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Tetrahedron Letters 49 (2008) 2575–2577

Tetrahedron Letters

$BF_3 \cdot SiO_2$: an efficient reagent system for the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles

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Received 7 December 2007; revised 29 January 2008; accepted 18 February 2008

Abstract

Silica-supported boron trifluoride ($BF_3 \cdot SiO_2$) is an efficient, readily available and reusable catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles using benzil, an aromatic aldehyde and an amine in the presence of ammonium acetate. This one-pot procedure is very simple, affording good to excellent yields.

Keywords: 1,2,4,5-Tetrasubstituted imidazoles; $BF_3 \cdot SiO_2$; Benzil; One-pot synthesis; Aromatic aldehyde

Multi-component reactions (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation.[1] The developing of new MCRs,[2] and improving known multi-component reactions are an area of considerable current interest. One such reaction, is the synthesis of imidazoles. Tetrasubstituted imidazole is a core section in many biological systems such as Losartan and Olmesartan.[3] The presence of an imidazole ring in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles.[4] However, despite intensive efforts, only a handful of general methods exist for the construction of tetrasubstituted imidazoles. Recently, the synthesis of 1,2,4,5-tetrasubstituted imidazoles has been catalyzed by silica gel or Zeolite HY,[5] silica gel/$NaHSO_4$,[6] molecular iodine,[7] $K_5CoW_{12}O_{40} \cdot 3H_2O$,[8] heteropolyacids[9] and $HClO_4$–SiO_2.[10]

BF_3, as a strong Lewis acid, has been used in small and large-scale reactions as an acid catalyst. In many synthetic reports, $BF_3 \cdot Et_2O$ has been used. The silica-supported form of BF_3 is a bench-top reagent which is easy to handle with better accessibility of the reactants to the active sites. When $BF_3 \cdot OEt_2$, or $BF_3 \cdot 2H_2O$ is added to a reaction mixture, particularly a protic medium, it can also function as a Brönsted acid. Exposure of high surface area oxides such as Si–O–Si or Al–O–Al to BF_3 at room temperature results in irreversible adsorption. The resulting surfaces possess surface species such as Al–OBF_2, Si–OBF_2, or the ion pairs, Al–OBF_3^- H^+ or Si–$OBF_3^-H^+$. It has been claimed that supported BF_3 is a solid superacid. If the complex $BF_3 \cdot OEt_2$ in EtOH is used to prepare a silica-supported BF_3 catalyst, Brönsted surface sites are obtained.[11]

BF_3 has been used for the rearrangement of 4-substituted-5,5-diphenyl-azepan-4-ols,[12] the Beckmann rearrangement,[13] the reduction of aromatic azides with EtSH,[14] the alkylation of acetals with manganate (R_3MnLi),[15] the synthesis of 2-substituted benzimidazoles and 3,1,5-benzoxadiazepines,[16] the conversion of alcohols to azides with NaN_3,[17] the reduction of 4,6-*o*-benzylidenes using triethylsilane,[18] the polymerization of styrene,[19] and the synthesis of 2′-*o*-cyanoethyluridine.[20] In continuation of our studies on solid acids in organic synthesis,[21] we investigated the synthesis of 1,2,4,5-tetrasubstituted imidazoles in the presence of various solid acids under thermal and sol-

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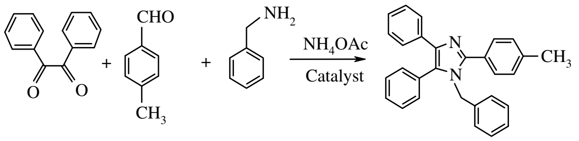
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.100

vent-free conditions. Herein, we report that $BF_3\cdot SiO_2$[22] is an efficient and reusable catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles and is comparable with other catalysts such as $K_5CoW_{12}O_{40}\cdot 3H_2O$, $HClO_4$–SiO_2 and $SiO_2/NaHSO_4$. To optimize the reaction conditions, the reaction of 4-methyl benzaldehyde, benzyl amine, benzil and ammonium acetate was used as a model reaction (Table 1). Reactions at different temperatures and various molar ratios of substrates in the presence of $BF_3\cdot SiO_2$ revealed that the best conditions were solvent-free at 140 °C and a molar ratio of aldehyde/amine/benzil/ammonium acetate/$BF_3\cdot SiO_2$ (37% w/w) of 1:1:1:1:0.21. The reusability of the $BF_3\cdot SiO_2$ catalyst was also examined. After each run, $CHCl_3$ was added and the product was filtered, the solvent evaporated and the residue (catalyst) was washed with $CHCl_3$ and reused. Apparently, treatment with $CHCl_3$ removes tars more efficiently from the catalyst surface (Table 1, entries 17 and 18). This catalyst was reusable, although a gradual decline in activity was observed.

Next, various aldehydes and amines were used as substrates for the synthesis of 1,2,4,5-tetrasubstituted imidazoles (Scheme 1 and Table 2).[23]

The products are known and were characterized by IR and ^1H NMR and through comparison of their physical properties with those reported in the literature.

