α-BENZENEDISULFONIMIDE AS A RECYCLABLE HOMOGENEOUS ORGANOCATALYST FOR AN EFFICIENT AND FACILE SYNTHESIS OF 4-AMIDOTETRAHYDROPYRAN DERIVATIVES THROUGH PRINS–RITTER REACTION

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GRAPHICAL ABSTRACT

Abstract A highly diastereoselective synthesis of 4-amidotetrahydropyran derivatives has been achieved using a catalytic amount of α-benzenedisulfonimide under mild conditions involving sequential allylation and Prins–Ritter amidation. The oxo-carbenium ion formed in Prins cyclization could be successfully trapped with nitriles through Ritter amidation. The catalyst is highly efficient in promoting both allylation and Prins cyclization with a net addition of nitrile. The catalyst can be easily recovered and reused in subsequent reactions.

Keywords 4-Amidotetrahydropyrans; Brønsted acid; Hosomi–Sakurai allylation; Prins–Ritter amidation; recyclable catalyst; spiro-tetrahydropyrans
INTRODUCTION

In recent years, o-benzenedisulfonimide (1, 1,3,2-benzodithiazole-1,1,3,3-tetraoxide; Fig. 1) has received great attention because of its versatility in organic synthesis. It has been used for various organic transformations such as etherification/acetalization,[1] esterification,[2] Hosomi–Sakurai reaction,[3] Ritter reaction,[4] Nazarov electrocyclization,[5] disproportionations of dialkyl diarylmethyl ethers,[6] and Strecker reaction.[7] It can be recovered and reused in subsequent reactions with economic and ecological advantages.

4-Aminotetrahydropyran ring is a core structure in several natural products[8] such as ambruticin VS3 and dysiherbaine (Fig. 2). Compound A is a heat-generating photosensitive material used in photographic films. Compound B, a nonmacrocyclic supramolecule, showed appreciable binding with alkali metals (Li⁺, Na⁺, and K⁺) with association constants (Ka) greater than 10⁷–10⁸, and compound C is a melanocortin receptor agonist.[9]

In literature, a few one-pot approaches have been reported for the synthesis of 4-amidotetrahydropyrans. Typically, these methods combine three reactions such as
(i) Sakurai–Hosomi, (ii) Prins cyclization, and (iii) Ritter amidation in a one-pot operation. However, most of these methods require activators such as acetyl chloride and stoichiometric amount of catalysts. Hence, there is still scope to develop catalytic methods with low catalytic loading and high efficiency for the synthesis of 4-amidotetrahydropyran derivatives.\textsuperscript{[10]} In this article, we report a new application of o-benzenedisulfonimide (I) to perform the Prins–Ritter amidation. The catalyst is a nontoxic, nonvolatile, and noncorrosive homogeneous Brønsted acid.

RESULTS AND DISCUSSION

Following our interest in Prins cyclization,\textsuperscript{[11]} we herein report an efficient and rapid approach for the synthesis of symmetrical 2,6-disubstituted 4-amidotetrahydropyrans through a sequential Sakurai–Hosomi–Prins/Ritter reaction. The Hosomi–Sakurai allylation of both aromatic and aliphatic aldehydes proceeds rapidly under the influence of the catalyst (I). Thus in situ–formed homoallylic alcohol underwent a smooth Prins cyclization with another equiv. of aldehyde in the presence of nitrile to afford the corresponding 4-amidotetrahydropyran. For instance, treatment of 2.1 equiv. of \(p\)-chlorobenzaldehyde with 1 equiv. of allylttrimethylsilane in acetonitrile in the presence of 10 mol\% catalyst (I) at room temperature gave the corresponding 4-acetamido-2,6-diphenyl-tetrahydropyran \(3\text{a}\) in 85\% yield with \(cis\)-selectivity. The reaction was completed within 1 h with excellent diastereoselectivity (Table 1, Scheme 1).

