

BF₃.SiO₂: An Efficient Heterogeneous Alternative for Regio-Chemo and Stereoselective Claisen-Schmidt Condensation

B. Sadeghi^a, B.F. Mirjalili^{b,*} and M.M. Hashemi^c

^aFaculty of Chemistry, Islamic Azad University, Science and Research Campus, Tehran, Iran

^bDepartment of Chemistry, College of Sciences, Yazd University, Yazd, Iran, P.O.Box 89195-741

^cDepartment of Chemistry, Sharif University of Technology, P.O. Box 11365-9516, Tehran, Iran

(Received 7 October 2007, Accepted 16 February 2008)

Under solvent free conditions between 40-50 °C, BF₃.SiO₂, a mild solid acid catalyst, is applied to regio-chemo and stereoselective Claisen-Schmidt condensation. The procedure is very simple and the products are isolated with an easy workup in good to excellent yields.

Keywords: Claisen-Schmidt and crossed aldol condensations, Silica supported boron trifluoride, Solid acid, Solvent free conditions, Aldehydes, Ketones

INTRODUCTION

BF₃, as a strong Lewis acid, has been used in small and large-scale reactions as an acid catalyst. In many synthetic reports, BF₃.Et₂O has been used. The silica supported form of BF₃ is a bench-top reagent which is easy to handle providing better accessibility of the reactants to the active sites [1]. When BF₃.OEt₂, or BF₃.2H₂O, is added to a reaction mixture, particularly in a protic medium, it can also function as a Brønsted acid. Exposure of high surface area oxides such as Si-O-Si or Al-O-Al to BF₃ at room temperature results in irreversible adsorption. The resulting surfaces possess surface species such as Al-OBF₂, Si-OBF₂, or the ion pairs, Al-OBF₃⁻ H⁺ or Si-OBF₃⁻ H⁺. It has been claimed that supported BF₃ is a solid superacid. When the complex BF₃.OEt₂ in EtOH is used to prepare a silica-supported BF₃ catalyst, Brønsted surface sites are obtained [2].

BF₃ has been used for the rearrangement of 4-substituted-

5,5-diphenyl-azepan-4-ols [3], the Beckmann rearrangement [4], the reduction of aromatic azides with EtSH [5], the alkylation of acetals with manganate [6], the synthesis of 2-substituted benzimidazoles and 3,1,5-benzoxadiazepines [7], the conversion of alcohols to azides with NaN₃ [8], the reduction of 4,6-*o*-benzylidenes using triethylsilane [9], the polymerization of styrene [10] and the synthesis of 2'-*o*-cyanoethyluridine [11].

In the Claisen-Schmidt condensation, a type of crossed aldol condensation, an aromatic aldehyde combines with alkyl ketones or aldehyde to form a β-hydroxyl ketone, which is easily dehydrated to form an α,β-unsaturated ketone. Note that dehydration is especially favorable because the resulting enone is also conjugated with the aromatic ring. The resulting α,β-unsaturated ketones are useful intermediates for a large variety of compounds. Mixed or crossed aldol condensation is an effective pathway for the preparation of α,α-bis (substituted benzylidene) cycloalkanones as precursors for the synthesis of bioactive pyrimidine derivatives or nikkomycine.

Aldol condensation can be catalyzed by acids, bases,

*Corresponding author. E-mail: fmirjalili@yazduni.ac.ir

organometallic compounds or metal ions such as Mg(HSO₄)₂ [12], TiCl₃(SO₃CF₃) [13], silica sulfuric acid [14], CsOH.SiO₂ [15], V₂O₅-P₂O₅ [16], RuCl₃ [17], LiClO₄ [18], TiCl₄ [19], ZrO₂/SO₄²⁻ [20], Cu(OTf)₂ [21], Mg/Al mixed oxides [22], [Cp*Rh(η⁶-C₆H₆)](BF₄)₂ [23], NaOAc/HOAc [24], FeCl₃.6H₂O [25], ZrCl₄ [26], LiOH.H₂O [27], I₂ [28], acid-base functionalized catalyst [29] and polymer supported sulphonic acid [30].

