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Synthesis and characterization of some thioether compounds by thiol-ene click chemistry

Abdulraoof saleh and Raed k. Zaidan

University of basrah, science collage, chemistry department

wxdwxd10@gmail.com

Abstract:

In this study, some thioether compounds were prepared by thiol-ene click reaction using cheap starting materials from natural source or plastic waste such as limonene from orange peel, and styrene by thermal degradation (cracking) of plastic waste like spoon and fork plastic, and different reaction conditions were achieved, some starting material did not need any catalyst or heat like limonene reacts with thioglycolic acid to give 2-(4-methylcyclohex-3-en-1-yl)propyl)thio)acetic acid , where the reaction was exothermic and very fast, while the styrene need the catalyst such as water or glycerol to start the reaction with thioglycolic acid through nucleophilic addition to give 2-(phenethylthio)acetic acid . The synthesized thioether compounds were prepared in high yield through anti-Markonickov rule at room temperature and diagnosed by FT- IR and H-NMR .

Introduction:

The using of biomass versus petroleum resources needs to determine the choice among them through the efficiency and sustainability of the production of this biomass, and this means the necessity to set priorities for the allocation of biomass, due to direct competition between food, energy, fodder and industrial raw materials in terms of price and Abundance and non-food competitiveness[1,2], so the materials used in this research were selected on this basis after studying the extent of their competitiveness and the possibilities of their work in medical and other fields, and all of that is from extracting the raw materials for their synthesis and treatment from available materials in nature or waste[3-7].

To achieve the goal of sustainability, innovation alone is not sufficient, and therefore more efforts should be made to develop catalytic pathways, synthetic methods, and moderate conditions which are of low cost, A fundamental key to achieving a fully sustainable approach is to design highly environmentally efficient reactions and by achieving a high production rate. One of reaction that can be used to achieve the goals that we mentioned above is click reaction.

Click reaction is the reaction between two materials, one of is the alkene for example and the other is thiol or azide, this reaction was introduced by Sharpless and

coworkers [8] in 2001, and the same was further expounded by Moses [9] and Becer.[10]

Therefore, this type of reaction and these raw materials were chosen, where the click reaction is considered one of the reactions in which the products are in a high proportion and is carried out through multiple, moderate and available reaction conditions and does not need expensive materials for the purpose of purification because it does not produce byproducts and materials The primary is extracted from nature and from waste, so it is possible to consider this reaction as the click, due to the compatibility with most of the characteristics such as the high reaction rate, thermodynamic strength, compatibility with water and oxygen, as the different functional groups bear regressive selectivity [11,12].

Experimental Part:

Boiling point of starting materials;

Limonene : 176 ℃

Styrene : 145 ℃

Thioglycolic acid : 96 ℃

Limonene extracted by using fractionation column ; water and orange peels mixture distilled by heating (100 ℃) , the product was two layer water and limonene by isolated them limonene was achieved.

1- (synthesis of 2-((2-(4-methylcyclohex-3-en-1-yl)propyl)thio)acetic acid);

Limonene (0.681 g, 5 mmol) was treated with thioglycolic acid (0.506 g, 5.5 mmol) with stirring at room temperature (25℃) till complete consumption of the starting material(by TLC) then leaving the mixture overnight.

The reaction mixture washed with distilled water and extracted with EtOAc the extract was dried by (Na_2SO_4) and concentrated under reduced pressure to afford a light yellow viscous oil in yield (96%).

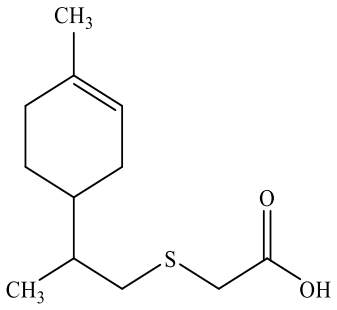


Figure (1) 2-((2-(4-methylcyclohex-3-en-1-yl)propyl)thio)acetic acid

2- (synthesis of (2-((2-(3-((carboxymethyl)thio)-4- methylcyclohexyl)propyl)thio)acetic acid);

Limonene (0.34 gm , 2.5 mmol) was treated with thioglycolic acid (0.506 gm ,5.5 mmol) with stirring at room temperature (25℃) till complete consumption of the starting material(by TLC) then leaving the mixture overnight.

