An Efficient $FeCl_3$-Catalyzed Condensation of Thiols with 1,3-Dicarbonyl Compounds under Solvent-Free Conditions

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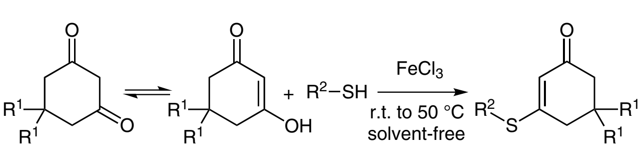
Abstract: A practical and environmentally friendly method has been developed for the synthesis of thiol-substituted cyclohex-2-enones using a $FeCl_3$-catalyzed condensation of cyclic 1,3-dicarbonyl compounds and aromatic/aliphatic thiols under solvent-free conditions at ambient temperature.

Key words: condensation, thiols, green chemistry, Lewis acids, iron

Organosulfur compounds represent an important class of bioactive organic molecules and have been widely used as pharmaceuticals, functional materials, and synthetic intermediates.[1] Indeed, a number of drugs in therapeutic areas such as inflammatory, diabetes,[2] cancer,[3] HIV,[4] and neurodegenerative (Alzheimer's and Parkinson's) diseases[5] contain a sulfide functional moiety. Due to their broad spectrum of pharmaceutical activity, organosulfur compounds have triggered ever-increasing attention in the synthetic and medicinal chemistry areas. Thiols, being the simplest organic sulfur compounds, are not only manifested in natural products, but are also utilized in the synthesis of valuable organosulfur compounds.[6,7]

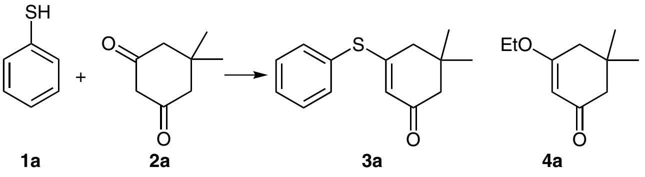
The exploration of transition-metal catalysts for the construction of carbon–sulfur bonds is of widespread interest due to the growing need for versatile, mild, and selective methods.[8] However, in comparison to C–N and C–O bond formation, the transition-metal-catalyzed construction of C–S bond has been less studied due to the deactivation of metal catalysts by the strongly coordinating sulfur compounds.[9] In recent years, iron-based catalysts have risen notably in popularity for promotion of a wide range of organic transformations.[10] The continued need for environmentally benign organic transformations has also focused on the replacement of volatile organic reaction media, leading to the development of solvent-free reactions.[11] Solvent-free conditions have many advantages[12] and are especially appealing as they provide the opportunity to work in an open vessel, circumventing the risk of pressure build up in a closed system.



Scheme 1 Synthesis of thiol-substituted cyclohex-2-enones

In view of the above and as a part of our ongoing research program,[13] we report herein a rapid and solvent-free anhydrous $FeCl_3$-catalyzed condensation of thiols and 1,3-diones to afford thiol-substituted cyclohex-2-enones in excellent yields (Scheme 1). In this regard, it is important to note that 3-substituted 5,5-dimethylcyclohex-2-ene-1-ones constitute an important class of agrochemicals.[14] Further, there exists only one report for their synthesis involving the solitary reaction of 4-methoxybenzyl mercaptan with cyclohexan-1,3-dione in acetonitrile using gold(III) catalysis.[15]

Table 1 Optimization of Reaction Conditions for **3a**[a]



1a **2a** **3a** **4a**

Entry	Catalyst (mol%)	Solvent	Yield (%)
1	–	–	–
2	Zn(L-proline)$_2$ (20)	–	19
3	CAN (20)	–	28
4	PTSA (20)	–	51
5	$AlCl_3$ (20)	–	75
6	$FeCl_3$ (20)	–	80
7	$FeCl_2\cdot 4H_2O$ (20)	–	–
8	$FeCl_3$ (20)	benzene	68
9	$FeCl_3$ (20)	MeCN	60
10	$FeCl_3$ (20)	DMF	50
11	$FeCl_3$ (20)	1,4-dioxane	65
12	$FeCl_3$ (20)	CH_2Cl_2	69
13	$FeCl_3$ (20)	H_2O	50
14	$FeCl_3$ (20)	EtOH	n.r.[b]
15	$FeCl_3$ (15)	–	81
16	$FeCl_3$ (10)	–	71

[a] Conditions: **1a** (1.2 mmol), **2a** (1 mmol), r.t., 5 h.
[b] Compound **4a** formed; n.r. = no reaction.

