

## A NEW READY ROUTE TO 1,4-KETOALDEHYDES AND 1,4-DIKETONES WITH APPLICATION TO THE SYNTHESIS OF Z-JASMONE AND DIHYDROJASMONE

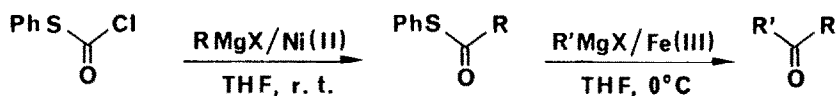
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**Summary:** A new three-step synthesis in good overall yield of 1,4-ketoaldehydes and 1,4-diketones is described. The method involves two sequential coupling reactions of Grignard reagents with *S*-phenyl carbonochloridothioate in the presence of nickel(II) or iron(III) complexes as catalysts. Application of this reaction to the synthesis of *Z*-jasmone and dihydrojasmone is also described.

In recent years, a great interest has been focused on the synthesis of 1,4-dicarbonyl compounds, since these compounds are useful starting materials for the synthesis of cyclopentenone rings which occur in many compounds of biological and commercial interest, such as prostaglandins, cyclopentanoid antibiotics, rethrolones, and jasmonoids<sup>1</sup>. Although many synthetic approaches to 1,4-dicarbonyl compounds are known<sup>1,2</sup>, most of these routes follow lengthy procedures, require multistep preparations of a special reagent, and/or involve expensive chemicals. Therefore, a simple and facile synthesis of this important class of compounds from easily accessible starting materials would be of great interest.

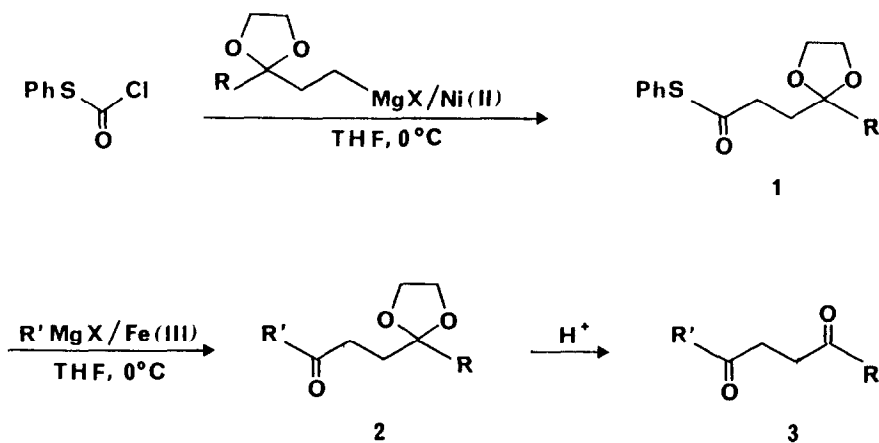
In the course of our studies on the carbon-carbon bond formation by the use of transition metal catalyzed Grignard reactions<sup>3,4</sup>, we have recently devised a new route for the synthesis of symmetrical and unsymmetrical ketones based on two sequential cross-coupling reactions between the commercially available *S*-phenyl carbonochloridothioate and Grignard reagents in the presence of nickel(II) or iron(III) complexes as catalysts<sup>4c</sup>:



**R, R' = alkyl, aryl**

As an extension of this work we now wish to report a simple and short route to 1,4-ketoaldehydes and 1,4-diketones according to the following Scheme<sup>5</sup>:

## Scheme

TABLE: Yields of products 1-3<sup>a</sup>

R	R'	1 (%)	2 (%)	3 (%)
H		85		
Me		80		
H	<i>n</i> -C <sub>6</sub> H <sub>13</sub>		85	95
H	<i>s</i> -C <sub>4</sub> H <sub>9</sub>		90	90
H	Ph		73	88
Me	<i>n</i> -C <sub>4</sub> H <sub>9</sub>		97	90
Me	<i>n</i> -C <sub>6</sub> H <sub>13</sub>		93	92
Me	<i>s</i> -C <sub>4</sub> H <sub>9</sub>		93	88
Me	Ph		75	90
Me	<i>Z</i> -C <sub>2</sub> H <sub>5</sub> CH=CHC <sub>2</sub> H <sub>4</sub>		93	86

<sup>a</sup>Yields of isolated purified products. All compounds show satisfactory spectral data (NMR, MS).

The starting point for our synthesis of 1,4-ketoaldehydes **3** (R=H) was the selective cross-coupling reaction between *S*-phenyl carbonochloridothioate and the Grignard reagent prepared from commercial 2-(2-bromoethyl)-1,3-dioxolane<sup>6</sup>, in the presence of catalytic amounts of dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II), Ni(dppe)Cl<sub>2</sub>. In the subsequent step the intermediate **1**<sup>7</sup> was reacted with several Grignard reagents in the presence of catalytic amounts of tris(acetylacetonate)iron(III), Fe(acac)<sub>3</sub>, yielding various 1,4-ketoaldehyde ethylene acetals **2**, which were converted into 1,4-ketoaldehydes **3** by deacetalization with dilute hydrochloric acid solution<sup>8</sup>.

