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Multicomponent, solvent-free synthesis of β-aryl-β-mercapto ketones using zirconium chloride as a catalyst☆

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Abstract—Zirconium chloride efficiently catalyzes the one-pot, three-component reaction of an aryl aldehyde, cyclic or acyclic enolizable ketones, and thiols under solvent-free conditions at room temperature to afford the corresponding β-aryl-β-mercaptoketones via aldol-Michael addition reactions. This methodology affords a large number of β-aryl-β-mercapto ketone derivatives in high yields and in short reaction times.

Multi-component reactions are useful and efficient methods in organic synthesis. The major advantages of these reactions are (1) a single purification step, (2) higher yields than stepwise assembly, (3) the use of simple and diverse precursors to construct complex molecules, and (4) the use of only a single promoter or catalyst. Thus, the development of new multi-component reactions is a popular area of research in current organic chemistry and is also acceptable from a 'Green Chemistry' point of view.[1]

β-Aryl-β-mercapto ketones are valuable synthetic scaffolds for medicinal as well as synthetic organic chemists. β-Aryl-β-mercapto ketones are useful for the synthesis of various biologically active compounds such as, thiochromans,[2] thiopyrans[3] benzothiazapines,[4] 4,5-dihydroisoxazoles, 4,5-dihydropyrazoles.[5] etc. Traditionally the synthesis of β-aryl-β-mercapto ketones is performed by a sequence of two separate reaction steps, (i) synthesis of an α,β-unsaturated ketone via an aldol reaction, (ii) 1,4-conjugate addition of a thiol to an α,β-unsaturated ketone via a thia-Michael addition. Michael addition of a thiol to chalcone is an efficient approach to prepare β-aryl-β-mercapto ketones. Consequently, there are several reports in the literature for thia-Michael addition utilizing natural and synthetic phosphates,[6] $InCl_3$,[7] $Cu(BF_4)_2{\cdot}xH_2O$,[8] $Zn(ClO_4)_2$[9] and NaOH,[10] KOH,[11] $Ba(OH)_2$,[12] hydrotalcites,[13] and Cp_2ZrH_2/$NiCl_2$,[14] for aldol condensation reactions. However, both of these reactions require cumbersome workup and purification steps. Most of these procedures have several drawbacks, are time consuming and produce lots of waste products.

Recently, zirconium chloride chemistry has attracted much attention as $ZrCl_4$ has emerged as an alternative safe, economical, air, and moisture tolerant Lewis acid which has been used in various organic transformations.[15]

Therefore, we investigated a zirconium chloride catalyzed one-pot, simple, mild, and efficient procedure for the rapid construction of β-aryl-β-mercapto ketones via a three-component aldol-Michael addition reaction between substituted cyclic or acyclic enolizable ketones **1**, aryl aldehydes **2**, and thiols **3** (Scheme 1).

To the best of our knowledge there is no report on the one-pot synthesis of β-aryl-β-mercapto ketones in the literature.

Initially, a model one-pot, three-component reaction of acetophenone **1a** (1.0 mmol), benzaldehyde **2a** (1.0 mmol) and thiophenol **3a** (1.8 mmol) was planned (Scheme 2). Several Lewis acids were screened in our model reaction (Table 1).

Interestingly, the use of other Lewis acids such as $AlCl_3$, $SnCl_4$, $ZnCl_2$, and $BF_3{\cdot}OEt_2$ slowed the reaction and

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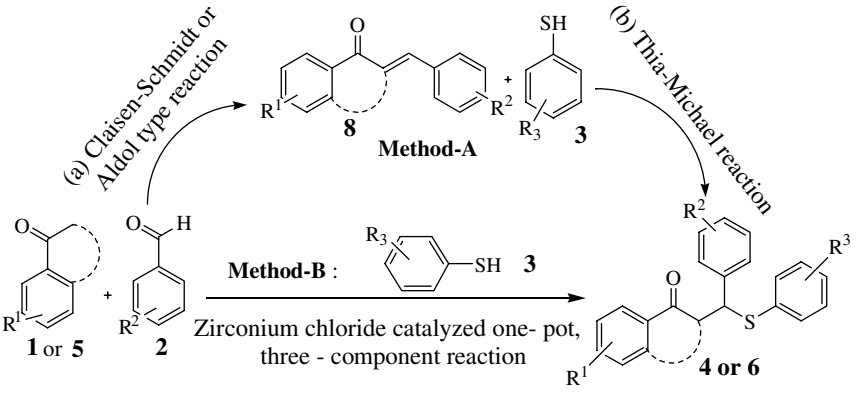
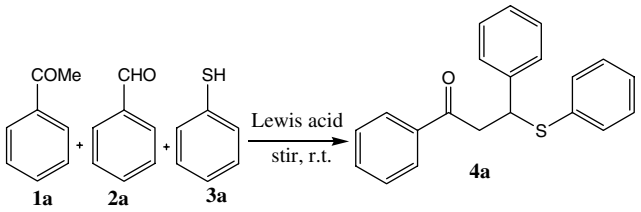
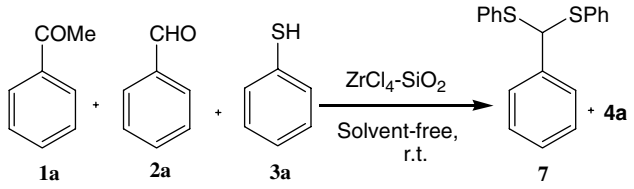


