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Short communication

Ytterbium perfluorooctanesulfonates catalyzed synthesis of benzimidazole derivatives in fluorous solvents

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Abstract

Catalytic condensation of *o*-phenylenediamine and aldehydes was accomplished using rare earth(III)perfluorooctane sulfonates ($RE(OPf)_3$), RE = Sc, Y, La ~ Lu) as catalysts in fluorous solvents. Ytterbium perfluorooctanesulfonates ($Yb(OPf)_3$) catalyzes the high-efficient synthesis of benzimidazole derivatives in fluorous solvents. By simple separation, fluorous phase containing only catalyst can be reused several times.

Keywords: Benzimidazole derivatives; Fluorous biphasic catalysis; Rare earth(III)perfluorooctanesulfonates; Perfluorocarbon

1. Introduction

Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics [1].

Due to their wide range of pharmacological activity, industrial and synthetic applications, a number of methods have been reported for the synthesis of benzimidazoles, which include the coupling of phenylenediamines and carboxylic acids [2] or their derivatives (nitriles, imidates, or orthoesters) [3], the reaction between *N*-ethoxycarbonylthiomides with 1,2-diamines [4], and the reaction of aldehydes with 1,2-diamines followed by *N*-halosuccinimides (X = Cl, Br, I) [5]. Recently, azalactones [6], 2-aryl-1,1-dibromoethane [7], nitriles [8] and amino amides [9] have been used as starting materials for this synthesis of benzimidazoles. However, all of these methods have problems, including drastic reaction conditions, low yields and severe side-reactions. Curini and co-workers reported that ytterbium triflate ($Yb(OTf)_3$) can catalyze the synthesis of benzimidazole derivatives from the condensation of *o*-phenylenediamines and aldehydes in good to excellent yield [10]. However, reusing of this catalyst required tedious work up procedures such as filtration, purification and drying. Dilip Konwar and co-workers reported that iodine (I_2) can catalyze the synthesis of benzimidazole derivatives from the condensation of *o*-phenylenediamines and aldehydes in good to excellent yield [11]. However, the catalyst iodine can not be recycled.

Recently, a new kind of Lewis acids of rare earth metal(III)perfluorooctanesulfonates ($RE(OSO_2C_8F_{17})_3$, $RE(OPf)_3$, RE = Sc, Y, La ~ Lu) has been of special interest in that they have characteristic features such as low hygroscopicity, ease of handling, robustness for the recycling using and high solubility in fluorous solvent [12]. On the other hand, perfluorocarbon solvents, especially perfluoro-alkanes have some unique properties which make them as attractive alternatives for conventional organic solvents [13]. The compounds functionalized with perfluorinated groups often dissolve preferentially in fluorous solvents and this property can be used to extract fluorous components from reaction mixtures [14]. As a part of our studies to explore the utility of lanthanide perfluorooctanesulfonates catalyzed reactions in fluorous solvents [15], we decided to investigate $Yb(OPf)_3$-catalyzed synthesis of benzimidazole derivatives by condensation of *o*-phenylenediamine with aldehydes (Scheme 1).

2. Results and discussion

The condensation of *o*-phenylenediamine with benzaldehyde was adopted for studying the effect of catalysts and

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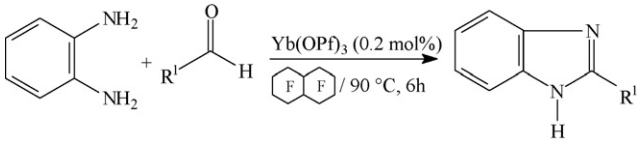


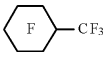
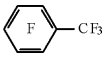
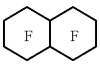
Scheme 1.

solvents. Table 1 shows the catalytic activity of 10 $RE(OPf)_3$ complexes in perfluorodecalin. It was found that $Yb(OPf)_3$ was the most effective catalyst, which produced almost quantitive yields of benzimidazole by condensation of *o*-phenylenediamine with benzaldehyde in perfluorodecalin ($C_{10}F_{18}$).

Next, perfluorohexane (C_6F_{14}), perfluoromethylcyclo-hexane (C_7F_{14}), perfluorotoluene (C_7F_8), perfluorooctane (C_8F_{18}), and perfluorooctyl bromide ($C_8F_{17}Br$) were also selected as fluorous solvents and the effect of such solvents was examined for the condensation of *o*-phenylenediamine with benzaldehyde (Scheme 1). Table 2 shows the influence of fluorous solvents on the reaction under the controlled conditions. The results show that yields of the desired benzimidazole in perfluorooctane (C_8F_{18}) and perfluorooctyl bromide ($C_8F_{17}Br$) are lower than other solvents. The fluorous solvents perfluorohexane (C_6F_{14}) and perfluorotoluene (C_7F_8) are in fact miscible with aromatic substrates such as benzaldehyde at room temperature. Thus, it is difficult to recover fluorous phase by phase-separation. At the same time, we found that during repeated condensations, the loss of fluorous solvent is very serious when using perfluor-omethyl-cyclohexane (C_7F_{14}) as a fluorous solvent because it is very volatile (b.p. 76 °C). Therefore, perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture) is the best fluorous solvent for condensation.