The reaction mixture washed with distilled water and extracted with EtOAc the extract was dried by (Na_2SO_4) and concentrated under reduced pressure to afford an light yellow viscous oil in yield (92%).

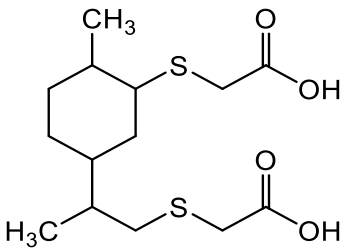


Figure (2) 2-((2-(3-((carboxymethyl)thio)-4-methylcyclohexyl)propyl)thio)acetic acid

Styrene achieved by thermal cracking on 150 ℃ of plastic spoons (poly-styrene) using fractionation column .

3- (synthesis of 2-(phenethylthio)acetic acid under light and benzil as catalyst).

Method A:

Styrene (0.52 gm, 5 mmol) was treated with thioglycolic acid (0.506 gm, 5.5 mmol) under LED light 5 volt with (0.05 gm) of benzil with magnetic stirring at room temperature (25℃) till complete consumption of the starting material.

The reaction mixture extracted with EtOAc, the extract was dried by (Na_2SO_4) and concentrated under reduced pressure to afford a clear viscous oil in yield (91%).

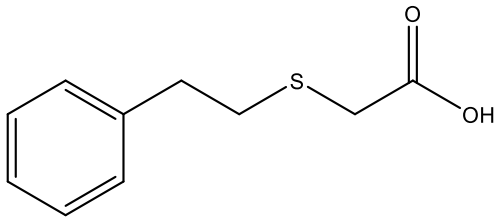


Figure (3) 2-(phenethylthio)acetic acid

Method B:

A mixture of the appropriate Styrene (0.374 gm , 3.6 mmole) and thioglycolic acid (0.276 gm, 3.0 mmole) in glycerol (9.0 mL) was stirred at room temperature (25 ℃) overnight, the reaction mixture was washed with hexanes (3×9.0 mL) and the upper organic phase was separated from glycerol , dried with Na_2SO_4 and evaporated under reduced pressure. The product was isolated by column chromatography using hexane/ethyl acetate (2:1) as eluents afford an clear viscous oil in yield (87%).

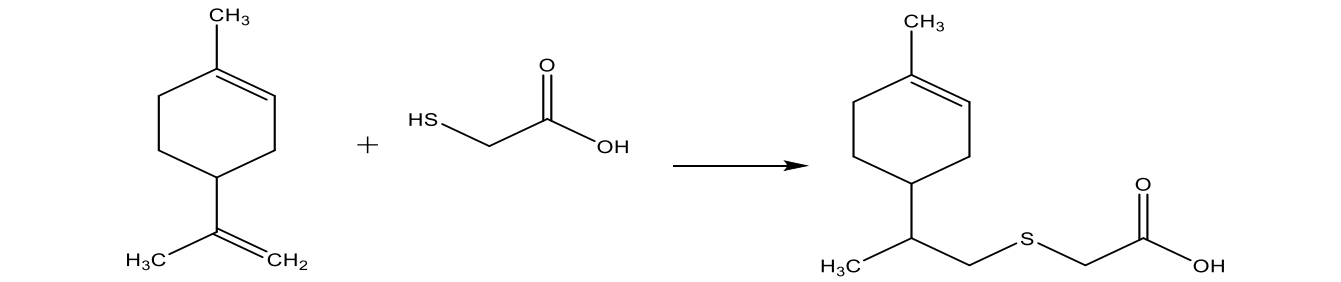
Method C:

Styrene (5 mmol, 0.52 gm) was treated with thioglycolic acid (0.506 gm ,5.5 mmol) in water (2.5ml) with stirring at room temperature (25℃) till complete consumption of the starting material(by TLC), then leaving the mixture overnight.

The reaction mixture washed with distilled water and extracted with EtOAc the extract was dried by (Na_2SO_4) and concentrated under reduced pressure. The product was isolated by column chromatography using hexane/ethyl acetate (2:1) as eluents to afford a clear viscous oil in yield (92%).

Results and Discussion.

