

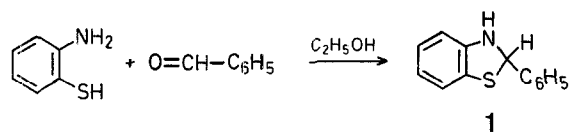
## 2-Phenylbenzothiazoline as a Reducing Agent in the Conjugate Reduction of $\alpha,\beta$ -Unsaturated Carbonyl Compounds

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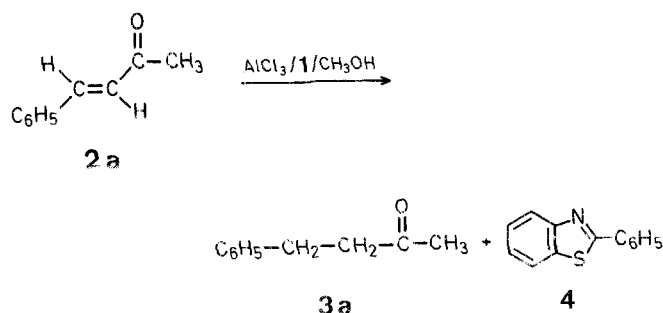
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Chemoselective hydrogenation of carbon-carbon double bonds, such as those of  $\alpha,\beta$ -unsaturated carbonyl compounds, has been a long desired synthetic transformation. Although the reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds has been effected by dissolving alkali metals in liquid ammonia<sup>1</sup> and amalgamated zinc in hydrochloric acid<sup>2</sup>, such methods are synthetically useless because of undesired side reactions. Sodium borohydride<sup>3,4</sup> also has been employed in certain cases, but lacks general utility. Recently, complex copper hydrides<sup>5,6,7</sup> or the reagents<sup>8,9</sup> obtained by the combination of complex metal hydrides with copper salts have been reported as effective reagents for conjugate reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds. However, these methods have not always afforded satisfactory results because of a lack of consistent regioselectivity. Moreover, the copper hydride reagents are quite difficult to prepare.

Recently, we reported that 2-phenylbenzimidazoline<sup>10,11</sup> prepared *in situ* was a good reducing agent for the selective reduction of carbon-carbon double bonds of  $\alpha,\beta$ -unsaturated dinitriles or  $\beta$ -nitrostyrenes. However, as yet, this method has been limited to the reduction of highly electron-deficient olefins. In continuation of our study to explore the synthetic utility of heterocyclic hydrogen donors, we have discovered that conjugate reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds by 2-phenylbenzothiazoline satisfactorily occurs in the presence of aluminium chloride. In this communication, we report results of the aluminium chloride-promoted reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds by using 2-phenylbenzothiazoline (**1**) as a reducing agent. Benzothiazoline **1** was readily prepared in quantitative yield by the reaction of *o*-aminothiophenol with benzaldehyde.



Benzylideneacetone (**2a**) was chosen as a model compound for preliminary assays of this study. Although the reduction of enone **2a** with **1** did not proceed without catalyst, we have discovered that it can be carried out with a 1.0:1.0:1.0 (mol/mol) ratio of enone **2a**:**1**:aluminium chloride in dry methanol at 80°C.



Thus, after the reaction time of 3 h, benzylacetone (**3a**), the conjugate reduction product, and 2-phenylbenzothiazole (**4**) were isolated in 87% and 98% yields, respectively. This shows evidently that carbon-carbon double bond in enone **2a** is reduced by **1** in complete selectivity and the compensating oxidation is that of **1** to 2-phenylbenzothiazole (**4**). Among the solvent tested, methanol gave best results. The use of aluminium chloride in amounts equimolar with enone **2a** is sufficient to promote the reaction, while the use of half mol of aluminium chloride relative to enone **2a** gave the reduced product in 49% yield (Table 1). In order to probe the catalytic efficiency of other Lewis acids, the reaction of enone **2a** with **1** in the presence of several kinds of Lewis acid was examined under the reaction conditions mentioned above. The results summarized in Table 1 show that the catalytic

