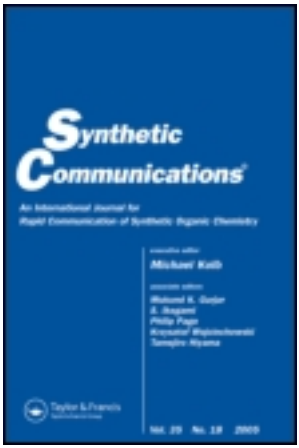

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An Efficient Procedure for the Synthesis of Benzimidazole Derivatives Using $Yb(OTf)_3$ as Catalyst Under Solvent-Free Conditions

Limin Wang [a] , Jia Sheng [a] , He Tian [a] & Changtao Qian [b]

[a] Institute of Fine Chemicals, East China University of Science and Technology, 130 Meilong Lu, Shanghai, 200237, P. R. China

[b] Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, P. R. China

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An Efficient Procedure for the Synthesis of Benzimidazole Derivatives Using $Yb(OTf)_3$ as Catalyst Under Solvent-Free Conditions

Limin Wang,[1,*] Jia Sheng,[1] He Tian,[1] and Changtao Qian[2]

[1]Institute of Fine Chemicals, East China University of Science and Technology, Shanghai, P. R. China
[2]Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, P. R. China

ABSTRACT

o-Diaminobenzene derivatives react smoothly with ortho-esters in the presence of 0.5 mol% of $Yb(OTf)_3$ under solvent-free conditions to afford the corresponding benzimidazole derivatives in good to excellent yields. In addition, $Yb(OTf)_3$ can be easily recovered almost quantitatively from the aqueous layer after the reaction was completed, and it could be reused with no loss of activity.

Key Words: $Yb(OTf)_3$; Benzimidazole; Solvent-free reaction.

*Correspondence: Limin Wang, Institute of Fine Chemicals, East China University of Science and Technology, 130 Meilong Lu, Shanghai 200237, P. R. China; Tel. (fax): 86-21-64252288, 64252758; E-mail: wanglimin@ecust.edu.cn or wcathy@china.com.

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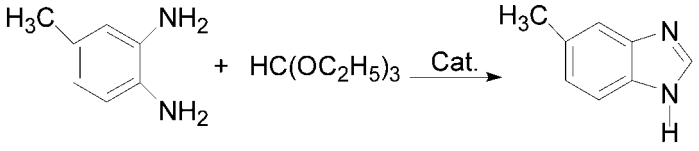
INTRODUCTION

It is well known that benzimidazole is an important structural element in medicinal chemistry, with a wide spectrum of pharmacological activities.[1] Recently, bisbenzimidazoles are being developed as DNA minor-groove binding agents with antitumor activity[2] and can act as ligands to transition metals for modeling biological systems.[3] Conventional synthesis of benzimidazoles involved refluxing the reactants in aqueous hydrochloric acid for 30 min[4a] or in a slurry of the dehydrating agent, such as polyphosphoric acid, at 250°C for 4 h,[4b] as the result of which generating abundant harmful waste to the environment. New research has recently been applied to the preparation of this sort of compound, including solid-phase[5] methods, a rapid microwave-assisted liquid-phase combinatorial approach,[6] the strategy of palladium-catalyzed intramolecular aryl-amination chemistry,[7,8] using high-temperature water[9] as the medium and Montmorillonite KSF or K10[10] as the catalyst.

Over the past decade, many efforts have gone into developing rare earth metal triflate, especially the $Yb(OTf)_3$ and $Sc(OTf)_3$ catalyzed organic synthesis. As a new type of strong water-compatible Lewis acid, they have been applied in a wide variety of reactions.[11] Only catalytic amounts of them are effective enough to complete the reactions in most cases. Furthermore, $RE(OTf)_3$ can be easily recovered and reused without any loss of activity. As a continuation of our interest in lanthanide triflates catalyzed reactions,[12] we wish to describe here a simple and convenient method for the synthesis of benzimidazole derivatives from *o*-diaminobenzene derivatives and ortho-esters using $Yb(OTf)_3$ under solvent-free conditions.

