

THE SYNTHESIS OF VANILLIN-SEMICARBAZONE IN CRUDE GLYCEROL AS A GREEN SOLVENT*

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Glycerol is usually obtained as a by-product in the transesterification of triglycerides in the production of natural derivatives of fatty acids that can be used in many areas of pharmaceutical and food industries and as an alternative fuel. Also, crude glycerol can be successfully used as an alternative green solvent in various catalytic and non-catalytic organic reactions. In the present work, vanillin-semicarbazone was synthesized by using vanillin and semicarbazide as carbonyl and amine components, respectively, in the standard solvents (methanol, ethanol) and crude glycerol. The obtained semicarbazone was identified by elemental microanalysis, as well as by FTIR, UV/VIS, ¹H NMR and ¹³C NMR spectroscopic methods. The yield of vanillin-semicarbazone in crude glycerol was higher by 17 % in a much shorter reaction time (25 min) than in the conventional solvents.

Keywords: Vanillin-semicarbazone, glycerol, green synthesis

Introduction

Glycerol is the main by-product in the production of biodiesel. In the past decade, the price of glycerol decreased steadily because of the increase in its production and use of fatty acids derivatives in food, drugs and cosmetics, as well as a biofuel [1].

Glycerol is a non-toxic, non-irritating and biodegradable liquid that is very stable under typical storage conditions and compatible with many other chemicals. Owing to these features, glycerol has a number of uses such as humectant, plasticizer, emollient, lubricant, sweetener and antifreeze. It is also used as an ingredient in cosmetics, personal care, medicines and food products [2]. In addition, glycerol derivatives, such as esters, are widely used in many industries.

Recent studies have shown that glycerol and crude glycerol from the biodiesel production can be successfully used as an alternative green solvent in various catalytic and non-catalytic reactions of organic synthesis, ensuring a high product yield and selectivity [3]. As a polar solvent, glycerol facilitates dissolution of inorganic salts, acids, bases, and many transition metals. It also dissolves organic compounds that are poorly miscible with water. Therefore, glycerol can be used for the removal of products from the reaction mixtures simply by solvent extraction [4]. In this regard, the use of glycerol as a green solvent is a significant improvement in terms of the solvent selection, excellent performance and environ-

mental safety.

On the other hand, semicarbazones are an interesting class of compounds due to a significant antimicrobial activity [5, 6]. Semicarbazones can also exhibit anticonvulsant [7], antitubercular [8], analgesic and anti-inflammatory activity [9]. Recently, vanillin-semicarbazone was *in vivo* tested on the anticancer activity against Ehrlich ascites carcinoma cells, and the results confirmed vanillin-semicarbazone as a potential anticancer agent [10].

Taking into account this significant biological activity of vanillin-semicarbazone, its synthesis was performed in crude glycerol derived by the alkali catalyzed transesterification of edible sunflower oil with methanol as a green solvent. The main goals were to increase the product yield and to reduce the time of synthesis.

Experimental

Chemicals

All chemicals, except crude glycerol, were of reagent grade and used without further purification. They were purchased from Sigma Aldrich. The crude glycerol, a by-product in the production of biodiesel from sunflower oil, was obtained from the Laboratory for Chemical Engineering, Faculty of Technology, Leskovac. The excess of methanol was removed from the crude glycerol by distillation. After distillation, the acidity of crude glycerol was

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adjusted to pH 5 by addition of 85 % phosphoric acid [11]. The inorganic salts formed in this stage were then removed by centrifugation at 400 rpm for 15 min.

Instruments

Carbon, hydrogen and nitrogen were determined by microanalysis using a Carlo Erba 1106 microanalyser. The melting point was determined in open capillary tubes in a Thomas-Hoover point apparatus and was uncorrected. The purity of the compound was gained by TLC on silica gel using benzene: chloroform = 55:45, the compound being visualized by iodine vapors. The FTIR spectrum was recorded with a Michaelson Bomen MB-series spectrophotometer, using the KBr pellet (1 mg/100 mg) technique. The UV/Vis spectrum of 1×10^{-5} mol·dm⁻³ ethanolic solution of synthesized vanillin-semicarbazone was recorded on a Perkin-Elmer Lambda 15 UV/Vis spectrophotometer. The ¹H NMR and ¹³C NMR spectra were obtained in DMSO-d₆ solution by Gemini-200 "HF NMR".

