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The facile and efficient organocatalytic platform for accessing 1,2,4-selenadiazoles and thiadiazoles under aerobic conditions

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ABSTRACT

The first organocatalytic approach towards synthesis of rarely explored 1,2,4-selenadiazole and thiadiazole scaffolds have been devised using corresponding carboxamides as substrates. The transformations were realized using two distinct conditions in the presence of catalytic vitamin B_3 or thiourea under aerobic conditions. Developed methods overcome the associated limitations of previous reported approaches and the desired products were obtained in high yields and selectivity without the formation of toxic side-products.

Introduction

During the recent years selenium and sulfur-based molecules have driven the concern of organic chemists due to their colossal engrossment in multidisciplinary research fields. These unique class of compounds are copiously inaugurated in pharmaceuticals and agrochemicals 1. Additionally, their attention has been lavishly elongated in the field of fluorescent molecular probes as well as in talented biomaterials 2. A broad spectrum of selenium and sulfur-based scaffolds are agnates to the drug molecules (Fig. 1), especially with human cancer cell growth inhibitor, antitumor agent, antioxidant, RAR agonist 1,3. In addition, their immense appeal to be used as potent catalysts and synthetic intermediates remain ambitious 4. Hence, a broad range of protocols have been investigated to realize the ideal synthesis of selenium-based molecules 5. Among, the selenium-founded nitrogen and oxygen containing molecules, the synthesis of acyclic structures such as diaryl-/heteroaryl selenides 6 and hydroxyselenides 7 attracted ample attention during the recent years. Towards the cyclic scaffolds, a numerous novel methods have been identified to synthesize medicinal candidates such as benzisoselenazolones, 8 benzoselenazines, 9 benzosultams, 10 ebselen, 11 seleno-chromenes, 12 selenadiazoles, 13 and benzoselenophene fused imidazopyridines 14. Albeit, tremendous recent progress has been recognized on the synthesis of selenium-containing nitrogen heterocycles, however the synthesis of selenium based azole derivatives have not been explored in details. In this regards, only limited number of protocols are executed for the preparation of 1,2,4-selenadiazoles 13.

Among the previous reported methods, a spectrum of stoichiometric strong and toxic oxidizing agents including precious metal-catalysts were introduced to accomplish the oxidative cyclization of the arylselenocarboxamides (Scheme 1a) 13a–h and imidamidines (Scheme 1b) 13i. However, the developed protocols suffers from a number of limitations such as use of metal as catalyst, toxic stoichiometric reagents and in most cases the yield of the desired products remains low. Therefore, an easy-to-operate and efficient approach has been described in our laboratory towards the synthesis of 1,2,4-selenadiazoles in the presence of catalytic amounts of vitamin B_3 using selenocarboxamides as substrates (Scheme 1c). Additionally, using the developed methods, we envisaged to upgrade the existing protocols (Scheme 1a) towards synthesis of 1,2,4-thiadiazoles. Our attention has been attracted towards finding surrogate methods for the preparation of 1,2,4-thiadiazoles is

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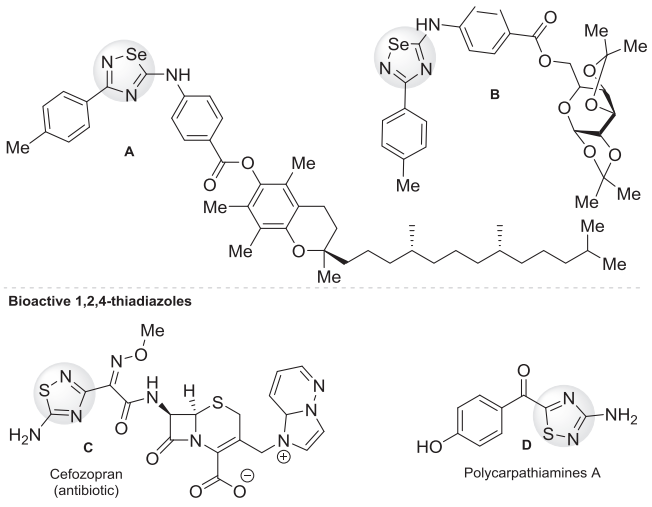
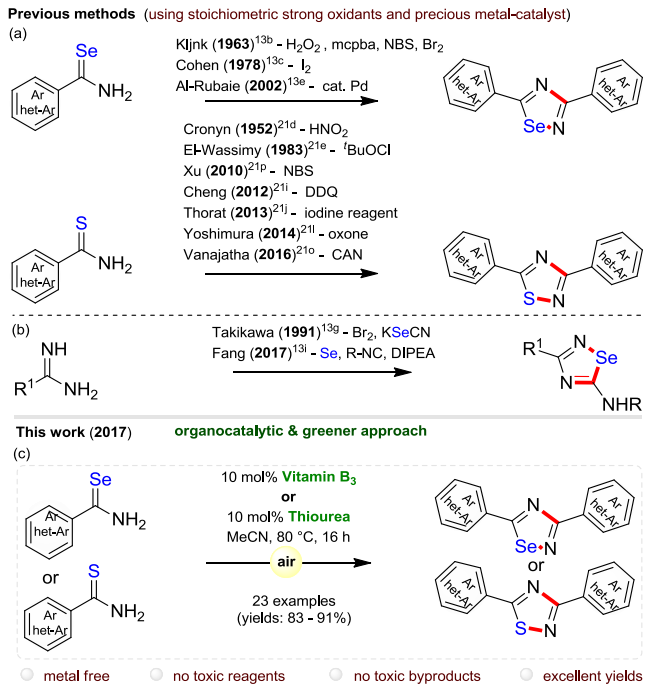


Fig. 1. Selected important 1,2,4-selenadiazoles and thiadiazole scaffolds.



