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A facile synthesis of novel biologically active 4-hydroxy-*N*′-(benzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxides

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ABSTRACT

A novel series of potentially biologically active 4-hydroxy-*N*′-(benzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxides were synthesized starting from ultrasonic mediated N-alkylation of sodium saccharin with methyl chloroacetate. Ring expansion of methyl(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate followed by its hydrazinolysis afforded 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide which was reacted in a straight forward manner with various benzaldehydes in an ultrasonic bath to get the title compounds. All of the synthesized compounds were subjected to preliminary evaluation for their antibacterial and DPPH radical scavenging activities.

1. Introduction

Various benzothiazine derivatives are known to possess a versatile range of biological activities and have been synthesized continuously since the very first synthesis by Abe et al. [1]. Among these, 1,2-benzothiazine-3-carboxamide-1,1-dioxides such as Piroxicam [2], Ampiroxicam [3] and Meloxicam [4] are familiar for their analgesic and anti-inflammatory activities and are being used worldwide as non-steroidal anti-inflammatory drugs (NSAIDs). Some of the 3,4-dihydro-1,2-benzothiazine-3-carboxylate 1,1-dioxide α-ketomide and P(2)–P(3) peptide mimetic aldehyde compounds act as potent calpain I inhibitors [5] while 1,2-benzothiazin-3-yl-quinazolin-4(3*H*)-ones possess antibacterial properties [6].

Various carbohydrazides and their derivatives are reported to show a plethora of biological activities. For example, some of these are found useful for the treatment of autoimmune and inflammatory diseases, tumors, osteoarthritis and hemorrhage [7] whereas some others exhibit antifungal [8], antiviral [9], bacteriostatic [10,11], antiparasitic [12], antituberculous [13–16], and insecticidal activities [17]. These have also been found useful as antifertility agents in pigeons and rats [18].

Prompted by the above mentioned biological properties of benzothiazines and hydrazides, it was contemplated to synthesize a novel series of *N*-arylmethylidene-4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides on the perception of getting biologically active compounds.

2. Chemistry

The synthetic route to prepare the 4-hydroxy-*N*′-(benzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxides **5a–o** (Scheme 1) employed N-alkylation of *o*-benzosulfimide **1** with methyl chloroacetate under ultrasonic waves followed by the known ring expansion of the five membered isothiazole ring to a six membered thiazine ring. The resulting methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide **3** was reacted with hydrazine hydrate followed by ultrasound mediated reaction with different aldehydes (Scheme 1).

3. Results and discussion

In recent years, synthetic applications of ultrasonic irradiation in various organic transformations have been widely demonstrated in literature [19]. Many procedures have been devised to carry out chemical reactions in shorter times and under milder and more environmentally benign conditions. Reduction of carbonyl

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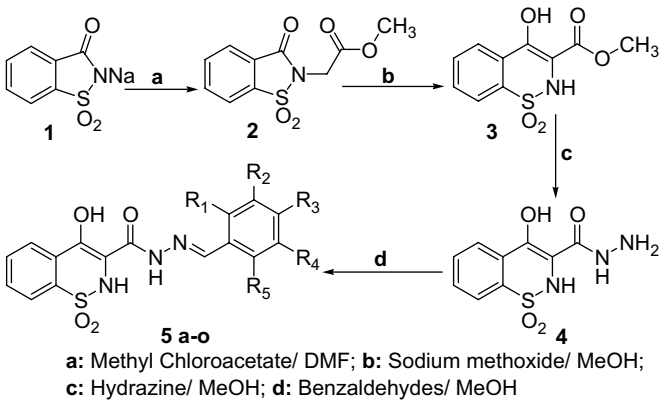

Scheme 1. Conversion of sodium saccharin to *N*-[(1*E*)-arylmethylidene]-4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides.

compounds [20], ring opening of epoxides [21], acetylation of alcohols [22], Suzuki cross-coupling reaction [23], aldol reaction [24] and oxime synthesis [25] are worth mentioning in this regard. Keeping in view the usefulness of this relatively unexplored technique, N-alkylation of 1,2-benzisothiazol-3(2*H*)-ones was carried out in an ultrasonic reaction bath; a mixture of sodium saccharin and methyl chloroacetate dissolved in dimethylformamide was subjected to ultrasonic irradiation. The reaction was completed in a shorter time and at lower temperature than the previously reported standard procedure [26].