The synthesis of 1,4-diketones **3** (R=Me) was carried out by a similar sequence of reactions. The Grignard reagent was prepared from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane<sup>9</sup>, which in turn was obtained from methyl vinyl ketone, ethylene glycol, and hydrogen bromide by a known procedure<sup>8</sup>. Then two sequential cross-coupling reactions with Grignard reagents on *S*-phenyl carbonochloridothioate were carried out, as described in the Scheme, to give half-protected diketones **2**, which were subjected to the hydrolytic cleavage of the dioxolane ring<sup>8</sup> yielding various 1,4-diketones **3**. Thus, as shown in the Table, our procedure represents a powerful and general three-step synthesis of 1,4-ketoaldehydes and 1,4-diketones in good overall yield starting from readily available reagents. Furthermore, this work opens a simple methodological path for the construction of substituted cyclopentenones. In fact, by using this method, we have easily synthesized in four steps and in good overall yield target molecules such as *Z*-jasmone and dihydrojasmone, important perfumery constituents<sup>1</sup>.

The following procedure for the synthesis of *Z*-undec-8-ene-2,5-dione **3** (R=Me, R'=Z-C<sub>2</sub>H<sub>5</sub>CH=CHC<sub>2</sub>H<sub>4</sub>), well known precursor of *Z*-jasmone, is representative. A 0.94 M freshly prepared solution of 2-(2-methyl-1,3-dioxolan-2-yl)ethylmagnesium bromide in THF (16 ml, 15 mmol) was added dropwise, under nitrogen, to a stirred solution of freshly distilled *S*-phenyl carbonochloridothioate (1.3 g, 7.5 mmol) and Ni(dppf)Cl<sub>2</sub> (0.24 g, 0.45 mmol) in 50 ml of dry THF at 0° C. After stirring for 1h at this temperature, the reaction mixture was quenched with water and the organic phase was extracted with ether, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure. Flash chromatography of the residue on a silica gel column, eluting with light petroleum/ether (80/20), afforded the pure compound **1** (R=Me, 1.5 g, 80%)<sup>7</sup> which was directly used in the subsequent step without further purification. A 0.8 M freshly prepared solution of *Z*-3-hexenylmagnesium iodide<sup>10</sup> in ether (15ml, 12 mmol) was added dropwise, under nitrogen, to a stirred solution of **1** (R=Me, 1.5 g, 6 mmol) and Fe(acac)<sub>3</sub> (0.13 g, 0.36 mmol) in 75 ml of dry THF at 0° C. After stirring for 30 min at this temperature the reaction mixture was quenched with water and the organic phase was extracted with ether, washed with NaOH 10%, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure. Flash chromatography of the residue on a silica gel column, eluting with light petroleum/ether (80/20), afforded the pure *Z*-1-(2-methyl-1,3-dioxolan-2-yl)non-6-en-3-one **2**<sup>8</sup> (R=Me, R'=Z-C<sub>2</sub>H<sub>5</sub>CH=CHC<sub>2</sub>H<sub>4</sub>, 1.25 g, 93%). The hydrolysis of the ketal function was performed by stirring **2** in acetone (60 ml) containing a catalytic amount (3-4 drops) of 3 M HCl solution for 7h at room temperature. After evaporation of the acetone, the residue was extracted with ether. The ether extracts were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent followed by distillation gave *Z*-undec-8-ene-2,5-dione (0.87 g, 86%), b.p. 136-137° C/2 torr (lit.<sup>11</sup>:138-141 °C/3 torr).

Base catalyzed cyclization<sup>12</sup> of the latter compound afforded *Z*-jasmone (0.7 g, 88%, b.p. 102-103°C /0.5 torr) which was spectroscopically (NMR, MS) identical to an authentic sample. The overall yield based on *S*-phenyl carbonochloridothioate was 56%. Careful GLC analysis on a SE 30 capillary column, 30 m, showed a *Z/E* ratio of 98/2 which is comparable to the isomer ratio in the starting *Z*-3-hexen-1-ol used for the synthesis of *Z*-3-hexen-1-yl iodide. This indicate that *Z* to *E* isomerization does not accompany the synthetic procedure.

The synthesis of the second target compound, dihydrojasmone<sup>13</sup>, was accomplished in a similar way and in 60% overall yield by using *n*-hexylmagnesium bromide as a reagent in the second step.

The main advantage of the present methodology is that the target molecules can be obtained in high purity and in good overall yields by a very short procedure using easily accessible chemicals. Now, we are continuing our efforts in exploring the application of our methodology to the synthesis of other valuable intermediates and natural products.

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- 7) **1** (R=H): b.p. 130-131° C/0.5 torr; <sup>1</sup>H-NMR (90 MHz, CDCl<sub>3</sub>/TMS): δ 2.03 (dt, 2H, J=7.6, 4.2 Hz), 2.73 (t, 2H, J=7.6 Hz), 3.60-3.95 (m, 4H), 4.88 (t, 1H, J=4.2 Hz), and 7.35 ppm (s, 5H); MS m/z (%): 129 (100), 109 (17), 85 (57), 73 (23), 45 (30). **1** (R=Me): b.p. 134-135° C/0.5 torr; <sup>1</sup>H-NMR (90 MHz, CDCl<sub>3</sub>/TMS): δ 1.29 (s, 3H), 2.03 (t, 2H, J=7.6 Hz), 2.71 (t, 2H, J=7.6 Hz), 3.89 (s, 4H), and 7.35 ppm (s, 5H); MS m/z (%): 237 (2), 143 (97), 109 (22), 99 (97), 87 (29), 43 (100).
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