We decided to use the relatively cheap and similarly active catalytic system including $Yb(OPf)_3$ and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture) as a fluorous solvent for condensation. The condensation of various aldehydes with *o*-phenylenediamine have been examined (Scheme 1). The results are summarized in Table 3. Not only aryl aldehydes but also acyclic aldehydes were efficient reagents for this reaction. In all cases, the reactions proceeded very cleanly (checked by TLC) and no side reaction products were observed. When the reaction

Table 2
Effect of fluorous solvents on the condensation[a]

Entry	PFC	Yield[b] (%)
1	$CF_3(CF_2)_4CF_3$	82
2		97
3		98
4	$CF_3(CF_2)_6CF_3$	80
5	$CF_3(CF_2)_6CF_2Br$	80
6		98

[a] All reactions were carried out in the presence of $Yb(OPf)_3$ at 90 °C for 6 h.
[b] Isolated yield.

was finished, the reaction mixture was cooled to room temperature, the fluorous phase with $RE(OPf)_3$ can separate from the organic layer return to the bottom layer. Based on GC–MS data, no distribution of perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture) to the organic phase was ascertained.

Attempts were made to recycle these catalytic systems. The condensation of *o*-phenylenediamine with benzaldehyde under the conditions described in Table 1 with $RE(OPf)_3$ as catalysts was run for five consecutive cycles, furnishing the corresponding benzimidazole, with 98, 98, 97, 96, 96% isolated yields. The robustness of the catalyst for recycling using may partly be attributed to the water-repellent nature of the perfluoroalkane group "$(–CF_2–CF_2–)_n$" of $RE(OSO_2C_8F_{17})_3$ which obstructs the approach of water or acid molecules to the central metal cation, thus maintaining its high Lewis acidity [15]. The separated fluorous phase containing only catalyst could be reused for the next condensation without any treatment, and this workup procedure of recycling was accomplished by simple phase-separation.

In conclusion, $RE(OPf)_3$ are demonstrated to be new and highly effective catalysts for preparation of 2-substituted benzimidazoles in fluorous biphasic system (FBS). By simple separation of the fluorous phase containing only catalyst, the reaction can be repeated many times. Further study on the

Table 1
Effect of the catalysts on the condensation[a]

Entry	Catalyst	Yield[b] (%)
1	$La(OPf)_3$	65
2	$Ce(OPf)_3$	64
3	$Nd(OPf)_3$	79
4	$Sm(OPf)_3$	62
5	$Eu(OPf)_3$	50
6	$Tb(OPf)_3$	76
7	$Dy(OPf)_3$	64
8	$Er(OPf)_3$	85
9	$Yb(OPf)_3$	98
10	$Lu(OPf)_3$	80

[a] All reactions were carried out in perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture) at 90 °C for 6 h.
[b] Isolated yield.

Table 3
Condensation of benzaldehydes with *o*-phenylenediamine[a]

Entry	R^1	Yield[b] (%)	m.p. (Lit. [16])/°C
1	Ph	98	290–292 (292)
2	C_2H_5	89	175–176 (176)
3	C_3H_7	87	159–161 (162)
4	*p*-CH_3OPh	96	225–226 (226)
5	*o*-NO_2Ph	99	209–210 (210)
6	*p*-NO_2Ph	93	312–314 (316)
7	*o*-HOPh	92	240–242 (242)
8	*p*-CH_3Ph	93	268–270 (270)
9	*o*-ClPh	95	232–234 (234)
10	*p*-ClPh	96	291–293 (294)
11	2-Furanyl	94	285–287 (288)

[a] All reactions were carried out in the presence of $Yb(OPf)_3$.
[b] Isolated yield.

application of FBS to other reactions, which can promote by such Lewis acids, is under way in this laboratory.

3. Experimental

3.1. General

MPs were obtained with Shimadzu DSC-50 thermal analyzer. IR spectra were recorded on a Bumem MB154S infra-red analyzer. ^{1}HNMR spectra were measured on Bruke Advance RX500. MS were recorded with a Saturn 2000 GC/MS instrument. Inductively coupled plasma (ICP) spectra were measured on Ultima2C apparatus. Elemental analyses were performed on a Yanagimoto MT3CHN corder.

