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Efficient synthesis of benzylidene semicarbazones from aromatic aldehydes by urea-hydrogen peroxide (UHP)

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Abstract: A facile and useful method for synthesis of 1-benzylidene semicarbazones was introduced in this work. The reaction of synthesis of the corresponding 1-benzylidene semicarbazone derivatives is carried out in the presence of acetonitrile-UHP/NH_4OAc. In this method, NH_4OAc was used as a source of ammonia and urea-hydrogen peroxide (UHP) as reagent. The key advantages of this process are elimination of semicarbazide, good yields and cheap reagents. All products were characterized by common techniques (infrared, ^1H NMR, and melting point).

Keywords: Benzylidene semicarbazone; UHP; aromatic aldehydes; acetonitrile. © 2024 ACG Publications. All rights reserved.

1. Introduction

Benzylidene semicarbazones are one of the most attractive compounds in organic synthesis. Therefore, the easy and green synthesis of these compounds is attractive and important for researchers because it includes environmentally clean synthesis, high atomic efficiency, elimination of hazardous reagents, easy separation from the reaction mixture and easy access to cheap and safe reagents[1].

2. Background

Semicarbazone derivatives were found to possess various pharmacological properties such as antimicrobial[2,3], anticonvulsant[4-6], antiepileptic[7], anti-inflammatory[8], antioxidant[9] and antiproliferative[10] activities. These are useful for the protection, purification and characterization of carbonyl compounds, and also act as intermediate for the synthesis of biologically important heterocyclic moieties such as 1,3,4oxadiazoles[12,13], 1,2,3- triazoles, 1,2,4-triazoles[14,15] and metal complexes[16,17]. The routine and common method for the synthesis of semicarbazone derivatives is the reaction of aldehydes/ ketones with semicarbazide in the presence of base or acid as catalyst[11]. Recently many methods have been developed using SiO_2/NaOH[18], sodium acetate supported on silica gel[19] and basic alumina[20] as catalysts. In the present paper, we have reported the synthesis of semicarbazone derivatives of aryl aldehydes by UHP/NH_4OAc in acetonitrile as solvent under reflux

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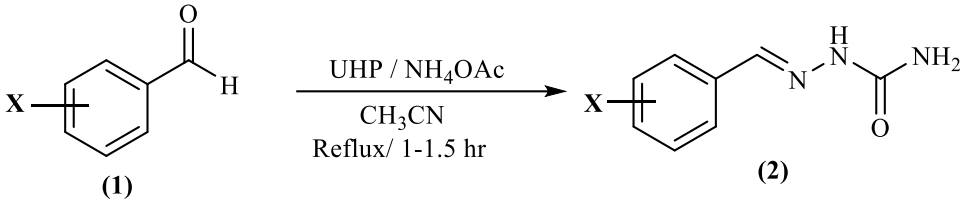
condition as facile synthesis.This method introduces the novel synthesis for the preparation of 1-benzylidene semicarbazone derivatives without using of semicarbazide. It can also be a good method to identify aryl hydrides.The general reaction is illustrated in scheme 1.



X= H, Me, OMe, Cl, Br, NO_2

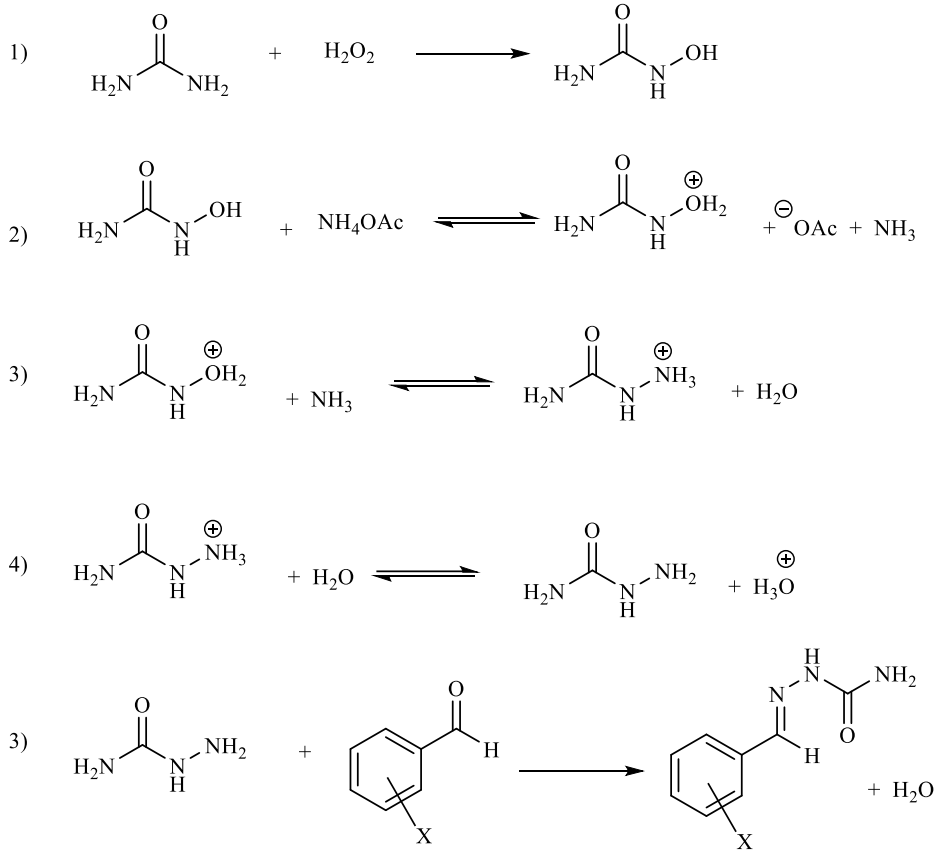
Scheme1. Synthesis of 1-benzylidene semicarbazones derivatives by UHP/NH_4OAc