Scheme 1. Method-A (a) Clasein–Schmidt reaction or aldol type reaction, (b) thia-Michael addition reaction. Method-B (c) zirconium chloride catalyzed one- pot, three-component reaction.



Scheme 2.



Scheme 3.

Table 1. One pot, three-component synthesis of **4a** using different Lewis acids[a]

Entry	Lewis acid	Time (h)	Yield[b] (%)
1	No cat	24	—
2	$ZnCl_2$	8	NR
3	$AlCl_3$	6	10
4	$SnCl_4$	10	Trace
5	$BF_3{\cdot}OEt_2$	12	14
6	$TiCl_4$	4	10
7	$ZrCl_4$	1	92
8	$ZrCl_4/SiO_2$	1	40/48[c]
9	SiO_2	2	45[c]

Reaction conditions:
[a] Benzaldehyde (1.0 mmol), acetophenone (1.0 mmol), thiol (1.8 mmol), catalyst (30–40 mol %), rt.
[b] Isolated yield.
[c] Isolated yield of product **7**.

resulted in a small or trace amount of the desired product. It was found that only $AlCl_3$ gave a minor amount of β-aryl-β-mercapto ketone **4a** along with other side products. While $ZrCl_4$ gave a high yield of **4a** within a short time, a high molar percentage of the catalyst was required. Thus, in order to enhance the reactivity of the catalyst, silica supported $ZrCl_4$ ($ZrCl_4$–SiO_2) was used. Surprisingly, and contrary to our expectations, thioacetylated product **7** was obtained as the major product along with **4a** as a minor product (Scheme 3).

Therefore, $ZrCl_4$ alone was found to be the most effective Lewis acid catalyst for the one-pot, three-component synthesis of β-aryl-β-mercapto ketone **4**.

Various solvents such as EtOH, MeCN, CH_2Cl_2, THF, Et_2O, and PhMe were also screened for this reaction. The best results were observed under solvent-free conditions.

In order to investigate the catalyst loading in our model reaction, the procedure was optimized using different molar concentrations of zirconium chloride under solvent-free conditions at room temperature (Table 2). A high yield of adduct **4a** was observed using 40 mol % of catalyst while with 20–30 mol % of catalyst, a mixture of aldol **8** and Michael adduct **4a** was obtained. From these results, it was evident that the catalyst concentration plays a crucial role in limiting the reaction to yield products **4a** or **8**. This supported the fact that the reaction proceeds via a one-pot aldol-Michael condensation. An increased mol % of catalyst did not improve the result to any greater extent.

Table 2. Effect of catalyst loading on the one-pot, three-component reaction[a]

Entry	$ZrCl_4$[b] (%)	Time (h)	Ratio[c]
			4a (Michael):**8** (Aldol)
1	10	4.5	1.0:4.0
2	20	2.5	2.0:5.2
3	30	2.0	6.0:2.2
4	40	1.0	9.2:0.2
5	50	0.8	9.0:0.1

Reaction conditions:
[a] Benzaldehyde (1.0 mmol), acetophenone (1.0 mmol), thiol (1.8 mmol), rt.
[b] Zirconium chloride (mol %).
[c] Ratio of **4a** (Michael):**8** (aldol, PhCOCH=CHPh) product.

Table 3. Zirconium chloride catalyzed one-pot, three-component reaction of substituted benzaldehydes with substituted acetophenones and thiols[a–d]

