Facile synthesis of benzothiadiazine 1,1-dioxides, a precursor of RSV inhibitors, by tandem amidation/intramolecular aza-Wittig reaction

Krishna C. Majumdar*§ and Sintu Ganai

Abstract

Reaction of o-azidobenzenesulfonamides with ethyl carbonochloridate afforded the corresponding amide derivatives, which gave 3-ethoxy-1,2,4-benzothiadiazine 1,1-dioxides through an intramolecular aza-Wittig reaction. The reaction was found to be general through the synthesis of a number of benzothiadiazine 1,1-dioxides. Acid-catalyzed hydrolysis of 3-ethoxy-1,2,4-benzothiadiazine 1,1-dioxides furnished the 2-substituted benzothiadiazine-3-one 1,1-dioxides in good yields and high purity, which is the core moiety of RSV inhibitors.

Introduction

Sultams have gained popularity in the scientific community especially among synthetic and medicinal chemists, because this basic moiety is present in many natural products and biologically active substances [1-8]. Especially, benzothiadiazine-3-one 1,1-dioxide and its derivatives possess potential activity, including hypoglycemic [9], antiscancer and anti-HIV activity [10-13], and also serve as selective antagonists of CXR2 [14]. 2-Substituted-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxides showed varying degrees of sedative and hypotensive activities [15]. A number of benzothiadiazine 1,1-dioxide derivatives have recently been reported that display potent activity [16-22], including hypoglycemic (1), anti-HIV (2), HIV-1 specific non-nucleoside reverse transcriptase inhibitor (3), sedative (4), and respiratory syncytial virus (RSV) inhibitory activity (5; Figure 1).

A literature search revealed that the 1,2,4-benzothiadiazine 1,1-dioxides are generally synthesized either by condensation of o-aminobenzenesulfonamides with urea at elevated temperature [23] or by the reaction of o-aminobenzenesulfonamide with isocyanates in DMF under reflux [24]. Although various approaches to the preparation of 1,2,4-benzothiadiazine 1,1-dioxide derivatives have been reported [25-32], the development of a simpler method for the synthesis of the 1,2,4-benzo-
The aza-Wittig reaction is employed for the construction of C=N, N=N and S=N double bonds in various heterocycles and heterocycle-containing natural products [33-43]. Recently, we have synthesized asymmetrically substituted piperazine-2,5-dione derivatives using the intramolecular aza-Wittig reaction [44]. In continuation of our earlier work [45-51], we have undertaken a study to synthesize 1,2,4-benzothiadiazine 1,1-dioxide derivatives using an intramolecular aza-Wittig reaction as the key step. Herein we report our results.

Retrosynthetic analysis of the RSV inhibitors 5 and 6 relied on benzothiadiazine-3-one 1,1-dioxide 7, which can easily be obtained by simple hydrolysis of the benzothiadiazine 1,1-dioxide derivative 8. Construction of this six-membered sultam 8 was thought to be achieved by intramolecular aza-Wittig reaction of the o-azido derivative 9. The following retrosynthetic analysis led us to the starting material o-azidobenzenesulfonic acid (11) for the synthesis of the intermediate 10 necessary for the synthesis of RSV inhibitors (Scheme 1).

**Results and Discussion**

Sulfonic acid 11 bearing an o-azido group [30] was converted into the corresponding sulfonyl chloride by treatment with oxalyl chloride followed by the reaction with appropriate amines to give the requisite 2-azido-N-substituted benzenesulfonamides 10a–i. The sulfonamide 10b was reacted with ethyl carbonochloridate to afford the corresponding amide derivative
required for our study. Initially, we turned our attention to the synthesis of a benzothiadiazine 1,1-dioxide derivative using substrate 9b by intramolecular aza-Wittig reaction. To test this premise, 9b was treated with triphenylphosphine in THF at room temperature, but no desired product was obtained, and only the intermediate iminophosphorane 12b was isolated, even under reflux (Scheme 2).

We next conducted a series of reactions with the replacement of the solvent THF by other solvents, such as toluene, CH₂Cl₂, and CH₃CN, but none of them afforded any cyclized product (Table 1, entries 2–4). Then the reaction conditions were modified through the use of a higher-boiling-point solvent, i.e., o-dichlorobenzene (DCB). The reaction was successful at higher temperature, affording the desired cyclized product 13b (54%) along with the by-product triphenylphosphine oxide (Table 1, entry 5).