In the next step, the five membered isothiazole ring was converted to a six membered thiazine ring using the known Gabriel–Colman type rearrangement having synchronous ring cleavage and ring closure steps in an inert atmosphere (nitrogen) [2] followed by its reaction with hydrazine. Hydrazinolysis of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide **3** was carried out conventionally; it was heated to reflux along with hydrazine hydrate for 1 h and excess hydrazine was removed under vacuum. The resulting 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide **4** was then reacted with different benzaldehydes to get the respective 4-hydroxy-*N*′-(benzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxides.

In the first attempt, these condensations were affected in a polar medium (methanol) and the resulting compounds **5a**–**o** were characterized by spectroscopic techniques.

Due to the encouraging results obtained for ultrasonic mediated N-alkylation of sodium saccharin (in the first reaction), condensations of 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide **4** with different aldehydes were carried out in an ultrasonic bath with promising results.

Ultrasonic mediation shortened the reaction times considerably (reactions completed in only 1.5–3.0 min compared with 30–120 min under standard reflux conditions) and with improved yields (90.7–96.6% compared with 76.5–87.1% under reflux). Shortening of the reaction time may be attributed to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in the irradiated medium. Cavitation creates very high local temperature and pressure inside the bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer [27]. Results are shown in Table 1.

IR spectra of all the compounds **5a**–**o** showed an absorption band at 1630–1685 cm^{-1}, typical of the stretching vibrations of the carbon–nitrogen double bond. No peaks were found due to starting material amino or aldehydic functionalities. ^{1}H NMR spectra of all the compounds showed the broad singlets due CON*H* protons and a singlet due to C*H*–N protons. The singlet due to two amino protons disappeared, indicating the transformation of the reactant **4**. All of these compounds were further confirmed through mass spectrometry and C, H, N analyses which were found in accordance with the calculated values (Table 2)

In order to determine the stereochemistry (*E* or *Z* configuration) of the compounds under investigation, a single crystal of the product (**5e**) was grown by dissolving the compound in 90% ethanol and studied by X-ray crystallography. The crystal structure indicates that it crystallizes with $Z = 4$ (in space group $P2_1/c$; monoclinic) and except for the thiazine ring, the molecule deviates only slightly from being planar as shown by the values of six torsion angles defining the conformation (Tables 3 and 4); none of these angles deviates from 180° by more than 5°. The thiazine ring exhibits a half-chair conformation with S(1)–C(1)–C(6)–C(7) planar within ±0.041 Å and N(1) showing significant departure from planarity with pyramidal geometry [Fig. 1]. Also, a look on C=N bond indicates the *E* configuration of the compounds of this type. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC deposition number is 658397).

4. Biological activity

4.1. DPPH radical scavenging activities

Compounds **5a**–**o** were screened for DPPH radical scavenging activity using the procedure of Shaheen et al. [28]. All the compounds showed interesting antioxidant activity compared to the standard, 3-*tert* butyl-4-hydroxy anisole (Table 5). The reaction

Table 1
Condensation of 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide and various aldehydes under normal and ultrasonic conditions

Entry	Reactant	Product	Alcoholic medium		Ultrasonic mediation	
			Reaction conditions (min)	Yield (%)[a]	Reaction conditions (°C; min)	Yield (%)[a]
1	**4**	**5a**	Reflux; 60	80.1	40; 3	93.2
2	**4**	**5b**	Reflux; 30	81.9	25; 3	94.7
3	**4**	**5c**	Reflux; 60	82	25; 3	91.1
4	**4**	**5d**	Reflux; 60	83.4	35; 2	92.0
5	**4**	**5e**	Reflux; 35	83	40; 2.5	93.4
6	**4**	**5f**	Reflux; 60	80.1	35; 2	96.6
7	**4**	**5g**	Reflux; 120	83.4	35; 3	90.9
8	**4**	**5h**	Reflux; 90	85	35; 3	92.3
9	**4**	**5i**	Reflux; 120	85.2	30; 5	93.2
10	**4**	**5j**	Reflux; 60	77.2	30; 1.5	95.4
11	**4**	**5k**	Reflux; 60	79.1	30; 2	92.8
12	**4**	**5l**	Reflux; 60	77.3	30; 1.5	90.7
13	**4**	**5m**	Reflux; 60	76.5	30; 3	93.9
14	**4**	**5n**	Reflux; 30	76.2	30; 2	91.1
15	**4**	**5o**	Reflux; 120	87.1	30; 2.5	92.7

[a] Isolated yields based on 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide.