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Highly Stereoselective Synthesis of Saccharin-Substituted β-Lactams via in Situ Generation of a Heterosubstituted Ketene and a Zwitterionic Intermediate as Potential Antibacterial Agents

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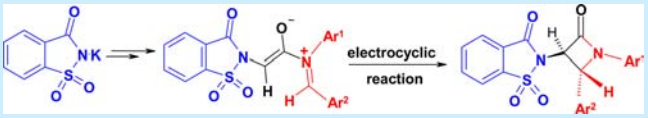
Supporting Information

ABSTRACT: Highly stereoselective synthesis of saccharin derivatives containing functionalized 2-azetidinone moiety was achieved starting from saccharin as an available precursor. The approach to these valuable heterocyclic scaffolds involves a formal [2π + 2π] cycloaddition between Schiff bases and the saccharinylketene as a novel ketene which was generated in situ and an electrocyclic reaction of a zwitterionic intermediate. The identification of the ketene was confirmed by reaction with the stable free radical TEMPO (TO•). Also, the antimicrobial activities of some new substituted saccharin against nine standard bacteria, four bacteria which were isolated from clinical samples and one yeast, were evaluated.

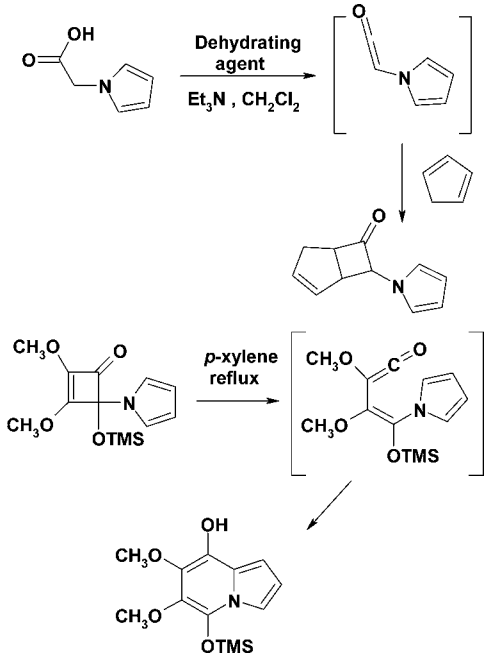


β-Lactams (2-azetidinones) have been recognized as the central motif of antibiotics such as penicillins, cephalosporins, and carbapenems.[1−4] The history of the first synthetic β-lactam dates back to 1907, when H. Staudinger reported that he added zinc powder to 2-chloro-2,2-diphenylacetyl chloride in the presence of an imine and 2-azetidinone was formed as the final product.[5] There are many reports in the literature about the synthesis and application of such compounds.[6−9] Practical chemistry for introducing new organic molecules with functional groups as potential synthons for new drug discovery is also an important current need in medicinal chemistry.[10−12] One of the most important methods for the synthesis of 2-azetidinones is the use of ketenes. Ketenes are highly reactive species in many organic reactions and are usually used in organic synthesis to prepare four- and six-membered rings (Scheme 1).[13−17]

Ketenes are remarkable for the variety of ways in which they can be prepared[18−21] and also for the range of useful products from their reactions with unsaturated compounds.[22,23] They have long been known for their unique reactivity in [2 + 2] cycloaddition reactions.[24,25] Saccharin, benzisothiazole derivative, is the foundation for many low-calorie and sugar-free products around the world.[26,27] It is used as sweeteners, baked goods, jams, chewing gum, canned fruit, candy, dessert toppings, and salad dressings.[26,28] It has been used in medicinal chemistry[29] and is a substituent in several drug molecules such as Ipsapirone (Figure 1).[30−32]

To the best of our knowledge, saccharin has not been employed as a substituent for the synthesis of β-lactam (2-azetidinone). In this present work, we have synthesized new saccharins including a β-lactam ring, as the central motif for antimicrobial properties, in a highly stereoselective manner by in situ producing the corresponding ketene and trapping it by different Schiff bases and from a zwitterionic intermediate. It is important to note that in this plan we used saccharin as a precursor which is safe for human consumption and there is an urgent need for new antibiotic capable of treating infection

Scheme 1. Synthesis of Four- and Six-Membered Rings by Reaction of the Ketenes



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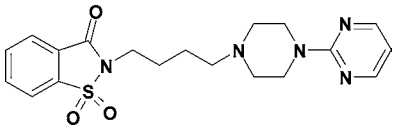
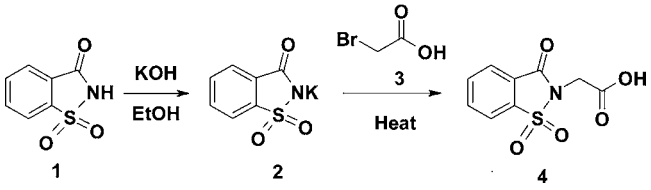


Figure 1. Ipsapirone drug.

caused by bacteria. Herein we would like to report the results of our investigation about novel heterocyclic compounds including two parts, saccharin and 2-azetidinone rings, as potential antibacterial compounds.

