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The synthesis of some new hydrazone derivatives containing the benzothiazole moiety

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Abstract: Hydrazones are an important class of compounds found in many synthetic products. Due to their importance in synthetic chemistry, the present article reports the synthesis of a new series of ten compounds based on the coupling of 2-oxo-3(2*H*)-benzothiazoleacetic acid, hydrazide and 2-thioxo-3(2*H*)-benzothiazoleacetic acid, hydrazide with different aldehydes. The structures of the synthesized compounds were confirmed by elemental analyses, IR, ¹H-NMR, ¹³C-NMR and FAB⁺-MS spectral data.

Keywords: hydrazone; 2-benzothiazolinone; 2-mercaptobenzothiazole; aromatic aldehydes.

INTRODUCTION

Hydrazone derivatives have attracted a great deal of interest in synthetic chemistry and considerable research on them in relation to their synthetic utility has been accomplished. Hydrazones are extensively studied as reactants or reaction intermediates since they can readily undergo various ring closure reactions.¹

Among the benzothiazole derivatives, benzothiazol-2-ones and 2-mercaptobenzothiazoles have received considerable attention in organic chemistry associated with their importance in nucleophilic substitution reactions.² The present study also confirmed that the ease of nucleophilic substitution depends on the nucleophilicity.

All these observations gave encouragement to commence a research program for the synthesis of new hydrazone derivatives containing a heterocyclic moiety. After careful screening of various heteronuclei, benzothiazole was chosen as the focus of attention. In this respect, it should be noted that this heterocyclic scaffold still attracts the attention of material chemists, because of its use as a chemically and thermally stable electron-withdrawing moiety in push-pull systems

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with potential application in nonlinear optics.^{3–6} Furthermore, various derivatives bearing the benzothiazole moiety display antimicrobial and anticancer activities.^{7–9} It was therefore expected that the newly synthesized hydrazone derivatives bearing a benzothiazole moiety might be of potential interest or could serve as potential intermediates in medicinal chemistry. Herein, the synthesis of new hydrazone derivatives bearing a benzothiazole moiety is described.

RESULTS AND DISCUSSION

Chemistry

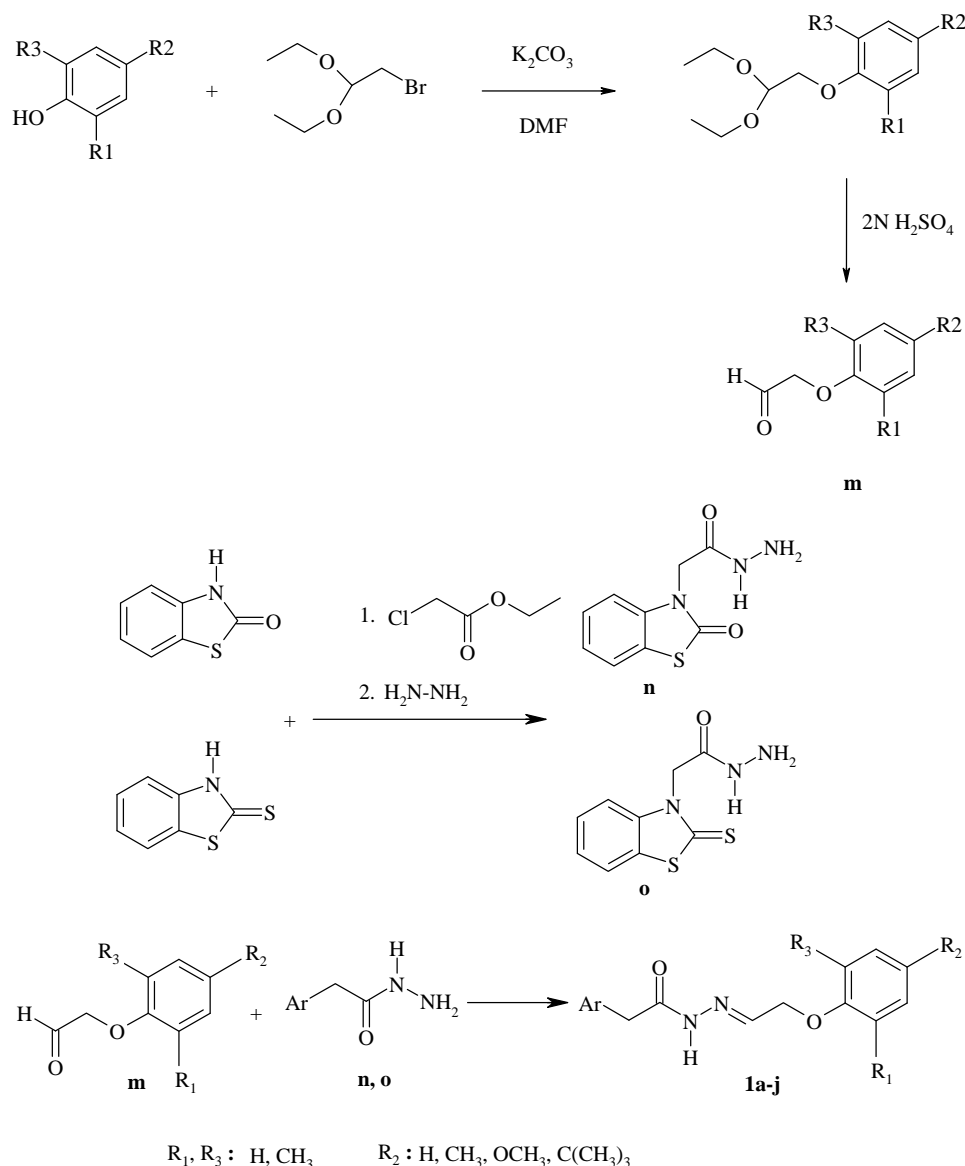
Among several synthetic routes to derivatives **1a–j**, it was decided to investigate the synthesis of acylhydrazone derivatives as key intermediates. This compound could be transformed to **1a–j** using classical functional group interconversion, *i.e.* $\text{CONHNH}_2 \rightarrow \text{CONHN}=\text{CH}-\text{CH}_2-\text{O}-\text{Ar}$. Finally, the new target compounds **1a–j** were obtained, in good yields (70–88 %), by condensing hydrazides (**n,o**) with the corresponding appropriate aldehydes in absolute ethanol, as illustrated in Table I and Scheme 1.

