Tetrahedron xxx (2017) 1–5

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of spiroisoxazolidinyl-benzoisothiazolines by 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidenes with nitrones

Guorui Cao, Shizheng Zhou, Dawei Teng*

College of Chemical Engineering, Qingdao University of Science and Technology, Qingdao 266042, China

ARTICLE INFO

Article history:
Received 16 November 2016
Received in revised form
6 March 2017
Accepted 10 March 2017
Available online xxx

Keywords:
1,3-dipolar cycloaddition
Spirobenzoisothiazole dioxide
Nitrone
Spiroisoxazolidinyl-benzoisothiazoline

ABSTRACT

The spiroisoxazolidinyl-benzoisothiazoline derivatives were synthesized through a highly diastereoselective 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidenes with nitrones. The regiochemistry of cycloaddition was assigned on the ^{1}H NMR chemical shift of methane-H in **3** and **5**. The relative stereochemistry of cycloadducts was determined from the single-crystal X-ray crystallography.

1. Introduction

Spirobenzoisothiazole dioxide derivatives are important molecules as they exhibit a wide range of biological activities. These motifs represent the substructures of many pharmaceutical agents. The potent bioactivities include phosphotyrosine phosphatase 1B (PTP1B) inhibitors for treatment of type I and II diabetes,[1] progesterone receptor antagonist[2] and opioid receptor-like 1 (ORL1) antagonist.[3] These biological activities render them attractive targets for synthesis (Fig. 1).

The 1,3-dipolar cycloaddition of nitrone and olefin is one of the versatile methods for the preparation of synthetically useful isoxazolidines[4,5] which are useful building blocks due to the easy cleavage of the oxygen-nitrogen bond to form β-amino acids,[4b,6] β-lactams,[7] pyrrolidinones,[8] and 1,3-amino alcohols.[9] To expand the molecular diversity of spirobenzoisothiazole dioxide derivatives, we have recently reported the synthesis of spiropyrrolidinyl-benzoisothiazolines and 3,4,5-trisubstituted isoxazoles by 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidenes with azomethine ylides[10] and nitrile oxides[11] respectively. In continuation of our work on the scope of 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidenes, we herein report a highly diastereoselective route for the synthesis of spiroisoxazolidinyl-benzoisothiazolines by the cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidenes with nitrones.

2. Results and discussion

Benzoisothiazole-2,2-dioxide-3-ylidenes **1** were prepared as described in our previous paper[10] and their geometrical configurations are assigned based on the ^{1}H NMR chemical shifts of their particular protons and confirmed by NOE analysis. Of the methods to generate nitrone, we initially investigated the oxidation of disubstituted hydroxylamine[12] and condensation of aldehyde or ketone with monosubstituted hydroxylamine.[13] After several attempts, the method of condensation of an aldehyde with monosubstituted hydroxylamine was chosen for its simplicity and easy work-up. The (*Z*)-3-ethylidene-1-methyl-1,3-dihydrobenzo[*c*]isothiazole-2,2-dioxide **1a** was used as the model substrate to react with the nitrone **2a** generated by condensation of 4-fluorobenzaldehyde with *N*-methylhydroxylamine.

As shown in Table 1, the reaction did not proceed when dichloromethane was used as solvent at room temperature. The spiroisoxazolidinyl-benzoisothiazoline **3a** was isolated in 19% yield with 86:14 diastereoselectivity when the reaction mixture was heated in dichloromethane at reflux (entry 1, 2). It was noted that

* Corresponding author.
E-mail address: dteng@qust.edu.cn (D. Teng).

http://dx.doi.org/10.1016/j.tet.2017.03.024
0040-4020/

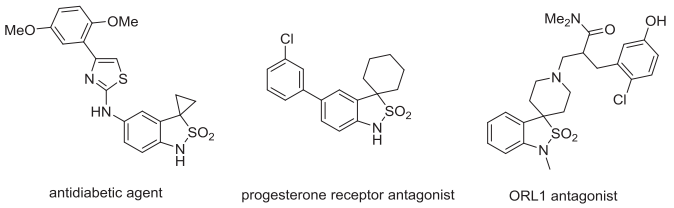


Fig. 1. The biologically important spirobenzoisothiazole dioxides.

