

Considerations on Obtaining Diethyl Chlorosuccinate

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Abstract: Anhydrous hydrogen chloride addition to diethyl maleate and maleic anhydride leads to a mixture of diethyl maleate and diethyl chlorosuccinate at a ratio of 5:4, respectively. The products were analysed by gas chromatography equipped with flame ionisation detector (GC-FID) and gas chromatography coupled to mass spectrometry (GC-MS), in order to determine their chemical composition.

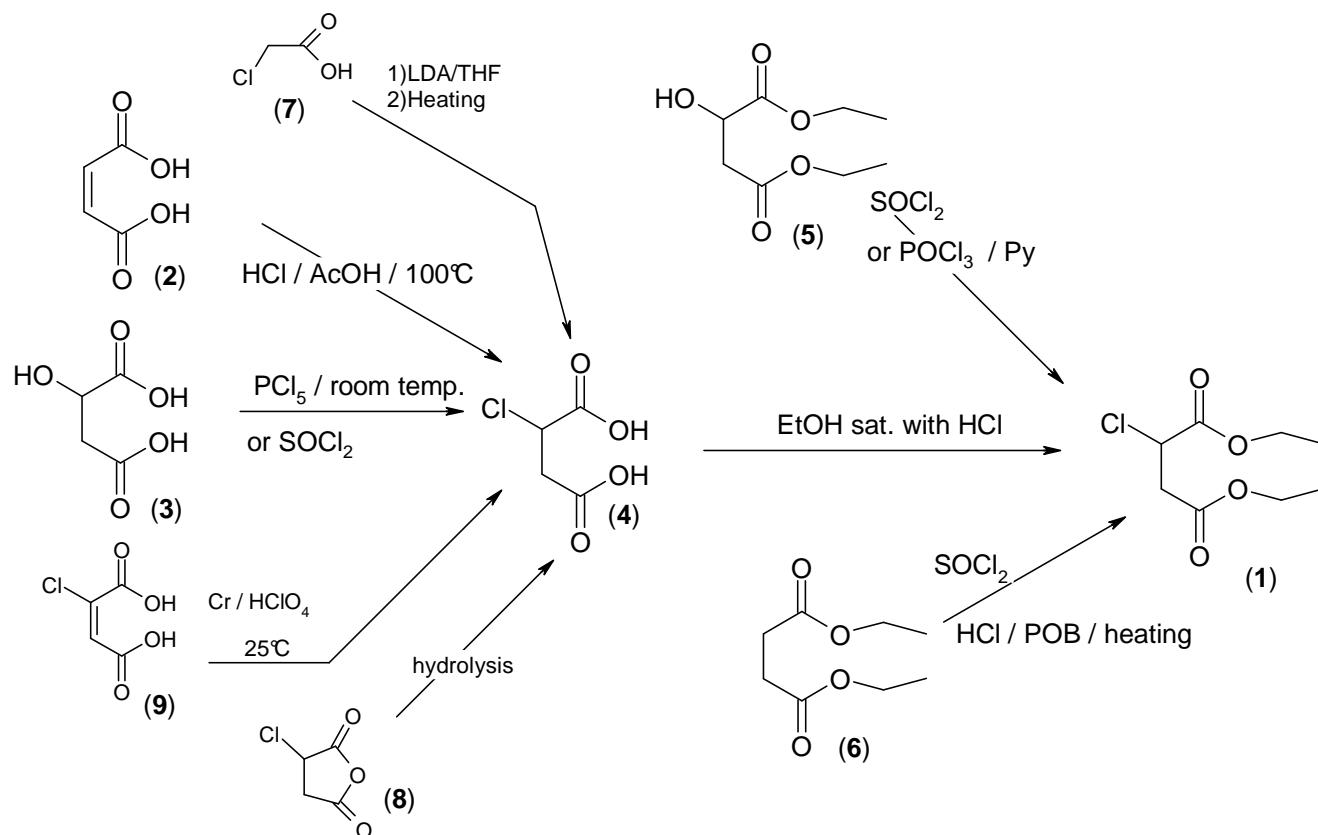
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1. Introduction

Chemical compounds containing the 4-amino-5-mercapto-1,2,4-triazole-3-substituted nucleus are important due to the biological activities they may possess: antibacterial, antitumoral, anticancerous, anticonvulsive, antiinflammatory and analgesic [1-6]. By functionalizing these compounds at the nitrogen or sulfur atoms new

compounds with improved biological activities can be obtained [7]. In order to functionalize the sulphur atom a number of halogen compounds may be used, including diethyl chlorosuccinate [10]. Given these aspects the aim of our paper is the elaboration of a method of synthesis for it.