In this study, which included the preparation of some crucial compounds that are expected to have biological activity, according to the literatures[13], the use of very cheap starting materials which produced from plastics and food wastes and they have been reacted with one of the active thiol compounds (thioglycolic acid) using thiol-ene click chemistry. The reaction was very fast and exothermic, and it did not need a catalyst to start the reaction process by free radicals. This is due to the reactivity of limonene containing two double bonds, which produces a stable free radical intermediate when it reacts with the thiol, as a result of the reaction of thiols with oxygen, which produces a reactive free radical that in turn it reacts with limonene. This intermediate will abstract hydrogen from the thiol to produce thioether according to the scheme below:



1-methyl-4-(prop-1-en-2-yl)cyclohex-1-ene | 2-mercaptoacetic acid | 2-((2-(4-methylcyclohex-3-en-1-yl)propyl)thio)acetic acid

Scheme(1)(reaction of lemonene with thioglycolic acid 1:1)

From FT-IR spectra, and proton 1H-NMR confirm that the compounds resulting from the thiol-ene click reaction of thioglycolic acid with limonene or styrene are as shown below due to the disappearance of SH group at 2500-2600 cm^{-1}. The number of protons and chemical shift in the NMR spectrum of the synthesized compounds are also confirmed due to the number of protons and Chemical shifts as shown below, and the disappearance of the olefinic protons in styrene and limonene are also good sign that the compounds as draw below:

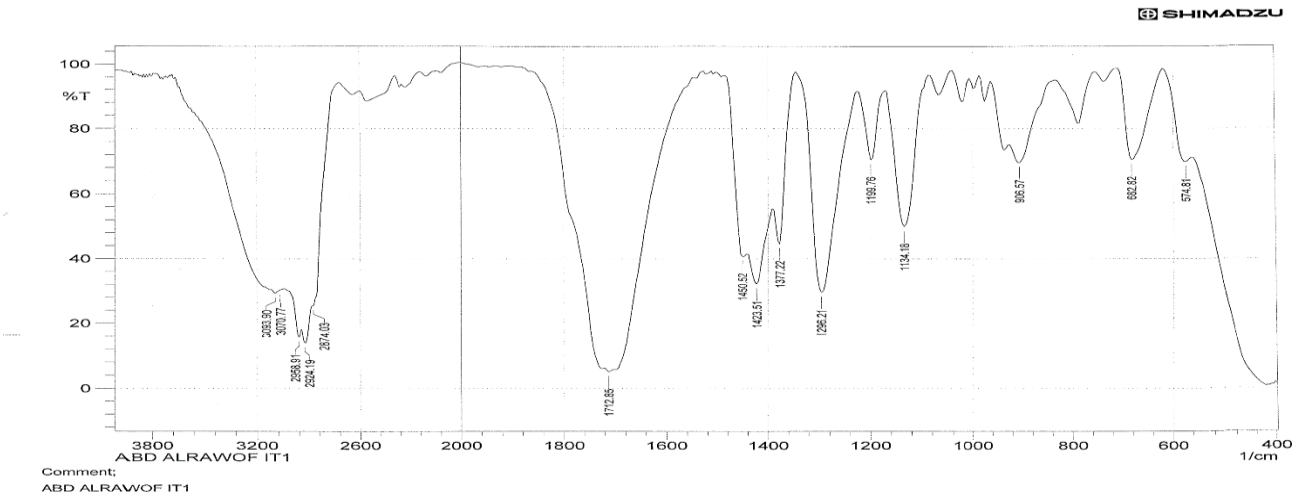


Figure 4(FT-IR chart of figure 1)

IR peaks: (carboxylic OH) appeared on range 2700-3200 cm^{-1}, C=O appeared on 1700 cm^{-1} and (C-S) ON 1134 cm^{-1}.