TABLE I. Some characteristics of the synthesized compounds

Compd.	Ar	R ₁	R ₂	R ₃	Yield, %	Molecular formula	M.W., g mol ⁻¹	M.p., °C
1a	n	H	CH ₃	H	71	C ₁₈ H ₁₇ N ₃ O ₃ S	355.42	213–214
1b	n	H	C(CH ₃) ₃	H	88	C ₂₁ H ₂₃ N ₃ O ₃ S	397.50	209–211
1c	n	H	OCH ₃	H	70	C ₁₈ H ₁₇ N ₃ O ₄ S	299.5	203–204
1d	n	CH ₃	CH ₃	H	77	C ₁₉ H ₁₉ N ₃ O ₃ S	369.45	218–220
1e	n	CH ₃	H	CH ₃	79	C ₁₉ H ₁₉ N ₃ O ₃ S	369.45	226–227
1f	o	H	CH ₃	H	80	C ₁₈ H ₁₇ N ₃ O ₂ S ₂	371.48	138–140
1g	o	H	C(CH ₃) ₃	H	78	C ₂₁ H ₂₃ N ₃ O ₂ S ₂	413.56	142–144
1h	o	H	OCH ₃	H	81	C ₁₈ H ₁₇ N ₃ O ₃ S ₂	387.48	145–147
1i	o	CH ₃	CH ₃	H	79	C ₁₉ H ₁₉ N ₃ O ₂ S ₂	385.51	136–137
1j	o	CH ₃	H	CH ₃	75	C ₁₉ H ₁₉ N ₃ O ₃ S ₂	385.51	86–88

The nucleophilic substitution of 2(3*H*)-benzothiazolone shows an important difference when compared with that of 2-mercaptobenzothiazole. The enolizable character of the amide moiety allows several useful substitutions at the level of the *N* position of the 2(3*H*)-benzothiazolone under base-catalyzed conditions¹⁰. On the other hand, the nucleophilic reactivity of 2-mercaptobenzothiazole associated with the presence of nitrogen and sulfur atoms holding a pair of electrons on either side of the $>\text{C}=\text{S}$ group increases the electron donating capacity of “S” to form a bond with a halogenated carbon atom.¹¹ The fact that the S-substituted

derivatives were the dominant species indicates that sulfur-containing anions are more stable and stronger nucleophiles due to d-orbital delocalization of sulfur compared to the nucleophilic properties of the nitrogen-containing anions.²



Scheme 1. The general synthetic reactions (see Table I for details of R, R₁ and R₂ of **1a-j**).

The purity of the synthesized compounds was checked by elemental analyses. The structures of the various synthesized compounds were determined based

on spectral data analysis, *i.e.*, IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and $\text{FAB}^+\text{-MS}$ spectral data. These data are given in the Supplementary material to this paper.

The IR data provided functional group evidence for the formation of the expected structures. In the IR spectra, some significant stretching bands due to N–H, C=O, C=C and C=N were observed at 3339–3175 cm^{-1} , 1687–1680 cm^{-1} and 1610–1485 cm^{-1} , respectively. The IR spectra of the acid hydrazides **1a–e** showed a peak at 1680–1683 cm^{-1} due to the exocyclic carbonyl function derived from hydrazide structure, beside the endocyclic carbonyl peak (1770–1768 cm^{-1}) at position 2 of the 2(3*H*)-benzothiazolone ring.

