TRANSESTERIFICATION REACTIONS WITH Mg$^0$/I$_2$ FOR THE SYNTHESIS OF SITOPHILATE, (2R*, 3S*)-1-ETHYLPROPYL-2-METHYL-3-HYDROXYPENTANOATE, AN AGGREGATION PHEROMONE FOR SITOPHILUS GRANARIUS LINNAEUS, 1785 (COLEOPTERA: CURCULIONIDAE)

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ABSTRACT
The concern to minimize the environmental impacts caused by the use of pesticides in agriculture has led researchers to develop new pest control methods. Thus, the technology based on the use of pheromones has been noted for being highly specific substances, that is act only on individuals of the same species. In this context, we describe the synthesis of sitophilate, aggregation pheromone of Sitophilus granarius, an important pest of stored cereal grains. The sitophilate was obtained by transesterification of methyl-2-methyl-3-oxopentanoate with 3-pentanol mediated by Mg$^0$/I$_2$, with subsequent reduction of the ketone group of 1-ethylpropyl-2-methyl-3-oxopentanoate using NaBH$_4$ in the presence of a Lewis acid (ZnCl$_2$, MgCl$_2$, CaCl$_2$ and MnCl$_2$). The experimental results showed that the MnCl$_2$ is the most effective for the formation of syn diastereoisomers, since these are the compounds that exert biological activity on the insect.

KEYWORDS: Synthesis, pheromone, sitophilate, Sitophilus granarius, β-keto ester.

RESUMO
A preocupação em minimizar os impactos ambientais ocasionados pelo uso de agrotóxicos na agricultura tem levado pesquisadores a desenvolver novos métodos de controle de pragas. Assim, a tecnologia baseada no uso de feromônios tem se destacado por serem substâncias altamente específicas, ou seja, agem apenas sobre indivíduos de uma mesma espécie. Neste contexto, descrevemos a síntese do sitofilato, feromônio de agregação do Sitophilus granarius, uma importante praga de grãos de cereais armazenados. O sitofilato foi obtido através da transesterificação do 2-metil-3-oxopentanoato de metila com 3-Pentanol mediada por Mg$^0$/I$_2$, com posterior redução do grupo cetona do 2-metil-3-oxopentanoato de 1-etilpropila utilizando NaBH$_4$ na presença de um ácido de Lewis (ZnCl$_2$, MgCl$_2$, CaCl$_2$ e MnCl$_2$). Os resultados experimentais mostraram que o MnCl$_2$ é o mais efetivo para a formação dos diastereoisômeros syn, uma vez que estes compostos são os que exercem atividade biológica no inseto.

PALAVRAS-CHAVE: Síntese, feromônio, sitofilato, Sitophilus granarius, β-cetoestérides.
1 INTRODUCTION

The β-keto esters are important intermediates in organic synthesis, as they are used in the preparation of various natural products in research laboratories, for the pharmaceutical and agrochemical industries, and for polymers manufacture (MA et al., 2016, NOVACEK et al., 2016, MINAMI et al., 2016, WANG et al., 2011, SAIRRE et al., 2005, BO et al., 2003, CHAVAN et al., 2002, WEST & GUNAWARDENA, 1993, HOLQUIST & ROSKAMP, 1990, KLIPA & HART, 1981, BARCO et al., 1980, BECKET et al., 1978). The transesterification reaction (Figure 1) is an important methodology for the transformation of one ester to another (LIU et al., 2016, SRIDHARAN et al., 2010, IWASAKI et al., 2008, YADAV et al., 2007). This may be carried out spontaneously at high temperature or by using homogeneous or heterogeneous catalysis in an acidic, basic (KIM & KIM, 2016, NAGANAWA et al., 2015, RAFIEE & EAVANI, 2012, PANDEY & KUMAR, 2007) or enzymatic (RAVIA et al., 2013, DHAKE et al., 2011, KALAITZAKIS et al., 2007, CORDOVA & JANDA, 2001, PUNTAMBEKAR & NAIK, 1998) medium by using a Dean Stark apparatus.

