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Microwave Assisted Synthesis of 4-Substituted 1-Ethoxycarbonyl Semicarbazides from Ethyl Carbazate and Isocyanates

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Summary. A rapid and simple method for the preparation of 4-substituted 1-ethoxycarbonyl semicarbazide is reported. The reaction is carried out under microwave irradiation by the reaction of five different isocyanates with ethyl carbazate.

Keywords. Microwave irradiation; Solid-state; Semicarbazide.

Introduction

4-Substituted 1-ethoxycarbonyl semicarbazides are important organic intermediates for the synthesis of 4-substituted urazoles and they are prepared by reaction of the corresponding isocyanates with ethyl carbazate in toluene solution [1]. However, some of the mentioned methods invariably require lower temperatures, long reaction times, and involve solvents which are toxic and detrimental to the environment. Therefore, there is a need for a simple, less expensive, and safer method for synthesis of semicarbazides. In recent years, there has been a growing interest in the application of microwave irradiation in chemical reaction enhancement, because of cleaner reactions, decreased reaction times, and easier work-up [2]. In continuation of our program [3] we now report a facile preparation of semicarbazides from ethyl carbazate and isocyanates accelerated under microwave irradiation.

Results and Discussion

One equivalent of ethyl carbazate and phenyl isocyanate were ground in a mortar until a homogeneous mixture is formed (1 min). Then, the reaction mixture was transferred

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Table 1. Microwave-assisted synthesis of 1-ethoxycarbonyl-4-substituted-semicarbazides (microwave oven was used at 70% of it's power)

Educt	Product	t/min	Yield/%	Ref.
1	**2**	2	95	[1a]
3	**4**	2	95	[1d]
5	**6**	2	96	[1e]
7	**8**	2	81	[1d]
9	**10**	2	94	[1d]

1	$R = Ph$	**2**	$R = Ph$
3	$R = 4\text{-Cl-}C_6H_4$	**4**	$R = 4\text{-Cl-}C_6H_4$
5	$R = 3,4\text{-}Cl_2C_6H_3$	**6**	$R = 3,4\text{-}Cl_2C_6H_3$
7	$R = C_6H_{11}$	**8**	$R = C_6H_{11}$
9	$R = n\text{-}C_3H_7$	**10**	$R = n\text{-}C_3H_7$

Formula 1

to an *Erlenmeyer* flask and irradiated in a microwave oven (2 min; after this time the temperature had risen to 80°C). The optimum molar ratio of ethyl carbazate and phenyl isocyanate was found to be 1:1. A variety of semicarbazides (aliphatic and aromatic) were prepared (Table 1). The yields of the reactions are high. The products were isolated by washing the reaction mixture with solvent followed by filtration of the mixture, which often produced pure product without any purification.

For comparison, according to the conventional method **2** has been prepared as follows: ethyl carbazate dissolved in toluene is cooled in an ice-water bath to about 10°C. To this solution **1** is added dropwise over a period of 75 min. The mixture is then stirred at room temperature for 2.5 h and heated under reflux for additional 2 h. After cooling to room temperature **2** is separated by filtration, washed with toluene, and dried for 24 h to provide a yield of 96% [1a].

In conclusion, we reported a new and efficient methodology for the synthesis of semicarbazides from ethyl carbazate and isocyanates under microwave irradiation. This method is superior to previously reported methods in terms of high yields, purity of products, facile work-up, short reaction time, and the cost of the solvent.

Experimental

All of the yields refer to isolated products after purification. All of the products were characterized by comparison of their spectral (IR, ^{1}H NMR) and physical data (melting and boiling points) with those of authentic samples [1]. All ^{1}H NMR spectra were recorded at 90 MHz in *DMSO*-d_6 relative to *TMS* as internal standard and IR spectra were recorded on a Shimadzu 435 IR spectrometer. A Samsung

domestic microwave oven (2450 MHz, 900 W) was used without any modification, but all of the reactions were carried out in a hood with strong ventilation.

Typical Procedure for the Preparation of Semicarbazides from Ethyl Carbazate and Isocyanates Under Microwave Irradiation

A mixture of 1 mmol ethyl carbazate (0.104 g) and 1 mmol phenyl isocyanate (0.11 g) was prepared and irradiated for the time specified in Table 1. When TLC showed complete disappearance of starting material, the mixture was treated with toluene, and pure 1-ethoxycarbonyl-4-phenyl semicarbazide was isolated by filtration. The yield was 0.20 g (95%) of a crystalline white solid, mp 141–143°C (Ref. [1a] 146–147°C).

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