According to data found in literature, diethyl chlorosuccinate can be obtained through the following methods (Scheme 1):



Scheme 1. Possibilities of obtaining diethyl chlorosuccinate (1)

According to literature data, diethyl chlorosuccinate(1) is obtained by esterification of chlorosuccinic acid (4) with ethyl alcohol in presence of gaseous hydrogen chloride [9], by treating diethyl malate(5) with thionyl chloride for one hour at room temperature or with phosphoryl chloride in pyridine at 0°C [9]; it can also be obtained from the reaction between diethyl diazosuccinate and chlorhydric acid at low temperature or by treating diethyl diazosuccinate with sodium chloride and chlorhydric acid 2N [10] or by heating diethyl succinate with sulfuryl chloride in carbon tetrachloride with benzoyl peroxide present [11].

In turn, chlorosuccinic acid can be obtained through the reaction of malic acid (3) and phosphorous pentachloride at room temperature [12] or with thionyl chloride [13], through the addition of hydrogen chloride to maleic acid (2) in acetic acid at 100°C [14]; also chlorosuccinic acid can be obtained by reduction of 2-chloro-butenedioic acid(9) with chromium powder in perchloric acid at 25°C [15], through the hydrolysis of chlorosuccinic acid anhydride (8) [16] and from the reaction of chloroacetic acid (7) with lithium diisopropyleamide at -80°C and heating at 50°C [17].

Surprisingly there are no synthesis methods for diethyl chlorosuccinate through the addition of hydrogen chloride to diethyl maleate or fumarate which are accesible raw materials. This is why we have tried synthesizing it starting from either diethyl maleate or diethyl maleate prepared „in situ” from maleic anhydride and absolute ethyl alcohol with gaseous hydrochloric acid (Scheme 2).

2. Experimental

The reagents were commercial products (Merck, Fluka, Aldrich) and used without further purification. Hydrogen chloride was prepared from natrium chloride and concentrated sulphuric acid and dried over concentrated sulphuric acid. Diethyl maleate were prepared according to the literature [18] with a purity of 90% and chlorosuccinic acid by addition of anhydrous hydrogen chloride to maleic anhydride in acetic acid at 100°C [19].

GC were performed on a HP5890 apparatus equipped with flame ionization detector and a non-polar, capillary column, 30 m x 0.32 mm, with Zebron ZB-5 stationary phase of a 0.50 µm thickness (Phenomenex). Analysis conditions were: temperature programe 100 – 280 °C, temperature gradient 10°/min., injector temperature 250 °C,

detector temperature 300 °C, carying gas: hydrogen at 12,5 psi.

Mass spectra GC-MS were performed on an Agilent G1701DA apparatus using methanol as carrying solvent.

Obtaining diethyl chlorosuccinate from the reaction of maleic anhydride in absolute ethyl alcohol media

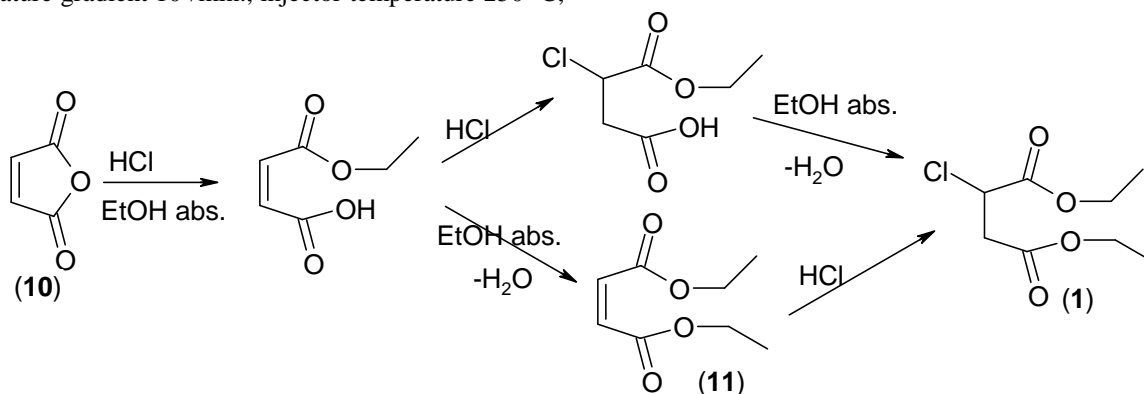
In the course of 3,5 h two moles of anhydrous hydrogen chloride were added at 0 °C to a solution formed by dissolving 49 g (0,5 moles) maleic anhydride in 200 mL of absolute ethyl alcohol. The mixture was afterwards refluxed for two hours in order to eliminate the excess hydrogen chloride. Afterwards the solution was distilled at low pressure and three fractions were obtained. There was no formation of fumaric acid since it would have precipitated easily in the reaction media, we assume that the first step in the reaction was the monoesterification of the maleic anhydride in the presence of gaseous hydrogen chloride (Scheme 2).