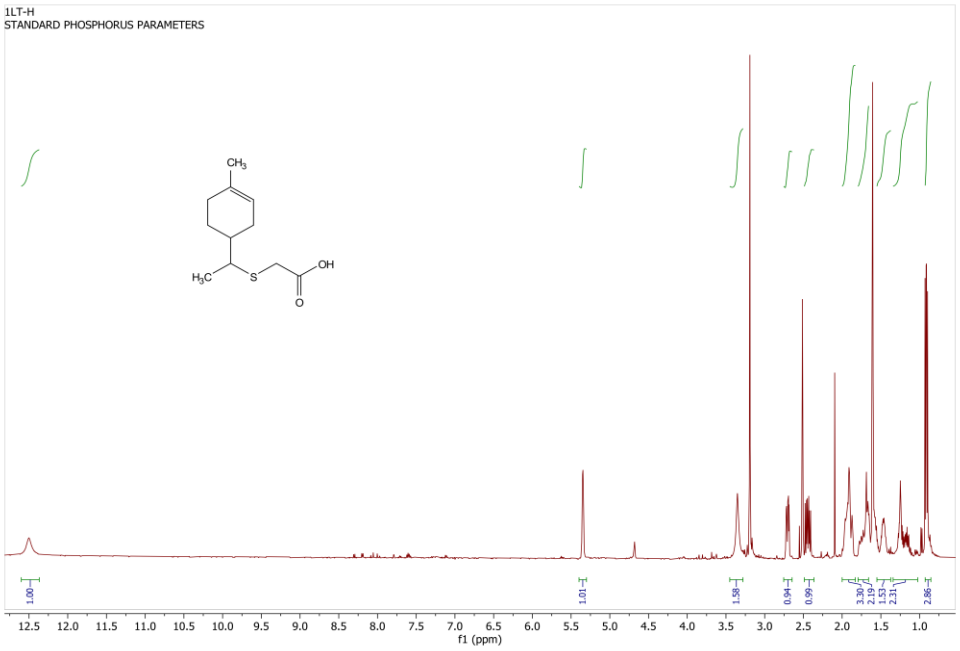
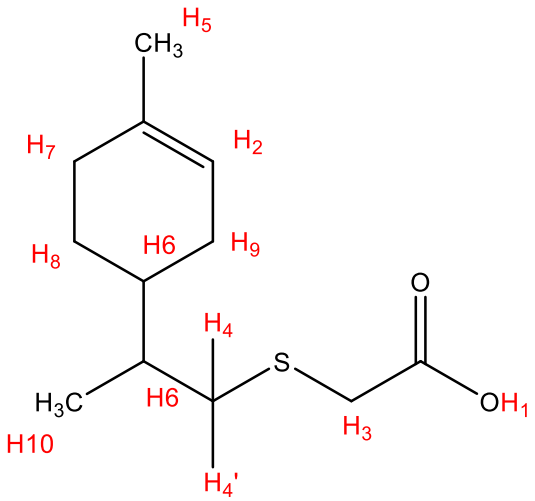
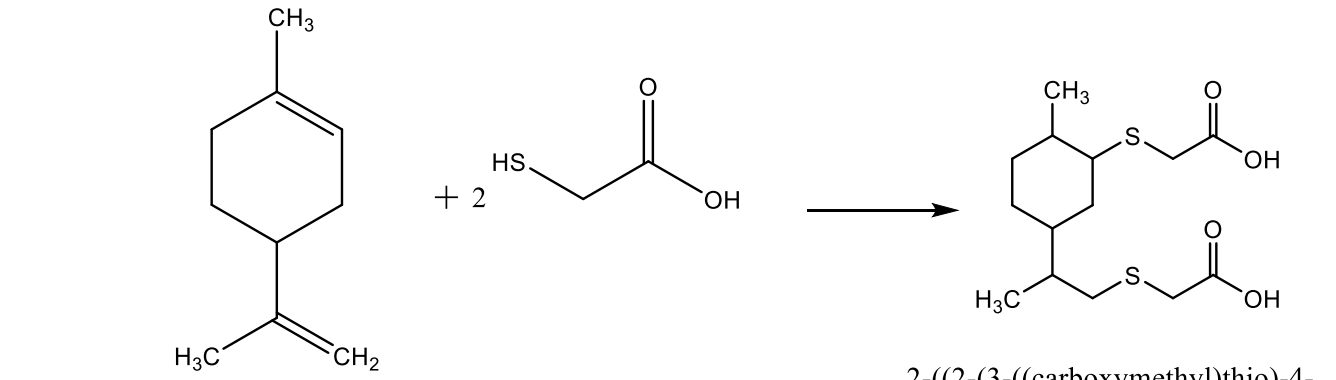


Figure 5(1H-NMR chart of Figure 1)



