$Zr(HSO_4)_4/SiO_2$ as an Efficient Alternative Catalyst for the Claisen-Schmidt Condensation

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Z. Naturforsch. **2008**, *63b,* 1421 – 1424; received June 4, 2008

$Zr(HSO_4)_4/SiO_2$ promotes the regio-, stereo- and chemoselective Claisen-Schmidt condensation of aromatic aldehydes with ketones under solvent-free conditions with improved yields. The work-up of the reaction mixture is simple, and the catalyst is easily removed from the products by simple filtration.

Key words: $Zr(HSO_4)_4/SiO_2$, Claisen-Schmidt Condensation, Crossed Aldol Condensation, Zirconium Hydrogensulfate, Aldehydes, Ketones, α,β-Unsaturated Ketones

Introduction

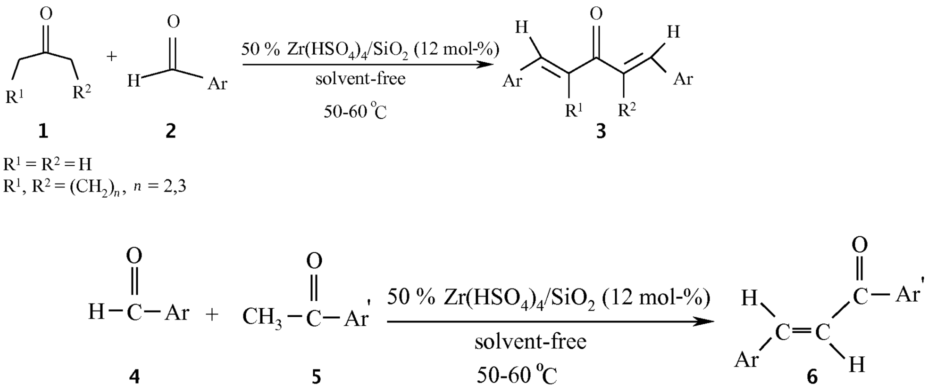
In the Claisen-Schmidt condensation, as a type of crossed aldol condensation, an aromatic aldehyde combines with alkyl ketones or aldehydes to form β-hydroxy ketones, which are easily dehydrated to form α,β-unsaturated ketones. It is worth mentioning that dehydration is especially favorable because the 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 [1]. Aldol condensation is carried out in the presence of acids or bases such as silica sulfuric acid [2], $Mg(HSO_4)_2$ [3], TiO_2 [4], $RuCl_3$ [5], $TiCl_3(SO_2CF_3)$ [6], $KHSO_4$ [7], [Cp*Rh-(η^6-C_6H_6)]$(BF_4)_2$ [8], NaOAc/HOAc [9], $ZrCl_4$ [10], $FeCl_3{\cdot}6H_2O$ [11], $LiOH{\cdot}H_2O$ [12], I_2 [13], acid-base functionalized catalysts [14], polymer-supported sulfonic acid [15], DBU-H_2O complex [16], among others. The use of toxic and expensive reagents, low yields, long reaction times and formation of a mixture of products are among the drawbacks of the reported procedures. Recently, more attention has been paid to catalysts for the Claisen-Schmidt condensation. Previously, inorganic solid acids such as $Mg(HSO_4)_2$ [3], $Al(HSO_4)_3$ [17] and $Zr(HSO_4)_4$ [18] have been used as bulk materials. The supported form of these acids is preferable because of the high dispersion and specific surface area compared with the the bulk materials, and better accessibility of reactants to the active sites. $Zr(HSO_4)_4$ has been used in reactions such as Friedel-Crafts acylation [19], cleavage of C=N bonds [20], acetylation of alcohols [21], and acylal formation [18].

Results and Discussion

In continuation of our studies on the application of solid acids in organic synthesis [18, 22 – 27], we have decided to investigate the Claisen-Schmidt condensation in the presence of some available catalysts under various conditions (Table 1).

The results indicate that the silica-supported $Zr(HSO_4)_4$ is the best catalyst system and the best molar ratio of aldehyde : ketone : 50 % $Zr(HSO_4)_4/SiO_2$ is 2 : 1 : 0.12. In the preparation of 50 % $Zr(HSO_4)_4/SiO_2$, we have used 0.2 mL of HCl (0.5 M) to prevent the dissociation of $Zr(HSO_4)_4$. Meanwhile, we found that silica-supported HCl in the absence of $Zr(HSO_4)_4$ promoted the crossed aldol condensation but gave very low yields (10 – 15 %).