\[
\begin{align*}
\text{Catalyst} \quad \text{Solvent, reflux} \\
\text{R}_1 \text{O} \text{R}_2 \text{O} \text{R}_3 + \text{R}_4\text{OH} & \rightarrow \quad \text{Catalyst} = \text{MgO/I}_2 \\
& \quad \text{Solvent} = \text{Toluene} \\
\text{R}_1 \text{O} \text{R}_4 \text{O} \text{R}_3 + \text{R}_2\text{OH}
\end{align*}
\]

Figure 1: General transesterification reaction.

In this study, some β-keto esters were prepared using ethyl acetoacetate as the substrate, and iodine and magnesium metal as the catalysts, in order to verify the feasibility and the best experimental conditions for the reaction. Afterward, this methodology was applied to the synthesis of syn stereoisomers of sitophilate, (2R*,3S*) 1-ethylpropyl-2-methyl-3-hydroxypentanoate (1a and 1b) (Figure 2). These compounds are major components of the aggregation pheromone of grain weevil Sitophilus granarius (KALAITZAKIS & SMONOU, 2008, PHILLIPS et al., 1987), an insect that severely damages wheat, barley, corn and other cereals. Such damage causes annual losses of millions of dollars to farmers in many countries (MATEUS et al., 2001, CHAMBERS et al., 1996).

\[
\begin{align*}
\text{1a} \\
\text{1b}
\end{align*}
\]

Figure 2: Structure of the syn stereoisomers of sitophilate.

In the biological studies, a racemic mixture of sitophilate (syn stereoisomers) showed attractiveness similar to the natural product, and unlike the anti stereoisomers (pure or racemic...
mixture), which was shown to be less attractive (MATEUS et al., 2001, BERGMANN et al., 2009, GIL et al., 2005, CHAVAN et al., 1996, RAZKIN et al., 1996, MORI & ISHIKURA, 1989, CHONG, 1989).

2 EXPERIMENTAL

2.1 General procedure for transesterification reactions

In a 125-mL bi-tubular flask coupled to a reflux condenser and under an inert atmosphere, activated metallic magnesium (1.2 g; 50 mmol) was introduced, and then the starting ester (volume and mass dependent on the respective esters; 7.7 mmol) in 10 mL of dry toluene, was slowly added. Under magnetic stirring, the alcohol (mass and volume dependent on the respective alcohols, 21 mmol) was slowly added. After 10 min, I$_2$ (0.3 g; 1.2 mmol) was added. The mixture was heated to reflux at the conditions shown in Table 1. The reactions were monitored by thin-layer chromatography and the plates were developed with the chromogen agent KMnO$_4$ in acidic solution. At the end of the reaction, 20 mL of saturated NH$_4$Cl solution was added. The reaction products obtained were extracted with three portions of 30 mL of ethyl ether, and the organic phase were poured together and washed three times with 40 mL of saturated solution of NaCl and dried over anhydrous Na$_2$SO$_4$, filtered and the solvent was then evaporated. The crude products were purified by column chromatography on silica gel by elution with a gradient of increasing polarity with hexane/ethyl acetate (5%, 10%, 15%, and 20%). The fractions corresponding to the transesterified products were analyzed and characterized by $^1$H NMR, $^{13}$C NMR and GC–MS.

Pentyl-3-oxobutanoate (2)

Yield = 77 %, (mass = 1.01 g ± 0.02).

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.91 (t, 3H, J 6.8 Hz, CH$_3$), 1.35–1.32 (m, 4H, CH$_2$), 1.65 (qt, 2H, J 6.9 Hz, CH$_2$), 2.27 (s, 3H, CH$_3$), 3.46 (s, 2H, CH$_2$), 4.14 (t, 2H, J 6.8 Hz), 4.99 (s, 1H, CH$_{\text{enolic}}$), 12.12 (s, 1H, OH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 13.95, 22.30, 27.99, 28.21, 30.13, 50.14, 65.54, 89.79, 167.26, 172.77, 175.42, 200.68. MS m/z (%) 172 ([M]+, 0.28), 130 (0.32), 115 (1.08), 103 (31.41), 85 (44.18), 70 (55.65), 55 (45.24), 43 (100.00), 42 (65.24).