EXPERIMENTAL

Preparation of BF₃.SiO₂

A mixture of BF₃.OEt₂ (0.57 g, 4 mmol) and preheated silica gel (0.5 g) in MeOH (5 ml) was prepared and 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 in an ambient temperature for 2 h and then was stored under dry atmosphere in a container for months.

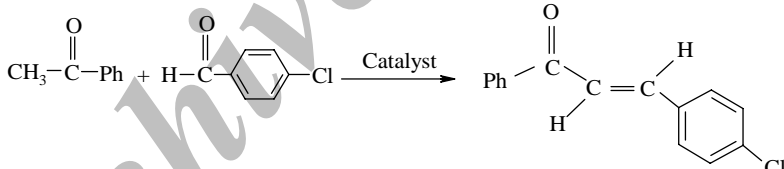
General Procedure for Claisen-Schmidt Condensation of Aldehydes with Ketones

Ketone (2 or 4 mmol), aldehyde (4 mmol) and BF₃.SiO₂ (0.32 g) were placed in a round bottom flask. The resulting mixture was mixed thoroughly and heated at 40-50 °C for 15-75 min (Table 3). The progress of the reaction was followed by TLC. After the completion of the reaction, the mixture was cooled to room temperature. Chloroform was added to the mixture which was filtered to remove the catalyst. Upon evaporation of the solvent, an oily residue or an impure solid was obtained. By adding ethanol and water to the resulting residue, a yellow to orange solid was obtained. The solid was then crystallized from ethanol. All products are known and were identified by comparing their physical or spectral data with those of authentic samples.

RESULTS AND DISCUSSION

Following the previous report about the application of solid acids in organic synthesis [31], in this work, we performed the Claisen-Schmidt condensation reaction in the presence of various available Lewis acids under thermal and solvent-free conditions or reflux (Table 1). The results showed

Table 1. Claisen-Schmidt Condensation of Acetophenone and 4-Chloro Benzaldehyde in Different Acidic Media



Entry	Catalyst	Condition/solvent	Yield (%) ^a
1	FeCl ₃ (28 mol%)	40-50 °C/-	45
2	AlCl ₃ (28 mol%)	40-50 °C/-	40
3	ZnCl ₂ (28 mol%)	40-50 °C/-	30
4	SnCl ₄ (28 mol%)	40-50 °C/-	45
5	SbCl ₅ (28 mol%)	40-50 °C/-	40
6	BF ₃ .Et ₂ O (28 mol%)	40-50 °C/-	60
7	BF ₃ .TiO ₂ (28 mol%)	40-50 °C/-	25
8	BF ₃ .ZrO ₂ (28 mol%)	40-50 °C/-	14
9	BF ₃ .SiO ₂ (28 mol%)	40-50 °C/-	90
10	BF ₃ .Al ₂ O ₃ (28 mol%)	40-50 °C/-	75
11	BF ₃ .SiO ₂ (28 mol%)	Reflux/ <i>n</i> -Hexane	85
12	BF ₃ .SiO ₂ (28 mol%)	Reflux/HOAc	86
13	BF ₃ .SiO ₂ (28 mol%)	Reflux/EtOH	81
14	BF ₃ .SiO ₂ (14 mol%)	40-50 °C/-	72
15	BF ₃ .SiO ₂ (21 mol%)	40-50 °C/-	85
16	BF ₃ .SiO ₂ (35 mol%)	40-50 °C/-	90

^aIsolated yield.

that, in this reaction, BF₃.SiO₂ is one of the best catalysts in comparison with the previously applied catalysts (Table 2). The best condition for this reaction was solvent free between 40-50 °C and the best ratio of aldehyde (mmol): BF₃.SiO₂ (g) was 1:0.08. Therefore, some aldehydes and ketones were subjected to Claisen-Schmidt condensation (Scheme 1 and Table 3).

The results showed that the reactions are completed within 45-60 min and α,β-unsaturated carbonyl compounds can be obtained with good to excellent yields (72-93%) without any self-condensation products.