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In a preliminary trial, a model reaction using thiophenol **1a** and dimedone **2a** was carried out without a catalyst under solvent-free conditions at room temperature, which led to no coupled product (Table 1, entry 1). The reaction was then examined using various catalysts under the same conditions (Table 1, entries 2–7). Poor conversions were observed using Zn(L-proline)$_2$ and ceric ammonium nitrate (CAN) (Table 1, entries 2 and 3). The use of Brønsted acid (PTSA) produced the coupled product in somewhat moderate yield (Table 1, entry 4). The best results were, however, obtained when Lewis acids were used as catalyst; $AlCl_3$ and $FeCl_3$ produced the condensation product **3a** in 75% and 80% yields, respectively (Table 1, entries 5 and 6), although no product was observed when $FeCl_2 \cdot 4H_2O$ was used as catalyst (Table 1, entry 7). Consequently, $FeCl_3$ was chosen as the best catalyst to carry out further studies. To explore the effect of solvent, the model reaction was studied in different solvents using 20 mol% of $FeCl_3$ at room temperature (Table 1, entries 8–14), but none of them could match the efficacy of the solvent-free conditions. When ethanol was used as a solvent, it reacted preferentially to form product **4a**. In terms of catalyst concentration, 15 mol% of $FeCl_3$ were found sufficient to bring about the highest conversion (Table 1, entry 15), as the reaction remained incomplete when 10 mol% of the catalyst was used (Table 1, entry 16).

Having the optimized conditions in hand, the scope of the reaction was extended using a variety of thiols **1** and 1,3-diones **2**, and the outcome is summarized in Table 2. It is evident that both the aromatic as well as aliphatic thiols participate well in the reaction. However, when 2-mercaptobenzothiazole (**1g**) was employed, it did not work at all (Table 2, entry 7) probably due to the lower nucleophilicity of the thiol. With reference to the reactivity of cyclic-1,3-diones, cyclohexan-1,3-dione (**2b**) afforded higher yields in general compared to **2a**. Other active methylene compounds viz. acetylacetone and Meldrum's acid were also tried but they did not react (Table 2, entries 14 and 15).

Table 2 Reaction of Various Thiols with 1,3-Diones[16]

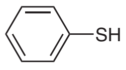
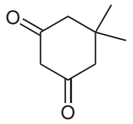
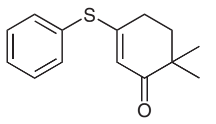
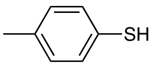
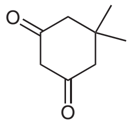
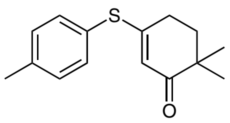
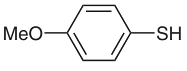
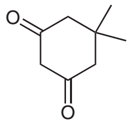
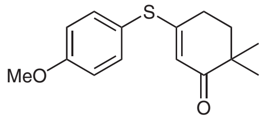
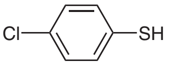
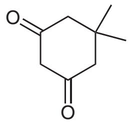
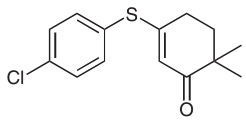
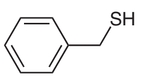
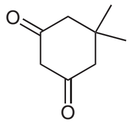
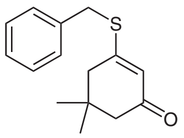
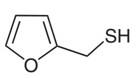
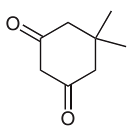
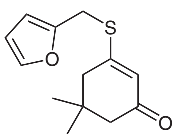
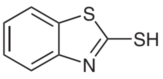
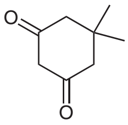
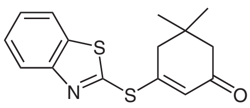
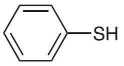
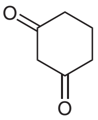
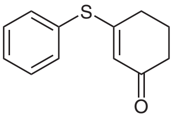
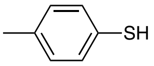
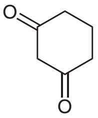
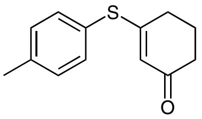
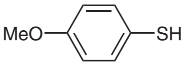
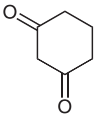
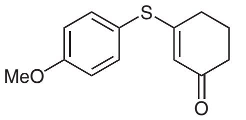
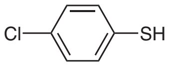
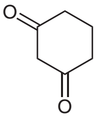
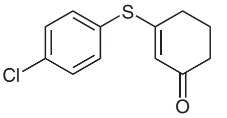
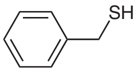
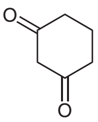
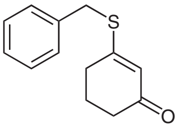
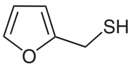
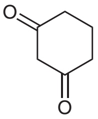
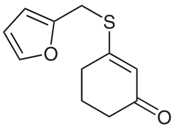
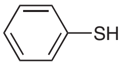
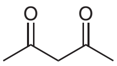
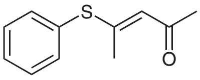
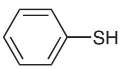
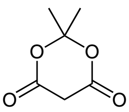
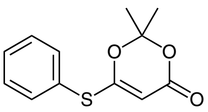
Entry	Thiol	1,3-Dione	Product	Time (h)	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	5	81
2	 **1b**	 **2a**	 **3b**	5	85
3	 **1c**	 **2a**	 **3c**	5	87
4	 **1d**	 **2a**	 **3d**	5	80[b]
5	 **1e**	 **2a**	 **3e**	4	97
6	 **1f**	 **2a**	 **3f**	4	81