3. Experimental

The details of the experimental procedures for all described reactions and the complete characterization data (infrared, ^1H NMR, ^{13}C NMR and melting point) for representative compounds can be found in the supporting information.

4. Present Study

1-benzylidene semicarbazone derivatives (**2a-h**) were synthesized by the condensation of aromatic aldehydes (**1a-h**) with *in-situ* semicarbazide, which was generated by reaction of UHP with ammonium acetate.The proposed mechanism of reaction is shown in Scheme 2.



Scheme 2. The proposed mechanism for the Synthesis of 1-benzylidene semicarbazones derivatives without using semicarbazide

To optimize the reaction conditions, initially the reaction between different ammonium salts with benzaldehyde was carried out in different solvents (ethanol, acetonitrile and water) and observed the maximum yield (90%) with ammonium acetate in acetonitrile (Table 1).

Table 1. Optimization of reaction conditions[a]

Entry	Solvent	$(NH_4)_2CO_3$ (mmol)	NH_4Cl (mmol)	NH_4OAc (mmol)	Yield[b] (%)
1	Water	1mmol	-	-	25
2	Water	-	1mmol	-	20
3	Water	-	-	1mmol	15
4	Ethanol	1mmol	-	-	65
5	Ethanol	-	1mmol	-	60
6	Ethanol	-	-	1mmol	50
7	Acetonitrile	1mmol	-	-	30
8	Acetonitrile	-	1mmol		45
9	Acetonitrile	-	-	1mmol	90

[a] Reactions were carried out with 1 mmol of the benzaldehyde , 1 mmol of UHP under reflux
[b] Isolated yield

With these optimal conditions (Acetonitrile as solvent and NH_4OAc as a source of ammonia), we have synthesized various 1-benzylidene semicarbazone derivatives of aromatic aldehydes with excellent yields (Table 2). The structures of products (**2a–h)** were deduced by ^1H NMR and FT-IR spectroscopy. The ^1H NMR spectrum of (**2a)** exhibited one singlet, arising from the imine group (δ 8.06 ppm). With regard to IR spectra, the presence of peaks around 1662 cm^{-1} (C=O stretching) and 1610 cm^{-1} (C=N stretching), which confirms the proposed structure.

Table 2. Synthesis of 1-benzylidene semicarbazones derivatives **2a-h** without using semicarbazide

Product[a]	Aldehyde	Time (min)	Yield[b] (%)	Mp (˚C)	
				Found	Reported[22]
2a	C_6H_5	60	90	218-220	222
2b	4-MeC_6H_4	75	88	230-234	234
2c	4-$MeOC_6H_4$	75	80	208-211	210
2d	4-ClC_6H_4	60	93	231-233	233
2e	4-$NO_2C_6H_4$	60	86	216-220	221
2f	2-$MeOC_6H_4$	75	90	208-212	215
2g	4-BrC_6H_4	75	89	223-226	229
2h	3-$NO_2C_6H_4$	60	90	239-243	246

[a]All known compounds were characterized by comparing their spectral data (FT-IR, ^1H-NMR) and physical data with those reported. [b] Isolated yield

In conlusion, as a novel synthesis method, benzylidene semicarbazones have been synthesized without using semicarbazide, which is a great advantage. Other advantages of this method are high efficiency and accessibility of cheap required reagents in the laboratory.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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