Unlike classical Prins cyclization, no formation of undesired 4-hydroxytetrahydropyrans was observed when a catalytic amount of catalyst (I) was employed. These results encouraged us to extend this protocol for various aldehydes and nitriles. Interestingly, aromatic aldehydes such as \(p\)-chlorobenzaldehyde and \(p\)-bromobenzaldehyde underwent a smooth reaction with allyltrimethylsilane in acetonitrile to give the corresponding 4-acetamido-2,6-diaryl-tetrahydropyrans in good yields (entries a and b, Table 1). This method is effective even for sterically hindered substrate, for example, 2-naphthaldehyde (entry c, Table 1). Similarly, benzaldehyde also reacted well with allyltrimethylsilane in benzyl cyanide to yield the corresponding 2,6-diaryl-4-phenylacetamido-tetrahydropyrans (entry d, Table 1). Next, we studied the reactivity of aromatic and aliphatic aldehydes in benzonitrile. Interestingly, \(p\)-chlorobenzaldehyde and \(n\)-butanal participated well in the Hosomi–Sakurai–Prins/Ritter amidation in benzonitrile to yield the respective 2,6-disubstituted-4-benzamidotetrahydropyrans (entries e and f, Table 1). Thus, it is very useful for the preparation of a diverse range of 2,6-diaryl- or 2,6-dialkyl-4-amidotetrahydropyrans. The structures of the products were established by NMR, infrared (IR), and mass spectroscopy. It is noteworthy to mention that the reaction was not successful in the absence of acid catalyst (I) even after an extended reaction time (12 h). The products were obtained in good yields with \(cis\)-selectivity as confirmed from the NMR spectrum of the crude product. Only a single diastereoisomer was formed in each reaction, the structure of which was confirmed by coupling constants (\(J\) values) and nuclear Overhauser effect (nOe) experiments.\textsuperscript{[8]} The scope of the catalyst I is illustrated with respect to various aldehydes and the results are presented in Table 1. As shown in Table 1, this method works well with both electron-donating as well as electron-withdrawing aldehydes.
Table 1. o-Benzene disulfonimide catalyzed Prins/Ritter reaction

| Entry | Aldehyde | Nitriles | Product (3) | Time (h) | Yield (%) |
|-------|----------|----------|-------------|----------|-----------|
| a     | \(\text{Cl-CHO} \) | \(\text{CH}_3\text{CN} \) | \[\text{NHCOCH}_3\] | 1.0      | 85        |
| b     | \(\text{Br-CHO} \) | \(\text{CH}_3\text{CN} \) | \[\text{NHCOCH}_3\] | 1.0      | 86        |
| c     | \(\text{CH}_3\text{CHC} \) | \(\text{CH}_3\text{CN} \) | \[\text{NHCOCH}_3\] | 1.5      | 82        |
| d     | \(\text{CHO} \) | \(\text{CN} \) | \[\text{NHCOCH}_2\text{Ph} \] | 1.0      | 80        |
| e     | \(\text{Cl-CHO} \) | \(\text{CN} \) | \[\text{NHCOPh} \] | 1.5      | 91        |
| f     | \(\text{CHO} \) | \(\text{CN} \) | \[\text{NHCOPh} \] | 1.5      | 80        |

\(^a\)All products were characterized by \(^1\text{H} \) NMR, IR and mass spectrometry.  
\(^b\)Yield refers to pure products after chromatography.

Scheme 1. Sequential allylation and Prins–Ritter amidation.
The simplicity of this procedure encouraged us to further extend it to the preparation of unsymmetrical 4-amidotetrahydropyran derivatives by means of Prins–Ritter reaction (entries 4a–g, Table 2). In a typical experiment, 1.2 eq of

Table 2. \( o \)-Benzenedisulfonimide–catalyzed Prins/Ritter reaction

| Entry | Aldehyde/Ketone | Nitriles | Homoallyl alcohol | Product (4) | Time (h) | Yield (%) |
|-------|-----------------|----------|-------------------|-------------|----------|-----------|
| a     | Cl-CHO          | CH₃CN    | \( \text{Homoallyl alcohol} \) | \( \text{Product (4)} \) | 1.0      | 87        |
| b     | \(-\text{CHC} | CH₃CN    | \( \text{Homoallyl alcohol} \) | \( \text{Product (4)} \) | 1.0      | 80        |
| c     | \(-\text{CHO} | \(-\text{CN} | \( \text{Homoallyl alcohol} \) | \( \text{Product (4)} \) | 1.2      | 80        |
| d     | \(-\text{CHO} | \(-\text{CN} | \( \text{Homoallyl alcohol} \) | \( \text{Product (4)} \) | 1.2      | 82        |
| e     | Cl-CHO          | CH₃CN    | \( \text{Homoallyl alcohol} \) | \( \text{Product (4)} \) | 1.0      | 90        |
| f     | Br-CHC          | \(-\text{CN} | \( \text{Homoallyl alcohol} \) | \( \text{Product (4)} \) | 1.2      | 83        |
| g     | \(-\text{MeO} | CH₃CN    | \( \text{Homoallyl alcohol} \) | \( \text{Product (4)} \) | 1.0      | 80        |

\( ^a \text{All products were characterized by} \) \(^1\text{H NMR, IR and mass spectrometry.} \)

\( ^b \text{Yield refers to pure products after chromatography.} \)
p-chlorobenzaldehyde was treated with 1.0 eq of 3-buten-1-ol in the presence of 10 mol% of catalyst 1 in acetonitrile. Interestingly, the reaction was completed within 1 h at room temperature and the corresponding 2-phenyl-4-acetamidotetrahydro- 
pyran 4a was obtained in 87% yield with cis-selectivity (Table 2, Scheme 2).

Subsequently, we found that this method works not only with aldehydes but also with ketones. For instance, N-methylisatin (1-methylindoline-2,3-dione) reacted smoothly with 3-buten-1-ol in the presence of catalyst 1 (10 mol%) in acetonitrile to furnish the corresponding spiro-tetrahydropyranyl amide[12] 4g in 80% yield (Scheme 3, entry g; Table 2).

Next, we tested the efficiency of o-benzenedisulfonimide with known acid catalysts for the condensation of homoallylic alcohol with N-methylisatin in acetonitrile at 25°C, and the results are presented in Table 3.

| Entry | Catalysts (10 mol%) | Reaction time | Yield (%)a |
|-------|---------------------|---------------|------------|
| a     | HCOOH               | 12 h          | Trace      |
| b     | BF3·OEt2            | 10 h          | 50         |
| c     | Phosphomolybdic acid| 12 h          | 40         |
| d     | TFA                 | 12 h          | 45         |
| e     | 4-MeC6H4SO3H        | 10 h          | 60         |
| f     | MeSO3H              | 10 h          | 63         |
| g     | NH4SO3H             | 10 h          | 40         |
| h     | o-Benzenedisulfonimide | 1.0 h | 80         |

aYield refers to pure product after chromatography.
As seen from Table 3, the product \(4g\) was obtained in 80% yield in a shorter reaction time (1 h) with \(\sigma\)-benzenedisulfonimide compared to other acid catalysts. Thus, \(\sigma\)-benzenedisulfonimide was found to be a superior catalyst in promoting Prins–Ritter amidation. It is the first example of Prins–Ritter amidation of \(N\)-methylisatin, which may find a useful application in medicinal chemistry to generate spiro-cyclic oxindole scaffolds.

The catalyst \(1\) is a strong acid\(^{[7]}\) and soluble in both water and organic solvents. One of the most remarkable aspects in the use of \(1\) is its ease of recovery in good yields from the reaction mixture owing to its complete solubility in water and its reuse in further reactions without significant loss of catalytic activity. The use of recyclable Brønsted acid (1) in this transformation makes this method an economically viable process for the synthesis of 4-amidotetrahydropyran derivatives. The recovered catalyst \(1\) was recycled in several consecutive runs and the results are presented in Table 4. The yields of \(4a\) and the recovery of \(1\) are always excellent throughout the course of different runs.

