

# A Convenient Synthesis of 2-Chlorophenyl Methylidene-5,5-dimethylcyclopentanone, a Key Intermediate for a Potent Fungicide against *Botrytis cinera*

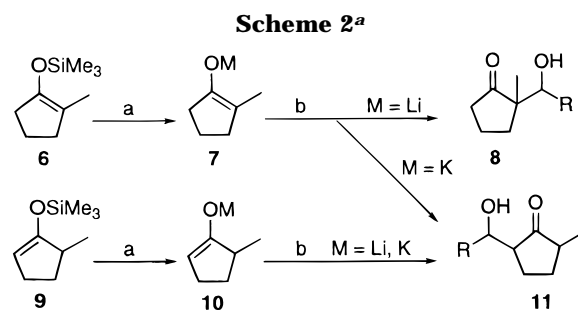
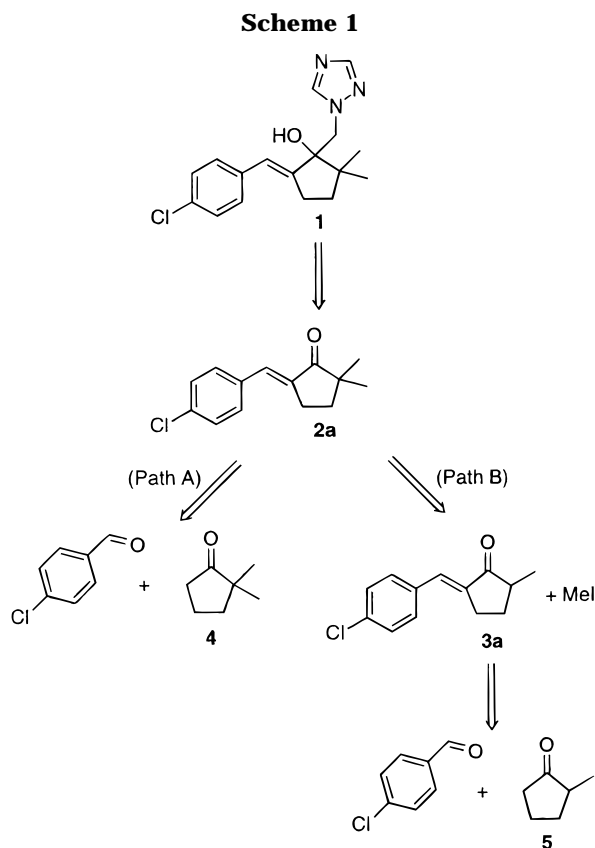
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Compound **1** is an efficient fungicide used to protect tomatoes against *Botrytis cinera* (efficiency >80%). In the reported synthesis of **1**, the key intermediate, 2-[(chlorophenyl)methylidene]-5,5-dimethylcyclopentanone (**2a**) has been obtained by aldolization of 2,2-dimethylcyclopentanone (**4**) with *p*-chlorobenzaldehyde followed by dehydration in situ of the aldol (Scheme 1, path A).<sup>1</sup> Then, ketone **2a** was condensed with dimethylsulfoxonium methylide (Corey ylide), and the resulting epoxide was opened with triazole.<sup>1</sup>

The drawback of this procedure is the access to the starting 2,2-dimethylcyclopentanone (**4**). Indeed, all methods using the monomethylation of 2-methylcyclopentanone (**5**)<sup>2</sup> and dimethylation of cyclopentanone<sup>3</sup> result in mixtures of polyalkylated cyclopentanones from which the wanted ketone **4** is very difficult to separate. Thus, many multistep procedures to prepare this ketone **4** have been reported. They either require the cyclization of 2,2-dimethyladipic acid,<sup>4</sup> 5-iodo-2,2-dimethylpentanitrile,<sup>5</sup> or 2-dimethylpent-4-enal<sup>6</sup> or pinacolic transposition reactions.<sup>7</sup> Our recent findings<sup>8,9</sup> led us to test another pathway to **2a** involving as a key step the synthesis of enone **3a** via the regioselective aldolization with *p*-chlorobenzaldehyde of commercial 2-methylcyclopentanone **5** (Scheme 1, path B).