**Table 1.** Catalytic Effect of Lewis Acids on the Yield of Benzylacetone (**3a**)<sup>a</sup>

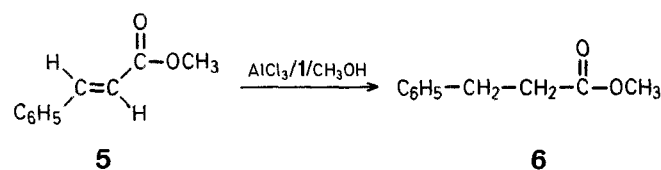
Lewis Acid	Molar Ratio of <b>2a</b> : <b>1</b> :Lewis Acid	Yield [%] <sup>b</sup> of <b>3a</b>
none	1:1:1	2
ZnCl <sub>2</sub>	1:1:1	6
FeCl <sub>3</sub>	1:1:1	43
SnCl <sub>4</sub>	1:1:1	69
AlCl <sub>3</sub>	1:1:1	100
AlCl <sub>3</sub>	1:1:0.5	49

<sup>a</sup> Reaction conditions: methanol (5 ml); benzylideneacetone **2a**, 1.0 mmol; **1**, 1.0 mmol; 80°C; 3 h.

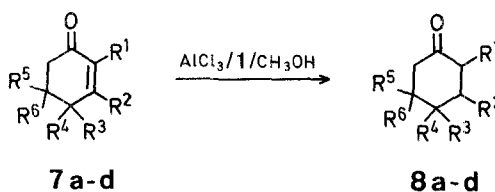
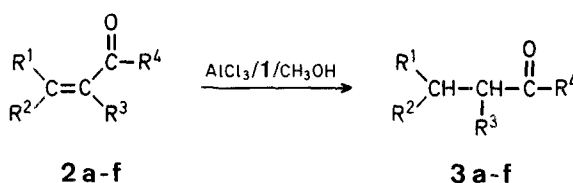
<sup>b</sup> Yield by G.L.C.

efficiency of a Lewis acid is proportional to the efficiency to form a complex with carbonyl compound<sup>12</sup>; the latter efficiency increase in the order ZnCl<sub>2</sub> < SnCl<sub>4</sub> < FeCl<sub>3</sub> < AlCl<sub>3</sub>. Thus, the Lewis acid was expected to act as an electrophilic catalyst to polarize a carbon-carbon double bond due to formation of a complex of the Lewis acid with carbonyl group. The conjugate reduction of  $\alpha,\beta$ -unsaturated ester and a similar aldehyde were also examined under the

optimum conditions. Methyl cinnamate (**5**) was less effectively reduced to give methyl 3-phenylpropanoate (**6**) in 18% yield; the conjugate reduction of cinnamic aldehyde was unsuccessful.

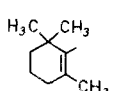


Thus, we have extended the method to a number of  $\alpha,\beta$ -unsaturated ketones **2** and **7** (Table 2).



The linear enones **2** except for 3-methyl-4-phenylbutenone (**2e**), were reduced in excellent yields. On the other hand, the reduction of cyclic enones **7** with **1** was correspondingly slower than that observed for linear enones but afforded satisfactory yields (50–65%) of saturated ketones **8**. In all cases, the conjugate reduction products were obtained in complete selectivity, and none of unsaturated alcohol, corresponding to the 1,2-reduction product, or saturated alcohol was detected. It should be noted that the rate of the reduction is influenced by the environment around the double bonds. The reduction of a linear enone possessing disubstitution at

**Table 2.** Conjugate Reduction of  $\alpha,\beta$ -Unsaturated Ketones **2** and **7** with Benzothiazoline **1** in the Presence of Aluminium Chloride<sup>a</sup>

Product	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	Reaction time [h]	Yield <sup>b</sup> [%]	m.p. [°C] or b.p. [°C/torr]		M.S. <i>m/e</i>
									found	reported	
<b>3a</b>	H	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	—	—	3	100(89) <sup>c</sup>	115–118°/16	110–112°/12 <sup>13</sup>	148
<b>3b</b>	H	C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	—	—	3	90(71)	72.5–73.5°	72° <sup>14</sup>	210
<b>3c</b>	H	C <sub>6</sub> H <sub>5</sub> -CO	H	C <sub>6</sub> H <sub>5</sub>	—	—	3	100(91)	145–146°	142–143° <sup>15</sup>	238
<b>3d</b>	CH <sub>3</sub>	CH <sub>3</sub>	H	CH <sub>3</sub>	—	—	24	76(63)	45.5–46.0°/80	117°/760 <sup>16</sup>	100
<b>3e</b>	H	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	CH <sub>3</sub>	—	—	24	26(16)	104–105°/18	102–104°/12 <sup>13</sup>	162
<b>3f</b>	H		H	CH <sub>3</sub>	—	—	3	100(98)	105–107°/3	122–122.5°/12 <sup>17</sup>	194
<b>8a</b>	H	H	H	H	H	H	24	55(26)	74.0–74.5°/45	153–156°/760 <sup>18</sup>	98
<b>8b</b>	H	CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	24	65(50)	54–56°/12	201–203°/750 <sup>19</sup>	140
<b>8c</b>	CH <sub>3</sub>	H	H	H	H	H	24	50(25)	46.5–47.0°/12	155–164°/760 <sup>20</sup>	112
<b>8d</b>	H	—(CH <sub>2</sub> ) <sub>4</sub>	—	CH <sub>3</sub>	H	H	24	52(11) <sup>d</sup>	( <i>cis</i> ) 175–176.5° <sup>e</sup> ( <i>trans</i> ) 178.5–180° <sup>e</sup>	175–176° <sup>21</sup> 178–179° <sup>21</sup>	—

