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Synthesis of Substituted Semicarbazone, Thiosemicarbazone and Aminoguanidine

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Abstract. A new simple, universal and highly-efficient method of substituted semicarbazone, thiosemicarbazone and aminoguanidine synthesis in presence of I_2 was developed. The method was applied for obtaining of the range of products, whose structures were confirmed by ^{1}H NMR Spectra.

Introduction

Currently, one of the urgent tasks is to develop methods for producing of new drugs with better pharmacological properties.

The aim of our work is to obtain substituted semicarbazones, thiosemicarbazones and aminoguanidines **(1-3)**, which is known by their antibacterial, anticonvulsive, antitubercular, and antitumor activity [1].

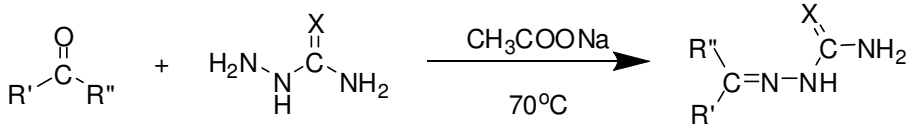
Semicarbazide, a raw material for the semicarbazone, has a biological activity. Even in small doses it can destroy tumor cells. The action of semicarbazide on human body is complex and differs from the standard drugs action. Semicarbazide is a powerful antioxidant. It blocks free radicals and protects cells from the damage caused by oxidative stress.

Semicarbazide effectively inhibits the activity of an enzyme called (SSAO) [2-6].

The improvement of substituted semicarbazone, thiosemicarbazone and aminoguanidine synthesis

The common procedure which usually used for semicarbazones preparation consists of interaction between carbonyl compounds and semicarbazide in the presence of appropriate buffer [1]. This method has been tested many times and attracts with its accessibility. We used this technique to prepare compounds **(3a-f)**, (Method 1).

Method 1



1a-b

1a, R'= Ph, R"= Ph
1b, R'= Ph, R"= H

1-3

1, X=O
2, X=S
3, X=NH

3a-f

3a, R'= Ph, R"= Ph, X=O
3b, R'= Ph, R"= Ph , X=S
3c, R'= Ph, R"= Ph, X=NH
3d, R'= Ph, R"= H, X=O
3e, R'= Ph, R"= H, X=S
3f, R'= Ph, R"= H, X=NH

However, it was discovered that aminoguanidine does not react with the carbonyl compounds **1a-b**. It was found earlier [3] that the reaction of urea with benzaldehyde can be activated by addition of catalytical amount of I_2 to the mixture. We applied this activation method for

aminoguanidine, and in this case the formation of the desirable product was detected. This method (Method 2) was also used in the reaction of compounds **1-3** with substrates **1a-b**. As a result, the reaction time was significantly reduced, and the product yields were increased (Table 1, Method 2).

Method 2

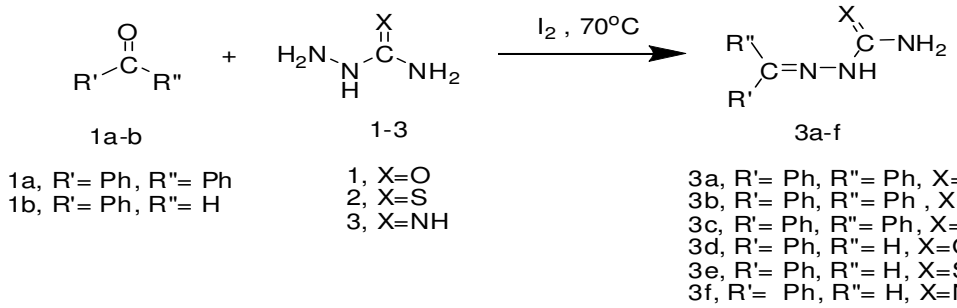
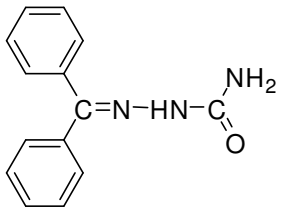
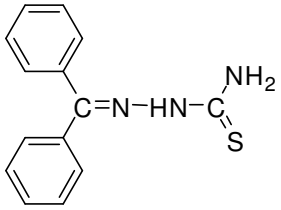
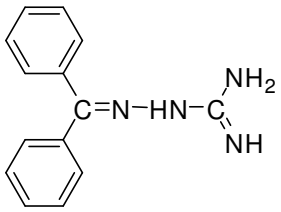
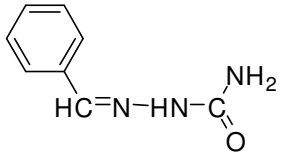
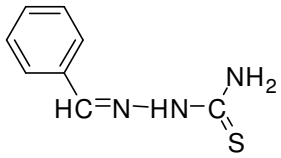
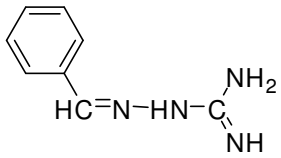