Scheme 1. Previous and present methods towards 1,2,4-selenadiazoles.

due to the use of stoichiometric and toxic reagents in their preparation as well as due to their immense pharmacological profiles, and availability of cefozopran as commercially available antibiotic 15. The derivatives of 1,2,4-thiadiazole are extensively used in medicinal chemistry, particularly for the treatment of Alzheimer's disease, 16 and human leukemia 17. Moreover, thiadiazole derivatives have been used as G-protein coupled receptors, 18 and acetylcholinesterase inhibitors 19. Recently, the alkaloid polycarpathiamines A has shown cytotoxic activity against L5178Y murine lymphoma cells 20. Hence, considering their capacious medicinal and biological attention, a significant progress has been made to devise efficient and convenient strategies for the synthesis of 1,2,4-thiadiazole derivatives using stoichiometric amounts of oxidants (Scheme 1a) 21. Here, we report a straightforward and facile synthetic protocol towards both 1,2,4-selenadiazoles and thiadiazoles using the novel organocatalytic and easy to operate synthetic tools (Scheme 1c).

To commence with the experiments, the corresponding arylselenocarboxamides 13e 1a-h, arylthiocarboxamides 22 3a-o have been synthesized using literature known methods.

The screening of the optimized reaction conditions have been attempted using benzoselenoamide (**1a**) as model substrate. The oxidative cyclization of substrate **1a** to obtain the corresponding product **2a** has been executed using transition metal-salts as catalysts in DMF as solvent (Table 1, Entries 1–6). Unfortunately, it was noted that both Cu(II) and Cu(I)-salts as catalysts delivered low yields of the product **2a** (Table 1, Entries 1–2). However, catalytic amounts of $FeCl_3$ remain inactive for the conversion of **1a** to **2a** (Table 1, Entry 3). More interestingly, when the reaction was carried out in presence of $Fe(NO_3)_3{\cdot}9H_2O$ as catalyst (Table 1, Entries 4–6), the product **2a** was isolated in high yields. Afterwards, a number of reagents have been tested towards the oxidative cyclization of **1a** (Table 1, Entries 7–20). It has been observed that the catalysts such as $NaNO_3$ and $K_2S_2O_8$ were effective to accomplish the transformation with yields 83% and 77% respectively (Table 1, Entries 7 and 10). However, when catalytic amounts of KI have been introduced the formation of the desired product **2a** was inhibited either in presence or in absence of $NaNO_3$ (Table 1, Entries 8–9). Similar result has also been observed using catalytic TBAI (Table 1, Entry 11), whereas the product **2a** was isolated in 49% yield under the influence of 30 mol% NIS as catalyst (Table 1, Entry 12). Next, the feasibilities of the transformation have been checked in presence of organocatalysts such as Ph_2Se_2, PhI, 3-nitropyridine, thiourea, TEMPO and Vitamin B_3 (Table 1, Entries 13–20). Among these conditions tested, combination of both catalytic amounts of Ph_2Se_2 and NIS, and catalytic PhI in presence of mcpba in DCM as solvent delivered the product **2a** in moderate yields (Table 1, Entries 13 and 14). Replacing solvent with DMSO and with increased reaction temperature, a combination of PhI and mcpba were effective to improve the yield of the product **2a** (Table 1, Entry 15). Interestingly, organocatalysts such as 3-niropyridine,thiourea, TEMPO and vitamin B_3 have shown excellent reactivity towards conversion of **1a** into **2a** (Table 1, Entries 17–20), when the reactions were executed in DMF or MeCN as solvent at 80 °C for 16 h. Considering the vitamin B_3 as the most effective catalyst (Table 1, Entry 20) for the selective and effective transformation of **1a** to **2a**, the reaction conditions have been further optimized with respect to solvents, reaction time, reaction temperature and amounts of catalyst (SI, Table 1). A detailed optimization of the conditions concluded that the maximum yield of **2a** was realized when 1 mmol of **1a** was reacted using 10 mol% vitamin B_3 in MeCN at 80 °C for 16 h (Table 1, Entry 20; Conditions **A**). Additionally, during the optimization studies it was also noticed that using 10 mol% thiourea as catalyst under the identical conditions accomplished the transformation with similar yields of **2a** (Table 1, Entry 19; Conditions **B**). Giving priority to the recent concern on "green & clean" synthetic methods using organocatalyst, 23 these two identified best organocatalytic conditions (Conditions **A** and **B**) were acknowledged as the optimal conditions which employed to other substrates in order to describe the further scope of the current protocol.

Having the optimized conditions in hand a broad range of aryl/heteroaryl selenocarboxamides **1a-h** has been reacted (Scheme 2). It was described that aryl moieties containing electron withdrawing substituents such as chloro- and trifluoromethyl-groups, and electron donating substituents such as methoxy-group were well tolerated to obtain the products **2b-f** in excellent yields (Scheme 2). Moreover, the corresponding heteroaryl selenocarboxamides containing furan- and thiophene-moieties **1 g-h** have undergone successful conversion towards the formation of products **2 g-h** in high yields under both conditions **A** and **B** (Scheme 2).

Further to extend the scope of the developed methods, both conditions **A** and **B** have been verified towards the preparation of