RESULTS AND DISCUSSION

Initially, the mixture of 4-methylorthophenylenediamine (**1b**) and triethyl orthoformate (**2b**), producing the 2,5-dimethylbenzimidazole (**3b**) in solvent-free conditions (Scheme 1) were chosen as the model reaction to determine whether the use of ytterbium triflate was efficient and to investigate



1b **2b** **3b**

Scheme 1.

the optimized conditions. The results are summarized in Table 1. Typical Lewis acids, such as $ZnCl_2$, $AlCl_3$, $SnCl_2$, and $FeCl_3$, did not efficiently catalyze the reaction, giving low yields at first use in a long-time-reaction. On the other hand, to our delight, 1 mol% $Yb(OTf)_3$ was found to effectively catalyze the reaction. The expected product 2,5-dimethylbenzimidazole (**3b**) was obtained in 92% yield (entry 7) after 1 h of stirring at 90°C. We also examined other rare earth metals salts [$YbCl_3$, $La(OTf)_3$], using them as potential catalysts, which were also not as good as $Yb(OTf)_3$. Considering that the amount of catalyst can affect the reaction, we tried to change it from 0.1 mol% to 5 mol% and found that 0.5 mol% was sufficient (entry 9). In addition, the catalyst could be reused three times without showing any loss of activity (entry 12).

Establishing the advantages of $Yb(OTf)_3$ as the catalyst, we continued to optimize the condition by varying the solvent effect (Table 2). Although C_2H_5OH was the best solvent among those tested, the best results were obtained under solvent-free conditions.

To explore the generality of this reaction, we applied $Yb(OTf)_3$ in the reaction of various *o*-diaminobenzene derivatives (**1**) with several orthoesters (**2**) under optimized conditions (Scheme 2, Table 3). In general, when the *R* represented the electron-withdrawing group such as nitro (entries 10, 11), the yield and purity of the product were obviously worse. In the case of SO_3H, no desired products were detected even after heating for 6 h (entry 13).

Table 1. The reaction of 4-methyl-1,2-phenylenediamine (**1b**) and triethyl orthoformate (**2b**) by various Lewis acids under solvent-free conditions.[a]

Entry	Catalyst[c]	Amount of catalyst (mol%)	Time (h)	Yield of **3b** (%)[b]
1	$ZnCl_2$	25	4	20
2	$AlCl_3$	25	4	50
3	$SnCl_2$	25	4	30
4	$FeCl_3$	25	4	50
5	$YbCl_3$	25	2	80
6	$La(OTf)_3$	1.5	1	83
7	$Yb(OTf)_3$	1	1	92
8	$Yb(OTf)_3$	5	1	92
9	$Yb(OTf)_3$	0.5	1	92
10	$Yb(OTf)_3$	0.25	1	85
11	$Yb(OTf)_3$	0.1	1	75
12	$Yb(OTf)_3$	1	1	92, 90, 88

[a]Refluxed at 90°C for 1–4 h under solvent-free conditions.
[b]Isolated yield.
[c]Catalyst was reused three times.

Table 2. Solvent effect on the reaction of 4-methyl-1,2-phenylenediamine (**1b**) and triethyl orthoformate (**2b**).

Entry	Solvent[a]	Reaction time (h)	Yield of **3b** (%)[c]
1	C_2H_5OH	2	80
2	CH_3CN	2	70
3	EtOAc	2	40
4	$C_2H_5OC_2H_5$	2	30
5	CH_2Cl_2	2	20
6	THF	2	Trace
7	None[b]	1	92

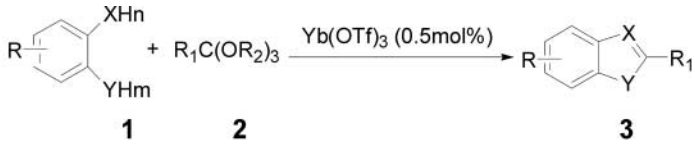
[a]Refluxed for 2 h.
[b]90°C for 1 h.
[c]Isolated yield.

The substituents R_1 and R_2 in ortho-ester had no influence on the reaction course. We also found that the reaction of *o*-aminophenol with triethyl orthoformate proceeded rapidly under the same reaction conditions to afford the corresponding benzoxazole (**3k**) in good yield (entry 14).

In summary, it can be concluded that $Yb(OTf)_3$ is an efficient catalyst in the reactions of *o*-diaminobenzene derivatives and ortho-esters to afford the benzimidazole derivates in good to excellent yields under solvent-free conditions in short reaction times. In contrast to the existing methods using many acidic catalysts, this method is general, simple, high yielding and environmentally friendly, avoiding the discharge of toxic volatile solvents and protic acids.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ or DMSO-d_6 using TMS as internal reference. Mass spectra were determined on Finigan 8230 mass spectrometer.