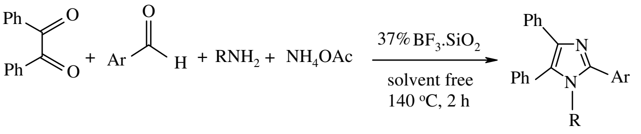
Table 1
Acid-catalyzed synthesis of 1-benzyl-4,5-diphenyl-2-*p*-tolyl-1*H*-imidazole[a]



Entry	Catalyst	Temp (°C)/time (min)	Yield[b] (%)	Ref.
1	$H_4[PMo_{11}VO_{40}]$ (1 mol %)	78/14	90	9
2	$K_5CoW_{12}O_{40}\cdot 3H_2O$	140/120	95	8
	(0.1 mol %)	MW/2	97	8
3	$SiO_2/NaHSO_4$ (0.4 g)	140/120	92	6
		MW/12	96	6
4	$SiO_2/HClO_4$ (1 mol %)	140/6	90	10
5	Zeolite HY (1 g)	MW/6	85	5
6	$ZnCl_2$ (21 mol %)	140/120	70	—
7	$SnCl_2\cdot 2H_2O$ (21 mol %)	140/120	55	—
8	$AlCl_3$ (21 mol %)	140/120	53	—
9	$MgCl_2$ (21 mol %)	140/120	50	—
10	$SnCl_4$ (21 mol %)	140/120	60	—
11	BF_3/SiO_2 (14 mol %) 33%	25/300	30	—
12	33% BF_3/SiO_2 (14 mol %)	70/240	73	—
13	33% BF_3/SiO_2 (14 mol %)	140/120	85	—
14	28% BF_3/SiO_2 (12 mol %)	140/120	80	—
15	37% BF_3/SiO_2 (16 mol %)	140/120	89	—
16	37% BF_3/SiO_2 (21 mol %)	140/120	92	—
17	37% BF_3/SiO_2 (21 mol %) 2nd run	140/120	85	—
18	37% BF_3/SiO_2 (21 mol %) 3rd run	140/120	82	—

[a] The molar ratio of 4-methylbenzaldehyde, benzylamine, benzil and ammonium acetate is 1:1:1:1.

[b] Isolated yield.



Scheme 1.

Table 2
BF_3/SiO_2-catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles[a]

Entry	Ar	R	Yield[b] (%)	Ref.	Mp °C
1	C_6H_5	C_6H_5	89	10	216–218
2	C_6H_5	$C_6H_5CH_2$	80	8	163–165
3	C_6H_5	Cyclohexyl	85	5	167–169
4	C_6H_5	CH_3CH_2	87	5	115–117
5	4-ClC_6H_4	C_6H_5	96	7	149–151
6	4-ClC_6H_4	$C_6H_5CH_2$	82	10	162–165
7	2-ClC_6H_4	$C_6H_5CH_2$	92	10	140–142
8	4-HOC_6H_4	C_6H_5	85	7	280–281
9	4-HOC_6H_4	$C_6H_5CH_2$	82	10	134–135
10	4-$CH_3C_6H_4$	C_6H_5	92	9	185–188
11	4-$CH_3C_6H_4$	$C_6H_5CH_2$	92	5	165–166
12	4-$CH_3C_6H_4$	Cyclohexyl	83	5	162–164
13	4-$CH_3C_6H_4$	CH_3CH_2	87	5	122–124
14	3-$MeOC_6H_4$	$C_6H_5CH_2$	92	10	128–130
15	2-$O_2NC_6H_4$	$C_6H_5CH_2$	93	10	152–155

[a] Ratio of benzil (mmol)/aldehyde (mmol)/amine (mmol)/ammonium acetate (mmol)/catalyst (g) is 1:1: 1:1:0.08.

[b] Isolated yield.

In conclusion, we have demonstrated a simple method for the synthesis of 1,2,4,5-tetrasubstituted imidazoles using $BF_3\cdot SiO_2$ as a reusable, eco-friendly, inexpensive and efficient reagent. Short reaction times, high yields, simplicity of operation and easy work-up are some advantages of this method.

Acknowledgments

The support for this study by the research affairs of Science and Research Branch of Azad University, Yazd University and Sharif University of Technology is gratefully acknowledged.

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22. *Preparation of silica-supported* BF_3: 5 ml of methanol containing 0.6 g (4.2 mmol) of $BF_3\cdot OEt_2$ and 0.4 g of unpreheated silica gel was stirred for 1 h at room temperature. The slurry was dried slowly on a rotary evaporator at 40 °C. The obtained solid was dried at ambient temperature for 2 h and then stored in a dry container for at least 3 months.
23. *General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles*: Benzil (4 mmol), amine (4 mmol), aldehyde (4 mmol), ammonium acetate (4 mmol) and $BF_3\cdot SiO_2$ (37% w/w) (0.32 g) were placed in a round bottom flask. The reactants were mixed and heated at 140 °C for 2 h (Table 2). The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was cooled to room temperature. Chloroform was added to the mixture which was filtered to remove the catalyst. After evaporation of the solvent, an oily residue or an impure solid was obtained. By adding ethanol and water to the residue, a milky to yellow solid was obtained. The solid was then crystallized from ethanol. All the products are known and were identified by comparison of their physical and spectral data with those of authentic samples.