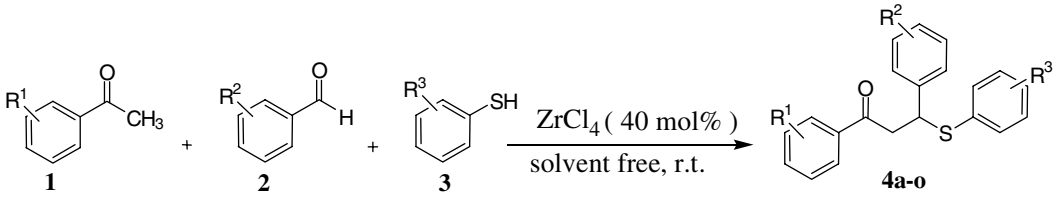
Entry	R^1	R^2	R^3	Product[c], [15]	Time (h)	Yield[d] (%)
1	H	H	H	**4a**	1.0	92
2	H	H	4-Me	**4b**	1.0	96
3	H	H	4-Cl	**4c**	1.2	90
4	4-OMe[b]	H	H	**4d**	1.5	95[17]
5	4-OMe[b]	H	4-Me	**4e**	1.2	94
6	4-OMe[b]	H	4-Cl	**4f**	1.0	92
7	H	3-NO_2[b]	H	**4g**	1.2	90
8	4-OH[b]	H	H	**4h**	1.8	88
9	H	4-OMe	H	**4i**	1.5	85
10	4- Me	3-Cl	H	**4j**	1.0	92
11	4- Me	3-Cl	4-Me	**4k**	1.0	90
12	4-OMe[b]	4-OMe	H	**4l**	0.5	92
13	4-OMe[b]	4-OMe	4-Me	**4m**	0.5	90[18]
14	H	2, 6-C l	H	**4n**	1.2	89
15	H	Ph	H	**4o**	1.5	87

Reaction conditions:
[a] Aldehyde (1.0 mmol), ketone (1.0 mmol), thiol (1.8 mmol), $ZrCl_4$ (40 mol %), solvent-free, rt.
[b] Dry CH_2Cl_2 (1–2 ml) used for solid reactants.
[c] Product characterized by IR, ^1H, ^{13}C NMR, and mass spectroscopy.
[d] Isolated yield (%) after crystallization.

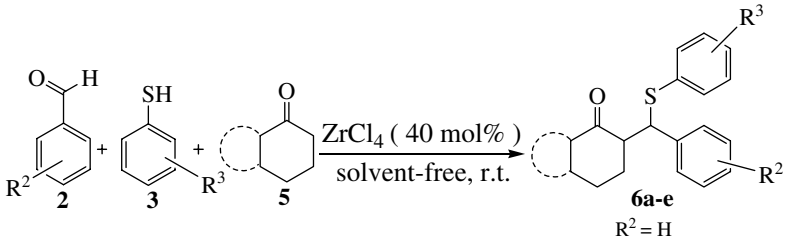
In a further investigation, a sequential one-pot reaction of benzaldehyde (1.0 mmol) and acetophenone (1.0 mmol) in the presence of zirconium chloride (20 mol %) was performed, leading to in situ generation of chalcone **8**. The progress of the reaction was monitored by TLC. After the complete consumption of benzaldehyde and acetophenone, thiophenol (2 mmol) and zirconium chloride (20 mol %) were added to the same flask. Product **4a** was obtained in 85–90% yield in 1–2 h. Encouraged by this initial result, a one-pot, three-component reaction was performed by the simple mixing of benzaldehyde (1.0 mmol), acetophenone (1.0 mmol), thiophenol (1.8 mmol), and 40 mol % of zirconium chloride. In comparison to the sequential one-pot reaction, the three-component procedure gave a comparatively high yield of **4a** within 1 h without any side product.[16]

To explore the generality and scope of this method, a wide variety of substituted aromatic aldehydes and acetophenones were reacted with substituted thiols under the same experimental conditions to afford the corresponding β-aryl-β-mercapto ketones. $ZrCl_4$ was found to be compatible with various substituents (electron withdrawing as well as donating substituents) such as OMe, OH, NO_2, Cl, and Me and the resultant products were obtained in good to excellent yields in short reaction times (Table 3) (Scheme 4).

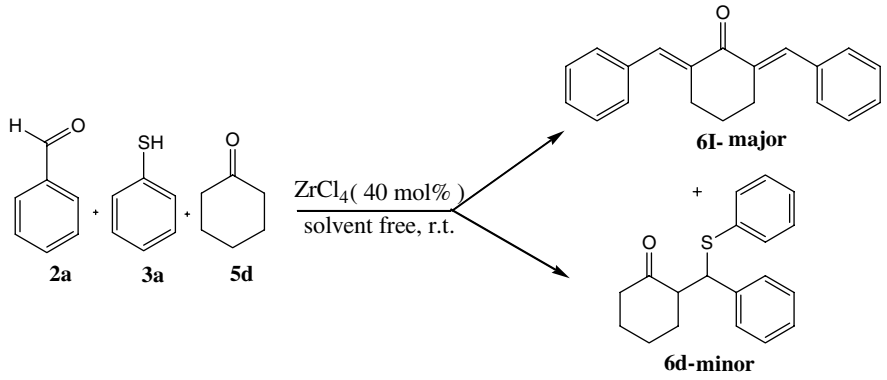
To further extend the scope and utility of this procedure, the reaction between an aromatic aldehyde **2**, a cyclic enolizable ketone (substituted tetralone, cyclohexanone) **5**, and substituted thiophenols **3** was investigated (Scheme 5).