Hexyl-3-oxobutanoate (3)

Yield = 72 %, (mass = 1.01 g ± 0.04).

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.89 (t, 3H, J 6.9 Hz, CH$_3$), 1.31 (sl, 6H), 1.64 (qt, 2H, J 7.0 Hz, CH$_2$), 2.27 (s, 3H, CH$_3$), 3.45 (s, 2H, CH$_2$), 4.13 (t, 2H, J 6.8 Hz, CH$_2$), 4.99 (s, 1H, CH$_{\text{enolic}}$), 12.13 (s, 1H, OH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.01, 22.57, 25.55, 28.52, 30.10, 31.44, 50.12, 65.51, 89.77, 167.26, 172.76, 175.42, 200.62. MS m/z (%) not observed [M]+, 158 (0.04), 129 (0.05), 103 (13.81), 85 (17.71), 69 (9.87), 56 (23.47), 55 (17.92), 43 (100.00), 42 (19.71).

1-Ethylpropyl-3-oxobutanoate (4)

Yield = 66 %, (mass = 0.87 g ± 0.03).

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.92–0.88 (m, 6H, CH$_3$), 1.61–1.57 (m, 4H, CH$_2$), 2.28 (s, 3H, CH$_3$), 3.46 (s, 2H, CH$_2$), 4.83–4.79 (m, 1H, CH), 4.99 (s, 1H, CH$_{\text{enolic}}$), 12.20 (s, 1H, OH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 9.56, 26.38, 26.59, 30.14, 50.44, 78.12, 90.03, 167.04, 172.70, 175.27, 200.74. MS m/z (%) 172 ([M]+, 0.13), 157 (0.01), 143 (1.26), 114 (0.39), 103 (19.93), 101 (11.06), 85 (66.96), 70 (23.24), 59 (29.12), 43 (100.00), 42 (24.22), 41 (23.97).

1-Methylpropyl-3-oxobutanoate (5)
Yield = 87 %, (mass = 1.13 g ± 0.02).

\[^{1}H\] NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.91 (t, 3H, \(J\) 7.4 Hz, CH\(_3\)), 1.25 (d, 3H, \(J\) 6.3 Hz, CH\(_3\)), 1.66–1.52 (m, 2H, CH\(_2\)), 2.27 (s, 3H, CH\(_3\)), 3.44 (s, 2H, CH\(_2\)), 4.91 (st, 1H, \(J\) 6.3 Hz), 4.99 (s, 1H, CH\(_{enolic}\)), 12.19 (s, 1H, OH).

\[^{13}C\] NMR (100 MHz, CDCl\(_3\)) \(\delta\) 9.65, 19.36, 28.70, 30.12, 50.51, 73.63, 90.16, 166.84, 172.47, 175.23, 200.78. MS m/z (%) 158 ([M\(^+\)], 1), 143 (0.05), 129 (0.43), 114 (0.13), 103 (10.92), 102 (3.37), 85 (34.79), 73 (4.94), 57 (17.85), 56 (15.25), 43 (100.00), 42 (9.58), 41 (19.39).