(Entries 1–13: X=N, Y=N, *n*=2, *m*=1; Entry 14: X=N, Y=O, *n*=2, *m*=1)

Scheme 2.

Table 3. $Yb(OTf)_3$-catalyzed synthesis of benzimidazole and other heterocycle derivatives under solvent-free conditions.[a]

Entry	R	R_1	R_2	Time (h)	Product	Yield (%)[b]
1	H	H	C_2H_5	1	**3a**	80
2	H	CH_3	C_2H_5	1	**3b**	40
3	H	C_2H_5	C_2H_5	1	**3c**	88
4	CH_3	H	CH_3	1	**3d**	92
5	CH_3	H	C_2H_5	1	**3d**	92
6	CH_3	CH_3	CH_3	1	**3e**	90
7	CH_3	CH_3	C_2H_5	1	**3e**	90
8	CH_3	C_2H_5	C_2H_5	1	**3f**	88
9	Cl	H	C_2H_5	2	**3g**	80
10	NO_2	H	C_2H_5	2	**3h**	75
11	NO_2	CH_3	C_2H_5	2	**3i**	75
12	OCH_3	H	C_2H_5	1	**3j**	90
13	SO_3H	H	C_2H_5	6	None	
14	H	H	C_2H_5	1.5	**3k**	80

[a]90°C for 1 h.
[b]Isolated yield.

$Yb(OTf)_3$ Catalyzed Synthesis of Benzimidazole Derivates Under Solventless Conditions

o-Diaminobenzene derivatives (1 mmol), ortho-esters (1.2 mmol), and $Yb(OTf)_3$ (0.005 mmol, 0.5 mol%) were mixed. The mixture was stirred for 1 h at 90°C. Thin-layer chromatography (TLC) showed that the initial materials almost disappeared. Then, water was added, and the product was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated, and the crude was recrystallized from diethyl ether to obtain products **3**. The catalyst remaining in the aqueous phase can be recovered by removing the H_2O by evaporation and then drying under reduced pressure at 100°C for 2 h. The following compounds were obtained:

Benzimidazole (3a): m.p. 171–172°C (lit.[1] 172–173°C); ^{1}H NMR ($CDCl_3$): $\delta = 8.10$ (*s*, 1H), 7.67–7.70 (*m*, 2H), 7.29–7.32 (*m*, 2H).

2-Methylbenzimidazole (3b): m.p. 176–177°C (lit.[1] 176–178°C); ^{1}H NMR ($CDCl_3$): $\delta = 7.53$–7.55 (*m*, 2H), 7.19–7.22 (*m*, 2H), 2.62 (*s*, 3H).

2-Ethylbenzimidazole (3c): m.p. 175–176°C (lit.[4a] 177°C); ^{1}H NMR ($CDCl_3$): $\delta = 7.54–7.56$ (*m*, 2H), 7.19–7.23 (*m*, 2H), 2.92–2.96 (*q*, 2H, $J = 7.6$ Hz), 1.47 (*t*, 3H, $J = 7.6$ Hz).

5-Methylbenzimidazole (3d): m.p. 115–116°C (lit.[13] 116–118°C); ^{1}H NMR ($CDCl_3$): $\delta = 12.49$ (*s*, 1H), 8.12 (*s*, 1H), 7.58 (*d*, 1H, $J = 8.2$ Hz), 7.48 (*s*, 1H), 7.12 (*d*, 2H, $J = 8.2$ Hz), 2.46 (*s*, 3H).

2,5-Dimethylbenzimidazole (3e): m.p. 201–203°C (lit.[14] 203–204°C); ^{1}H NMR ($CDCl_3$): $\delta = 7.43$ (*d*, 1H, $J = 8.1$ Hz), 7.33 (*s*, 1H), 7.48 (*s*, 1H), 7.06 (*d*, 1H, $J = 8.1$ Hz), 2.63 (*s*, 3H), 2.42 (*s*, 3H). MS-EI: m/z (%): 146 (M, 98), 131 (10).

2-Ethyl-5-methylbenzimidazole (3f): m.p. 163–164°C (lit.[15] 168–169°C); ^{1}H NMR ($CDCl_3$): $\delta = 7.44$ (*d*, 1H, $J = 8.2$ Hz), 7.32 (*s*, 1H), 7.04 (*d*, 1H, $J = 8.2$ Hz), 2.95 (*q*, 2H, $J = 7.6$ Hz), 2.45 (*s*, 3H), 1.14 (*t*, 3H, $J = 7.6$ Hz); MS-EI: m/z (%): 159 (M, 100), 145 (18).