Table 2 Reaction of Various Thiols with 1,3-Diones[16] (continued)

Entry	Thiol	1,3-Dione	Product	Time (h)	Yield (%)[a]
7	 **1g**	 **2a**	 **3g**	8	nr[c]
8	 **1a**	 **2b**	 **3h**	4	80
9	 **1b**	 **2b**	 **3i**	4	88
10	 **1c**	 **2b**	 **3j**	4	89
11	 **1d**	 **2b**	 **3k**	4	90[b]
12	 **1e**	 **2b**	 **3l**	3.5	96
13	 **1f**	 **2b**	 **3m**	3.5	92
14	 **1a**	 **2c**	 **3n**	8	n.r.[c]
15	 **1a**	 **2d**	 **3o**	8	n.r.[c]

[a] Isolated yield.

[b] Reaction at 50 °C.

[c] n.r. = no reaction.

In conclusion, we have developed an efficient and mild protocol for the condensation of 1,3-dicarbonyl compounds with thiols (aliphatic and aromatic) to afford thiol-substituted cyclohex-2-enones in excellent yields. The procedure uses FeCl$_3$ as catalyst under solvent-free conditions and may serve as a practical alternative to the existing methods for the synthesis of agriculturally important compounds.

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(16) **General Experimental Procedure**
The requisite thiol **1** (1.2 mmol), cyclic 1,3-dione **2** (1mmol), and anhydrous FeCl$_3$ (15 mol%) were placed in a round-bottomed flask and then stirred at r.t. to 50 °C for the specified time (Table 2). After completion of the reaction (as monitored by TLC), H$_2$O was added to the reaction mixture, and then it was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated on a rotary evaporator. The crude product was purified by column chromatography using EtOAc–hexane as eluent to afford pure product **3**.
Representative Data
5,5-Dimethyl-3-(phenylthio)cyclohex-2-enone (3a)
Solid; mp 50–52 °C (lit.[17] mp 50–51 °C). FTIR (KBr): 2955, 2868, 1662, 1574, 1454, 1305, 1279, 1239, 1021, 716 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.07 (s, 6 H), 2.22 (s, 2 H), 2.39 (s, 2 H), 5.47 (s, 1 H), 7.40–7.48 (m, 5 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 27.8, 34.1, 43.7, 50.9, 119.6, 127.9, 129.7, 130.0, 135.3, 164.8, 196.1 ppm.
3-(Phenylthio)cyclohex-2-enone (3h)
Solid; mp 44–45 °C (lit.[18] mp 43–44 °C). FTIR (KBr): 2950, 2868, 1655, 1580, 1454, 1310, 1280, 1240, 1020, 710 cm^{-1}. ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.99–2.03 (m, 2 H), 2.32–2.36 (m, 2 H), 2.48–2.51 (m, 2 H), 5.47 (s, 1 H), 7.38–7.47 (m, 5 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 22.8, 29.8, 36.8, 120.5, 127.6, 129.5, 129.8, 135.1, 166.5, 195.6 ppm.

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