NMR peaks; (H_1:12.5, H_2:5.35, H_3: 3.35,H_4,$H_{4'}$:2.75(DiisoAropic effect),H_5 :2.45,H_6:1.8,H_7:1.75

2-



1-methyl-4-(prop-1-en-2-yl)cyclohex-1-ene

2-mercaptoacetic acid

2-((2-(3-((carboxymethyl)thio)-4-methylcyclohexyl)propyl)thio)acetic acid

scheme (2)(reaction of limonene with thioglycolic acid 1:2)

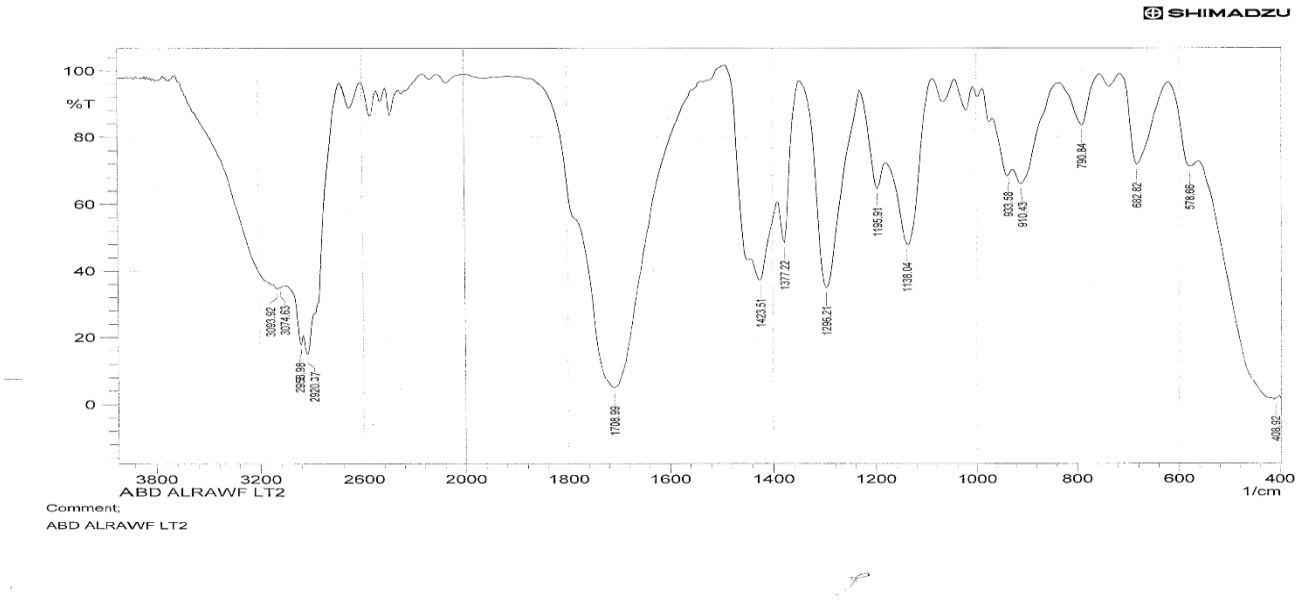


Figure 6(FT-IR chart of Figure 2)

IR peaks ; (carboxylic OH) appeared on range 2700-3200 cm^{-1} , C=O appeared on 1700 cm^{-1} and (C-S) on 1128 cm^{-1}.