Methods

Synthesis of vanillin-semicarbazone in ethanol/methanol

Vanillin-semicarbazone was prepared by the reaction of vanillin (1.52 g) and semicarbazone (0.52 g) in

95% ethanol or methanol as a conventional solvent following the standard procedure [12,13]. The mixture was refluxed at 50 °C for 45 min. The product, precipitated as a yellow solid, was collected by filtration and washed out with solvent.

Synthesis of vanillin-semicarbazone in glycerol

Vanillin-semicarbazone was also prepared by the reaction of vanillin (1.52 g) and semicarbazone (0.52 g) in crude glycerol as a green solvent. The mixture was refluxed at 65 °C for 20 min. The product, precipitated as a yellow solid, was filtered and washed out with water.

Results and Discussion

The synthesis of vanillin-semicarbazone was done using the carbonyl-amine condensation reaction of vanillin and semicarbazide in standard solvents (methanol, 95 % ethanol) and crude glycerol (Figure 1). The molecular formula of the synthesized compound, C₉H₁₁N₃O₃, was confirmed by the elemental analysis (see Table 1).

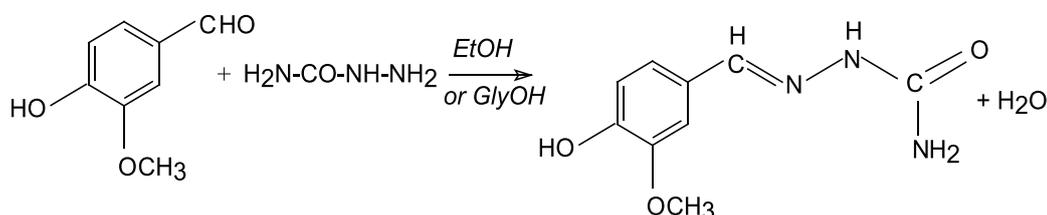


Figure 1. The synthesis of vanillin-semicarbazone using the carbonyl-amine condensation reaction

Table 1. Physico-chemical characteristics of synthesized vanillin-semicarbazone

Compound	Color	Melting point	C	Analysis (%)		Solubility
				H Exp. (Calc.)	N (20.02)	
Vanillin-semikarbazone	Yellow	230°C	51.68 (51.62)	5.26 (5.27)	20.09 (20.02)	Ethanol, Methanol, DMF, DMSO

UV/VIS spectral analysis of vanillin-semicarbazone

The UV/VIS spectrum of the ethanolic solution of vanillin-semicarbazone recorded in the wavelength region from 200 to 600 nm is represented in Figure 2, while the details about absorption bands and their assignment are given in Table 2. The spectrum shows two absorption

bands due to $\pi \rightarrow \pi^*$ transitions at $\lambda_{\max} = 220$ nm and $\lambda_{\max} = 289$ nm, and the third one at $\lambda_{\max} = 316$ nm due to the $n \rightarrow \pi^*$ transition in the synthesized compound. These transitions are characteristic for vanillin-semicarbazone as a Schiff base [5,14]. The spectrum shows no transitions above 450 nm, which makes vanillin-semicarbazone convenient for many nonlinear optical applications [5,14].

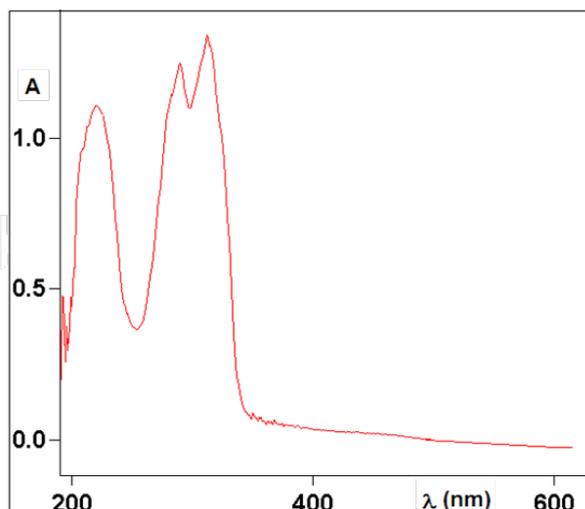


Figure 2. UV/VIS spectrum of vanillin-semicarbazone in 95 % ethanol

Table 2. UV/VIS spectral data of vanillin-semicarbazone recorded in 95 % ethanol

Compound	$\lambda(\text{nm})/\varepsilon \cdot 10^{-3}(\text{mol}^{-1} \cdot \text{dm}^3 \cdot \text{cm}^{-1})$	Band assignment
Vanillin-semicarbazone	220/1.089	$\pi \rightarrow \pi^*$
	289/1.231	$\pi \rightarrow \pi^*$
	316/1.338	$n \rightarrow \pi^*$