3-Methylbutyl-3-oxobutanoate (6)
Yield = 72 %, (mass = 0.95 g ± 0.08).

\[^{1}H\] NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.92 (s, 3H, CH\(_3\)), 0.93 (s, 3H, CH\(_3\)), 1.55 (qt, 2H, \(J\) 6.9 Hz, CH\(_2\)), 1.69 (oct, 1H, \(J\) 6.7 Hz, CH), 2.27 (s, 3H, CH\(_3\)), 3.45 (s, 2H, CH\(_2\)), 4.18 (t, 2H, \(J\) 6.9 Hz, CH\(_2\)), 4.98 (s, 1H, CH\(_{enolic}\)), 12.12 (s, 1H, OH).

\[^{13}C\] NMR (100 MHz, CDCl\(_3\)) \(\delta\) 22.41, 24.99, 30.14, 37.16, 50.15, 64.07, 89.79, 167.24, 172.76, 175.42, 200.65. MS m/z (%) 172 ([M\(^+\)], 0.06), 157 (0.17), 143 (0.05), 129 (0.93), 115 (1.29), 103 (17.96), 102 (8.02), 85 (36.85), 71 (35.15), 70 (64.72), 69 (23.10), 55 (57.67), 43 (100.00), 42 (33.13), 41 (45.64).

1-Methylethyl-3-oxobutanoate (7)
Yield = 83 %, (mass = 0.92 g ± 0.04).

\[^{1}H\] NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.26 and 1.28 (d, 6H, \(J\) 6.2 Hz, CH\(_3\)), 2.27 (s, 3H, CH\(_3\)), 3.42 (s, 2H, CH\(_2\)), 4.95 (s, 1H, CH\(_{enolic}\)), 5.07 (sp, 1H, CH, \(J\) 6.3 Hz), 12.18 (s, 1H, OH).

\[^{13}C\] NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.67, 30.08, 50.47, 69.01, 90.17, 166.66, 200.81. MS m/z (%) 144 ([M\(^+\)], 0.82), 129 (0.05), 102 (36.45), 87 (18.13), 85 (80.62), 84 (53.56), 69 (42.00), 60 (51.04), 59 (20.97), 57 (11.66), 45 (100.00), 44 (25.94), 42 (80.21).

1-Ethylpropyl-2-methyl-3-oxopentanoate (10)
Yield = 61 %, (mass = 0.93 g ± 0.03).

\[^{1}H\] NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.88 (t, 6H, \(J\) 7.2 Hz, CH\(_3\)), 1.08 (t, 3H, \(J\) 7.2 Hz, CH\(_3\)), 1.34 (d, 3H, \(J\) 7.1 Hz, CH\(_3\)), 1.62–1.54 (m, 4H, CH\(_2\)), 2.70–2.48 (m, 2H, CH\(_2\)), 3.54 (q, 1H, \(J\) 7.2 Hz, CH), 4.79 (qt, 1H, \(J\) 6.2, Hz CH).

\[^{13}C\] NMR (100 MHz, CDCl\(_3\)) \(\delta\) 7.71, 9.52, 9.57, 12.95, 25.97, 34.80, 77.88, 170.61, 206.57. MS m/z (%), not observed [M\(^+\)], 186 (0.22), 172 (0.29), 153 (0.21), 144 (0.68), 130 (11.66), 113 (25.84), 102 (0.87), 83 (1.82), 75 (3.08), 57 (100.00), 43 (40.42).

2.2 Preparation of Methyl-2-methyl-3-oxopentanoate (12)

![Diagram of preparation](attachment://diagram.png)

In a 250-mL tri-tubular flask attached to a 25-mL addition funnel, a thermometer and a reflux condenser and under an inert atmosphere, NaH (0.6 g; 25 mmol) and dimethylcarbonate (2.7 g; 30 mmol) in 12 mL of dry THF were introduced. The mixture was brought to reflux at 60 °C under constant stirring. After the start of reflux, a solution of 3-pentanone (11) (2.1 mL; 20 mmol) in 2 mL of dry THF was poured in and maintained under reflux for 2 h. After this time, it was cooled to room temperature and the mixture was transferred to a 50 mL extraction funnel. The product obtained was washed successively with three fractions of 5 mL of distilled water, five fractions of 3 mL of 10% NaHCO\(_3\) solution and three fractions of 5 mL of saturated NaCl solution. The organic
solution was dried over anhydrous Na$_2$SO$_4$, filtered and the solvent evaporated. The crude product was analyzed and characterized by $^1$H NMR, $^{13}$C NMR and GC–MS.