Scheme 4.



Scheme 5.



Scheme 6.

Table 4. Zirconium chloride catalyzed one-pot, three-component coupling reaction of benzaldehyde with cyclic enolizable ketones and substituted thiophenols[a,d]

Entry	R^3	Cyclic ketone	Product[c]	Time (h)	Yield[d]
1	H	Tetralone	**6a**	1.0	90
2	4-Me	Tetralone	**6b**	1.8	94
3	H	6-OMe tetralone[b]	**6c**	1.5	88
4	H	Cyclohexanone	**6d**	1.8	10
5	4-Me	6-OMe tetralone[b]	**6e**	1.2	80

Reaction conditions:
[a] Aldehyde (1.0 mmol), ketone (1.0 mmol), thiol (1.8 mmol), $ZrCl_4$ (40 mol %), solvent-free, rt.
[b] Dry CH_2Cl_2 (1–2 ml) used for solid reactants.
[c] Product characterized by IR, ^1H, ^{13}C NMR, and mass spectroscopy.
[d] Isolated yield (%) after crystallization.

It was noticed that the reaction of cyclohexanone, benzaldehyde, and thiophenol with a catalytic amount of zirconium chloride (40 mol %) furnished the unexpected bis aldol product **6I** as the major product along with a minor amount of the desired product (**6d**) (Scheme 6).

Prolonging the reaction time and increasing the amount of $ZrCl_4$ catalyst to 80 mol % did not improve the yield of the addition product **6d**. On increasing the concentration of thiophenol, many other side products were obtained. Good results were obtained with tetralones. The results are summarized in Table 4.

All the products (Tables 3 and 4) obtained were fully characterized by spectroscopic methods including IR, ^1H NMR, ^{13}C NMR, and mass spectroscopy and also by the comparison of the spectral data with reported values.[17,18]

In conclusion, this method provides an efficient multicomponent approach for the synthesis β-aryl-β-mercapto ketones. The reaction is versatile and also offers several advantages, such as high yields, shorter reaction times, cleaner reaction profiles and simple experimental and work-up procedures.

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16. *General experimental procedure*: Solvent-free: A mixture of aromatic ketone **1** (1.0 mmol), aromatic aldehyde **2** (1.0 mmol), and zirconium chloride (40 mol %) and thiol (1.8 mmol) was stirred vigorously at room temperature for 1.5–2 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and filtered and concentrated under vacuum. The crude product was obtained in 80–96% yield and purified by simple crystallization to afford pure β-aryl-β-mercapto ketone. All the products were characterized by ^1H and ^{13}C NMR spectroscopy.
17. *Spectral data of selected compounds*. 1-(4-Methoxy-phenyl)-3-phenyl-3-phenylsulfanyl-propan-1-one, (**4d**); white solid, ^1H NMR (200 MHz, $CDCl_3$); δ 3.52–3.59 (m, 2H), 3.83 (s, 3H), 4.91 (t, 1H, $J = 6.2$ Hz), 6.86 (d, 2H, $J = 8.8$ Hz), 7.16–7.34 (m, 10H), 7.83 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 44.7, 48.7, 55.8, 114.1, 127.7, 127.8, 128.2, 128.8, 129.2, 130.3, 130.7, 133.0, 134.7, 141.7, 164.0, 195.8. MS (FAB^+) 348. Anal. Calcd for $C_{22}H_{20}O_2S$: C, 75.83; H, 5.79. Found: C, 75.80; H, 5.77.
18. *1,3-Bis-(4-methoxy-phenyl)-3-p-tolyl-sulfanyl-propan-1-one*. (**4m**); white solid, ^1H NMR (200 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.47–3.55 (m, 2H), 3.74 (s, 3H), 3.84 (s, 3H), 4.81 (t, $J = 6.1$ Hz, 1H), 6.75 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.05 (d, $J = 7.9$ Hz, 2H), 7.20–7.25 (m, 4H), 7.82 (d, $J = 8.8$ Hz, 2H,).^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5, 44.7, 48.6, 55.6, 55.8, 114.1, 114.2, 129.2, 130.0, 130.3, 130.7, 131.0, 133.7, 138.0, 159.0, 163.9, 196.2. MS (FAB^+) 392. Anal. Calcd for $C_{24}H_{24}O_3S$: C, 73.44; H, 6.16. Found: C, 73.46; H, 6.46.