<sup>a</sup> 1.2:1 molar ratio of benzothiazoline **1** and aluminium chloride to enone (1 mmol) was used.

<sup>b</sup> Yield determined by G.L.C.

<sup>c</sup> The values in the parentheses indicate the yield of pure, isolated product.

<sup>d</sup> Yield of isomeric mixture; *cis/trans* ratio: 65/35 (G.L.C. analysis on Silicon OV-7).

<sup>e</sup> m.p. of 2,4-dinitrophenylhydrazone derivative.

the  $\alpha$ - or  $\beta$ -carbon of the enone was more sluggish than that observed for benzylideneacetone (**2a**) and relative reactivities decrease in the order  $\alpha,\beta$ -monosubstitution >  $\alpha$ -mono- $\beta$ -disubstitution >  $\alpha$ -di- $\beta$ -monosubstitution. A similar trend was also observed in the case of cyclic enones.

The mechanism of the present reduction has not been studied yet. The reaction may proceed through an initial formation of a complex produced from the enone and aluminium chloride. The next redox reaction may be interpreted by a mechanism involving hydride transfer from the C-2 carbon in **1** to the enone.

The present study is the first example of the conjugate reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds by a heterocyclic hydrogen donor, and provides a unique and convenient method for this type of reaction. The present method has following advantages:

- complete regioselectivity,
- no side reactions,
- operational simplicity,
- easy preparation of the reducing agent.

Further studies on the scope and limitations, as well as applications to other systems, are now in progress.

#### 2-Phenylbenzothiazoline (**1**):

Benzaldehyde (10.6 g, 0.1 mol) is added to a solution of *o*-aminothiophenol (12.5 g, 0.1 mol) in ethanol (20 ml) and the mixture is stirred at room temperature. Pale yellow needles separate after 40 min and are collected by filtration and dried in vacuo. Recrystallization is carried out from ethanol; yield: 20.1 g (94%); pale yellow needles; m.p. 77°C (Ref.<sup>22</sup>, m.p. 77°C).

C<sub>13</sub>H<sub>11</sub>NS calc. C 73.20 H 5.20 N 6.57  
(213.3) found 73.22 5.14 6.45

<sup>1</sup>H-N.M.R. (CDCl<sub>3</sub>/TMS):  $\delta$  = 4.19 (s, 1H, NH); 6.26 (s, 1H, CH); 6.45–6.95 (m, 4H, C<sub>6</sub>H<sub>4</sub>); 7.03–7.55 ppm (m, 5H, C<sub>6</sub>H<sub>5</sub>).

I.R. (KBr):  $\nu$  = 3390, 1580, 1300, 740, 700 cm<sup>-1</sup>.

#### Saturated Ketones **3** and **8**; General Procedure:

A solution of unsaturated ketone **2** or **7** (1.0 mmol) in dry methanol (5 ml) and aluminium chloride (0.16 g, 1.2 mmol) are mixed in a glass tube under ice-water cooling. After the aluminium chloride has completely dissolved, 2-phenylbenzothiazoline (**1**; 0.26 g, 1.2 mmol) is added and the mixture is degassed several times in vacuo. The tube is sealed in vacuo and kept at 80°C for the appropriate time (Table 2). After 0.1 normal hydrochloric acid (5 ml) has been added to the mixture in the tube under ice-water cooling, the aqueous mixture is extracted with chloroform (2 × 5 ml). The chloroform extract is washed thoroughly with 0.5 normal hydrochloric acid (3 × 5 ml) and dried with anhydrous sodium sulfate. The oily residue obtained by evaporation of solvent is subjected to short column chromatography on silica gel. Elution with hexane/benzene affords the pure product.

In a large scale synthesis, the reaction could be also carried out in a three necked flask under nitrogen and the same reaction conditions. After workup as above, the product is isolated by distillation or short column chromatography on silica gel.

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