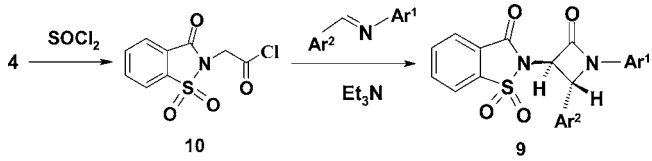
To prepare saccharinylacetic acid **4** as a precursor by modified Gabriel synthesis, potassium saccharin **2** was mixed with 2-bromoacetic acid **3** and heated until they melted then heating was continued for 6 h. Upon cooling to room temperature, the desired product **4** was formed as a solid and recrystallized from water and was used in the next reactions (Scheme 2).

Scheme 2. Synthesis of Saccharinylacetic Acid 4



Several methods are used for activating carboxylic acids. In many cases where a carboxylic acid with strongly sensitive functional groups to acid media such as amide group, the use of Mukaiyama reagent **6** is better than other reagents. We previously used this reagent for the synthesis of 2-azetidinones at room temperature.[33,34] While this method is certainly very promising and provides the mentioned products, it suffers from one or more disadvantages such as low yield of products. For overcoming this problem, we investigated the effect of reagent ratios. Our studies commenced with the reaction of saccharinyl-acetic acid **4**, Mukaiyama reagent **6**, and benzylidenephenyl-amine **8** in the presence of Et_3N **5** in CH_2Cl_2 at room temperature, and the corresponding β-lactam was obtained in a 20% yield (Table 1, entry 1). Then the mentioned reaction was run in two steps: first, compound **4** was heated under reflux conditions with Mukaiyama reagent **6** in the presence of Et_3N for time t_1 and then Schiff base and the base were added and the reaction continued to reflux for t_2 (Table 1, entries 2 and 3). Also, the preparation of the same β-lactam was performed in toluene and hexane by the reaction of saccharinyl acetyl chloride **10** with compound **8** in the presence of triethylamine **5** at different temperatures (Scheme 3). The results revealed that the corresponding product was not observed in hexane at room temperature (Table 1, entry 4) and it was obtained in

Scheme 3. Synthesis of 9 from Saccharinylacetyl Chloride



toluene and hexane at reflux condition in a 64% and 49%, respectively (Table 1, entries 5 and 6). The best result was obtained when the reaction was run in two steps using an acid/reagent/base/Schiff base ratio of 2.0:2.1:2.0:2.0 in 80% yield (Table 1, entry 3).

The reaction of *N*-saccharinylacetic acid **4** and Mukaiyama reagent **6** with Et_3N **5** in CH_2Cl_2 in the presence of imines **8** led to the formation of azetidinones **9**. The reaction was found to be highly stereoselective, and the *trans*-isomers were formed as the only products (Table 2).

Table 2. Saccharin Derivatives 9 from *N*-Saccharinylktene 7 and Imines

9	Ar^2	Ar^1	yield[a] (%) *trans*
9a	Ph	Ph	80
9b	Ph	4-BrC_6H_4	65
9c	Ph	4-ClC_6H_4	55
9d	Ph	4-MeC_6H_4	50
9e	Ph	4-$MeOC_6H_4$	77
9f	4-ClC_6H_4	Ph	69
9g	4-MeC_6H_4	Ph	67
9h	4-$MeOC_6H_4$	Ph	63
9i	Ph	Naphthyl	51
9j	4-MeC_6H_4	Naphthyl	56
9k	4-$MeOC_6H_4$	Naphthyl	86

[a]Isolated yield of pure product.

The structure of the products was fully characterized by IR and ^1H and ^{13}C NMR spectra along with elemental analysis data. ^1H NMR spectroscopy is generally used for distinguishing between *cis* and *trans*-isomers of β-lactam using H−H coupling constants. The *J* value is smaller (2−2.5 Hz) in a *trans*-isomer than in a *cis*-isomer (5−6 Hz).[24] ^1H NMR spectra of products exhibiting the *trans*-β-lactams were formed as the only product. The ^1H NMR spectrum of **9a** exhibited two doublets at δ = 5.49 and 5.04 ppm ($^3J_{HH}$= 2.6 Hz) for vicinal methine protons along with a multiplet at δ = 8.11−7.13 ppm for phenyl ring protons. The ^1H-decoupled ^{13}C NMR spectrum of **9a** showed 18 distinct resonances in agreement with the suggested structure; partial assignment of these resonances is given in the Supporting Information (SI). Characteristic ^{13}C NMR signals were shown due to two carbonyl groups at δ = 159.79 and 158.38 ppm and signals at δ = 63.11 and 61.08 ppm for CH

