A Simple and One-Pot Synthesis of β-Sultams by Using the Vilsmeier Reagent

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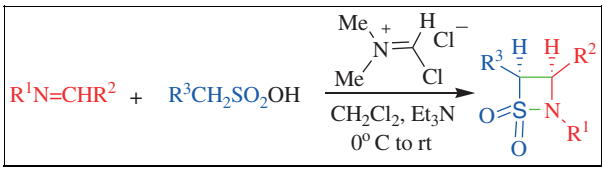

Mild and efficient one-pot synthesis of β-sultams with the Vilsmeier reagent proceeded in good to excellent yield. [2 + 2] Cycloaddition of imines with sulfenes (prepared *in situ*) afforded the corresponding *cis*-β-sultams. Optimization of solvents, molar ratio of reagents,and temperature was performed. Toxic and corrosive compounds have been avoided in this novel method.

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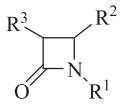
INTRODUCTION

The sulfonamide moiety has long been established to display biological activity and, as such, is widely found in molecules of medicinal interest, particularly antibacterial agents [1]. It is generally assumed that the antibacterial activity of β-lactam antibiotics depends on the stability and reactivity of the four-membered ring [2]. Replacement of the carbonyl group in β-lactams **1** by the sulphonyl group results in 1,2-thiazetidine-1,l-dioxides (β-sultams). β-Sultams **2** are regarded as sulfonyl analogs of β-lactam antibiotics as well as cyclic derivatives of taurine **3** (2-aminoethanesulfonic acid). Taurine, which is present in mammals, shows various biological activities [3].



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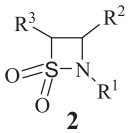

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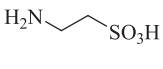

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Their reactivity is usually higher compared with the analogous β-lactam systems (approx. 10^3-fold) [4] and at least 10^7-fold more reactive than acyclic sulfonamides [5]. β-Lactams are stabilized by the π-bond overlap between the lone-pair electrons of the nitrogen atom and the carbonyl group and are much more stable than β-sultams. The overlap between the nitrogen lone-pair electrons and the sulfonyl group in β-sultams is much less compared with the stabilization of the β-lactam ring [6]. In addition, β-sultams are destabilized by the increased distortion of the β-sultam ring because of the C–S and N–S bonds, which are longer than the corresponding C–C and C–N bonds of the β-lactam ring [7]. Therefore, β-sultams are important subunits for chemical and pharmaceutical applications.

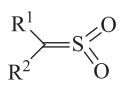
β-Sultams can act as irreversible active-site-directed inhibitors of elastases such as the human neutrophil elastase [8], β-lactamase [9], and *D,D*-peptidase inhibitors [10]. The anti-inflammatory roles of these compounds have also been reported [11].

The β-sultam ring consists of three different kinds of hetero single bonds, namely, C–N, C–S, and N–S bonds, which could be utilized as various synthetic equivalents as well as building blocks for the construction of other heterocycles [12].

To synthesize β-sultams, a number of methods has been developed [13], most notably (a) cyclization of 2-aminosulfonyl halides [14]; (b) cyclization of activated β-hydroxysulfonamides [15]; (c) cyclization of α-(halomethylsulfonamido) ketones, esters, or nitriles [16]; (d) [2 + 2] cycloaddition reactions of sulfonylamines with particularly electron-rich olefins [17]; (e) ring contraction of five-membered rings of pentafluorophenyl sulfonates [18]; and (f) [2 + 2] cycloaddition reactions of sulfenes with imines [19]. Among these methods, a widely used method is via the [2 + 2] cyclocondensation of nucleophilic imines and sulfenes.

Sulfenes **4** are molecules of the formula $RR'C{=}SO_2$ and may be regarded either as the sulfonyl analogs of ketenes **5**, although sulfenes are far less stable than ketenes [20], or as derivatives of sulfur trioxide formally obtained by replacement of one oxygen atom by a CRR′ group [21]. Sulfenes are formed by elimination of HCI from primary sulfonyl chlorides in the presence of a base [22], reaction of diazoalkanes with sulfur dioxide [23], thermolysis and photolysis of appropriate compounds [24], and elimination of nitrogen from α-diazosulfones [25]. Generally, sulfonyl chlorides are used as precursor of sulfenes in the synthesis

of β-sultams, but sulfonyl chlorides are highly corrosive and hygroscopic.