According to the literature, hydrazones may exist as *E/Z* geometric isomers about the C=N double bonds and *cis/trans* amide conformers. In addition, hydrazones derived from aldehydes and substituted hydrazides are present in solution in the *E* form. It was reported that when hydrazones are dissolved in d_6 -dimethyl sulfoxide solution, the *E* geometrical isomers of these compounds undergo a rapid *cis/trans* amide equilibrium, in which the *cis* conformer predominates.^{12,13}

In the 400 MHz $^1\text{H-NMR}$ spectra of the compounds, the –O–CH₂–CO protons were observed as singlets at 4.55 and 4.87–4.90 ppm. The –O–CH₂–CH= protons appeared as multiplets at 4.63–4.72 ppm. The –N=CH– proton was observed as a triplet at 7.47–7.94 ppm. The –NH–N= proton was observed as two broad singlets at 11.41–11.47 ppm. All the other aliphatic and aromatic protons were observed within the expected regions.

The $^1\text{H-NMR}$ data were also consistent with the assigned structures. In the $^1\text{H-NMR}$ spectra of the compounds, paired peaks for each of the protons –O–CH₂–CH=, –N=CH– and –NH–N=, corresponding to the (*E*)- and (*Z*)-forms of the compounds, were observed. For each compound, the intensities of these paired peaks differed from others, due to the variable amounts of the (*E*)- and (*Z*)-isomers, which are usually unequal.

Additional support for the structures of the synthesized compounds was provided by their $^{13}\text{C-NMR}$ spectra, in which chemical shift values of the carbon atoms at around 164.56–164.64 ppm (hydrazide C=O), and 142.61–142.99 ppm (imine N=CH) corroborated the hydrazide character deduced from the $^1\text{H-NMR}$ data. The mass spectra of compounds showed [M+1] peaks in agreement with their molecular formula.

EXPERIMENTAL

All chemicals were obtained from Aldrich (Steinheim, Germany). All melting points (m.p.) were determined in open capillaries on a Gallenkamp apparatus (Weiss-Gallenkamp, Loughborough, UK) and are uncorrected. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using silica gel 60G (Merck, Darmstadt, Germany). Elemental analyses were performed on a Perkin Elmer EAL 240 elemental analyzer. Spectroscopic data were recorded using the following instruments: $^1\text{H-NMR}$, a Bruker 400 MHz spectrometer; $^{13}\text{C-NMR}$, a Bruker 100 MHz spectrometer (Bruker, Billerica, Massachusetts,

USA) and MS-FAB, a VG Quattro Mass spectrometer (Agilent, Minnesota, USA). The NMR spectra were recorded in DMSO- d_6 using TMS as an internal standard.

General procedure for the synthesis of the compounds

Synthesis of substituted phenoxyacetaldehyde (m). These compounds used in the syntheses were prepared according to methods reported in the literature.^{14,15}

Synthesis of 2-oxo-3(2H)-benzothiazoleacetic acid, hydrazide (n). This compound was prepared according to the literature, by reacting 2-oxo-3(2H)-benzothiazoleacetic acid, ethyl ester with hydrazine hydrate.^{16,17}

Synthesis of 2-thioxo-3(2H)-benzothiazoleacetic acid, hydrazide (o). This compound was prepared in accordance with a previously described method, by reacting 2-thioxo-3(2H)-benzothiazoleacetic acid, ethyl ester with hydrazine hydrate.^{16,17}

Synthesis of the 2-phenoxyethylidene hydrazide derivatives (1a-j). Equimolar quantities of acetylhydrazines (30 mmol) and an appropriate aldehyde in 25 ml of absolute ethanol were refluxed for 10–12 h. The reaction mixture was then cooled and the solid precipitated was recrystallized from an appropriate solvent. Some characteristics of the synthesized compounds are given in Table I.

CONCLUSIONS

In the present work, appropriate aldehyde derivatives were synthesized *via* the treatment of the compounds bearing an acetal group with sulfuric acid, which catalyzes the hydrolysis of acetals affording aldehydes prone to nucleophilic addition reactions. Hydrazone derivatives were obtained by reaction of the aldehyde derivatives with appropriate hydrazides.

SUPPLEMENTARY MATERIAL

Characteristics and spectral data of synthesized compounds are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

ИЗВОД

СИНТЕЗА НОВИХ ХИДРАЗОНСКИХ ДЕРИВАТА КОЈИ САДРЖЕ БЕНЗОТИАЗОЛСКУ СТРУКТУРУ

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Хидразони су важна класа једињења која се садржи у многим синтетичким производима. Због њихове важности у синтетској хемији, у овом раду је приказана синтеза нове серије од десет једињења. Синтеза се заснива на купловању хидразида 2-оксо-3(2H)-бензотиазолсирћетне киселине и хидразида 2-тиоксо-3(2H)-бензотиазолсирћетне киселине са различитим алдехидима. Структуре синтетисаних једињења одређене су на основу елементалне анализе, ИС, ¹H-NMR, ¹³C-NMR и FAB⁺-MS спектроскопских података.

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