Reaction of 2-alkylidene-3,1-benzoxathiin-4-ones with nitrones

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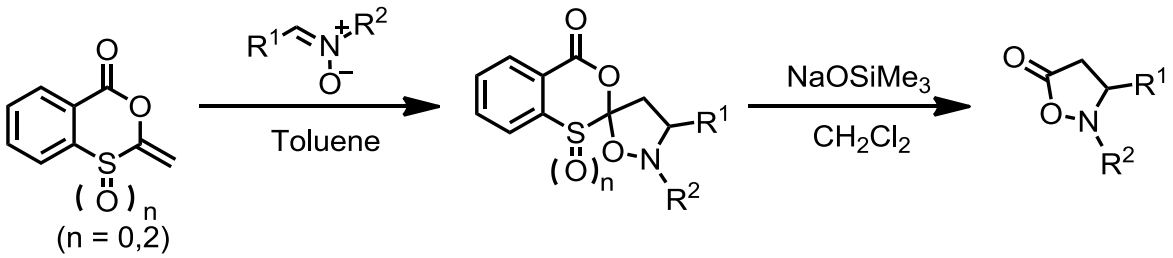
GRAPHICAL ABSTRACT



Abstract

2-Methylene-3,1-benzoxathiin-4-ones reacted with nitrones at methylene moieties of 3,1-benzoxathiine rings to yield spiro 1,3-dipolar cycloadducts. The benzoxathiin-4-one rings easily occurred ring opening reaction with $NaOSiMe_3$ and isoxazolidin-5-one derivatives were obtained in good yields. As a result, 2-methylene-3,1-benzoxathiin-4-ones can be used as a ketene equivalent.

Keywords

1,3-Dipolar addition; spiro cycloadduct; isoxazolidin-5-one; ketene equivalent

INTRODUCTION

3,1-Benzoxathiin-4-ones can be used as starting materials for other heterocycles. We have reported that 3,1-benzoxathiin-4-one 1-oxides were synthetic intermediates of 1,2-benzisothiazol-3-ones.[1] When 3,1-benzoxathiin-4-ones were treated with nucleophiles, ring opening reaction occurred and carbonyl compounds derived from the C-2 carbons of the rings are formed. During our study of synthesis of 3,1-benzoxathiin-4-ones which have a variety kind of substituents on the C-2 carbons, we have recently succeeded in two synthetic methods of 2-alkylidene-3,1-benzoxathiin-4-one derivatives: synthesis from the reaction of *S*-acylthiosalicylic acids with dehydrate reagents,[2] and from the Pummerer type reaction of 2-alkyl-3,1-benzoxatuiin-4-ones with trifluoroacetic anhydride.[3] Because the 2-alkylidene-3,1-benzoxathiin-4-ones were regarded as masked ketenes with thiosalicylic acid, it is expected that they operate as ketene equivalents. Therefore, we carried out 1,3-dipolar cycloaddition of 2-alkylidene-3,1-benzoxathiin-4-ones with nitrones, and following nucleophilic ring opening reaction.

RESULTS AND DISCUSSION

Reaction of 2-Methylene-3,1-benzoxathiin-4-one with Nitrones

When 2-methylene-3,1-benzoxathiin-4-one (**1a**) was treated with *N*-(4-chloro-benzylidene)methylamine oxide (**2a**) in 1,2-dichloromethane at 140 ºC for 20 min, imide derivative (**3**) was obtained in 75% yield. This product was formed by nucleophilic ring-opening reaction of the 1,3-oxathiine ring with the nitrone oxygen atom instead of 1,3-dipolar cycloaddition, and successive rearrangement occurred to give **3**. It was reported that the similar product was obtained from the reaction of nitrones with acid chlorides.[4]

On the contrary, when the reaction was carried out in toluene, cycloadduct **4a** was obtained in 52% yield. Cyclization occurred by attack of the nitrone oxygen atom to the C-2 carbon of 3,1-benzoxathiine ring. The product which the nitrone oxygen atom attacked to the terminal methylene group did not obtained. For various kinds of nitrones, similar cycloadducts **4** were obtained (Table 1). Reactivity of an *E*-form cyclic nitrone was high and the reaction proceeded lower reaction temperature (Entry 3) than that of *Z*-form nitrones. The same type of cycloaddition also occurred for 2-methylene-3,1-benzoxathiin-4-one 1,1-dioxide (**1b**) (Entry 4).

Carbonyl Group Formation from Cycloadducts

When 3,1-benzoxathiin-4-ones were treated with some nucleophiles, the reaction occurred at their carbonyl groups and the following ring-opening reaction produce carbonyl groups derived from the C-2 carbons of 3,1-benzoxathiin-4-ones. Therefore, we carried out the reaction of the cyclization products **4** with nucleophiles. Although amines, thiols, and alkoxides were used as nucleophiles, the aimed product was not obtained. It was reported that sodium timethylsilanolate was used for hydrolysis of lactone rings.[5] This reagent was applied for cycloadduct **4**. As a result, the nucleophile attacked to the benzoxathiine carbonyl group and not to the carbonyl groups of a product; deprotected products, isoxazolidin-5-one derivatives **5**, were obtained in a good yield. In the case of sulfone derivatives **4d**, product purification was easier than **4a-c** because of formation of sulfinic acid derivatives, which was able to be soluble in water, instead of thiosalicylic acid; purification was possible by extraction for aqueous reaction mixture.