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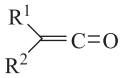

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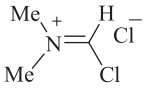

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We utilized alkoxymethylene-*N,N*-dimethyliminium salts as acid activators in the synthesis of 2-azetidinone ring by the ketene-imine cycloaddition [26]. In a recent communication, Yadav and co-workers used this reagent in the synthesis of β-sultams from imines with sulfonic acids [27]. Previously, we reported the synthesis of 2-azetidinone from imines and carboxylic acids via the Vilsmeier reagent ((chloromethylene)dimethylammonium chloride) [28]. The Vilsmeier reagent **6** was easily prepared from DMF and oxalyl chloride or thionyl chloride in dry CH_2Cl_2 [28], although it is commercially available [29]. The Vilsmeier reagent, unlike alkoxymethylene-*N,N*-dimethyliminium salt, does not need the toxic Me_2SO_4. Also, it was obtained as white solid and can be kept for a long time by storage in a well-capped bottle.

According to the earlier reports, in this letter, we describe the versatility and utility of the Vilsmeier reagent in the one-pot synthesis of β-sultams from imines and sulfonic acids under simple and mild conditions.

RESULTS AND DISCUSSION

Treatment of imine **7a** with phenylmethanesulfonic acid **8a** and the Vilsmeier reagent **6** in dry dichloromethane at room temperature in the presence of triethylamine afforded β-sultam **9a**. After purification by short-column chromatography, the pure *cis*-β-sultam was obtained in high yield. Indication of stereochemistry of the β-sultam **9a** was deduced from the coupling constant of H-3 and H-4, which were calculated to be $J = 8.6$ Hz for the *cis*-stereoisomer. The β-sultam ring is more distorted than the β-lactam ring, which presumably causes a decrease in its outer H–C–C bond angles and results in the higher J value of the *cis*-configured β-sultams than the corresponding β-lactams [27].

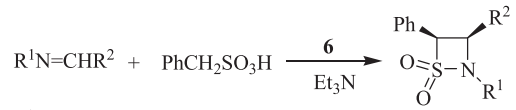
As part of the efforts to arrive at the optimal set of reaction parameters and choice of appropriate conditions, we considered the effect of solvents, temperature, and mole ratio of the reagents (Table 1).

As shown in Table 1 among the solvents considered, dichloromethane showed the best result. When the reaction started at 0 or −15°C and then stirred overnight at room temperature, the yield of **9a** increased perhaps because of low stability of sulfenes (Entries 6 and 7). It was found that 1.5 equiv. of the Vilsmeier reagent **6** was needed for the complete disappearing of imine **7**.

On the basis of these successful results, β-sultams **9a–k** were synthesized by treatment of 1.0 mmol of imines, 1.5 mmol of corresponding sulfonic acids, and 1.5 mmol of reagent **6** in the presence of triethylamine in dry dichloromethane at 0°C (Scheme 1, Table 2). Then, the mixtures were stirred overnight at room temperature. The β-sultams **9a–k** were obtained with complete *cis*-selectivity by mild and simple reactions, and by-products (DMF and salts) were removed by a simple aqueous work-up. The purification of β-sultams was performed by short-column chromatography on silica gel (EtOAc/hexane 3:7), and all products were characterized by their spectral data and elemental analyses.

Table 1

Reaction condition in the synthesis of β-sultam **9a**.



7a, R^1= 4-$MeOC_6H_4$, R^2= 4-$NO_2C_6H_4$ **8a** **9a**

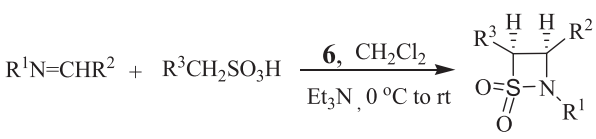
Entry	Solvent	Temperature (°C)	Reagent (equiv.)	Yield (%)
1	THF	RT	1.5	73
2	1,4-Dioxane	RT	1.5	56
3	CH_2Cl_2	RT	1.5	80
4	DMF	RT	1.5	40
5	Toluene	RT	1.5	51
6	CH_2Cl_2	0	1.5	94
7	CH_2Cl_2	−15	1.5	92
8	CH_2Cl_2	0	1.3	78

The data in Table 2 indicate that the yields are decreased when ethanesulfonic acid was used as a source of sulfene (Entries 2, 4, and 6). This may be due to lower stability of alkyl sulfenes than those corresponding to the aryl sulfenes.