Table 1. Optimization of Reaction Conditions for the Synthesis of 9

entry	compd	ratio (**4** or **10**)/(**6**)/(**5**)/(**8**)	solvent	base	t_1 (h)	conditions	t_2 (h)	yield (%)
1	**4**	2.0:2.4:5.0:2.4	CH_2Cl_2	Et_3N	17	rt	0	20
2	**4**	2.0:2.1:2.0:1.0	CH_2Cl_2	Et_3N	10	reflux	10	70
3	**4**	2.0:2.1:2.0:2.0	CH_2Cl_2	Et_3N	10	reflux	10	80
4	**10**	1.5:0.0:1.6: 2.2	hexane	Et_3N	17	rt	0	0
5	**10**	1.5:0.0:1.6:2.2	hexane	Et_3N	0.5	reflux	0	49
6	**10**	1.5:0.0:1.6:2.2	toluene	Et_3N	0.5	reflux	0	64

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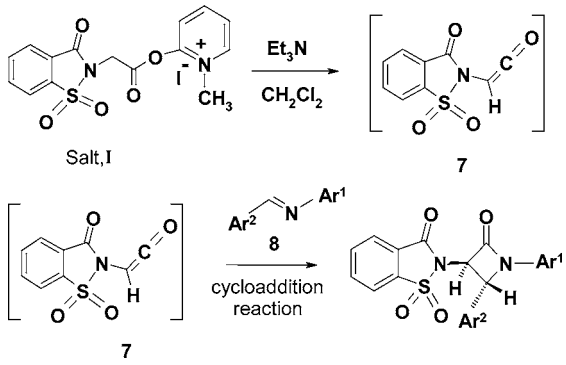
groups, respectively. The ^{1}H NMR and ^{13}C NMR spectroscopic data of compounds **9b−k** are presented in the SI. It is not clear to us why the reaction efficiency increases when the reaction take places in two steps. It seems the reaction goes in different paths. Two possible explanations for the formation of products are shown in Schemes 4 and 6. In the first mechanism, salt **I** is

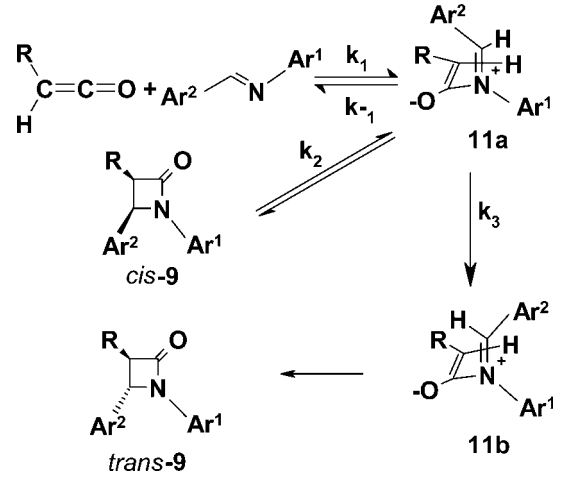
Scheme 4. Synthesis of *β*-Lactam from Ketene as an Intermediate



formed as an intermediate from the reaction of saccharinyl-acetic acid **4** and Mukaiyama reagent **6** in the presence of Et_3N and then the saccharinylketene **7** is actually formed as an intermediate.

The stereochemistry in the cycloaddition reaction between ketene and imine involves initial attack of the imine onto the ketene with formation of intermediate **11a** which can undergo ring closure to the *cis*-*β*-lactam **9** or it can convert to the less crowded intermediate **11b** and ring closure to *trans*-*β*-lactam **9** (Scheme 5).

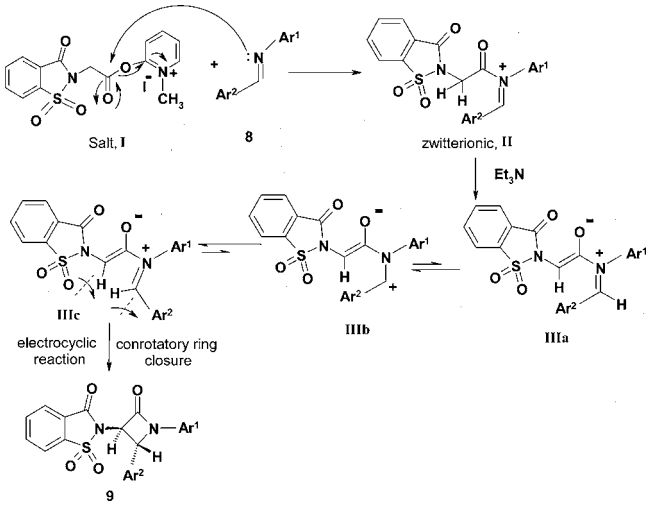
Scheme 5. A Plausible Mechanism for Highly Stereoselective Formation of *trans*-*β*-Lactam from Saccharinyl Ketene