Obtaining diethyl chlorosuccinate through the esterification of chlorosuccinic acid with ethyl alcohol

A mixture composed of 100 mL benzene, 20 mL absolute ethyl alcohol, 0.5 g of p-toluenesulfonic acid and 16.4 g (0,107 moles) chlorosuccinic acid is refluxed until all of the water from the reaction mixture is collected through ternary azeotrope distillation. Afterwards the solution is washed with saturated NaHCO₃ and after the water traces are removed and then the solvent is also removed at atmospheric pressure.

Obtaining diethyl chlorosuccinate through the addition of hydrogen chloride to diethyl maleate

1.5 moles of anhydrous hydrogen chloride are added at 0°C to a solution made up of 25 mL chloroform and 161 mL (172 g, 1 mole) diethyl maleate. The reaction mixture is then maintained at low temperature for another thirty minutes after which it is refluxed for an hour. Then it is mixed with ice and afterwards neutralized with KOH 40% and then extracted with methylene chloride. Water traces are then removed from the extract and then the solvent is also removed at low pressure.



Scheme 2. Obtaining diethyl chlorosuccinate (1) starting from maleic anhydride (10)

3. Results and Discussion

In the GC-MS analysis of diethyl maleate (Fig. 1) (RT=12,55) no molecular peak can be observed at $m/z=172$ a.m.u., only fragmentation peaks that correspond to losing of the OC_2H_5 group at $m/z=127$ a.m.u. (base peak) and another fragmentation peak corresponding to losing the COOC_2H_5 group at $m/z=99$ a.m.u.

When obtaining diethyl chlorosuccinate by adding hydrogen chloride to diethyl maleate a mixture made up of 45% diethyl chlorosuccinate and 35% raw material that did not react (Fig. 2).

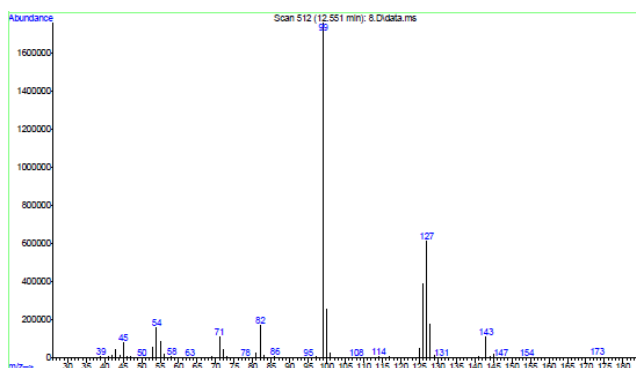
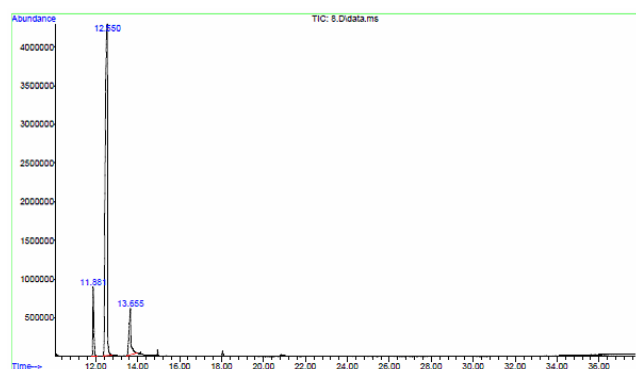