The mechanism of β-sultam formation is a [2 + 2] cycloaddition reaction in which the nucleophilic imine attacks the electrophilic sulfene [13b,19]. The sulfene was prepared *in situ* by reaction of sulfonic acid and the Vilsmeier reagent **6** in the presence of triethylamine (Scheme 2).

In conclusion, the use of the Vilsmeier reagent for the one-pot synthesis of β-sultams from imines and sulfonic acids under mild conditions has been reported. The method is simple and versatile. The solvents, molar ratio of reagent, and temperature have been optimized.

Scheme 1



7 **8** **9a-k**

Table 2

Synthesis of β-sultams **9a–k** by reagent **6**.

Entry	R^1	R^2	R^3	Product	Isolated yield (%)
1	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	Ph	**9a**	93
2	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	Me	**9b**	67
3	*c*-C_6H_{11}	4-MeC_6H_4	Ph	**9c**	88
4	*c*-C_6H_{11}	4-MeC_6H_4	Me	**9d**	65
5	*c*-C_6H_{11}	4-ClC_6H_4	Ph	**9e**	92
6	*c*-C_6H_{11}	4-ClC_6H_4	Me	**9f**	72
7	Me	4-$NO_2C_6H_4$	Ph	**9g**	86
8	Me	Ph	Ph	**9h**	88
9	Me	4-$MeOC_6H_4$	Ph	**9i**	85
10	Me	4-$NO_2C_6H_4$	Ph	**9j**	84
11	$PhCH_2$	Ph	Ph	**9k**	90

EXPERIMENTAL

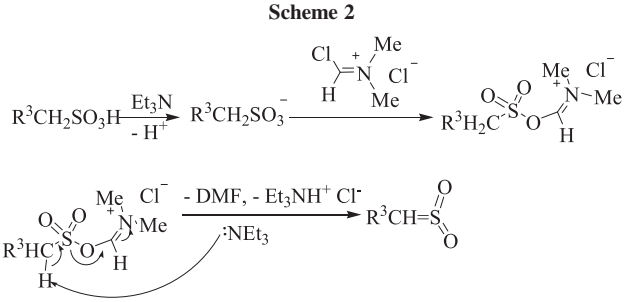
All needed chemicals were purchased from Merck, Fluka, and Acros chemical companies. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ by using a Bruker Avance DPX instrument (^{1}H NMR 250 MHz, ^{13}C NMR 62.9 MHz). Chemical shifts were reported in ppm (δ) downfield from TMS. All of the coupling constants (*J*) are in Hertz. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series. Melting points were determined in open capillaries with a Buchi 510 melting point apparatus. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was performed on Merck Kiesel gel (230–270 mesh). Compounds **9c–k** were known, and their spectral data have been previously reported [6a, 19b,c, 27].

General procedure. The Vilsmeier reagent ((Chloromethylene)-dimethylammonium chloride) (1.5 mmol) was added to a solution of sulfonic acids (1.5 mmol), imines (1 mmol), and triethylamine (5.0 mmol) in dry CH_2Cl_2 (20 mL) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was washed successively with saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed to give the crude product, which was purified by short-column chromatography on silica gel (EtOAc/hexane 3:7) to give pure β-sultams **9a–k**.

4-Phenyl-2-(p-methoxyphenyl)-3-(p-nitrophenyl)-1,2-thiazetidine-1,1-dioxide (9a). White solid; mp: 184–186°C. IR (KBr) cm^{-1}: 1118, 1306 (SO_2), 1337, 1515 (NO_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.68 (OMe, s, 3H), 4.60 (H-4, d, 1H, J = 8.6 Hz), 4.91 (H-3, d, 1H, J = 8.6 Hz), 6.71–8.12 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.3 (OMe), 55.9 (C-3), 56.5 (C-4), 116.3, 117.8, 119.0, 123.9, 125.0, 128.5, 129.2, 129.9, 135.7, 141.4, 143.8, 154.6 (aromatic carbons). *Anal*. Calcd for $C_{21}H_{18}N_2O_5S$: C, 61.45; H, 4.42; N, 6.83. Found: C, 61.53; H, 4.55; N, 6.88.