It is our perception that $Zr(HSO_4)_4$ combines the properties of a Lewis acid (Zr^{4+}) and a Brønsted acid (HSO_4^-), which are both useful to catalyze the



Scheme 1.

Claisen-Schmidt condensation. To support this idea, the Claisen-Schmidt condensation was carried out separately in the presence of the same amount of $Zr(HSO_4)_4$, $ZrCl_4$, $NaHSO_4$, and H_2SO_4 (Table 1). The results show that $Zr(HSO_4)_4$ has the highest efficiency in this reaction.

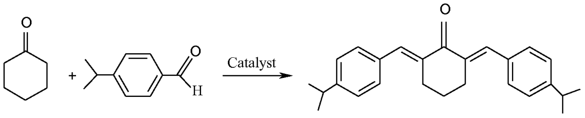
Various types of cyclic and acyclic ketones were subjected to different aromatic aldehydes containing electron-releasing or electron-withdrawing groups in the presence of 50 % $Zr(HSO_4)_4/SiO_2$ under solvent-free conditions at 50 – 60 °C (Scheme 1, Table 2).

The reactions were completed whitin 45 – 60 min with improved yields, especially from aromatic aldehydes with electron-withdrawing groups, and no self-condensation products were detected. Attempts at mono-condensation of acetone or cycloalkanones were not successful and only di-aldol products were obtained.

The stereoselectivity of this method was confirmed by the formation of a *trans* double bond in the Claisen-Schmidt condensation of methyl ketones (Table 2, entries 14 – 19).

The *trans* stereochemistry of the double bounds in the adduct of cyclopentanone with 3-nitrobenzaldehyde (Table 2, entry 11) was confirmed by NOE experiments. Irradiation of the cyclopentanone protons does not change the intensity of the vinylic protons. The regioselectivity of this method was examined by crossed aldol condensation of 2-butanone and 4-methyl-2-pentanone with 4-chlorobenzaldehyde. Because of the preference for acid-catalyzed enolization to give the more substituted enol, under $Zr(HSO_4)_4/SiO_2$-catalyzed condensation, the branched-chain ketol was formed in high yield (Scheme 2).

Table 1. Claisen-Schmidt condensation of 4-isopropyl benzaldehyde (2 mmol) and cyclohexanone (1 mmol) under various conditions.