Figure 1. GC-MS analysis of diethyl maleate

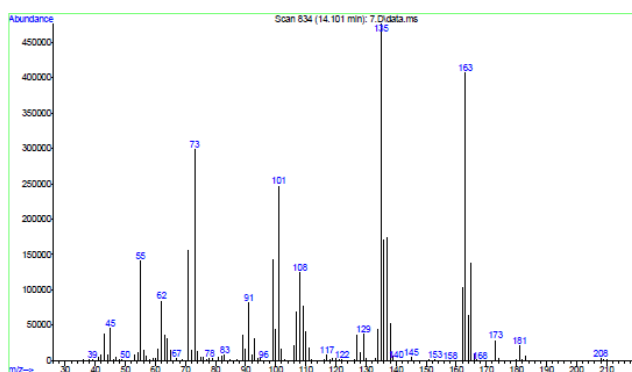
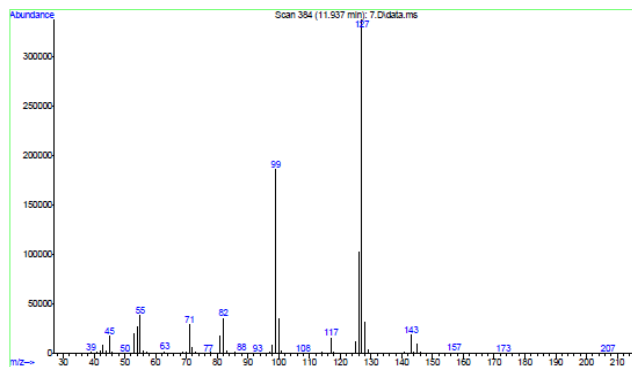
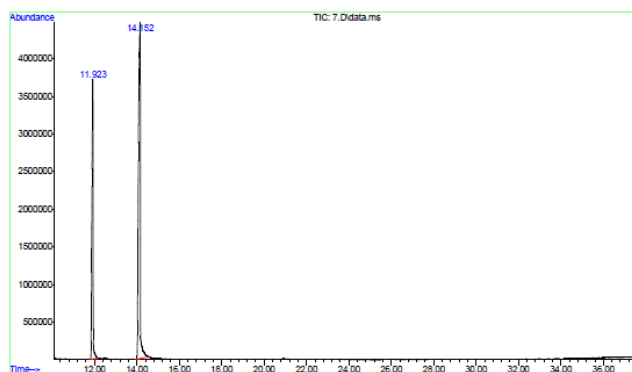


Figure 2. GC-MS analysis of diethyl chlorosuccinate obtained through hydrogen chloride addition to diethyl maleate

When obtaining diethyl chlorosuccinate by adding hydrogen chloride to maleic anhydride in absolute ethyl alcohol three fractions are separated, of which two (bp= 40-50°C/8mmHg and residue, respectively) were analysed through GC (Fig. 3) and GC-MS (Fig. 4).

Two components are observed in the second fraction. These were identified as being diethyl maleate (RT=3,303) (58,2%) and diethyl chlorosuccinate (RT=4,278) (36,5%).

Just as with the authentic sample of diethyl maleate, through the GC-MS analysis of the second fraction's first component, no molecular peak is visible at $m/z=172$ a.m.u.; only fragmentation peaks corresponding to the loss of the OC_2H_5 group at $m/z=127$ a.m.u. (base peak) and the loss of the COOC_2H_5 group at $m/z=99$ a.m.u.