The \(cis\)-selectivity of the Prins–Ritter amidation reaction can be explained by the formation of oxo-carbenium ion in the presence of an acid catalyst. Attack of the alkene to oxo-carbenium ion through a chair-like transition state generates a tetrahydropyranyl cation. In the ring closure step, the \(C_2\) substituent occupies favorably in equatorial position to produce (\(E\))-oxo-carbenium ion over the (\(Z\))-oxo-carbenium ion. Therefore, the stereochemistry of the \(C_2\) substituent is transferred to the newly formed carbon–carbon bond. The stereochemistry at \(C_4\) is controlled by the extensive delocalization of the tetrahydropyranyl cation. The optimal geometry for this delocalization places hydrogen at \(C_4\) in a pseudoaxial position, so the nucleophilic attack occurs from the equatorial side to deliver the \(cis\)-tetrahydropyran skeleton.\(^{[13]}\)

In summary, a direct one-pot method has been developed for the synthesis of 4-amidotetrahydropyran derivatives by means of Prins cyclisation using a recyclable Brønsted acid catalyst (1). The synthetic usefulness of \(\sigma\)-benzenedisulfonimide (1) as an organocatalyst in Prins–Ritter reaction has been demonstrated. This strong bench-stable Brønsted acid has been shown to catalyze the three-component Prins–Ritter amidation under mild conditions. This method provides easy access to the synthesis of a wide range of symmetrical, unsymmetrical, and spiro-cyclic 4-amidotetrahydropyran derivatives with excellent yields (Scheme 4).

### Table 4. Reusability of the catalyst (1) in the preparation of \(4a\)\(^a\)

| Entry | Yield (%) \((4a)\) | Recovery (%) \((1)\) |
|-------|------------------|-------------------|
| 1     | 87               | 85 (18.6 mg)      |
| 2     | 82               | 81 (15.06 mg)     |
| 3     | 80               | 78 (11.75 mg)     |
| 4     | 78               | 75 (8.23 mg)      |

\(^a\)All the reaction were performed in 1 h.
\(^b\)Yield refers to the pure product.
\(^c\)The reaction was performed in 1 mmol scale using 0.1 mmol of the catalyst (1).
EXPERIMENTAL

Representative Procedure for the Synthesis of 4-Amidotetrahydropyran Derivatives

A solution of allyltrimethylsilane (0.5 mmol) was added to a mixture of aldehyde (1.05 mmol) and o-benzenedisulphonimide (I) (10 mmol%) in nitrile (4 mL). The resulting mixture was stirred at room temperature for the specified time. After completion, as indicated by TLC, the reaction mixture was poured into dichloromethane/water (20 mL, 1:1). The aqueous layer was separated and extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with water (3 × 4 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuo. The resulting crude mass was then subjected to flash column chromatography using a 7:3 mixture of n-hexane and ethyl acetate as eluent to afford the pure 4-amidotetrahydropyran. The products thus obtained were characterized by infrared (IR), NMR, and mass spectroscopy. The spectroscopic data of products 3a, 3c, and 3f (Table 1) and 4a (Table 2) are known in the literature.[10]

The aqueous layer and aqueous washings were collected and evaporated under reduced pressure. The residue was passed through a column of Dowex AG 50W-X8 ion-exchange resin (acidic in nature, 100–200 mesh, 160 mg resin/100 mg product) with water as eluent. After removal of the water under reduced pressure, virtually the pure catalyst I was recovered as a white solid; mp 190–192°C (toluene) (lit.[14] 192–194°C). The recovered catalyst I was employed in further catalytic cycles under the conditions described previously.

FUNDING

S. G. thanks the Council of Scientific and Industrial Research, New Delhi, for the award of a fellowship.

SUPPLEMENTAL MATERIAL

Full experimental details and ¹H and ¹³C NMR spectra are available online. Supplemental data for this article can be accessed on the publisher’s website.
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