CONCLUSIONS

2-Methylene-3,1-benzoxathiin-4-ones reacted with nitrones to yield 1,3-dipolar cycloadducts, spiro-isoxazolidines, and the products hydrolyzed to isoxazolidin-5-ones.

Therefore, 2-methylene-3,1-benzoxathiin-4-ones were regarded as one of the ketene equivalents in the 1,3-dipolar cycloaddition with nitrones.

Graphic for Table of Contents

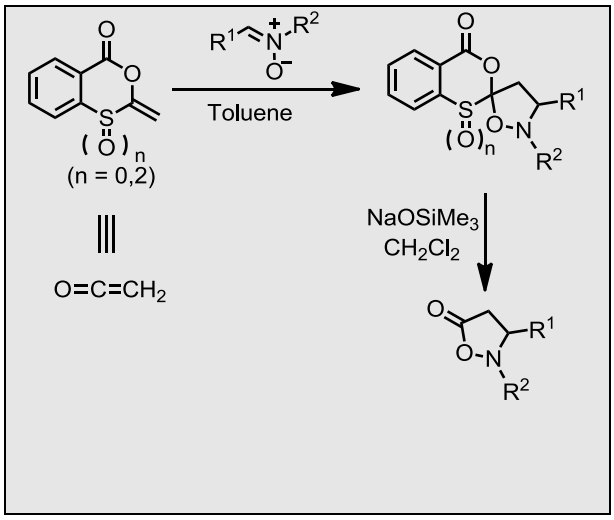


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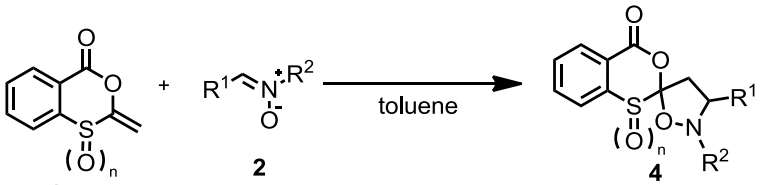
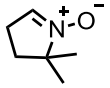
Table 1 Reaction of **1** with nitrones in toluene



1a: n=0
1b: n=2

2

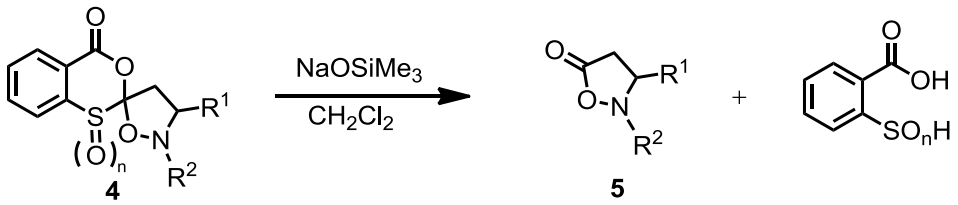
4

Entry	n	**2**	*E*/*Z*	R^1	R^2	Temp.(°C)	Time (min)	**4**	Yield[a] (%)
1	0	**2a**	*Z*	*p*-ClC_6H_4	Me	140	20	**4a**	52
2	0	**2b**	*Z*	Ph	Me	140	20	**4b**	54
3	0	**2c**	*E*			80	60	**4c**	75
4	2	**2c**	*E*			80	60	**4d**	62

Reaction conditions: **1**: 1.0 mmol; **2**: 1.5 mmol; toluene: 2 mL.

[a] Isolated product.

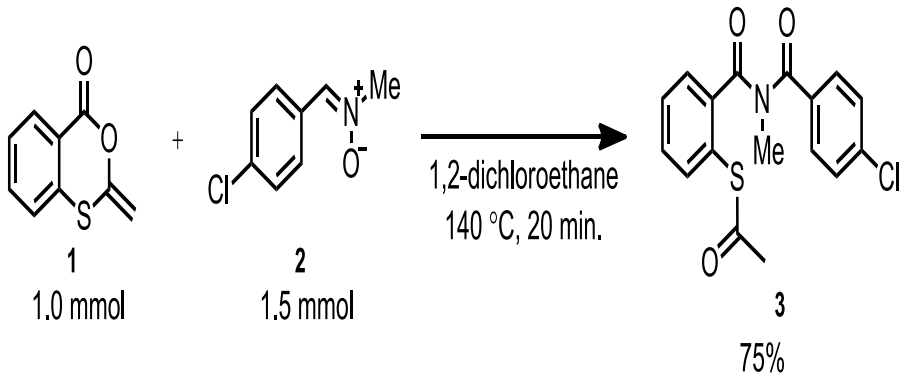
Table 2 Deprotection reaction of **4** with $NaOSiMe_3$



4 **5**

Entry	**4**	n	R^1	R^2	**5**	Yield[a] (%)
1	**4a**	0	*p*-ClC_6H_4	Me	**5a**	69
2	**4b**	0	Ph	Me	**5b**	65
3	**4c**	0			**5c**	66
4	**4d**	2			**5c**	92

Reaction conditions: **4**: 0.5 mmol; $NaOSiMe_3$: 1.0 mmol; CH_2Cl_2: 3 mL, r.t.; 15 min.
[a] Isolated product.



Scheme 1 Reaction of **1** with a nitrone in 1,2-dichloroethane