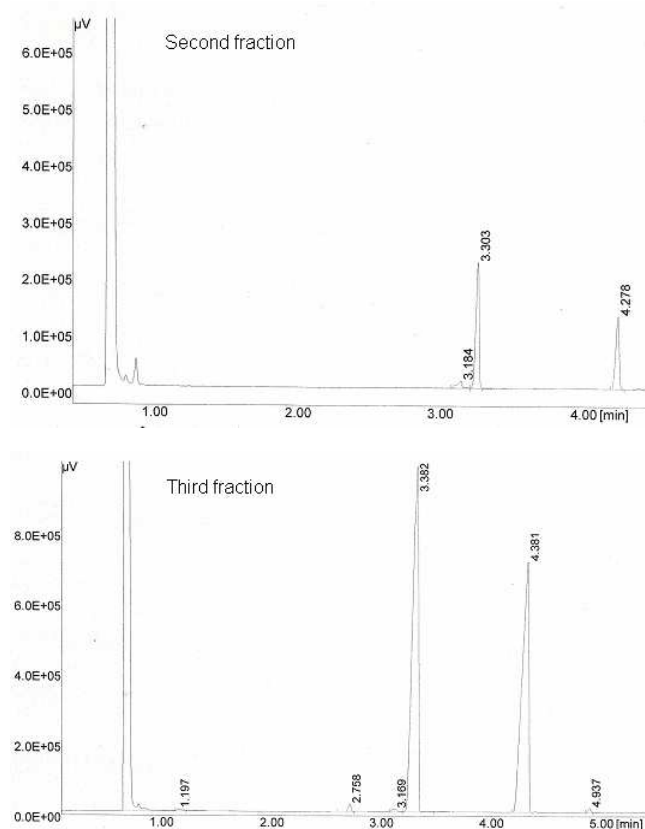


Figure 3. GC analysis of diethyl chlorosuccinate fractions obtained from hydrogen chloride addition to maleic anhydride

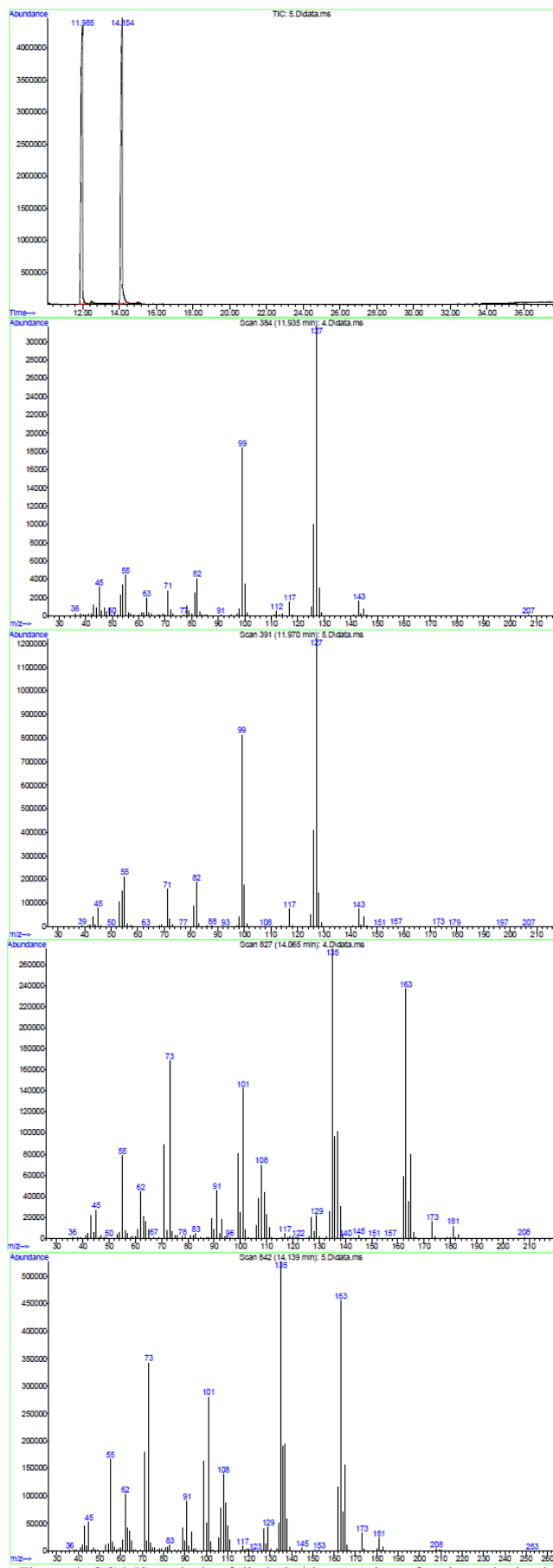
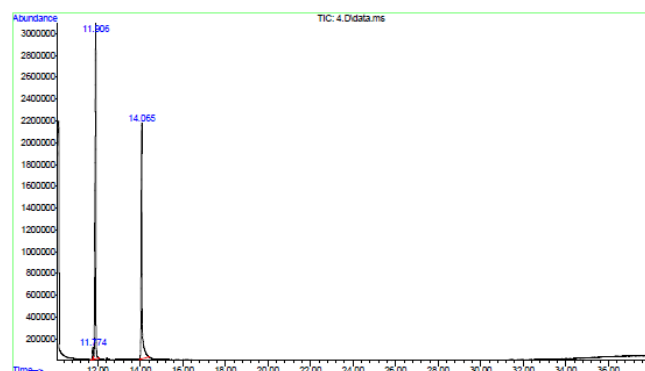


