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Synthesis of spiropyrrolidinyl-benzoisothiazoline derivatives by 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidenes and azomethine ylide

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ABSTRACT

The new spirocyclic compounds, spiropyrrolidinyl-benzoisothiazoline derivatives were synthesized by the 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidenes and azomethine ylide. The stereochemistry of 1,3-dipolar cycloaddition as well as the stereochemistry of Knoevenagel condensation of benzoisothiazole-2,2-dioxide with aldehydes were studied.

1. Introduction

Benzoisothiazole dioxides, which possess similar structure with oxindoles, have been shown to exhibit a variety of biological activities. Many benzoisothiazole dioxides derivatives substituted in the C-3 position are useful pharmaceutical agents such as central nervous system stimulants and antihypertensive agents.[1] Spirobenzoisothiazole dioxide derivatives inhibit the activity of phosphotyrosine phosphatase 1B, which is suitable for the treatment of type I and II diabetes.[2] They are also progesterone receptor antagonists[3] and potent HIV-1 inhibitors.[4] Although considerable efforts have been made to develop efficient methods for the synthesis of benzoisothiazole dioxides and their derivatives,[5] molecular diversity is only varied on the C-3 position by alkylation[6] and Knoevenagel condensation.[7] As part of our effort on exploring biologically important heterocyclic and spirocyclic compounds[8] and inspired by the biological activities of naturally occurring spirooxindole derivatives and their synthetic intermediates,[9] we started to examine the 1,3-dipolar cycloadditions of benzoisothiazole-2,2-dioxide-3-ylidene derivatives **5a**, **5b**, and **5c** to different 1,3-dipoles such as azomethine ylides, nitrones, and nitrile oxides. To the best of our knowledge, there are no reports on the synthetic application of benzoisothiazole-2,2-dioxide-3-ylidene **5** with 1,3-dipoles.

Herein, we demonstrate the application of a [3+2] cycloaddition reaction toward the synthesis of novel benzoisothiazole dioxide derivatives. The results of our studies will lead to an unprecedented synthesis of spiropyrrolidinyl-benzoisothiazoline derivatives using 1,3-dipolar cycloaddition reaction of **5** with azomethine ylide **6**.

2. Results and discussion

Our research started with a modified literature synthesis of benzoisothiazole-2,2-dioxide,[5c] 1-methyl-1,3-dihydro-benzo[*c*]isothiazole-2,2-dioxide **1** was prepared by sequential *N*-alkylation of 2-bromoaniline with mesyl chloride and iodomethane to afford *N*,*N*-disubstituted aniline, which was smoothly converted to **1** under sodium amide in ammonia condition. Knoevenagel condensation of **1** with aldehydes **2a**–**j** to afford α,β-unsaturated dipolarophiles **5a**–**j**. For acetaldehyde and propylaldehyde, Knoevenagel condensation products **3k** and **3l** are obtained, the corresponding dipolarophiles **5k** and **5l** are obtained by O-alkylation of **3** with mesyl chloride and subsequent elimination under basic condition (Scheme 1).

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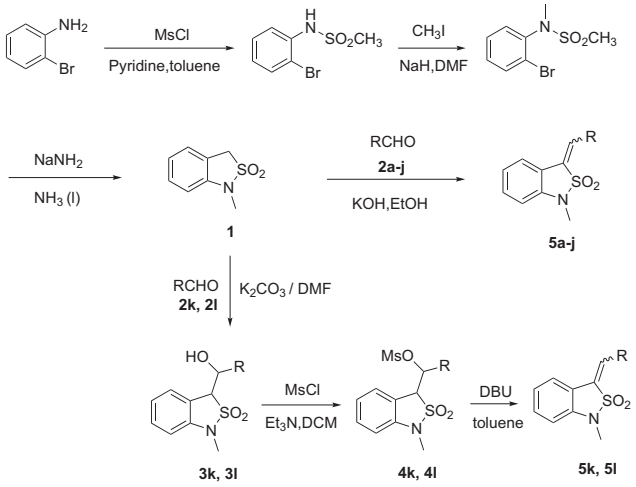
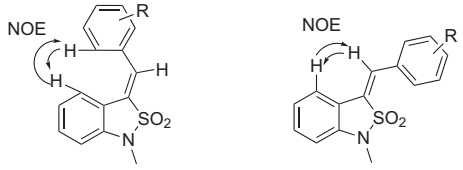


Scheme 1. Synthetic route of benzoisothiazole-2,2-dioxide-3-ylidene derivatives **5**.

Two stereoisomers of the 1-methyl-3-alkylidene-1,3-dihydrobenzo[*c*]isothiazole 2,2-dioxide **5**, either by direct Knoevenagel condensation or by elimination of the corresponding mesylates, are found in ^{1}H NMR spectra and thin-layer chromatography analysis. The geometrical configurations of compound **5** could be partly assigned on the chemical shifts of particular proton, H-2′, H-6′, and H-vinyl, in the molecules and confirmed using NOE analysis. The *Z* configured compounds **5a**–**f** showed NOE between the proton at the C-4 position and the vinyl proton, whereas the *E*-configured compounds showed NOE between the C-4 and hydrogen at the C-2′ (or C-6′) (see Scheme 2). The ^{1}H NMR chemical shift of their particular protons (H-2′,6′, H-4, and H-vinyl) are summarized in Table 1.