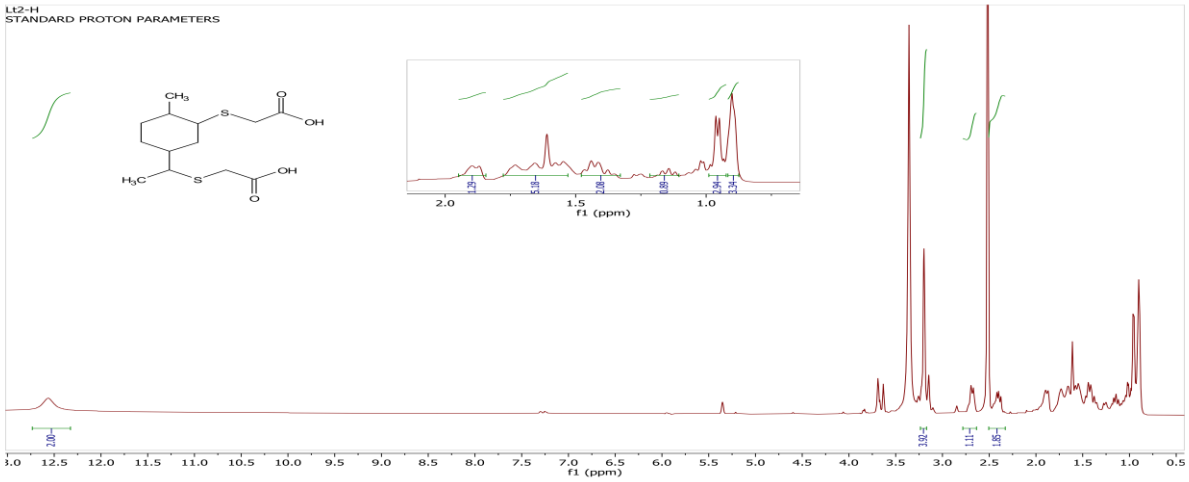
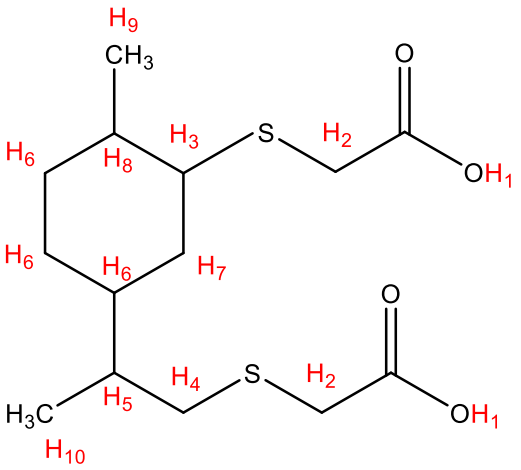


Figure 7(1H-NMR chart of figure(2))



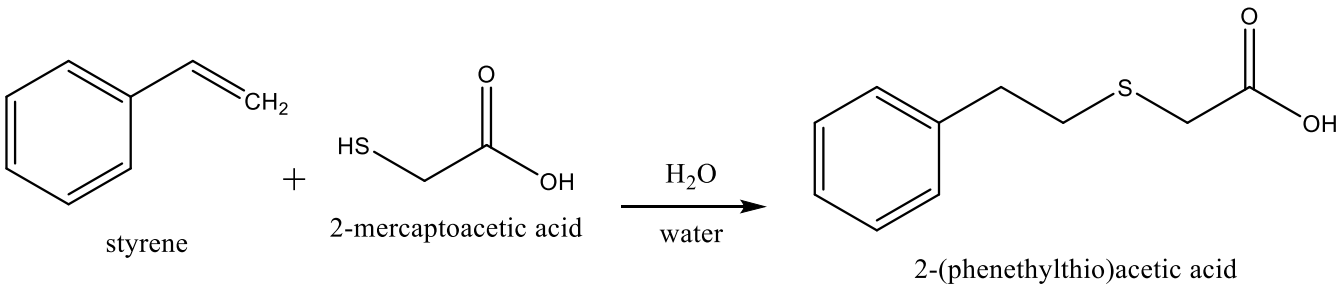
NMR peaks;H_1:12.6,H_2:3.2,H_3:2.7,H_4:2.46,H_5:1.85,H_6:1.6,H_7:1.4,

H_8:1.15, H_9:0.9, H_{10}:0.8

The second thioether compound which it was synthesized using styrene as starting material, which was prepared from plastic waste such as spoons, and the resulting thioether is one of the crucial compounds which it has been tested as anti covid19 in 2020[12], according to the literature. In this reaction, no product was obtained without a catalyst, as happened with limonene, due to the low reactivity of styrene compared to limonene, and therefore the reaction was carried out in several ways and using different catalysts to find the optimum conditions in terms of temperature, time and yield as well as the cost of catalyst and the results were excellent from Where the outcome, as well as the use of water as a catalyst, gave very good results in terms of yield and ease of purification. The mechanism does not include the formation of free radicals, but rather by the formation of ion, which in turn abstract hydrogen to form the product.