Methyl-2-methyl-3-oxopentanoate (12)
Yield = 90 %, (mass = 2.6 g ± 0.2).

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.70 (t, 3H, J 7.4 Hz, CH$_3$), 0.97 (d, 3H, J 7.2 Hz, CH$_3$), 2.36–2.17 (m, 2H, CH$_2$), 3.27 (q, 1H, J 7.2 Hz, CH), 3.38 (s, 3H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 6.79, 11.99, 33.92, 51.40, 51.45, 170.36, 205.50.

MS m/z (%) 144 ([M]+, 2.63), 129 (0.02), 115 (5.30), 97 (0.06), 88 (10.73), 69 (0.46), 57 (100.00), 43 (6.83).

2.3 Preparation of 1-Ethylpropyl-2-methyl-3-hydroxypentanoate (1)

In a 50-mL bi-tubular flask, under an inert atmosphere, 1-ethylpropyl-2-methyl-3-oxopentanoate (0.5 g; 2.5 mmol), compound 10, 6 mL of methanol, and 5 mmol of Lewis acid (ZnCl$_2$, MgCl$_2$, CaCl$_2$, or MnCl$_2$) were introduced. The reduction of the carbonyl ketone in the absence of a Lewis acid was also evaluated. The flask was cooled to 0 °C in an ice bath. After 30 min, NaBH$_4$ (0.19 g; 5 mmol) was slowly added. The reaction was stirred for 2 h, and then 20 mL of a saturated solution of NH$_4$Cl was slowly added. The product obtained was extracted with three portions of 20 mL of ethyl ether and the organic phases were poured together, washed with three portions of 40 mL of saturated NaCl solution. The organic phase was dried over anhydrous Na$_2$SO$_4$, and then filtered and the solvent was evaporated. The product was purified by chromatography on silica gel with elution by a gradient of increasing polarity with hexane/ethyl acetate (5%, 10%, and 15%). The fractions corresponding to the reduced products were analyzed and characterized by $^1$H NMR, $^{13}$C NMR and GC–MS. Yield = 89 %, (m = 0.045 g ± 0.004).

Anti-stereoisomer: 1-Ethylpropyl-2-methyl-3-hydroxypentanoate (sitophilate)

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.89 (t, 6H, J 7.4 Hz, CH$_3$), 0.99 (t, 3H, J 7.4 Hz, CH$_3$), 1.22 (d, 3H, J 7.1 Hz, CH$_3$), 1.52–1.40 (m, 2H, CH$_2$), 1.64–1.53 (m, 4H, CH$_2$), 2.57–2.50 (m, 1H, CH), 2.85 (m, 1H, OH), 3.61–3.56 (m, 1H, CH), 4.84–4.76 (m, 1H, CH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 9.60, 9.96, 14.57, 26.49, 27.65, 45.10, 74.68, 77.44, 176.18. MS m/z (%), not observed [M]+, 181 (0.04), 173 (3.95), 155 (0.08), 144 (2.94), 133 (0.69), 115 (64.28), 103 (54.93), 85 (18.02), 74 (100.00), 57 (37.89), 42 (90.03).

Syn-stereoisomer: 1-Ethylpropyl-2-methyl-3-hydroxypentanoate (sitophilate)

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.90 (t, 6H, J 7.4 Hz, CH$_3$), 0.98 (t, 3H, J 7.4 Hz, CH$_3$), 1.19 (d, 3H, J 7.1 Hz, CH$_3$), 1.53–1.43 (m, 2H, CH$_2$), 1.63–1.54 (m, 4H, CH$_2$), 2.57–2.51 (m, 1H, CH), 2.87 (sl, 1H, OH), 3.83–3.79 (m, 1H, CH), 4.83–4.76 (m, 1H, CH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 9.64, 10.41, 10.98, 26.44, 26.85, 44.28, 73.30, 77.48, 176.41. MS m/z (%), not observed [M]+, 181 (0.02), 173 (1.51), 155 (0.08), 144 (3.33), 132 (0.69), 115 (49.19), 103 (26.91), 85 (10.84), 74 (100.00), 57 (36.95), 42 (74.85).
3 RESULTS AND DISCUSSION