3.2. Typical procedure for preparation of RE(OPf)$_3$

RE(OPf)$_3$ was prepared according to the literatures [17]. **(Method A)**. The mixture of PfOH solution (aq) and $YbCl_3{\cdot}6H_2O$ solution (aq) was stirred at room temperature. **(Method B)**. The mixture of PfOH solution (aq) and Yb_2O_3 powder was stirred at boiling temperature. In both methods, the resulting gelatin-like solid was collected, washed with H_2O and dried at 150 °C in vacuum to give a white solid, which does not have a clear melting point up to 500 °C, but shrinks around 380 °C and 450 °C. IR (KBr) ν 1 230 (CF_3), 1 150 (CF_2), 1 080 (SO_2), 1 060 (SO_2), 740 (S–O) and 650 (C–S) cm^{-1}. ICP: Calcd. for $C_{24}O_9F_{51}S_3Yb$: Yb, 10.30%. Found: Yb, 9.88%. Anal. calcd. for $C_{24}O_9F_{51}S_3Yb{\cdot}H_2O$: C, 17.21%; H, 0.10%. Found: C, 17.03%; H, 0.18%.

3.3. Typical procedure for preparation of benzimidazole derivatives

A mixture of Yb(OPf)$_3$ (67 mg, 0.04 mmol), *o*-phenylenediamine (1.08 g, 10 mmol), benzaldehyde (1.17 g, 11 mmol), toluene (2 mL) and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture, 1.5 mL). The mixture was stirred at 90 °C for 6 h. Then, the fluorous layer on the bottom was separated for the next condensation. The organic solvent in the reaction mixture (organic phase) was removed under reduced pressure and the residue was purified by SiO_2 gel column chromatography using CH_2Cl_2:MeOH 99:1 as eluent. All products are known compounds and their structures were characterized by IR, NMR and mass spectra.

2-Phenyl-benzimidazole (Lit. [18]). A white solid; m.p. 290–292 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 7.21–7.73 (7H, m, Ar), 8.16–8.22 (2H, m, Ar), MS (EI) *m*/*z* 194 (M$^+$).

2-Ethyl-benzimidazole (Lit. [19]). A white solid; m.p. 175–176 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 2.30–2.50 (5H, m, C_2H_5), 7.20–7.43 (4H, m, Ar), MS (EI) *m*/*z* 146 (M$^+$).

2-Propyl-benzimidazole (Lit. [19]). A white solid; m.p. 159–161 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 2.20–2.60 (7H, m, C_3H_7), 7.21–7.43 (4H, m, Ar), MS (EI) *m*/*z* 160 (M$^+$).

2-(4-Methoxy-phenyl)-benzimidazole (Lit. [18]). A white solid; m.p. 225–226 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 3.52 (3H, m, CH_3), 7.20–7.60 (6H, m, Ar), 8.00 – 8.08 (2H, m, Ar), MS (EI) *m*/*z* 224 (M$^+$).

2-(2-Nitro-phenyl)-benzimidazole (Lit. [20]). A yellow solid; m.p. 209–210 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 7.20–7.60 (6H, m, Ar), 8.00–8.08 (2H, m, Ar), MS (EI) *m*/*z* 239 (M$^+$).

2-(4-Nitro-phenyl)-benzimidazole (Lit. [20]). A yellow solid; m.p. 312–314 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 7.20–7.60 (6H, m, Ar), 8.00–8.08 (2H, m, Ar), MS (EI) *m*/*z* 239 (M$^+$).

2-(2-Hydroxy-phenyl)-benzimidazole (Lit. [21]). A white solid; m.p. 240–242 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 4.60 (1H, d, OH), 7.21–7.73 (6H, m, Ar), 8.16–8.22 (2H, m, Ar), MS (EI) *m*/*z* 210 (M$^+$).

2-(4-Methyl-phenyl)-benzimidazole (Lit. [18]). A white solid; m.p. 268–270 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 2.60 (3H, m, CH_3), 7.20–7.60 (6H, m, Ar), 8.00–8.08 (2H, m, Ar), MS (EI) *m*/*z* 208 (M$^+$).

2-(2-Chloro-phenyl)-benzimidazole (Lit. [20]). A white solid; m.p. 232–234 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 7.20–7.60 (6H, m, Ar), 8.00–8.08 (2H, m, Ar), MS (EI) *m*/*z* 228.5 (M$^+$).

2-(4-Chloro-phenyl)-benzimidazole (Lit. [18]). A white solid; m.p. 291–293 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 7.20–7.60 (6H, m, Ar), 8.00–8.08 (2H, m, Ar), MS (EI) *m*/*z* 228.5 (M$^+$).

2-Furanyl-benzimidazole (Lit. [22]). A white solid; m.p. 285–287 °C. IR (KBr) υ 1640 cm^{-1} (C=N), 3250 cm^{-1} (NH). ^{1}HNMR (DMSO) δ 6.80–7.00 (3H, m, Furanyl), 7.21–7.43 (4H, m, Ar), MS (EI) *m*/*z* 184 (M$^+$).

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