<sup>a</sup> Reagents and conditions: (a) M = K: *t*-BuOK (1 equiv), THF, -15 °C, 45 min; M = Li: *t*-BuOK (1 equiv), THF, -15 °C, 45 min, then LiBr (5 equiv), THF, -15 °C, 15 min; (b) (i) RCHO, -78 °C, THF, 1 h, (ii) H<sub>2</sub>O, -78 °C.

We have recently reported that the condensation of potassium enolates **7** and **10** (M = K) with carbonyl compounds leads to the thermodynamically most stable aldols **11**, whereas the corresponding lithium enolates **7** and **10** (M = Li) yield the expected aldols **8** and **11**, respectively.<sup>8</sup> The potassium enolates can be easily generated from the corresponding enoxy silanes **6** and **9** and potassium *tert*-butoxide (Scheme 2).<sup>9</sup>

We studied the methodology of pathway B with two aromatic aldehydes. Our first approach required a two-step procedure: aldol **11b** (R = Ph) obtained from enoxy silanes **6** or **9** according to Scheme 2<sup>8</sup> (82% yield) was successively treated with potassium *tert*-butoxide and methyl iodide, yielding directly ketone **2b** (R = Ph, 60% yield from **11b**, 49% overall yield from **6** or/and **9**). The dehydration of the aldol occurred in situ.

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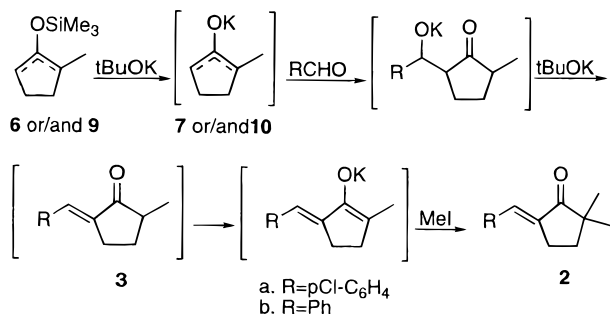
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Scheme 3



We then developed a one-pot synthesis. Mixtures of enoxy silanes **6** and **9** (**6/9** = 95/5, 50/50, 1/99) were treated with potassium *tert*-butoxide, and corresponding mixtures of potassium enolates **7** and **10** ( $M = K$ ) were condensed with *p*-chlorobenzaldehyde or benzaldehyde. Reaction of the resulting potassium aldolates with potassium *tert*-butoxide allowed their transformation into enones **3a** or **3b** which yielded, after enolization and alkylation with methyl iodide, ketones **2a** ( $R = p\text{-Cl-C}_6\text{H}_4$ ) or **2b** ( $R = \text{Ph}$ ) with an overall yield of 80% (**2a**) and 79% (**2b**) after a single crystallization (Scheme 3).

Ketone **2b** was already reported in the literature by a three-step procedure: reaction of benzaldehyde with the kinetic lithium enolate **10** of 2-methylcyclopentanone **5**, dehydration of aldol **11b** ( $R = \text{Ph}$ ) via its mesylate, and methylation of the resulting enone **3b** (overall yield 72%).<sup>10</sup> It is to be noted that in our case the potassium aldolates of **11** were spontaneously transformed into enones **3** at  $-15^\circ\text{C}$ , whereas this reaction did not occur at  $-78^\circ\text{C}$ .<sup>8,11</sup>

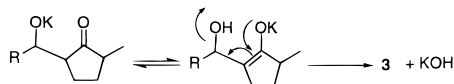
In conclusion, the highly regioselective condensation of carbonyl compounds with potassium enolates **7** or **10** led to an expeditious synthesis of the key ketone **2a** in one pot from enoxy silanes **6** or **9**. The other advantages of this procedure are that we can start from any mixture of enoxysilanes **6/9** obtained from 2-methylcyclopentanone **5** and avoid the laborious preparation of 2,2-dimethylcyclopentanone **4**.

### Experimental Section

**General Methods.** Prior to use, tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl and kept under argon.

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(11) The transformation of initial potassium aldolate into enone **3** can occur via the following equilibrium:



Potassium *tert*-butoxide was purchased from Aldrich and sublimed prior to use. Lithium bromide was dried by heating under reduced pressure. Silyl enol ethers **6** and **9** were prepared according to literature procedures<sup>12,13</sup> (according to ref 12, **6/9** = 95/5, and to ref 13, **6/9** = 1/99). NMR spectra were recorded on a Bruker A. C. spectrometer in chloroform-*d* (200 MHz for <sup>1</sup>H and 50 MHz for <sup>13</sup>C).