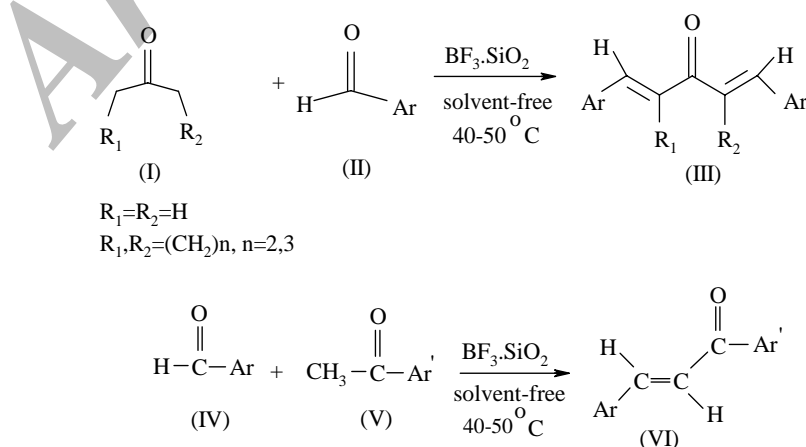
The stereoselectivity of this method was confirmed by the formation of a *trans* double bond in the Claisen-Schmidt

condensation of methyl ketones (Table 3, entries 13-18). The regioselectivity of this method was examined by the crossed aldol condensation of 2-butanone and 4-methyl-2-pentanone with 4-chloro benzaldehyde (Scheme 2). Because of the preference for acid catalyzed enolization to give more substituted enol under BF₃.SiO₂ catalyzed condensation, the branched chain ketol was formed rapidly (Scheme 2).

Also, the chemoselectivity of the reaction was evaluated via a competitive BF₃.SiO₂ catalyzed Claisen-Schmidt reaction of 4-chloro benzaldehyde (2 mmol) with a mixture of cyclohexanone (1 mmol) and acetone (1 mmol). It was found that cyclohexanone reacts with benzaldehyde in a high yield. No chemoselectivity was observed for cyclohexanone vs.

Table 2. Comparison of BF₃.SiO₂ with Previously Applied Catalysts in Condensation Reaction of Cyclohexanone and Benzaldehyde

Entry	Catalyst	Condition	Time (h)/Yield (%)	Ref.
1	Silica sulfuric acid (95 mol%)	80 °C/solvent-free	2.5/91	[14]
2	Mg(HSO ₄) ₂ (100 mol%)	60 °C/solvent-free	2.5/88	[12]
3	RuCl ₃ (1 mol%)	120 °C/solvent-free	6/95	[17]
4	TiCl ₃ (SO ₃ CF ₃) (5 mol%)	R.T./solvent-free	0.7/99	[13]
5	FeCl ₃ .6H ₂ O (50 mol%)	80 °C/solvent-free	6/90	[25]
6	I ₂ (14 mol%)	R.T./CH ₂ Cl ₂	4.5/92	[28]
7	Polymer supported sulphonic acid (35.5 mol%)	Reflux/CHCl ₃	4/86	[30]
8	NaOAc/HOAc (10 mol%)	80 °C/solvent-free/N ₂	7/86	[24]
9	BF ₃ .SiO ₂ (28 mol%)	40-50 °C/solvent-free	0.5/85	-