4-Methyl-2-(p-methoxyphenyl)-3-(p-nitrophenyl)-1,2-thiazetidine-1,1-dioxide (9b). White solid; mp: 138–140°C. IR (KBr) cm^{-1}: 1133, 1318 (SO_2), 1332, 1528 (NO_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.14 (Me, d, 3H, J = 7.1 Hz), 3.66 (OMe, s, 3H), 4.45 (H-4, dq, 1H, J = 7.1, 8.8 Hz), 4.84 (H-3, d, 1H, J = 8.8 Hz), 6.84–8.07 (ArH, m, 8H); ^{3}C NMR (62.9 MHz, $CDCl_3$) δ 12.7 (Me), 55.5 (OMe), 55.8 (C-4), 56.2 (C-3), 117.1, 118.5, 122.4, 123.9, 126.2, 128.5, 140.8, 152.4 (aromatic carbons). *Anal*. Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63; N, 8.04. Found: C, 55.26; H, 4.76; N, 7.97.

Scheme 2



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[29] CAS No. 3724-43-4. For example Acros product No. 29577 or Aldrich product no. 280909.

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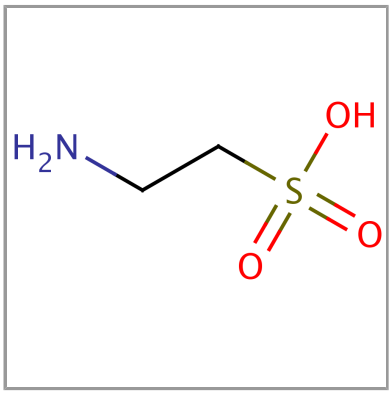

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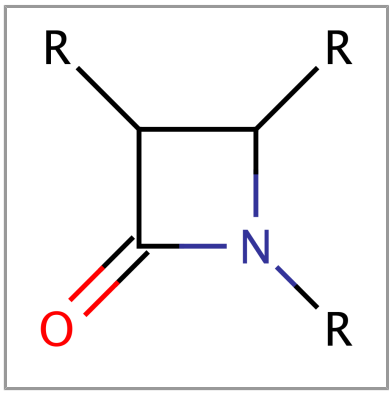

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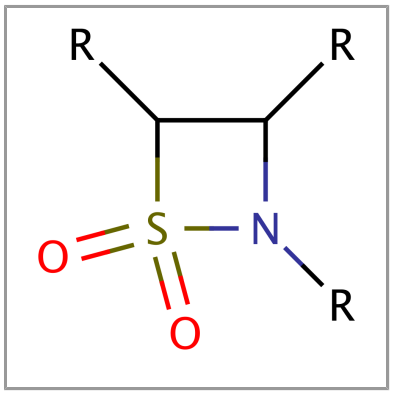

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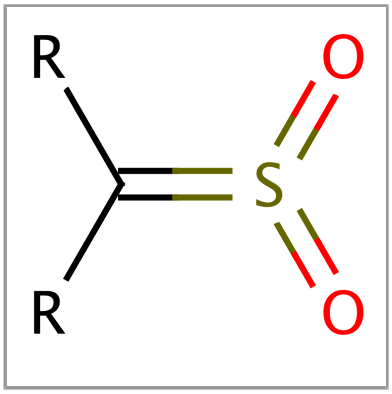

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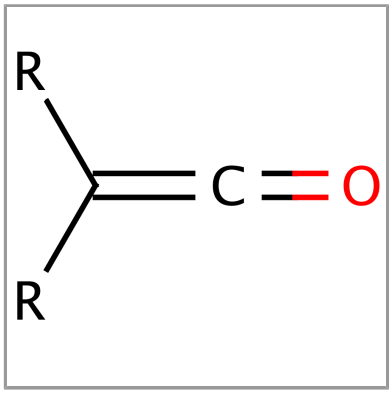

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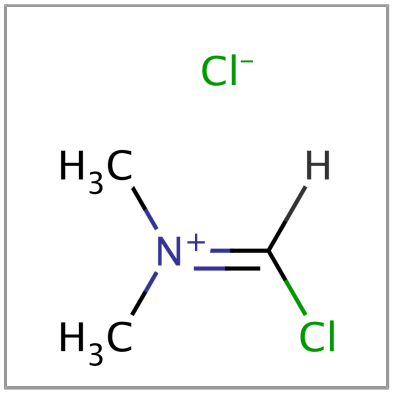