The use of magnesium in organic synthesis gained prominence in the beginning of the 18th century with the work of Professor Victor Grignard (1900). It continues to be used efficiently today in many other synthetic methodologies (SZUROMI, 2000, GOLDBACH et al., 2016, GAIR et al., 2016, FREITAS et al., 2011). Its application as a mediator of transesterification reactions, listed in Table 1 (entries 1–25), served as a model for obtaining the best experimental conditions for the synthesis of 1-ethylpropyl-2-methyl-3-oxopentanoate (10), the intermediate ester in the synthesis of sitophilate.

The reaction parameters used for analysis were the reaction time, the use and non-use of toluene as a solvent, as well as the ratio of alcohol to β-keto ester. The most feasible conditions for the synthesis of compound 10 are shown in entry 25.

<table>
<thead>
<tr>
<th>Entry</th>
<th>β-Keto ester</th>
<th>Alcohol</th>
<th>Time of reaction</th>
<th>Purified yield (%)</th>
<th>Ratio (alcohol:β-keto ester)</th>
<th>Product</th>
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<td>1</td>
<td></td>
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<td>3 h W/S</td>
<td>24</td>
<td>1:1</td>
<td>2</td>
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<tr>
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<td>33</td>
<td>2:1</td>
<td>4</td>
</tr>
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<td>77</td>
<td>2:1</td>
<td>10</td>
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<td>24</td>
<td>1:1</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>HOH</td>
<td>3 h W/S</td>
<td>24</td>
<td>1:1</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>HOH</td>
<td>3 h W/S</td>
<td>63</td>
<td>1:1</td>
<td>7</td>
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<td></td>
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<td>6 h W/S</td>
<td>72</td>
<td>2:1</td>
<td>8</td>
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<td>66</td>
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<td>No reaction</td>
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<td>6 h W/S</td>
<td>No reaction</td>
<td>2:1</td>
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<td>HOH</td>
<td>3 h W/S</td>
<td>No reaction</td>
<td>2:1</td>
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<tr>
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<td>6 h W/S</td>
<td>No reaction</td>
<td>2:1</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>HOH</td>
<td>6 h W/S</td>
<td>61</td>
<td>2:1</td>
<td>10</td>
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</table>

Reaction carried out without solvent (WO/S).
Reaction carried out with solvent (W/S).

The formation of the enolate of 3-pentanone (11) with NaH in THF, and subsequent nucleophilic attack to the dimethylcarbonate led to the formation of methyl-2-methyl-3-oxopentanoate (12) at a yield higher than 90%.

HOLOS, Year 32, Vol. 4
The carbonyl reduction reaction of 10 to an alcohol proceeded without problems under all experimental conditions at yields higher than 80%.

Taniguchi et al. (1993) performed experiments to determine the induction of chirality. The authors investigated the diastereoselectivity of the reduction of some β-keto esters with NaBH₄ when the reaction is performed in the absence and presence of a Lewis acid in the chloride form, such as ZnCl₂, MgCl₂, CaCl₂, and MnCl₂. The results of this study concluded that when there is no Lewis acid used in the reduction, the main product obtained is the anti diastereoisomer (a compound known as a Cram or Felkin product). However, when the reduction reaction is performed with the use of a Lewis acid, the preferential product is the syn diastereoisomer (a compound known as a Cram-chelated or anti-Felkin product) (EVANS et al., 2001, MENGEL & REISER, 1999, CRAM & ELHAFEZ, 1952).

