Iranian Journal of Organic Chemistry Vol. 8, No. 1 (2016) 1731-1735

$BF_3.SiO_2$: an efficient catalyst for the synthesis of tetrasubstituted pyrrole derivatives

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Received: November 2015; Revised: January 2016; Accepted: January 2016

Abstract: Silica supported boron trifluoride ($BF_3.SiO_2$) was prepared by boron trifluoride diethyl etherate and powder of silicon dioxide. This catalyst was used for the synthesis of tetrasubstituted pyrrole derivatives by condensation of amine, aldehyde, 1, 3-dicarbonyl compound and nitromethane. Silica supported boron trifluoride is readily available and reusable catalyst which results good to excellent yield of products in the proposed reaction. After each run, the catalyst residue was washed with chloroform and reused. This reaction was considered by different solvents at room temperature and the reflux condition. The best conditions can be obtained using $BF_3.SiO_2$ under solvent free condition at room temperature within 90 min.

Keywords: Silica supported boron trifluoride, Tetrasubstituted pyrroles, Reusable catalyst.

Introduction

The pyrrole nucleus is the characteristic structural motif of numerous natural (storniamide A, lamellarin P, marinopyrrole B) and synthetic products [1-5]. Many polyfunctionalized pyrroles are known to display interesting biological activities, as antilipidemics (atorvastatin, Lipitor) [6, 7], antioxidants [8], and anti-inflammatories [9, 10]. They are also antibacterials [11, 12], antitumorals [13], as well as antifungal [14], antitubercular [15-17], and central nervous system agents [18]. Several methods have been developed for the preparation of tetrasubstituted pyrrole derivatives. In general, simple procedures have been employed for the synthesis of tetrasubstituted pyrroles using of 1,3-dicarbonyl compounds, amines, aldehydes, and nitroalkanes in the presence of catalysts such as iron(III) chloride [19], nickel(II) chloride [20], iodine [21], gluconic acid [22] and cerium(III) chloride heptahydrate [23].

Silica supported boron trifluoride, $BF_3.SiO_2$, which is easy to prepare and shows unusually high acidity which can be controlled by activation temperature, and exhibits considerable catalytic activity [24], enables better accessibility of the reactants to the active sites. The $BF_3.SiO_2$ is used in several organic transformations, such as *Claisen-Schmidt* condensations [25], syntheses of 14-aryl or alkyl-14*H*-dibenzo[*a*,*j*]xanthenes [26], 1,2,4,5-tetrasubstituted imidazoles [27], tetrahydrobenzo[*a*]xanthenes-11-one [28], polyfunctionalized piperidin-4-ones [29], *α*-amino phosphonates [30], quinoxalines [31], 3,4-dihydropyrimidin-2(1*H*)-ones [32] and polymerization of styrene [33], . In this study we report a new strategy for the synthesis of tetrasubstituted pyrrole derivatives by condensation of amine, aldehyde, 1,3-dicarbonyl compound and nitromethane at room temperature under solvent free.

Results and discussion

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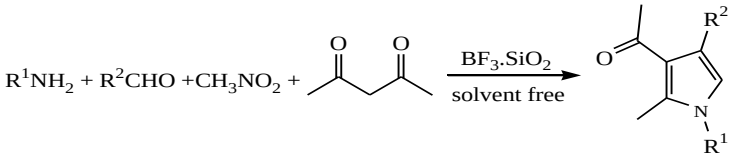
Initially, we have examined the synthesis of 3-acetyl-4-(4-chloro-phenyl)-1-(4-methoxy-phenyl)-2-methyl-1*H*-pyrrole using 4-methoxyaniline (10 mmol, 1.23 g), 4-chlorobenzaldehyde (10 mmol, 1.41 g), acetylacetone (10 mmol, 1.1 mL), nitromethane (12 mmol, 0.6 mL) and $BF_3.SiO_2$ as the catalyst under various conditions (Scheme **1**, Table **1**). We have found that the best conditions are $BF_3.SiO_2$ (10 mol%) under solvent free at room temperature in 90 min (Table **1**, entry 8). Among other condition that were used solvents such as ethanol, chloroform and water provided the desired product at room temperature for 60 min 28, 32 and scare % yield respectively. This reaction also worked by the above solvent in the reflux condition (Table **1**). The recyclability of the catalyst is an important parameter for any catalytic reaction. After each run, the catalyst residue was washed with chloroform and reused. Treatment with chloroform removes tars more efficiently from the catalyst surface (Table **1**, entries 13 and 14). The catalyst was reusable, although a gradual decline in activity was observed.



Scheme 1: Synthesis of pyrazoles under solvent free condition

Table 1: Optimization of the reaction conditions for the synthesis of 1-(1-(4-Methoxyphenyl)-2-methyl-4-Chlorophenyl-1H-pyrrol-3-yl) ethanone.