Subsequently, we turned our attention to develop a simpler one-step procedure by heating the sulfonamide 10b with ethyl carbonochloridate, Et₃N and PPh₃ in DCB at 135 °C for 6 h, which gave the cyclized product 13b in 78% yield (Table 2, entry 1). The base Et₃N was then replaced by Cs₂CO₃ or K₂CO₃, but no better result was obtained (Table 2, entries 2 and 3). Only DIPEA gave 69% yield of the product (Table 2, entry 4). However, surprisingly the use of xylene as the solvent improved the yield of the cyclized product (Table 2, entry 5). The replacement of NET₃ by DIPEA as the base also gave a similar

![Scheme 2: Preparation of 3-ethoxy-1,2,4-benzothiadiazine 1,1-dioxide. Reagent and conditions: (i) (COCl)₂, DMF, CH₂Cl₂, reflux, 3 h; (ii) RNH₂, NaOAc, MeOH + water, 60 °C; (iii) ClCO₂C₂H₅, acetone, Et₃N, rt, 5 h; (iv) PPh₃, THF, reflux, 10 h; (v) PPh₃, DCB, 135 °C, 8 h.](image)

**Table 1: Summary of the intramolecular aza-Wittig reactions.**

| Entry | Solvent | Temp (°C) | Time (h) | Yield (%) |
|-------|---------|-----------|----------|-----------|
| 1c    | THF     | reflux    | 6        | 0         |
| 2c    | toluene | 120 °C    | 8        | 0         |
| 3c    | CH₂Cl₂  | reflux    | 8        | 0         |
| 4c    | CH₃CN   | reflux    | 6        | 0         |
| 5c    | DCB     | 135 °C    | 8        | 54        |

*aAll the reactions were carried out with 1 equiv 9b and 1.5 equiv PPh₃; bisolated yields of 13b; conly 12b was separated.*
yield of the product (Table 2, entry 6). The decomposition of the iminophosphorane intermediate into the corresponding amine derivative 14b was found to occur at higher temperature (150 °C) producing a low yield of the cyclized product (Table 2, entry 7). The reaction did not occur at all in the absence of a base (Table 2, entry 8). The observations are summarized in Table 2.

It is notable that xylene appears to be a suitable solvent for this reaction. We then carried out the reactions with a variety of substrates 10a–i under the optimized conditions (ethyl carbonochloridate, PPh3, Et3N, xylene at 135 °C) in order to generalize the method, and the results are summarized in Table 3. The reactions of all the substrates having electron-deficient R-substituents at the 2-position proceeded smoothly,
Scheme 3: Rationalization of the formation of compound 13.

providing excellent yields, whereas the substrates having electron-donating R-substituents gave lower yields.

The proposed mechanism for the formation of the products 13 may involve amidation of SO₂NH₂ by the reaction of nucleophilic sulfonamide 10 with anhydrous carbonochloridate in the presence of Et₃N to form the intermediates 9, which may then undergo intramolecular aza-Wittig reaction via the formation of iminophosphorane intermediate 1. We isolated iminophosphorane intermediate 12b from the reaction with 10b at room temperature. In the presence of heat the iminophosphorane intermediate 1 leads to the formation of the product 3-ethoxy-1,2,4-benzothiadiazine 1,1-dioxide 13 (Scheme 3). However, in all other cases we did not carry out the reactions at room temperature for isolation of the intermediates.

We have also demonstrated the conversion of the products 13 to the 2-substituted benzothiadiazine-3-one 1,1-dioxide 15 by hydrolysing 13 with ethanolic HCl. The benzothiadiazine-3-one 1,1-dioxide derivatives 15c,e,h were obtained in excellent yields from the compounds 13c,e,h (Scheme 4). These 2-substituted benzothiadiazine-3-one 1,1-dioxides may further be alkylated at the 4-position with suitable halides to yield the RSV inhibitors 5 and 6 by using the reported [13] procedure.

Previously, Jung and Khazi [52] reported the synthesis of the benzothiadiazine 1,1-dioxide moiety from the reaction of o-aminobenzenesulfonamide with the costlier triphosgene, whereas in our case the synthesis of benzothiadiazine 1,1-
dioxide derivatives was achieved from o-azidobenzenesulfonamides and required cheaper ethyl carbonochloridate as the reagent.

Conclusion

In conclusion, we have developed a simple and efficient method for the synthesis of 3-ethoxybenzothiadiazine 1,1-dioxide and benzothiadiazine-3-one 1,1-dioxide derivatives starting from an easy precursor, by the application of an intramolecular aza-Wittig reaction. The reaction procedure is very simple and gives good to excellent yields of the products. This benzothiadiazine-3-one 1,1-dioxide can further be alkylated at the 4-position, following a literature procedure, to give the bioactive RSV inhibitors.

Supporting Information

Supporting Information File 1
Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-54-S1.pdf]

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