5-Chlorobenzimidazole (3g): m.p. 124–125°C (lit.[1] 125–126°C); ^{1}H NMR ($CDCl_3$): $\delta = 8.47$ (*s*, 1H), 7.76 (*s*, 1H), 7.67 (*d*, 1H, $J = 8.7$ Hz), 7.29 (*d*, 1H, $J = 8.7$ Hz).

5-Nitrobenzimidazole (3h): m.p. 206–208°C (lit.[16] 203–205°C); ^{1}H NMR (DMSO-d_6): $\delta = 8.56$ (*s*, 1H), 8.51 (*s*, 1H), 8.11 (*d*, 1H, $J = 8.9$ Hz), 7.76 (*d*, 1H, $J = 8.9$ Hz).

2-Methyl-5-nitrobenzimidazole (3i): m.p. 218–221°C (lit.[16] 220–221°C); ^{1}H NMR (DMSO-d_6): $\delta = 8.38$ (*s*, 1H), 8.08 (*d*, 1H, $J = 8.9$ Hz), 7.65 (*d*, 1H, $J = 8.9$ Hz), 2.58 (*s*, 3H).

5-Methoxybenzimidazole (3j): m.p. 123–124°C (lit.[13] 123–124°C); ^{1}H NMR ($CDCl_3$): $\delta = 8.26$ (*s*, 1H), 7.58 (*d*, 1H, $J = 8.3$ Hz), 7.22 (*s*, 1H), 6.91 (*d*, 1H, $J = 8.3$ Hz), 3.80 (*s*, 3H).

Benzoxazole (3k): m.p. 30–31°C (lit.[17] 30°C); ^{1}H NMR ($CDCl_3$): $\delta = 8.42$ (*s*, 1H), 7.77 (*d*, 1H, $J = 8.2$ Hz), 7.70 (*d*, 1H, $J = 8.3$ Hz), 7.41 (*m*, 2H).

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REFERENCES

1. Valdez, J.; Cedillo, R.; Campos, A.H.; Yepez, L.; Luis, F.H.; Vazquez, G.N.; Tapia, A.; Cortes, R.; Hernandez, M.; Castillo, R. Synthesis and Antiparasitic Activity of 1H-Benzimidazole Derivatives. Bioorg. Med. Chem. Lett. **2002**, *12*, 2221–2224.
2. Tanious, F.A.; Hamelberg, D.; Bailly, C.; Czarny, A.; Boykin, D.W.; Wilson, W.D. DNA Sequence Dependent Monomer–Dimer Binding Modulation of Asymmetric Benzimidazole Derivatives. J. Am. Chem. Soc. **2004**, *126*, 143–153.
3. Fekner, T.; Gallucci, J.; Chan, M.K. Ruffling-Induced Chirality: Synthesis, Metalation, and Optical Resolution of Highly Nonplanar, Cyclic, Benzimidazole-Based Ligands. J. Am. Chem. Soc. **2004**, *126*, 223–236.
4. (a) Phillips, M.A. The Formation of 2-Substituted Benziminazoles. J. Chem. Soc. **1928**, 2393–2399; (b) Hein, D.W.; Alheim, R.J.; Leavitt, J.J. The use of Polyphosphoric Acid in the Synthesis of 2-aryl- and 2-alkyl-Substituted Benzimidazoles, Benzoxazoles and Benzothiazoles. J. Am. Chem. Soc. **1957**, *79*, 427–429.
5. Hoesl, C.E.; Nefzi, A.; Houghten, R.A. Halogenoalkyl Isocyanates as Bifunctional Reagents in an Aza-Wittig/Heterocyclization Reaction on the Solid Phase: Efficient Entry into New Tetracyclic Benzimidazole Systems. J. Comb. Chem. **2004**, *6*, 220–223.
6. Bendale, P.M.; Sun, C.-M. Rapid Microwave-Assisted Liquid-Phase Combinatorial Synthesis of 2-(Arylamino)benzimidazoles. J. Comb. Chem. **2002**, *4*, 359–361.
7. (a) Brain, C.T.; Brunton, S.A. An Intramolecular Palladium-Catalysed Aryl Amination Reaction to Produce Benzimidazoles. Tetrahedron Lett. **2002**, *43*, 1893–1985; (b) Brain, C.T.; Steer, J.T. An Improved Procedure for the Synthesis of Benzimidazoles Using Palladium-Catalyzed Aryl-Amination Chemistry. J. Org. Chem. **2003**, *68*, 6814–6816.
8. Evindar, G.; Batey, R.A. Copper- and Palladium-Catalyzed Intramolecular Aryl Guanidinylation: An Efficient Method for the Synthesis of 2-Aminobenzimidazoles. Org. Lett. **2003**, *5*, 133–136.
9. Dudd, L.M.; Venardou, E.; Garcia-Verdugo, E.; Licence, P.; Blake, A.J.; Wilson, C.; Poliakoff, M. Synthesis of Benzimidazoles in High-Temperature Water. Green Chem. **2003**, *5*, 187–192.
10. Bougrin, K.; Soufiaoui, M. Nouvelle voie de synthèse des arylimidazoles sous irradiation micro-ondes en "milieu sec". Tetrahedron Lett. **1995**, *36*, 3683–3686.
11. Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W.W.-L. Rare-Earth Metal Triflates in Organic Synthesis. Chem. Rev. **2002**, *102*, 2227–2302.