Figure 4. GC-MS analysis of diethyl chlorosuccinate fractions obtained from hydrogen chloride addition to maleic anhydride

The GC-MS analysis of the second fraction's second component a very small molecular peak can be observed at $m/z = 208$ a.m.u., yet there is no molecular peak at $M+2$. However, the following fragmentation peaks can be observed:

$m/z=173$ a.m.u. ($M-^{35}\text{Cl}$)

$m/z= 165$ a.m.u. ($M+2- \text{OC}_2\text{H}_5$) at a ratio of 1/3 to $m/z= 163$ a.m.u. ($M- \text{OC}_2\text{H}_5$)

$m/z= 137$ a.m.u. ($M+2- \text{COOC}_2\text{H}_5$) at a ratio of 1/3 to $m/z=$ a.m.u. ($M- \text{COOC}_2\text{H}_5$)

In the third fraction the presence of diethyl maleate (RT=3,382) (54,2%) and diethyl chlorosuccinate (RT=4,381) (44,2%) can be observed.

These results show that through the addition-esterification reaction of maleic anhydride a mixture of diethyl maleate and diethyl chlorosuccinate in approximately equal quantities (5:4) is formed.

When obtaining diethyl chlorosuccinate through the esterification of chlorosuccinic acid with ethyl alcohol in the presence of p-toluenesulfonic acid through the azeotrope method, the raw product was analysed through GC (Fig. 5) and GC-MS (Fig. 6) and contains, in both cases, four components. Based on retention times, these components were identified as being diethyl fumarate (RT=3,197) (6%), diethyl maleate (RT=3,32) (18%) and diethyl chlorosuccinate (RT=4,402) (59%).

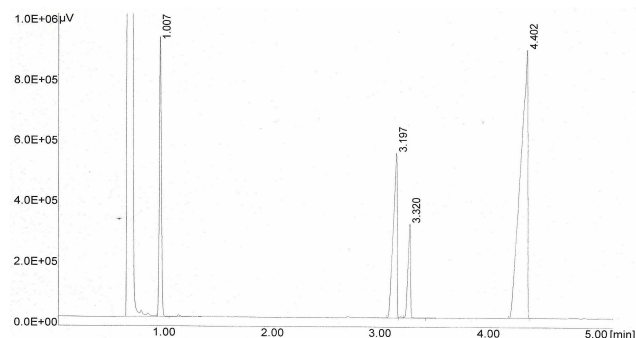


Figure 5. GC analysis of diethyl chlorosuccinate obtained through direct esterification