Because saccharin is a large group, steric hindrance between Ar of the imine and the saccharin side chain of the ketene in the intermediate **11a** causes k_3 to be enhanced relative to k_2 ($k_3 \gg k_2$), *trans*-*β*-lactam **9** formed as the only isomer.

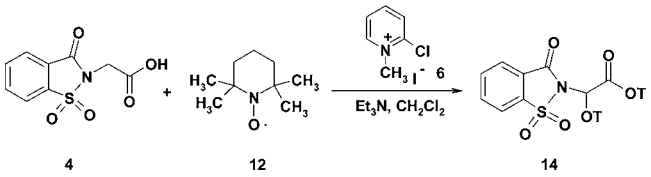
In the second possible mechanism, the reaction of imine **8** with salt **I** generates a zwitterionic intermediate **II**, which proceeds onto lactam products. Zwitterionic intermediate **II** is converted to an equilibrium mixture of **IIIa** and **IIIc** involving **IIIb**. The *trans*-*β*-lactam is formed as an only product from **IIIc** by an electrocyclic ring closure reaction via conrotatory mode (Scheme 6). In the last mechanism, ketene has not been generated and the zwitterion intermediate **II** has completely converted to *β*-lactams **9**.

Scheme 6. Zwitterion Formation in *β*-Lactam Formation



To identify the saccharinylketene as an intermediate in the synthesis of *β*-lactam ring, we have undertaken further reaction of the mentioned ketene with aminoxyl radicals. Reaction of *N*-saccharinylacetic acid **4** with Mukaiyama reagent **6** and Et_3N in the presence of TEMPO **12** [(2,2,6,6-tetramethyl-piperidin-1-yl) oxyl] in CH_2Cl_2 at room temperature leads to capture of ketene **7** by addition of two TEMPO radicals forming **14** (Scheme 7). ^{1}H NMR spectrum of **14** showed signals in agreement with the suggested structure. This spectrum exhibited clearly one single proton at 5.95 ppm for methine group.

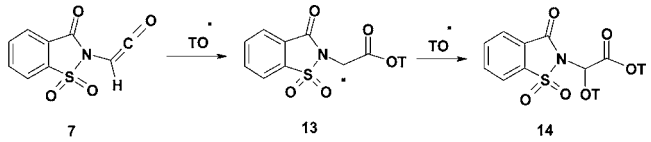
Scheme 7. Reaction of *N*-Saccharinylacetic Acid with TEMPO 12



Ketene **7** reacts with the stable free radical TEMPO (TO•) by initial attack of the radical on the carbonyl carbon of the ketene forming intermediate enolic radical **13**, followed by addition of a second TEMPO giving the 1,2-di-addition product **14** (Scheme 8).

Five of the 11 *β*-lactams **9b**, **9c**, **9e**, **9f**, and **9g** have been screened for their antimicrobial activities. The results showed

Scheme 8. Reaction Mechanism of TEMPO Radical



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that only compounds **9b** and **9f** exhibited antibacterial effects and they did not have any antifungal effect. Compound **9b** including bromine atom was effect on eight bacterial strains, and the mean diameter of inhibition zone was 23.5 mm. The minimum and maximum IZ measured in *Micrococcus luteus* PTCC 1110 (19 mm) and in *Staphylococcus aureus* PTCC 1112 (26 mm). Compound **9f** containing chlorine atom was more effective than **9b** on bacteria (see SI).

In summary, we synthesized new saccharins bearing trisubstituted β-lactam ring from the reaction of *N*-saccharinyl-acetic acid with Mukaiyama reagent and aromatic imines in the presence of Et_3N. Two distinct mechanisms have been proposed to explain the formation of the final products from saccharinylacetic acid. In the first mechanism, the reactions proceed via in situ generation of unstabilized saccharinylketene as a novel ketene and in the second mechanism the reactions proceed through the formation of a zwitterionic intermediate. Among newly synthesized compounds, two compounds **9b** and **9f** exhibited potential antibacterial activity which may guarantee their future applications in a moderate antibiotic therapy.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, compound characterization data, ^1H and ^{13}C NMR spectra of compounds **9a−9k** and compound **14**. Antibacterial procedure and the SAS system calculation. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01309.

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Notes

The authors declare no competing financial interest.

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