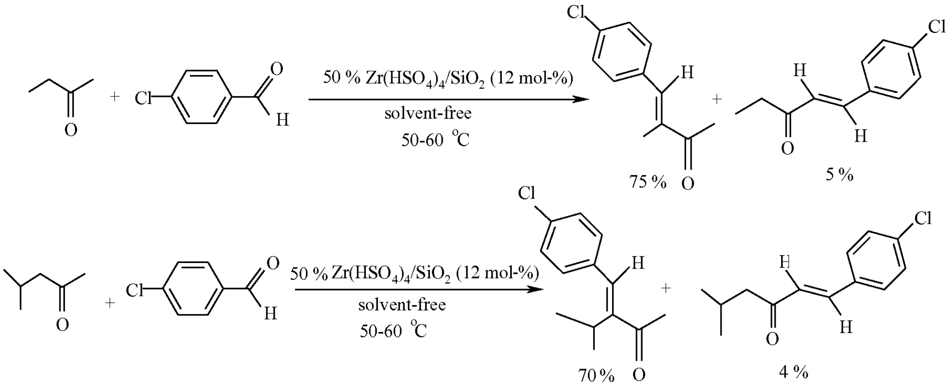
Entry	Catalyst	Condition/ Solvent	Time (min)/ Yield (%)[a]
1	$FeCl_3$ (20 mol-%)	50 – 60 °C/–	45/45
2	$AlCl_3$ (20 mol-%)	50 – 60 °C/–	45/40
3	$ZnCl_2$ (20 mol-%)	50 – 60 °C/–	54/30
4	$SnCl_4$ (20 mol-%)	50 – 60 °C/–	55/45
5	$SbCl_5$ (20 mol-%)	50 – 60 °C/–	45/60
6	ZrO_2 (20 mol-%)	50 – 60 °C/–	45/15
7	$ZrCl_4$ (20 mol-%)	50 – 60 °C/–	45/45
8	$ZrCl_4$ (20 mol-%)	reflux/CH_2Cl_2	60/52
9	$NaHSO_4$ (20 mol-%)	50 – 60 °C/–	45/35
10	$NaHSO_4$ (20 mol-%)	reflux/CH_2Cl_2	60/41
11	H_2SO_4 (20 mol-%)	50 – 60 °C/–	45/15
12	H_2SO_4 (20 mol-%)	reflux/CH_2Cl_2	60/10
13	$Zr(HSO_4)_4$ (20 mol-%)	50 – 60 °C/–	45/75
14	$Zr(HSO_4)_4$ (20 mol-%)	reflux/toluene	60/63
15	$Zr(HSO_4)_4$ (20 mol-%)	reflux/ acetonitrile	60/ 67
16	$Zr(HSO_4)_4$ (20 mol-%)	reflux/THF	60/67
17	$Zr(HSO_4)_4$ (20 mol-%)	reflux/HOAc	60/65
18	$Zr(HSO_4)_4$ (20 mol-%)	reflux/EtOH	60/68
19	$Zr(HSO_4)_4$ (20 mol-%)	reflux/CH_2Cl_2	60/70
20	$Zr(HSO_4)_4$ (20 mol-%)	ultrasound/ CH_2Cl_2	100/ 10
21	$Zr(HSO_4)_4$ (20 mol-%)	MW/HOAc	5/42
22	50 % $Zr(HSO_4)_4/SiO_2$ (12 mol-%)	50 – 60 °C/–	45/93
23	50 % $Zr(HSO_4)_4/SiO_2$ (12 mol-%)	reflux/CH_2Cl_2	60/80
24	40 % $Zr(HSO_4)_4/SiO_2$ (12 mol-%)	50 – 60 °C/–	45/78
25	60 % $Zr(HSO_4)_4/SiO_2$ (12 mol-%)	50 – 60 °C/–	45/94
26	40 % $Zr(HSO_4)_4/SiO_2$ (12 mol-%)	50 – 60 °C/–	45/81
27	50 % $Zr(HSO_4)_4/TiO_2$ (12 mol-%)	50 – 60 °C/–	45/83
28	50 % $Zr(HSO_4)_4/SiO_2$ (8 mol-%)	50 – 60 °C/–	45/80
29	50 % $Zr(HSO_4)_4/SiO_2$ (10 mol-%)	50 – 60 °C/–	45/85
30	50 % $Zr(HSO_4)_4/SiO_2$ (14 mol-%)	50 – 60 °C/–	45/94

[a] Isolated yield.

Table 2. Claisen-Schmidt condensation promoted by 50 % $Zr(HSO_4)_4/SiO_2$ under solvent-free conditions at 50 – 60 °C[a].

Entry	Product	Time (min)/ Yield (%)[b]	Ref.[c]	M. p., °C[d]
1	III: R^1,R^2 = $(CH_2)_3$, Ar = 4-NO_2-C_6H_4	45/78	11	161 – 163
2	III: R^1,R^2 = $(CH_2)_3$, Ar = 4-CH_3-C_6H_4	60/75	11	165 – 166
3	III: R^1,R^2 = $(CH_2)_3$, Ar = C_6H_5	45/93	11	116 – 117
4	III: R^1,R^2 = $(CH_2)_3$, Ar = 3-OCH_3, 4-OH-C_6H_3	50/76	13	168 – 170
5	III: R^1,R^2 = $(CH_2)_3$, Ar = 2-Cl-C_6H_4	50/88	12	88 – 89
6	III: R^1,R^2 = $(CH_2)_3$, Ar = 4-OCH_3-C_6H_4	45/79	6	202 – 204
7	III: R^1,R^2 = $(CH_2)_2$, Ar = 4-OCH_3-C_6H_4	45/74	6	215 – 216
8	III: R^1,R^2 = $(CH_2)_2$, Ar = 4-CH_3-C_6H_4	45/73	11	245 – 246
9	III: R^1,R^2 = $(CH_2)_2$, Ar = 4-NO_2-C_6H_4	45/88	6	230 – 231
10	III: R^1,R^2 = $(CH_2)_2$, Ar = C_6H_4	45/85	11	189 – 190
11	III: R^1,R^2 = $(CH_2)_2$, Ar = 3-NO_2-C_6H_4	45/87	12	201 – 203
12	III: R^1,R^2 = $(CH_2)_2$, Ar = 2-Cl-C_6H_4	45/79	11	152 – 153
13	III: R^1,R^2 = $(CH_2)_3$, Ar = 4-Cl-C_6H_4	45/76	2	147 – 148
14	VI: Ar′ = Ph, Ar = 4-NO_2-C_6H_4	60/87	10	159 – 160
15	VI: Ar′ = Ph, Ar = 3-NO_2-C_6H_4	60/89	10	144 – 145
16	VI: Ar′ = Ph, Ar = 4-Cl-C_6H_4	60/85	2	108 – 109
17	VI: Ar′ = Ph, Ar = 4-OMe-C_6H_4	60/75	2	75 – 76
18	VI: Ar′ = Ph, Ar = 4-CH_3-C_6H_4	60/78	2	97 – 98
19	VI: Ar′ = 4-Cl-C_6H_4-C=C-, Ar = 4-Cl-C_6H_4	60/78	12	192 – 194