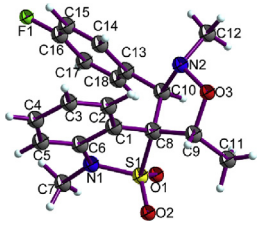
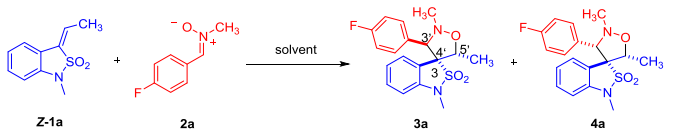


Fig. 2. The X-ray crystallography of compound **3a**.

Table 1
The optimization of the [3 + 2] cycloaddition.[a]



Entry	Solvent	Lewis acid[b]	Temp. (°C)	Yield[c] (%)	dr[d] (3a)
1	CH_2Cl_2	–	r.t.	0	–
2	CH_2Cl_2	–	40	19	86:14
3	1,2-Dichlorethane	–	40	35	86:14
4	$CHCl_3$	–	40	29	86:14
5	THF	–	40	18	86:14
6	CH_3CN	–	40	15	86:14
7	Toluene	–	40	45	85:15
8	Toluene	–	60	60	86:14
9	Toluene	–	80	73	86:14
10	Toluene	–	100	50	65:35
11	Toluene	$AlCl_3$	80	6	–
12	Toluene	Ti(*Oi*-Pr)4	80	7	–
13	Toluene	$Zn(OTf)_2$	80	7	–
14	Toluene	$Cu(OTf)_2$	80	5	–

[a] Reaction condition: (Z)-alkene **1a** (1 mmol), nitrone **2a** (1.5 mmol), solvent (5 mL).
[b] 10 mol% Lewis acid (relative to alkene **1a**).
[c] Isolated yields of major diastereomer **3a**.
[d] Diastereomer ratios (dr) were determined by LC-MS from the reaction crude.

the reaction yield varied significantly with solvents, but the diastereoselectivity remains unchanged. Investigation on the effect of solvent showed that toluene was the best solvent of choice. (entry 2–6). Examination of different reaction temperature disclosed that 80 °C was the best choice (entry 7–10). Though some examples of Lewis acid catalyzed cycloaddition,[14] quite low yields were observed when catalytic amount of Lewis acids were used (entry 11–14).

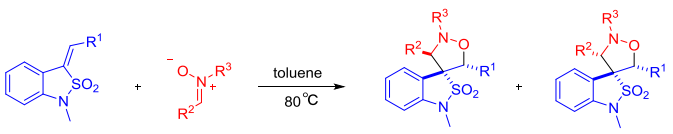
The structure of cycloadduct **3a** was determined by ^{1}H NMR, ^{13}C NMR, and HRMS analysis. The regiochemistry of cycloaddition was assigned on the ^{1}H NMR chemical shift of methine-H (C5′–H) in **3a** at δ 4.74 ppm, and this downfield shift clearly indicated that the methine carbon C5′ was attached to oxygen in **3a**. The formation of cycloadduct **3a** as the major regioisomer of addition could be rationalized by the frontier molecular orbital interaction.[15] For nitrone cycloaddition with very electron-deficient dipolarophile, the dominant interaction was HOMO (dipole) – LUMO (dipolarophile),[16] and the cycloadduct with electron-withdrawing group (SO_2) adjacent to spirocarbon C4′ was obtained predominately.