FTIR spectral analysis of vanillin-semicarbazone

The main IR spectral bands and their numerical data are given in Table 3. The strong absorption band at 3516 cm^{-1} in the IR spectrum (Figure 3) is due to phenolic $\nu(\text{OH})$ stretching vibration [5,15]. The symmetrical and asymmetrical NH_2 stretching bands can be observed 3465 and 3295 cm^{-1} in the IR spectrum according to the Davydov coupling [5,16]. Such a position showed the existence of the possible intramolecular hydrogen bond. The band at 1686 cm^{-1} comes from the $\nu(\text{C}=\text{O})$ stretching from the

semicarbazone part of the molecule. The $\nu(\text{C}=\text{N})$ stretching vibration of vanillin-semicarbazone appears at 1646 cm^{-1} as a characteristic band for Schiff bases, confirming the carbonyl-amine condensation reaction between vanillin and semicarbazide. The band at 1604 cm^{-1} can be assigned to the $\nu(\text{C}=\text{C})$ stretching vibration, and the peak at 1513 cm^{-1} is due to the N-H bending vibrations. The positions of other bands present in the spectra show that they are not involved in the vanillin-semicarbazone formation.

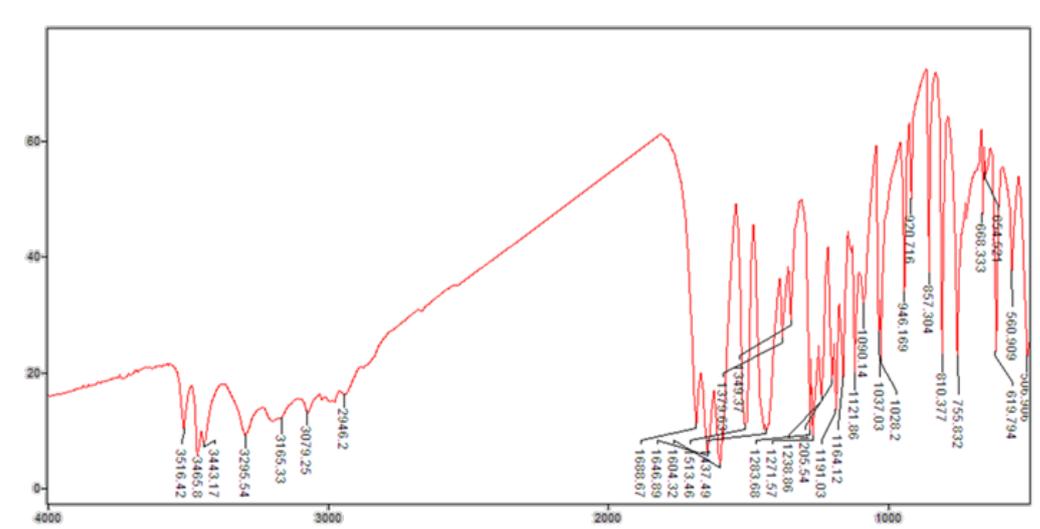


Figure 3. FTIR spectrum of vanillin-semicarbazone

Table 3. FTIR spectral data of vanillin-semicarbazone

$\nu(\text{cm}^{-1})$	Band assignment	$\nu(\text{cm}^{-1})$	Band assignment
3516	$\nu(\text{OH})$	1513	$\delta(\text{NH})$
3456	$\nu_{\text{as}}(\text{NH})$	1437	Ar-bending
3295	$\nu_{\text{s}}(\text{NH})$	1379	$\delta(\text{CH})$ from OCH_3
3165, 3079	Ar(CH)	1205	$\nu(\text{C-O})$
2946	$\nu(\text{CH})$ from OCH_3	1191	$\nu(\text{C-N})$
1688	$\nu(\text{C=O})$	1121	$\delta(\text{CH})$ in plane
1646	$\nu(\text{C=N})$	1090	$\delta(\text{NH})$ in plane
1604	$\nu(\text{C=C})$	810	$\delta(\text{CH})$ out of plane