12. (a) Ma, Y.; Qian, C.; Wang, L.M.; Yang, M. Lanthanide Triflate Catalyzed Biginelli Reaction One-Pot Synthesis of Dihydropyrimidines under the Solvent-Free Condition. J. Org. Chem. **2000**, *65*, 3864; (b) Chen, R.; Qian, C.; Vries, J.G.; Sun, P.P.; Wang, L.M. Asymmetric Catalytic Epoxidation of Enones by Chiral Binaphthol-Derived Lanthanum Catalyst. Chinese Journal of Chemistry **2001**, *19*, 1225; (c) Sun, P.P.; Qian, C.; Wang, L.M.; Chen, R. La(O-i-Pr)$_3$ Catalyzed Three-Component Condensation Reaction: A Convenient Synthesis of *N*,*N*-Dialkyl-α-Cyanoamines. Synth. Commun. **2002**, *32*, 2973; (d) Wang, L.M.; Qian, C.; Tian, H.; Ma, Y. Lanthanide Triflate Catalyzed One-Pot Synthesis of Dihydropyrimidin-2(1H)-thiones by a Three-Component of 1,3-Dicarbonyl Compounds, Aldehydes, and Thiourea Using a Solvent-Free Biginelli Condensation. Synth. Commun. **2003**, *33*, 1459; (e) Wang, L.M.; Xia, J.J.; Tian, H.; Qin, F.; Qian, C.; Sun, J. Yb(OTf)$_3$ Catalyzed One-Pot Synthesis of Quinazolin-4(3H)-ones from anthranilic acid, amine, and orthoesters (or formic acid) in Solvent-Free Conditions. Synthesis **2003**, *8*, 1241; (f) Wang, L.M.; Liu, J.J.; Tian, H.; Qian, C. Ytterbium Triflate Catalyzed Heterocyclization of 1,2-Phenylenediamines and Alkyl oxalates under Solvent-Free Conditions via Phillips Reaction: A Facile Synthesis of Quinoxaline-2,3-diones derivatives. Synth. Commun. **2004**, *34*, 1.
13. Rabiger, D.J.; Joullié, M.M. The Ionization Constants, Ultraviolet and Infrared Spectra of Some Substituted Benzimidazoles. J. Org. Chem. **1964**, *29*, 476–482.
14. Green, H.; Day, A.R. The Tautomeric Character of the Imidazole Ring. J. Am. Chem. Soc. **1942**, *64*, 1167–1173.
15. Murray, M.; Ryan, A.J.; Little, P.J. Inhibition of Rat Hepatic Microsomal Aminopyrine *N*-Demethylase Activity by Benzimidazole Derivatives. Quantitative Structure–Activity Relationships. J. Med. Chem. **1982**, *25*, 887–892.
16. Rabinowitz, J.L.; Wagner, E.C. Restriction of Tautomerism in the Amidine System by Hedrogen Bonding. The Case of 4(7)-Nitrobenzimidazole. J. Am. Chem. Soc. **1951**, *73*, 3030–3037.
17. Bredereck, H.; Simchen, G.; Kantlehner, W. Reaktionen Von Dimethylamino-alkoxy-acetonitrilen. Chem. Ber. **1971**, *104*, 932–940.

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