Compound Details Structure Search

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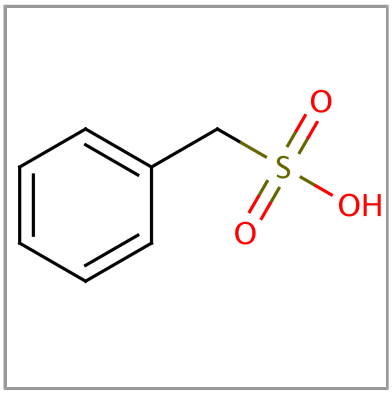

Compound Details Structure Search

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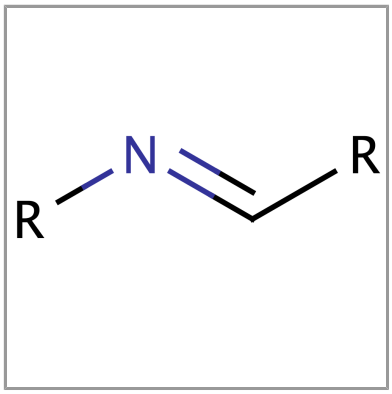

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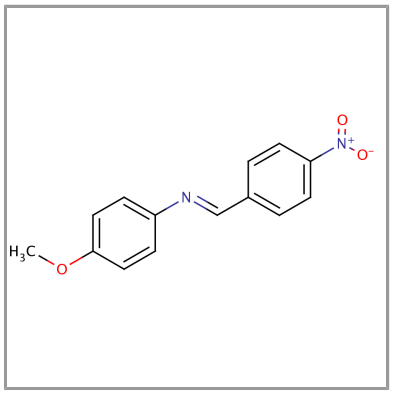

Compound Details Structure Search

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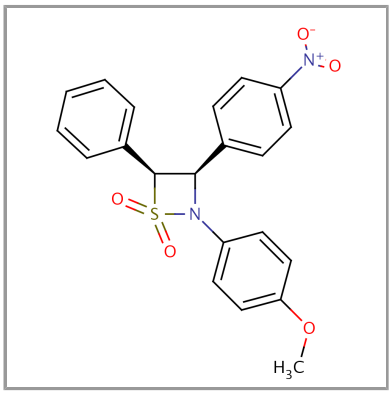

Compound Details Structure Search

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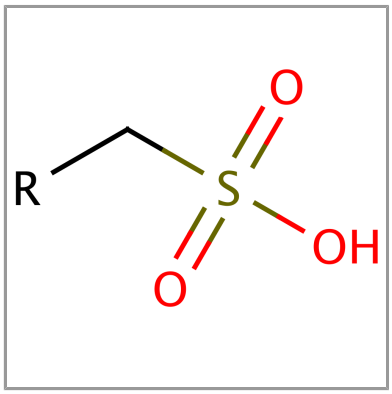

Compound Details Structure Search

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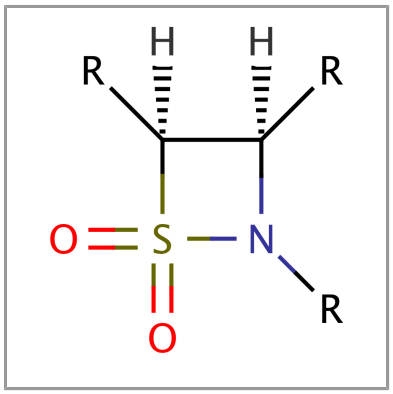

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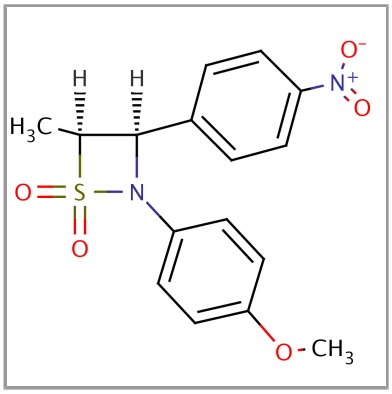

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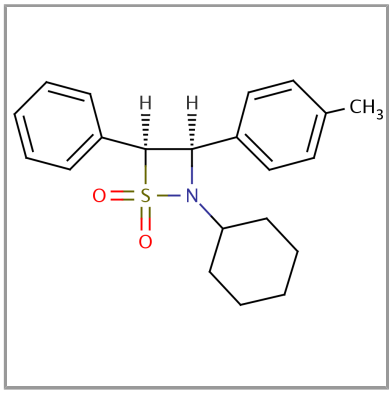