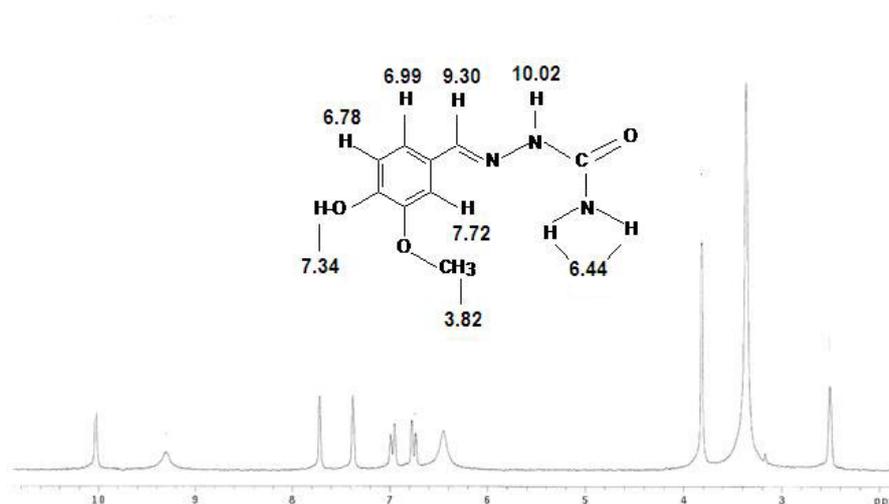
NMR spectral analysis of vanillin-semicarbazone

The NMR spectra of vanillin-semicarbazone recorded in DMSO-d₆ as a solvent provide further confirmation of the compound structure. The spectra and spectral assignments are given in Figures 4 and 5.

The ¹H NMR spectrum shows a singlet given from the proton in the secondary amine group at $\delta(\text{NH}) = 10.02$ ppm. As it can be seen, the position of this proton is shifted down the field, since it is attached to the heteroatom and decoupled by the quadrupole effects. The protons from the primary amine group give a characteristic broad signal at $\delta(\text{NH}_2) = 6.44$ ppm. The proton of the azome-

thine group gives a singlet at $\delta(\text{CH=N}) = 9.30$ ppm, and has no coupling interactions with protons of vicinal atoms. A strong singlet observed in the spectrum is given by protons from the methoxy group in the position of $\delta(\text{OCH}_3) = 3.82$ ppm.

The ¹³C NMR spectrum of vanillin-semicarbazone was recorded in DMSO-d₆. The proton decoupled ¹³C spectrum of the compound contains eight peaks corresponding to eight sets of carbonatoms. The peaks are assigned to the corresponding carbons according to the literature values [5]. The assignments of different resonating peaks to respective carbon atoms are presented in Figure 5.

**Figure 4.** ¹H NMR spectrum and proton assignments of vanillin-semicarbazone

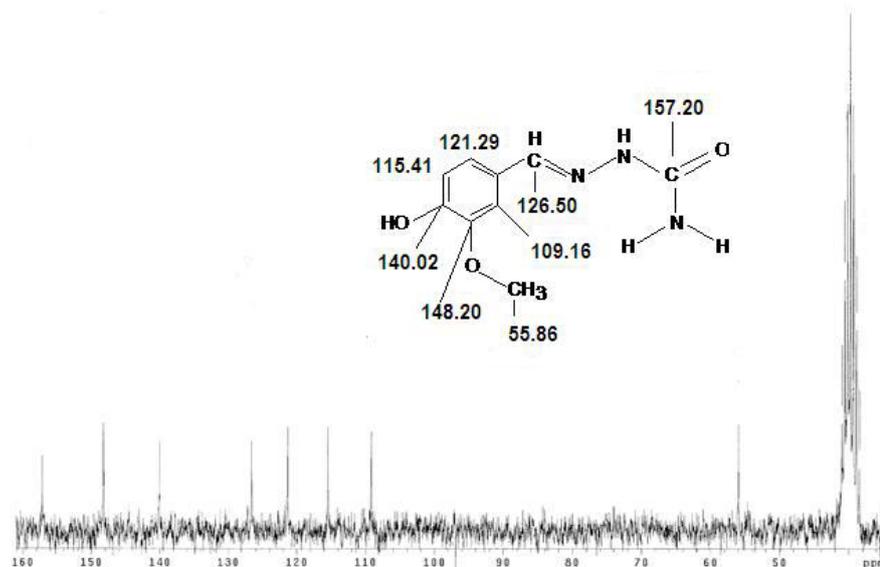


Figure 5. ^{13}C NMR spectrum and proton assignments of vanillin-semicarbazone

Synthesis in ethanol and crude glycerol

The formation of vanillin-semicarbazone in ethanol as a standard solvent is catalyzed with sulfuric acid, since the water elimination after the nucleophilic attack of semicarbazide on vanillin and acid medium is necessary for the synthesis. The reaction runs at 50 °C for 45 min (Table 4).