The studies by Taniguchi et al. (1993) and the model proposed by Cram and Elhafiez for the α-substituted β-keto ester (10) were used in this study to explain the diastereoselective formation of the syn isomers of the pheromone of interest, 1-ethylpropyl-2-methyl-3-hydroxypentanoate (1a and 1b), since these are the stereoisomers that exert biological activity on the insect.

When there is no Lewis acid used in the reduction reactions, the structure of 10 does not show a rigid conformation. The groups attached to the stereogenic carbon, are found positioned in such a way that a lowest interaction occurs between them. Accordingly, the hydrogen transfer occurs at the less sterically hindered face, i.e. at the Si face of the carbonyl group of the ketone, thus leading to the anti product of 1-ethylpropyl-2-methyl-3-hydroxypentanoate (1c and 1d) as the major product (Figure 3). However, when experiments are conducted with the use of a Lewis acid, a chelate is formed between the metal atom and the two oxygen atoms of the carbonyl groups of the ketone and the ester, leaving the molecule with a rigid conformation. The hydrogen transfer also occurs on the less sterically hindered side, the Re face, such as in this case. Here, the syn diastereoisomers of 1a and 1b are preferentially produced (Figure 4).

![Figure 3: Cram and Elhafiez model without the use of Lewis acids for the reduction of 1-ethylpropyl-2-methyl-3-hydroxypentanoate (10) with NaBH₄.](image-url)
Figure 4: Cram and Elhafez model with the use of Lewis acids for the reduction reaction of 1-ethylpropyl-2-methyl-3-oxopentanoate (10) with NaBH₄.

Table 2 indicates the Lewis acid, the reaction yield and the relative proportion of each pair of diastereoisomers determined by GC–MS.

Table 2: Yields and diastereoisomeric excess obtained in the reduction reactions with NaBH₄ to form sitophilate (1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Reaction yield</th>
<th>* Diastereoisomeric excess &lt;br&gt;anti/syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-----------</td>
<td>85 %</td>
<td>70 / 30</td>
</tr>
<tr>
<td>2</td>
<td>ZnCl₂</td>
<td>77 %</td>
<td>40 / 60</td>
</tr>
<tr>
<td>3</td>
<td>MgCl₂</td>
<td>81 %</td>
<td>34 / 66</td>
</tr>
<tr>
<td>4</td>
<td>CaCl₂</td>
<td>81 %</td>
<td>24 / 76</td>
</tr>
<tr>
<td>5</td>
<td>MnCl₂</td>
<td>89 %</td>
<td>13 / 87</td>
</tr>
</tbody>
</table>

*Proportions calculated by the base area relative to each peak in GC–MS analysis.

According to data presented in Table 2, the more effective chloride in this transformation is MnCl₂ (entry 5), because in addition to having provided the best reaction yield, it led to the highest extent of formation of syn diastereoisomers. In this case, there was a near reversal of diastereoselectivity compared with that obtained in the reaction without the use of a Lewis acid (entry 1). These results are consistent with those reported by Taniguchi et al. (1993).

Figure 5 shows a comparison between the chromatograms of the products obtained using different Lewis acids in the reduction reactions.
4 CONCLUSIONS

The transesterification reactions were considered satisfactory, with yields ranging from 61 to 87%. The choice of MgO/I₂ to mediate such reactions came from the work of Chavan et al. (2002) who conducted transesterifications of β-keto esters with different alcohols and phenols using ZnO/I₂ and applied the coumarin synthesis. These reactions served as a model to establish the best experimental conditions for use in the synthesis of sitophilate.

In respect to the use or not of Lewis acids (ZnCl₂, MgCl₂, CaCl₂ e MnCl₂) in the reduction step with NaBH₄, we conclude that the non-use of such compounds leads to a majority formation of the anti diastereoisomers, while the use MnCl₂ takes the majority formation of the syn diastereoisomers, since these latter compounds are that exert biological activity on the insect.

5 REFERENCES


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