[a] Ratio of aldehyde : ketone : 50 % Zr $(HSO_4)_4/SiO_2$ was 2 : 1 : 0.12; [b] isolated yield; [c] all products are known and were identified by their melting points, IR and ^1H NMR spectra; [d] melting points were determined with a Büchi melting point B-540 B.V.CHI apparatus.



Scheme 2.

Additionally, the chemoselectivity of the reaction was evaluated *via* a competitive $Zr(HSO_4)_4/SiO_2$-catalyzed Claisen-Schmidt reaction of 4-chlorobenzaldehyde (2 mmol) with a mixture of cyclohexanone (1 mmol) and acetone (1 mmol). It was found that cyclohexanone reacted with benzaldehyde in high yield. No chemoselectivity was observed for cyclohexanone *versus* acetophenone, or for 4-nitrobenzaldehyde *versus* 4-methylbenzaldehyde.

Conclusion

$Zr(HSO_4)_4/SiO_2$ as a solid acid has a high efficiency as catalyst of the Claisen-Schmidt condensation reaction under solvent-free conditions. This simple methodology offers several advantages including a simple work-up, opportunities for scale-up, improved yields, regio-, and stereo- and chemoselectivity.

Experimental Section

General

Carbonyl compounds were purchased from Fluka, Merck and Aldrich companies. Zirconium hydrogensulfate was synthesized according to the reported protocol [13]. We have modified the reported protocol by washing the $Zr(HSO_4)_4$ with dry acetone and drying at r. t. Products were characterized by comparison of their spectroscopic data (FT-IR, ^1H NMR) and physical properties. IR spectra were run on a Bruker, Eqinox 55 spectrometer. ^1H NMR spectra were obtained using a Bruker Avance 400 MHz spectrometer and a Bruker Avance 500 MHz spectrometer (DRX). Melting points were determined with a Büchi melting point B-540 B. V. CHI apparatus. A Kenwood domestic microwave oven, 800 Watt and 1300 MHz, was used.

Preparation of silica-supported $Zr(HSO_4)_4$

A mixture of 0.3 g of $Zr(HSO_4)_4$ and 0.3 g of silica gel was ground into fine particles. A suspension of this mixture in 0.5 mL of 0.5 M HCl was stirred for 20 min at r. t. The solvent of the suspension was evaporated at about 80 – 90 °C until dryness. The obtained solid was dried in a domestic microwave oven for 20 min at a power of 800 W.

General procedure for crossed aldol condensation of ketones with aldehydes using SiO_2-$Zr(HSO_4)_4$ under solvent-free conditions

Ketone (1 or 2 mmol), aldehyde (2 mmol) and 50 % SiO_2-$Zr(HSO_4)_4$ (0.12 mmol, 0.1 g) were placed in a round bottom flask. The materials were mixed and heated at 50 – 60 °C for 45 – 60 min. The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was cooled to r. t. Dichloromethane was added to the mixture, and the catalyst was removed by filtration. After evaporation of the solvent, an oily residue or an impure solid was obtained. By washing the residue with ethanol and water, usually a yellow to orange solid were obtained. The solid was recrystallized from ethanol. All products are known and were identified by comparison of their physical or spectral data with those of authentic samples.

Acknowledegment

Financial support for this work by the Research Council of Yazd University is gratefully acknowledged.

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