The synthesis of vanillin-semicarbazone in crude glycerol was carried out with no catalyst, since pH had already been adjusted by phosphoric acid in the previous stage. The reaction took place at 65 °C in order to reduce the negative impact of the glycerol viscosity. The duration of the reaction was 20 min (Table 4).

Table 4. The difference between the reaction time and the yield of reaction in ethanol/methanol and

Compound	Solvent							
	Ethanol/Methanol			Crude glycerol				
Vanillin-semicarbazone	Reaction time t(min)	Yield (%)	Catalyst	Reaction time t(min)	Yield (%)	Catalyst	Δt	$\Delta\%$
	45	72	Yes	20	89	No	25	17

As it can be seen from Table 4, the use of crude glycerol has significant advantages over the conventional solvent such as ethanol:

- The reaction time is faster for 25 min.
- The product yield is increased by 17 %.
- No catalyst is used.
- Crude glycerol is a by-product of the biodiesel production, which decrease the prize of synthesis.

vapor pressure and lower toxicity makes glycerol a more suitable solvent for the synthesis compared to ethanol and methanol.

Besides, the advantages of glycerol, compared to the conventional solvents, ethanol and methanol, are listed in Table 5. As it can be seen, a higher boiling point, lower

Table 5. Some physico-chemical characteristics of glycerol and standard solvents [4]

Characteristics	Glycerol	Ethanol	Methanol
Boiling point (°C)	290	78	65
Vapor pressure (mmHg/50°C)	<1	210	414
Dielectric constant (25°C)	42.5	24.3	32.66
Viscosity (cP/30°C)	629	0.949	0.521
Density (g/ml/25°C)	1.29	0.785	0.791
LD ₅₀ (Oral-rats) (mg/kg)	12 600	7060	5628
Biodegradability	Yes	Yes	Yes

Conclusion

The synthesis of vanillin-semicarbazones was carried out using the carbonyl-amine condensation reaction of vanillin and semicarbazide in standard solvents, methanol and 95 % ethanol, and crude glycerol, a green solvent obtained as a major by-product of the biodiesel production. The use of crude glycerol has significant advantages over the conventional solvents, since the reaction time is reduced for 20 min, the yield of the reaction is increased by 17 %, no catalyst is needed and glycerol is a by-product in the production of biodiesel. A higher boiling point, lower vapor pressure, lower toxicity and lower flammability of glycerol, compared to methanol and ethanol, are also its advantages.

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Izvod

SINTEZA VANILIN-SEMIKARBAZONA U SIROVOM GLICEROLU KAO ZELENOM RASTVARAČUMarija B. Jovanović¹, Sandra S. Konstantinović^{1**}, Slavica B. Ilić¹, Vlada B. Veljković¹(ORIGINALAN NAUČNI RAD)
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Glicerol je glavni nusproizvod u produkciji biodizela. Glicerol i sirovi glicerol se mogu uspešno iskoristiti kao alternativni zeleni rastvarači u različitim katalitičkim i ne-katalitičkim organskim reakcijama sinteze, pri čemu se ostvaruju visok prinos i selektivnost. Rastvarači se koriste svakodnevno u mnogim industrijskim procesima kao reakcioni medijumi. U tom smislu, utvrđeno je da je korišćenje glicerola kao zelenog rastvarača dobar izbor zbog njegovih odličnih fizičko-hemijskih karakteristika i neškodljivosti po okolinu. U ovom radu sintetisan je vanilin-semikarbazon korišćenjem vanilina kao karbonilne i semikarbazida kao amino komponente u standardnim rastvaračima (metanol, etanol) i sirovom glicerolu. Identifikacija dobijenog semikarbazona je rađena metodom elementarne mikroanalize, kao i primenom FTIR, UV/VIS, ¹H NMR i ¹³C NMR spektroskopskih metoda. Prinos vanilin-semikarbazona je u sintezi sa sirovim glicerolom povećan za 17 %, a reakciono vreme je kraće 25 min u odnosu na sinteze rađene u metanolu i etanolu kao standardnim rastvaračima.

Ključne reči: Vanilin-semikarbazon, glicerol, zelena sinteza