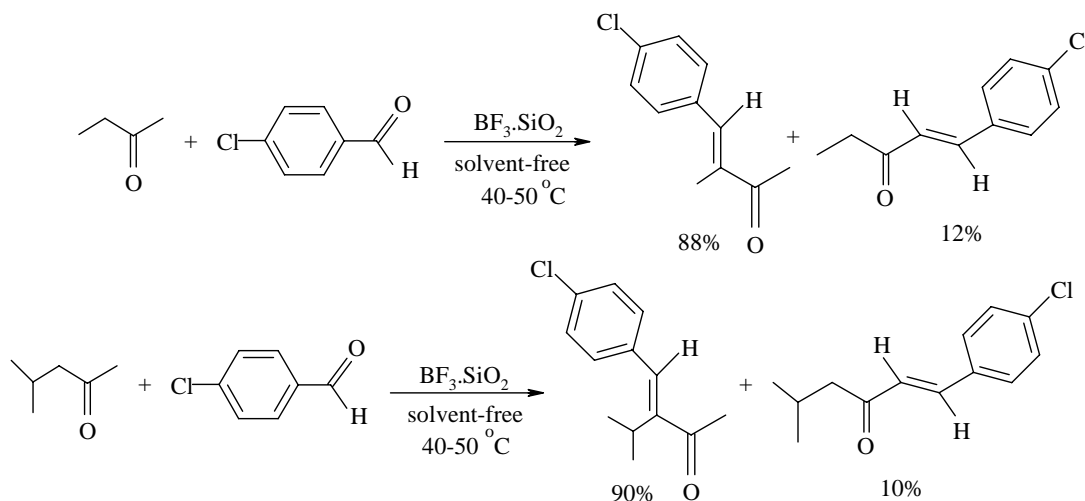


Scheme 1

Table 3. Claisen-Schmidt Condensation Promoted by $\text{BF}_3 \cdot \text{SiO}_2$ Under Solvent-Free Conditions Between 40-50 °C^a

Entry	Product	Time (min)/Yield (%) ^b	Ref. ^c	M.P. (°C)
1	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_3$, Ar = 3- NO_2 - C_6H_4	20/84	[25]	89-90
2	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_3$, Ar = 4- CH_3 - C_6H_4	83/60	[25]	165-166
3	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_3$, Ar = - C_6H_5	85/30	[18]	116-117
4	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_3$, Ar = 3- OCH_3 , 4- OH - C_6H_3	72/50	[28]	168-170
5	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_3$, Ar = 2- Cl - C_6H_4	87/30	[27]	88-89
6	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_3$, Ar = 4- OCH_3 - C_6H_4	60/73	[18]	202-204
7	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_2$, Ar = 4- OCH_3 - C_6H_4	60/75	[28]	215-216
8	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_2$, Ar = 4- CH_3 - C_6H_4	45/73	[18]	245-246
9	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_2$, Ar = 4- NO_2 - C_6H_4	88/35	[12]	230-231
10	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_2$, Ar = - C_6H_4	85/45	[25]	189-190
11	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_2$, Ar = 2- Cl - C_6H_4	79/25	[25]	152-153
12	III: $\text{R}_1, \text{R}_2 = (\text{CH}_2)_2$, Ar = 4- Cl - C_6H_4	73/25	[14]	225-226
13	VI: Ar' = Ph, Ar = 4- NO_2 - C_6H_4	70/77	[26]	159-160
14	VI: Ar' = Ph, Ar = 3- NO_2 - C_6H_4	20/75	[26]	144-145
15	VI: Ar' = Ph, Ar = 4- Cl - C_6H_4	45/90	[14]	108-109
16	VI: Ar' = Ph, Ar = 4- OMe - C_6H_4	45/80	[14]	75-76
17	VI: Ar' = Ph, Ar = 4- CH_3 - C_6H_4	40/77	[14]	97-98
18	VI: Ar' = 4- Cl - C_6H_4 - $\text{C}=\text{C}$ -, Ar = 4- Cl - C_6H_4	45/86	[29]	192-194

^aratio of aldehyde (mmol):catalyst (g) is 1:0.08. ^bIsolated yield. ^cAll products are known and were identified by their melting points, IR and ¹H-NMR spectra.



Scheme 2

acetophenone or 4-nitro benzaldehyde vs. 4-methyl benzaldehyde.

It can be inferred that silica supported boron trifluoride (BF₃.SiO₂), an inexpensive solid acid, has a high efficiency and catalyzes the Claisen-Schmidt condensation reaction in solvent-free conditions. This simple procedure offers several advantages, such as; a simple work up, easy to scale up, improved yields, regio-, stereo- and chemo-selectivity and a clean reaction.

ACKNOWLEDGEMENTS

The researchers gratefully acknowledge the financial support granted for the study by the research affairs of Science and Research Campus of Azad University, Yazd University and Sharif University of Technology.