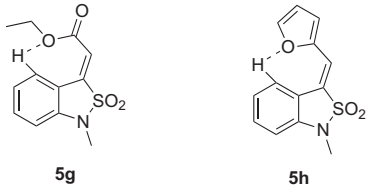


Scheme 2. Determination of the configurations for **5a**–**f** by NOE analysis.

Due to the deshielding effect of the sulfuryl group of the benzoisothiazoline ring, the chemical shift of H-2′ and H-6′ protons in the phenyl ring are approximately 7.79–8.03 ppm for the *Z*-isomers and 7.45–7.74 ppm for the *E*-isomers. These findings are in accordance with the similar results of 3-substituted indolin-2-ones, where it has been demonstrated that the H-2′ and H-6′ protons in the phenyl ring of 3-substituted-indolin-2-ones display a slight down-field shift in the *Z*-isomers as compared with *E*-isomers.[10]

The chemical shifts of the vinyl protons are approximately 6.57–7.45 ppm for the *Z*-isomers and 6.62–7.47 ppm for the *E*-isomers. The downfield of the vinyl proton chemical shift of the *E*-isomer relative to its *Z*-isomer (except for **5f**–**h**) is due to the vinyl proton of the *E*-isomer being deshielded by the sulfuryl group of the benzoisothiazoline ring. The results coincide with the similar α,β-unsaturated oxindole reported by Teichert, where the vinyl protons of the *E*-isomers always appear at lower field in the ^{1}H NMR spectra than the corresponding signal of the *Z*-isomers.[11]

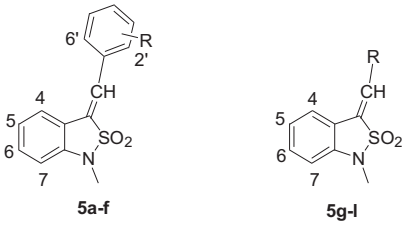
The H-4 chemical shifts of the respective *Z* and *E* isomers are also listed in Table 1. It is clear that the shifts of compound **5g** and **5h** move to 8.72 and 8.48 ppm, which are attributed to the hydrogen bond between C-4 hydrogen and the oxygen of ester group in **5g** and furanyl in **5h**. It means that there is a favorable electrostatic interaction between the electron-rich oxygen (possesses $\delta-$) and C-4 hydrogen (possesses $\delta+$) (Scheme 3).



Scheme 3. Hydrogen bond between C-4 hydrogen and O-3 atom in **5g** and **5h**.

The relative ratios of the two isomers in the mixtures are determined by ^{1}H NMR spectral analysis or column chromatography. In most cases, the more thermodynamically stable *Z*-isomer is predominantly formed, with the exception of compound **5h** (Table 1, Entry 8). In the condensation of furfural **2h** with **1**, a larger amount of the *E*-isomer was observed (*E*-isomer: *Z*-isomer=3.4:1),

Table 1
Yields and ^{1}H NMR chemical shift values of key protons of compound **5**



Entry	5	R	Isomer ratio (*Z*:*E*)[a]	Total yield (%)	NMR data chemical shift in ppm					
					Z-isomer H-2′,6′	*E*-isomer H-2′,6′	*Z*-isomer H-4	*E*-isomer H-4	*Z*-isomer H-vinyl	*E*-isomer H-vinyl
1	**5a**	H	1.4:1	83	7.90	7.45	7.51	7.51	7.45	7.47
2	**5b**	p-CH_3	1.5:1	81	7.79	7.49	7.47	7.49	7.40	7.43
3	**5c**	4-OCH_3	1:1	80	7.87	7.55	7.46	7.66	7.36	7.39
4	**5d**	4-Cl	1.7:1	88	7.81	7.51	7.46	7.47	7.35	7.38
5	**5e**	4-F	1.8:1	85	7.90	7.57	7.48	7.48	7.39	7.40
6	**5f**	4-NO_2	1:1	65	8.03	7.74	7.54	7.34	7.45	7.43
7	**5g**	CO_2Et	1.5:1	70	N/A	N/A	7.47	8.72	6.68	6.62
8	**5h**	Furan-2-yl	1:3.4	90	N/A	N/A	7.41	8.48	7.21	7.07
9	**5i**	Cyclopentyl	1.7:1	93	N/A	N/A	7.28	7.56	6.57	6.74
10	**5j**	Pentan-3-yl	2.5:1	94	N/A	N/A	7.40	7.62	6.68	6.75
11	**5k**	CH_3	1.8:1	65	N/A	N/A	7.28	7.35	6.67	6.74
12	**5l**	CH_2CH_3	1.2:1	62	N/A	N/A	7.37	7.53	6.643	6.644

[a] Determined by ^{1}H NMR from the crude reaction mixture.