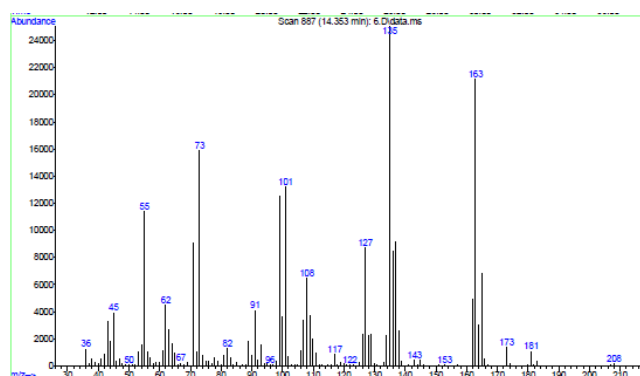
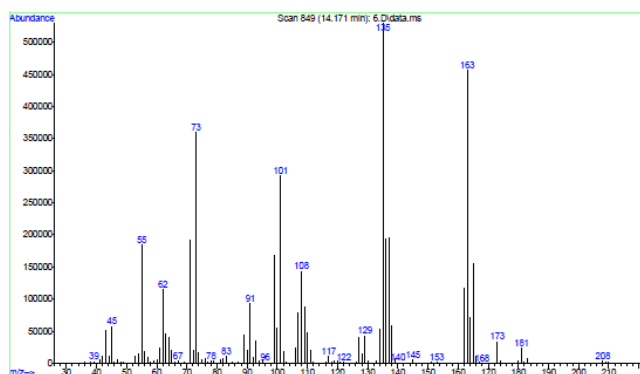
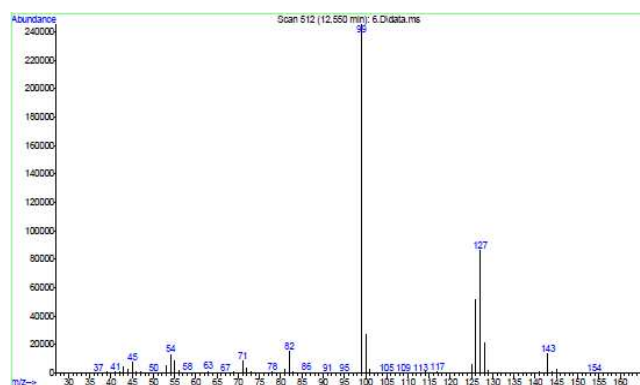
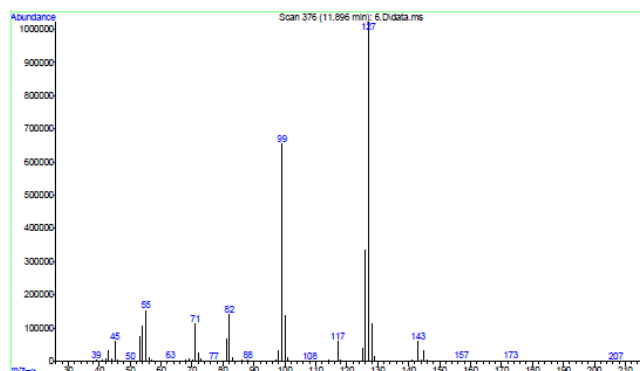
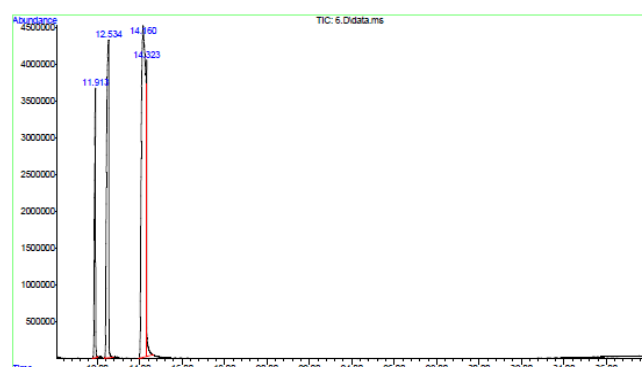


Figure 6. GC-MS analysis of diethyl chlorosuccinate obtained through direct esterification

The GC-MS analysis shows that the first two components with close retention times have the same type of fragmentation (characteristic peaks at $m/z=127$ a.m.u. and $m/z=99$ a.m.u.), these being diethyl fumarate and maleate, respectively. The last two components with $RT=14,16$ and $RT=14,323$ were attributed to diethyl chlorosuccinate having its characteristic fragmentations. The fact that the chlorosuccinic acid used in this method was obtained in a previous synthesis and contained fumaric acid explains the presence of diethyl fumarate in the chromatograms.

The existence of a better proportion of diethyl chlorosuccinate in the mixture, 59% compared to 44% from the previous method, is noteworthy.

4. Conclusions

Direct esterification of chlorosuccinic acid is the best method for obtaining diethyl chlorosuccinate.

When obtaining diethyl chlorosuccinate by adding hydrogen chloride to diethyl maleate and maleic anhydride, respectively, in absolute ethyl alcohol media, diethyl maleate is present as a secondary product, either due to very slow reaction speed or due to the reversibility of the reaction that makes the elimination of hydrogen chloride from diethyl chlorosuccinate possible.

To support the reversibility of the reaction theory we consider the formation of diethyl maleate in the direct esterification method of chlorosuccinic acid through the azeotrope method, in acid catalysis with p-toluenesulfonic acid.

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