**Preparation of Ketone 2b from 11b.** To a solution of hydroxy ketone **11b** (5 mmol, 1.02 g, T/E = 1.4/1, *cis/trans* = 2.6/1) in THF (10 mL) under argon was added a solution of potassium *tert*-butoxide (10 mmol, 1 equiv, 1.12 mg) in THF (5 mL) at  $-20^\circ\text{C}$ , and the mixture was then stirred for 1 h. A solution of methyl iodide (2 equiv, 7.5 mmol, 412  $\mu\text{L}$ ) was added dropwise, and the mixture was stirred for additional 1 h. The mixture was quenched with water (10 mL) at  $-20^\circ\text{C}$  and extracted with diethyl ether. The extract was dried over anhydrous MgSO<sub>4</sub> and concentrated in vacuo. Ketone **2b** was obtained in 60% yield after purification by flash chromatography using petroleum ether/ether = 96/4 as eluent.

**Preparation of Ketones 2a and 2b in One Pot from 6 or 9.** To a solution of silyl enol ether **6** or **9** (or any mixture of **6** and **9**) (5 mmol, 0.85 g) in THF (10 mL) under argon was added a solution of potassium *tert*-butoxide (5 mmol, 0.56 g) in THF (5 mL) at  $-15^\circ\text{C}$ , and the mixture was then stirred for 45 min. The aromatic aldehyde (5 mmol) in THF (5 mL) was added and stirred for 1 h at this temperature. A solution of potassium *tert*-butoxide (2 equiv, 10 mmol, 1.12 g) in THF (10 mL) was then added, and the resulting mixture was stirred for 2 h. A solution of methyl iodide (1.5 equiv, 7.5 mmol, 412  $\mu\text{L}$ ) in THF (5 mL) was added dropwise, and the mixture was stirred for additional 2 h at this temperature. The mixture was quenched with water (10 mL) and extracted with diethyl ether. The extract was dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to provide a pale yellow solid. A single crystallization in pentane afforded a white solid in 80% yield (**2a**, 0.94 g, 4 mmol) and 79% yield (**2b**, 0.79 g, 3.95 mmol).

**2-Benzylidene-5,5-dimethylcyclopentanone (2b):**<sup>10</sup> mp 134  $^\circ\text{C}$ ; <sup>1</sup>H NMR  $\delta$  7.53–7.30 (m, 6H), 2.84 (d, 2H,  $J = 2.8, 6.9$  Hz), 1.80 (t, 2H,  $J = 6.9$  Hz), 1.09 (s, 6H); <sup>13</sup>C NMR  $\delta$  210.0, 125.5, 135.4, 133.2, 130.4, 129.1, 128.6, 44.7, 35.8, 25.8, 23.8; IR (neat) 2963, 1725, 1649, 1578, 1452; MS (EI,  $m/z$ ) 200, 185, 116, 91. Anal. Calcd for C<sub>14</sub>H<sub>16</sub>O: C, 83.95; H, 8.05. Found: C, 83.82; H, 7.82.

**2-[(*p*-Chlorophenyl)methylidene]-5,5-dimethylcyclopentanone (2a):**<sup>1</sup> mp 122  $^\circ\text{C}$  (lit.<sup>1</sup> mp 121  $^\circ\text{C}$ ); <sup>1</sup>H NMR  $\delta$  7.44–7.33 (4H, 2d,  $J = 8.6, 12.6$  Hz), 7.32 (s, 1H), 2.83 (2H, d,  $J = 2.7, 7.3$  Hz), 1.83 (2H, t,  $J = 7.3$  Hz), 1.10 (s, 6H); <sup>13</sup>C NMR  $\delta$  210.9, 135.8, 134.9, 134.0, 131.6, 131.5, 128.8, 44.7, 35.6, 25.7, 23.8; IR 2958, 1704, 1622, 1458, 1100, 834  $\text{cm}^{-1}$ . Anal. Calcd for C<sub>14</sub>H<sub>15</sub>ClO: C, 71.64; H, 6.44. Found: C, 71.59; H, 6.59.

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