3-

Method A;



Scheme(3) (reaction of styrene with thioglycolic acid in distilled water)

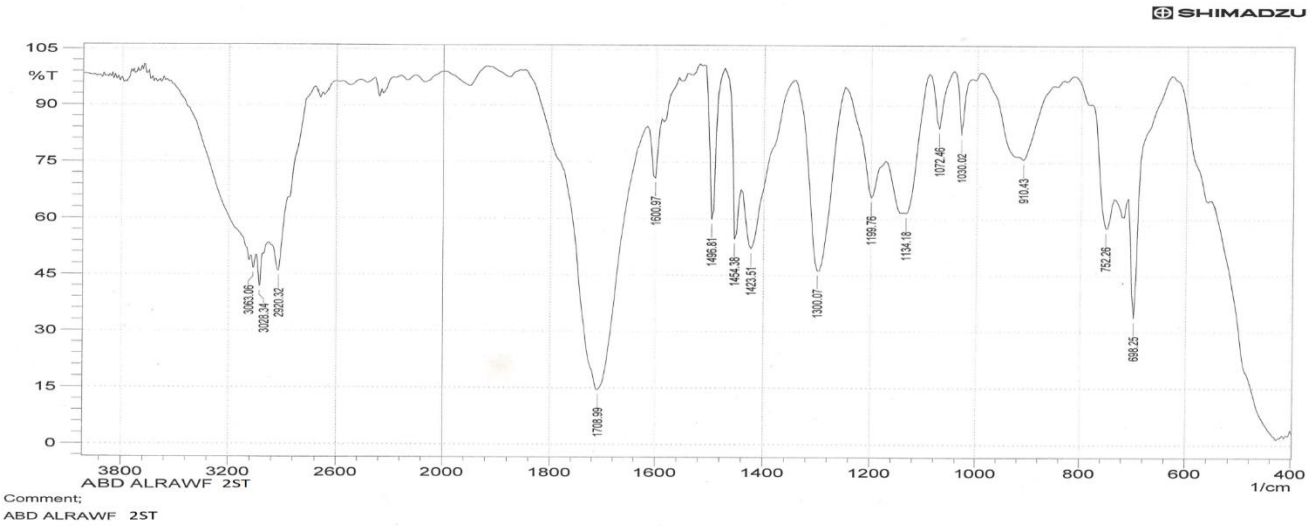


Figure 8(FT-IR chart of Figure 3)

IR peaks : Aromatic carbon on 1600 cm^{-1},(carboxylic OH) appeared on range 2700-3200 cm^{-1} , C=O appeared on 1700 cm^{-1}.