Entry	Catalyst (mol %)	Solvent	Conditions	Time (min)	Yield[a] %
1	$BF_3.SiO_2$ (10)	Chloroform	r.t.	60	32
2	$BF_3.SiO_2$ (10)	Chloroform	Reflux	60	57
3	$BF_3.SiO_2$ (10)	Ethanol	r.t.	60	28
4	$BF_3.SiO_2$ (10)	Ethanol	Reflux	60	63
5	$BF_3.SiO_2$ (10)	Water	r.t.	60	scarce
6	$BF_3.SiO_2$ (10)	Water	Reflux	60	38
7	$BF_3.SiO_2$ (10)	Solvent-free	r.t.	60	86
8	$BF_3.SiO_2$ (10)	Solvent-free	r.t.	90	91
9	$BF_3.SiO_2$ (10)	Solvent-free	r.t.	120	92
10	$BF_3.SiO_2$ (8)	Solvent-free	r.t.	90	85

11	$BF_3.SiO_2$ (12)	Solvent-free	r.t.	90	92
12	$BF_3.SiO_2$ (10)	Solvent-free	60°C	90	93
13	$BF_3.SiO_2$ (10) 2nd run	Solvent-free	r.t.	90	91
14	$BF_3.SiO_2$ (10) 2nd run	Solvent-free	r.t.	90	90

[a] Isolated yield

Next, the synthesis of tetrasubstituted pyrrole derivatives were studied and summarized in Table **2**. In all cases, the reaction proceeded smoothly to give the corresponding tetrasubstituted pyrroles in moderate to good yields. In summary, we have described $BF_3.SiO_2$ is an efficient, catalyst for synthesis of tetrasubstituted pyrrole derivatives. All of the products were characterized by FT-IR and ^{1}H-NMR.

Table 2: The synthesis of tetrasubstituted pyrrole derivatives in the presence of $BF_3.SiO_2$ via Scheme **1**.[a]

Entry	R^1	R^2	Yield (%)[b]	m.p.(°C)
1	4-$CH_3OC_6H_5$	C_6H_5	96	90-91
2	4-$CH_3OC_6H_5$	4-$OMeC_6H_4$	88	134-135
3	4-$CH_3OC_6H_5$	4-ClC_6H_4	94	117-118
4	4-$CH_3OC_6H_5$	4-FC_6H_4	97	121-122
5	4-ClC_6H_5	C_6H_5	96	127-128
6	4-ClC_6H_5	4-$OMeC_6H_4$	88	139-140
7	4-ClC_6H_5	4-ClC_6H_4	94	126-128
8	4-ClC_6H_5	4-FC_6H_4	93	133-135
9	4-BrC_6H_5	C_6H_5	88	141-143
10	4-BrC_6H_5	4-$OMeC_6H_4$	94	153-154
11	4-BrC_6H_5	4-ClC_6H_4	97	138-140
12	4-BrC_6H_5	4-FC_6H_4	96	132-134

13	4-$CF_3C_6H_5$	C_6H_5	88	145-147
14	4-$CF_3C_6H_5$	4-$OMeC_6H_4$	94	141-143
15	4-$CF_3C_6H_5$	4-ClC_6H_4	97	130-132
16	4-$CF_3C_6H_5$	4-FC_6H_4	96	147-149
17	C_6H_5	C_6H_5	88	78-79
18	C_6H_5	4-ClC_6H_4	97	105-107

[a]Amine (10 mmol), aldehyde (10 mmol), acetylacetone (10 mmol), nitromethane (12 mmol) $BF_3.SiO_2$ (10 mol%). [b]Isolated pure yield.

Conclusion

In conclusion, we have demonstrated a simple method for the synthesis of tetrasubstituted pyrrole derivatives using $BF_3.SiO_2$ as an eco-friendly, inexpensive and efficient reagent. Short reaction times, high yield, simplicity of operation and easy work-up are some advantages of this method.

Experimental

The materials were purchased from Sigma–Aldrich and Merck and were used without any additional purification. Products were characterized by FT-IR, ^{1}H-NMR and comparison of their physical properties with those reported in the literature. FT-IR spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-500 Avanes) NMR was used to record the ^{1}H NMR spectra.

Preparation of $BF_3.SiO_2$:

3.7 g of BF_3 (7.0 ml of $BF_3.Et_2O$) was added dropwise to a mixture of 6.3 gr of silicagel and 10 ml of chloroform. The mixture was stirred for 1 h at room temperature. The resulted suspension was filtered. The obtained solid was washed with chloroform and dried in a domestic microwave oven for 20 min in power 100.

General procedure for the synthesis of tetrasubstituted pyrrole derivatives:

The mixture of amine (10 mmol), aldehyde (10 mmol), 1,3-dicarbonyl compound (10 mmol), and nitromethane (10 ml) with the $BF_3.SiO_2$ (10 mol%) at the room temperature under solvent free condition. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with ethyl acetate and filtered to recover the catalyst. The obtained organic layer was dried over sodium sulfate and organic solvent was evaporated under reduced pressure and solid compound was crystallized from absolute ethanol to afford the pure corresponding tetrasubstituted pyrrole derivatives in excellent yields. All products were identified by comparison of their physical and spectral data with those of authentic samples.

Acknowledgement

The support for this study by the Research Council of University of Jiroft and Yazd University is gratefully acknowledged.

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