalcohol **C**. Subsequent dehydration proceeds via intermediate X to give the α,β-unsaturated imine **D**. The Michael-type annulation with the intermediate **D** and the intermediate **B** proceeds to give the tetrahydropyridine **E**. Finally elimination of amine from **E** affords the DHP **F**.

Conclusion

We have found that $Yb(OTf)_3$ is a suitable catalyst for one-pot DHP synthesis, and 2,6-unsubstituted DHPs tolerated various functional groups were synthesized easily, which is expected to provide a useful tool for medicinal chemistry and materials science.

Acknowledgments

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Supplementary data

Supplementary data (general experimental procedure and spectral data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.070.

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