REFERENCES

- [1] K. Wilson, D.J. Adams, G. Rothenberg, J.H. Clark, J. Mol. Catal. A: Chem. 159 (2000) 309.
- [2] T.M. Klapotke, F. Mc Monagle, R.R. Spence, J.M. Winfield, J. Fluorine Chem. 127 (2006) 1446.
- [3] M.-Y. Chang, Y.-H. Kung, T.-C. Wu, Tetrahedron 63 (2007) 3098.
- [4] M.A. Iglesias-Arteaga, A.A. Alvarado-Nuno, Tetrahedron Lett. 47 (2006) 5351.
- [5] A. Kamal, N. Shankaraiah, K.L. Reddy, V. Devaiah, Tetrahedron Lett. 47 (2006) 4253.
- [6] M. Hojo, N. Ushioda, A. Hosomi, Tetrahedron Lett. 45 (2004) 4499.
- [7] V. Tandon, M. Kumar, Tetrahedron Lett. 45 (2004) 4185.
- [8] H.M.S. Kumar, B.V.S. Reddy, S. Anjaneyulu, J.S. Yadav, Tetrahedron Lett. 39 (1998) 7385.
- [9] S.D. Debenham, E.J. Toone, Tetrahedron Asym. 11 (2000) 385.
- [10] Y. Qian, H. Zhang, X. Qian, J. Huang, C. Shen, J. Mol. Catal. A: Chem. 192 (2003) 25.
- [11] H. Saneyoshi, I. Okamoto, Y. Masaki, A. Ohkubo, K. Seio, M. Sekine, Tetrahedron Lett. 48 (2007) 8554.
- [12] P. Salehi, M.M. Khodaei, M.A. Zolfigol, A. Keyvan, Monatsh. Chem. 133 (2002) 1291.
- [13] N. Iranpoor, B. Zeynizadeh, A. Aghapour, J. Chem. Res. s (1999) 554.
- [14] P. Salehi, M. Dabiri, M.A. Zolfigol, M.A. Bodaghi Fard, J. Braz. Chem. Soc. 15 (2004) 773.
- [15] A.S. Canning, S.D. Jackson, E. Mcleod, E.M. Vass, Appl. Catal. A: General 289 (2005) 59.
- [16] M. Ai, J. Catal. 107 (1987) 201.
- [17] N. Iranpoor, F. Kazemi, Tetrahedron 54 (1998) 9475.
- [18] M.S. Abaee, M.M. Mojtahedi, R. Sharifi, M.M. Zahedi, H. Abbasi, K. Tabar-Heidar, J. Iran. Chem. Soc. 3 (2006) 293.
- [19] Y. Yoshida, N. Matsumoto, R. Hamasaki, Y. Tanabe, Tetrahedron Lett. 28 (1999) 4227.
- [20] W. Ji, Y. Chen, H.H. Kung, Appl. Catal. A: General 161 (1997) 93.
- [21] S. Orlandi, M. Benaglia, F. Cozzi, Tetrahedron Lett. 45 (2004) 1747.
- [22] M. Campanati, S. Franceschini, O. Piccolo, A. Vaccari, A. Zicmanis, Catal. Commun. 5 (2004) 145.
- [23] H. Terai, H. Takaya, T. Naota, Tetrahedron Lett. 47 (2006) 1705.
- [24] A.F.M.M. Rahman, B.S. Jeong, D.H. Kim, J.K. Park, E.S. Lee, Y. Jahng, Tetrahedron 63 (2007) 2426.
- [25] X. Zhang, X. Fan, H. Niu, Wang, J. Green Chem. 5 (2003) 267.
- [26] A. Kumar, Akanksha. J. Mol. Catal. A: Chem. 274 (2007) 212.
- [27] S. Bhagat, R. Sharma, A.K. Chakraborti, J. Mol. Catal. A: Chem. 260 (2006) 235.
- [28] B. Das, P. Thirupathi, I. Mahender, K.R. Reddy, J. Mol. Catal. A: Chem. 247 (2006) 182.
- [29] R.K. Zeidan, M.E. Davis, J. Catal. 379 (2007) 379.
- [30] L.-T. An, J.-P. Zou, L.-L. Zhang, Catal. Commun. 9 (2008) 349.
- [31] B.F. Mirjalili, M.A. Zolfigol, A. Bamoniri, M.A. Karimi Zarchi, Z. Zaghaghi, M. Parvideh, J. Iran. Chem. Soc. 4 (2007) 340.