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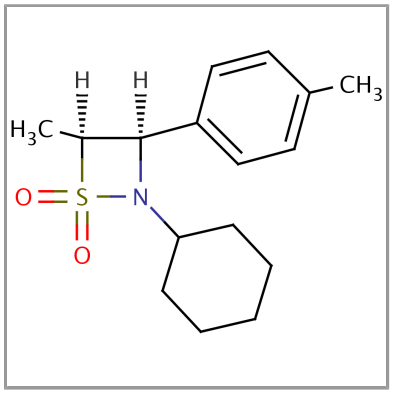

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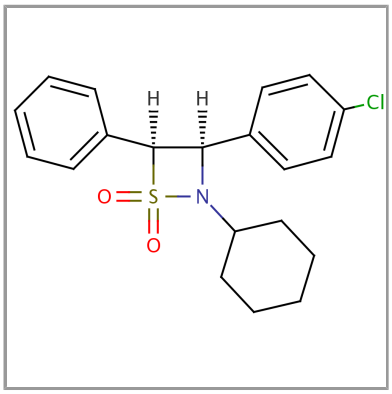

Compound Details Structure Search

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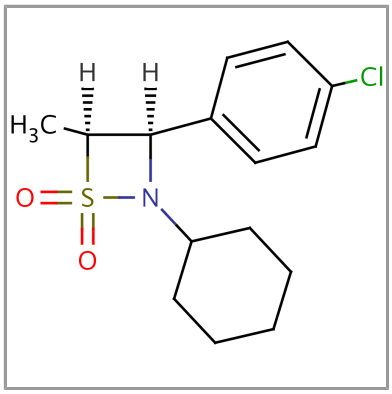

Compound Details Structure Search

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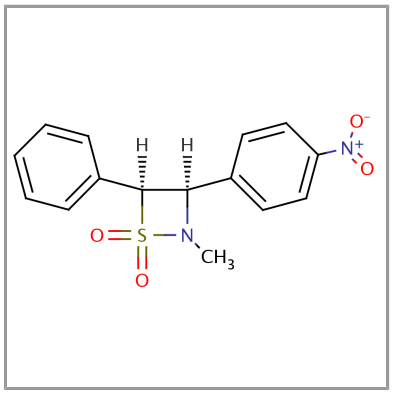

Compound Details Structure Search

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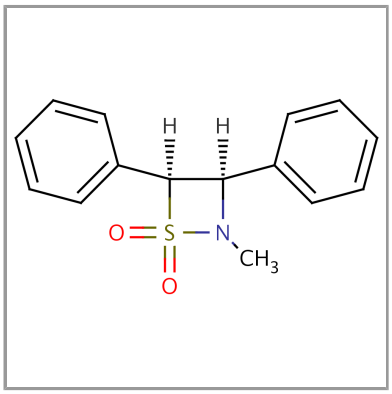

Compound Details Structure Search

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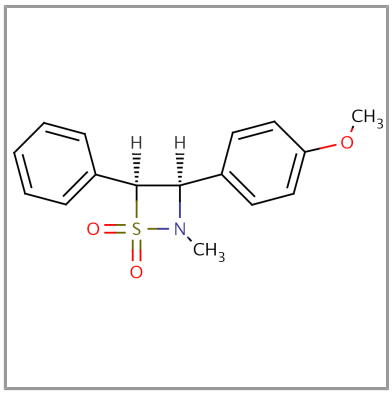

Compound Details Structure Search

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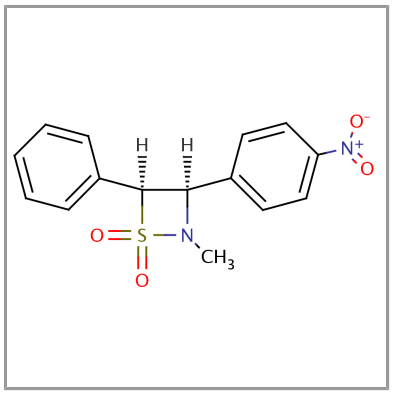

Compound Details Structure Search

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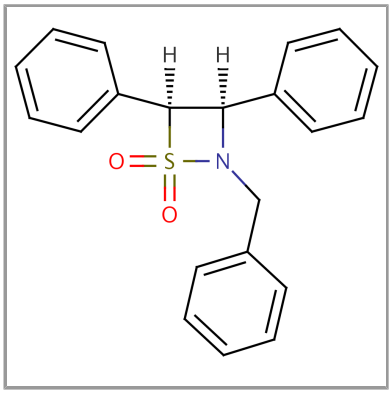

Compound Details Structure Search