Table 1. Comparison of methods 1 and 2

Product	Method 1			Method 2		
	time, h.	yield, %	m.p, ºC	time, h.	yield, %	m.p, ºC
3a 	2.5	70	163-165	1.5	75	163-164
3b 	4	76	170-171	2	80	169-170
3c 	-	-	-	3	83	275-278

3d 	1,5	80	213-215	0.5	84	214-215
3e 	2	85	158-161	1	89	159-160
3f 	-	-	-	2.5	68	135-136

Conclusions

Thus, as a result of this research we developed a new universal method for the synthesis of substituted semicarbazones, thiosemicarbazones and aminoguanidine in presence of I_2. The simple and highly-efficient method provides a good yields of products in short reaction time and requires only commercially available reagents.

Experimental

All chemicals are commercially avaliable products and were used without preliminary purification. The products were characterized by comparison of their physical properties with literature data or by comparison of ^{1}H NMR spectra. ^{1}H NMR spectra were recorded with a Bruker MMX300 spectrometer in DMSO with tetramethylsilane as the internal standard. The TLC eluent – benzene: ethanol (9:1).

General Procedure for the Synthesis of [3a-f]

A solution of semicarbazide, thiosemicarbazide, aminoguanidine hydrochloride **(1-3)** (0.02 mol in 25 ml water) was added to a solution of the carbonyl compound **(1a-b)** (0,01 mol in 15 mL of ethanol) containing sodium acetate (2 g) . To the resulting solution was added I_2 (0,5 g; 0,004 mol). The reaction mixture was refluxed under stirring the required amount of time (Table 1). The reaction was monitored by TLC (Rf of the product is about 0,2). After completion of the reaction the mixture was cooled to the room temperature, and the white crystals were filtered and washed with water. Obtained product were recrystallized from ethanol.

Analytical Data of 3a-f

2-(diphenylmethylene)hydrazinecarboxamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.731(s, 2H, NH_2); 7.9(s, 1H, NH); 7.633-7.2(m, 10H, Ar-H).

2-(diphenylmethylene)hydrazinecarbothioamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.4(s, 2H, NH_2); 8.654(s, 1H, NH); 8.410-7.327(m, 10H, Ar-H).

2-(diphenylmethylene)hydrazinecarboximidamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.9 (s, 1H); 7.9 (sl); 7.618–7.407 (m, 10H).

2-benzylidenehydrazinecarboxamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.840(s, 2H, NH_2); 7,699 (s, 1H, NH); 6.500(s, 1H, CH); 7.410-7.309(m, 10H, Ar-H).

2-benzylidenehydrazinecarbothioamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.051(s, 2H, NH_2); 8.201(s, 1H, NH); 7.993(s, 1H, CH); 7.803-7.381(m, 10H, Ar-H).

2-benzylidenehydrazinecarboximidamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.11 (s, 1H); 8.188 (s, 1H); 7.864-7.842(m, 10H, Ar-H); 7.444-7.423(m, 2H, 1H).

Acknowledgements

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