The relative stereochemistry at the C3′, C5′ and spirocarbon C4′ in **3a** could be determined from the single-crystal X-ray crystallography[17] in *endo*-selective manner (Fig. 2). Although there was the possibility of nitrone **2a** undergoing *E-Z* isomerisation under reaction condition, the observed diastereoselective cycloaddition could be rationalized in terms of the *endo*-selective addition of alkene **1a** with the *Z*-isomer of nitrone **2a** that was reported to be more stable than its *E*-isomer.[18]

The 1,3-dipolar cycloadditions of *Z*-alkene **1** with a series of nitrones **2** were investigated under the optimized reaction conditions (Table 2). Reaction of *Z*-**1a** with nitrones **2a-f** bearing both electron-withdrawing and electron-donating groups on the aryl ring gave spiro cycloadducts **3a-f** in moderate to good yields. For all of the nitrones examined, high diastereoisomer ratios were observed in each of the cycloaddition (up to 98:2, entry 1–6). The cycloaddition took place in highly regioselective and stereoselective manner. Electron-deficient aryl substituents on nitrones (entry 1–3) facilitated the cycloaddition with higher yields than the reactions of electron-rich aryl nitrones (entry 5–6). However, the diastereoselectivities obtained from the reaction of electron-rich aryl nitrones were higher than those obtained from the reactions of electron-deficient aryl nitrones. The cycloaddition with *N*-benzyl-C-aryl-nitrones **2g-i** (R^3 = Bn) showed similar yields and diasteroselectivities with the less-hindered *N*-methylhydroxylamine-derived nitrones (entry 7–9).

Investigations into the scope of benzoisothiazole-2,2-dioxide-3-ylidenes *Z*-**1** was carried out by using **2d** (R^2 = Ph, R^3 = CH_3) as the reaction partner (entry 10–13). Steric hindrance played important role in the 1,3-dipolar cycloaddition. For aliphatic substituted alkene, relatively lower yields were obtained in the case of alkene **1b** (R^1 = CH_2CH_3) and **1c** (R^1 = cyclopentyl) (entry 10–11). For aryl-substituted alkene, the cycloaddition either proceeded in low yield (10%, entry 12) or hardly proceeded (entry 13) even after prolonged heating time (72 h). Higher diastereoselectivities were observed

Table 2
The substrate scope of the [3 + 2] cycloaddition.[a]



Entry	R^1	R^2	R^3	3	Time	Yield[b] (%)	3 dr[c]
1	CH_3	4-FPh	CH_3	**3a**	24 h	78	86:14
2	CH_3	4-ClPh	CH_3	**3b**	24 h	85	90:10
3	CH_3	4-CF_3Ph	CH_3	**3c**	24 h	74	93:7
4	CH_3	Ph	CH_3	**3d**	24 h	65	96:4
5	CH_3	4-CH_3Ph	CH_3	**3e**	24 h	63	90:10
6	CH_3	4-CH_3OPh	CH_3	**3f**	24 h	60	98:2
7	CH_3	Ph	Bn	**3g**	24 h	73	93:7
8	CH_3	4-CH_3Ph	Bn	**3h**	24 h	71	92:8
9	CH_3	4-ClPh	Bn	**3i**	24 h	79	89:11
10	CH_2CH_3	Ph	CH_3	**3j**	24 h	53	>99:1
11	cyclopentyl	Ph	CH_3	**3k**	48 h	34	>99:1
12	4-ClPh	Ph	CH_3	**3l**	48 h	10	>99:1
13	Ph	Ph	CH_3	**3m**	72 h	0	–

[a] Reaction condition: (*Z*)-alkene **1** (1 mmol), nitrone **2** (1.5 mmol), toluene (5 mL).
[b] Isolated yields of major diastereomer **3**.
[c] Diastereomer ratios (dr) were determined by LC-MS from the reaction crude.

Please cite this article in press as: Cao G, et al., Synthesis of spiroisoxazolidinyl-benzoisothiazolines by 1,3-dipolar cycloaddition of benzoisothiazole-2,2-dioxide-3-ylidenes with nitrones, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.03.024