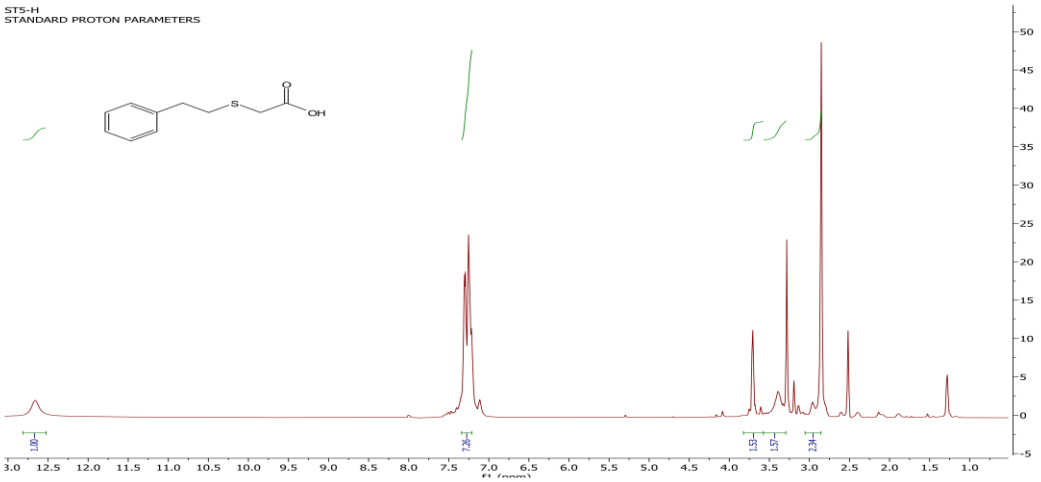
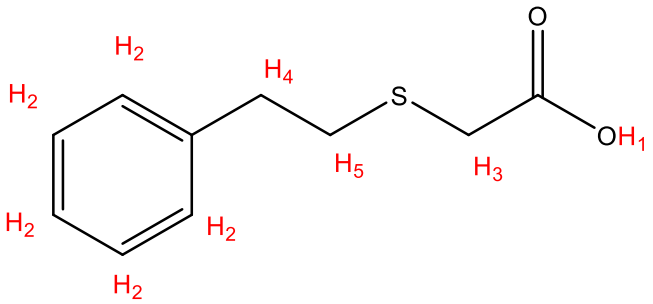
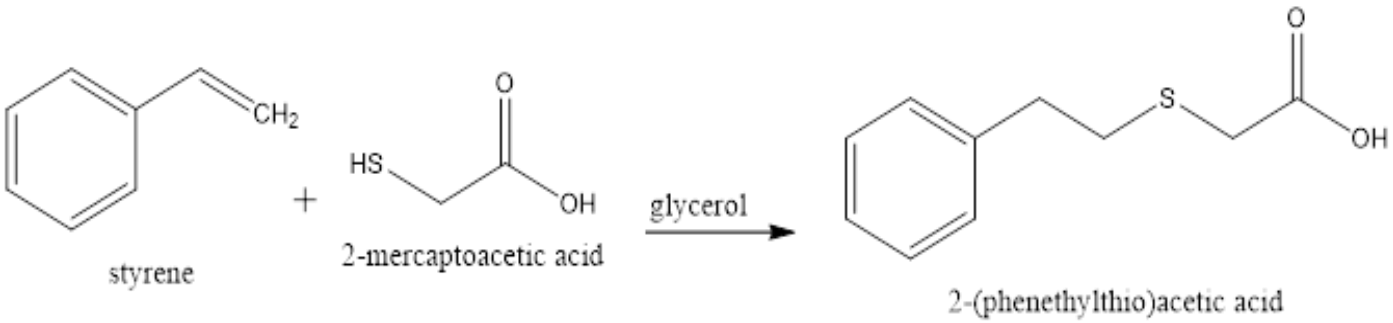


Figure 9(1H-NMR chart of Figure 3)



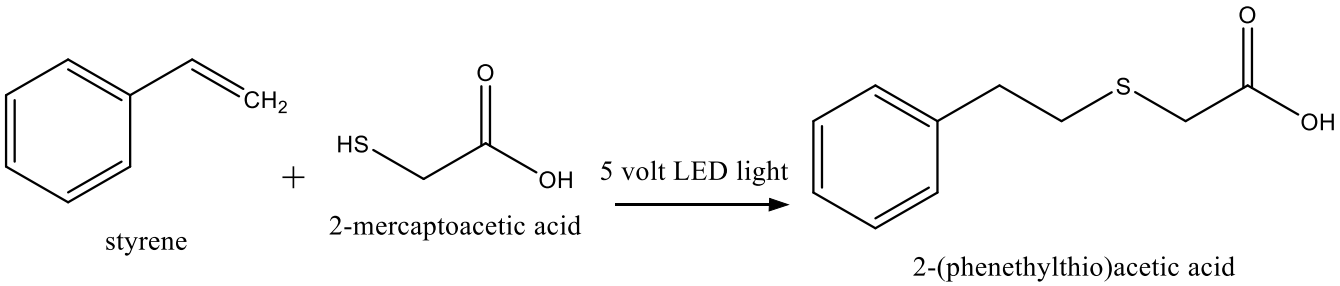
NMR peaks; H_1:12.65, H_2:7.25,H_3:3.74,H_4:3.48,H_5:2.9

Method B;



Scheme (4) (reaction of styrene with thioglycolic acid in glycerol)

Method C;



styrene 2-mercaptoacetic acid 2-(phenethylthio)acetic acid

scheme (5) (reaction of styrene with thioglycolic acid in LED light)

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[13] Repurposing of SARS Inhibitors Against COVID 19,Priyanka Rajbhar, Dikshant Singh, Ruchi Yadav Submitted date: 20/04/2020 • Posted date: 24/04/2020,Licence: CC BY-NC-ND 4.0 Citation information: Rajbhar, Priyanka; Singh, Dikshant; Yadav, Ruchi (2020): Repurposing of SARS Inhibitors Against COVID 19. ChemRxiv. Preprint.