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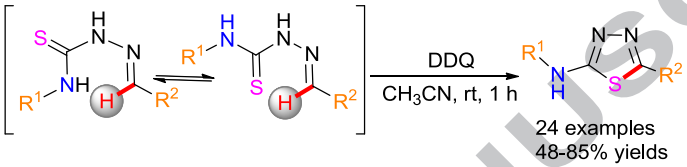

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ABSTRACT

An effective oxidative intramolecular cyclization (C–S bond formation) of thiosemicarbazones using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been developed to afford a diverse array of 2-amino-substituted-1,3,4-thiadiazoles. The attractive features of this protocol are operational simplicity, obviates the need of expensive transition-metal catalysts and broad substrate scope.

Introduction

1,3,4-Thiadiazoles are important five membered *N*,*S*-heterocycles with wide range of applications in medicine,[1] agriculture[2] and materials chemistry.[3] In particular, 1,3,4-thiadiazoles display a broad spectrum of biological activities including anti-inflammatory,[4a] antimicrobial,[4b] anticonvulsant[4c] and antihypertensive.[4d] The most familiar thiadiazole containing drugs are acetazolamide (**I**), megazol (**II**), and cefazedone (**III**) (Figure 1).[1b]

To date, various methods have been reported for the synthesis of 1,3,4-thiadiazoles (Scheme 1): (i) dehydrative cyclization of thiosemicarbazides with acidic reagents such as orthophosphoric acid and sulfuric acid (route a, Scheme 1);[5] (ii) reaction of acid hydrazides and dithiocarbamates using triethylamine in water (route b, Scheme 1);[6] (iii) dehydrative cyclization of thiosemicarbazide mediated by *p*-TsCl/TEA in *N*-methyl-2-pyrrolidone (route c, Scheme 1);[7] (iv) cyclization of thiosemicarbazone using iron (III) salts (route d, Scheme 1)[8] and (v) condensation of thiosemicarbazide and corresponding aldehyde followed by an iodine mediated oxidative cyclization (route e, Scheme 1).[9] Although, the above reported approaches are useful for the synthesis of 1,3,4-thiadiazoles, there are still disadvantages associated with these methodologies such as harsh reaction conditions, longer reaction time, the use of relatively harmful reagents and lacking of broad substrate scope. Therefore, the development of simple and mild routes for the synthesis of 1,3,4-thiadiazole derivatives is highly appealing and would be of great relevance to both synthetic and medicinal chemists.

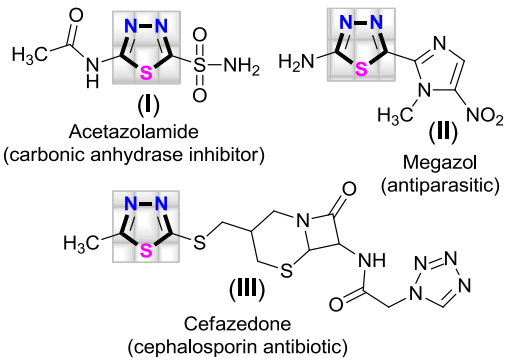

Figure 1. Representative examples of 1,3,4-thiadiazole containing drugs.

The development of transition metal catalyzed reactions using C–H bond functionalization/oxidation strategy is a challenging and powerful strategy for preparing valuable sulfur containing heterocycles.[10] Various catalytic systems based on palladium,[11] rhodium,[12] ruthenium,[13] copper[14] and iron[15] have been identified as efficient catalysts for C–S bond formation. Transition metal free transformations are more preferred in pharmaceutical industries over transition metal catalyzed reactions because the later are not only expensive, but are associated with difficulties in their removal from the desired products. To overcome these limitations, metal free approaches for direct C–S bond formation through C–H bond oxidation has drawn considerable interests. Recently, many groups reported significant progress on C–S bond formation under metal free conditions with various oxidants

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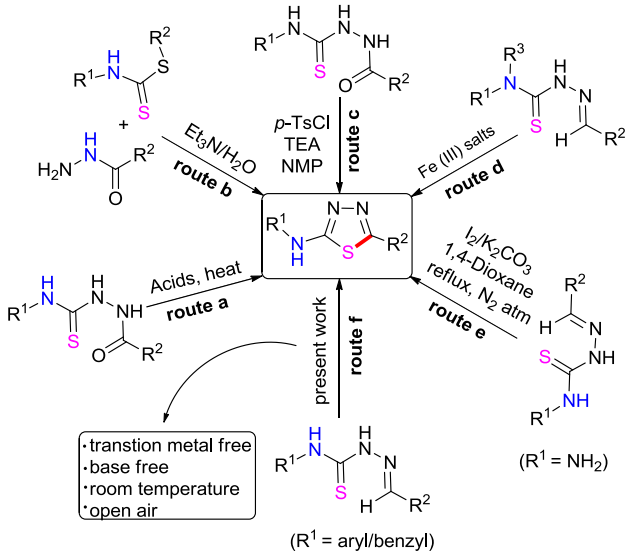
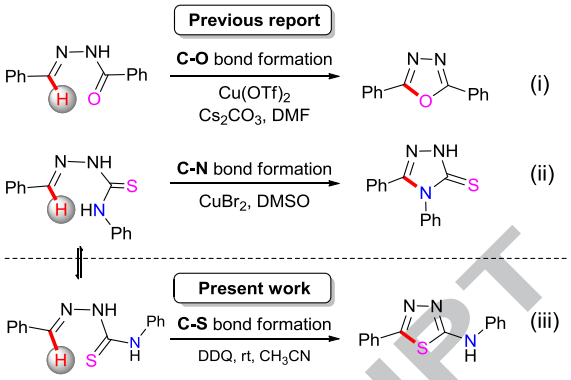
such as *tert*-butyl hydroperoxide (TBHP),[16a] *tetra-n*-butylammonium fluoride (TBAF),[16b] *di-tert*-butyl peroxide (DTBP)[16c] and iodine (I_2).[16d] Despite the significant advance on metal free oxidative C–S bond formation, the synthesis of biologically active heterocycles through oxidative cyclization (C–S bond formation) is rarely studied.[9,17]



Scheme 1. Various methods for the synthesis of 2-amino-1,3,4-thiadiazole.

Previously, we have achieved a direct access for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles *via* the imine C–H bond functionalization (C–O bond formation) of *N*-arylidenearoylhydrazides using a catalytic quantity of $Cu(OTf)_2$ (Scheme 2 (i)).[18a] Very recently, we have demonstrated a Cu(II) catalyzed imine C–H bond functionalization of thiosemicarbazones where selective C–N bond over C–S bond formations afforded 4,5-disubstituted 1,2,4-triazole-3-thiones (Scheme 2 (ii)).[18b] However, the formation of 1,3,4-thiadiazole (C–S bond over C–N) was observed only when any one of the aryl rings in thiosemicarbazones is *ortho*-disubstituted. This is probably due to the extreme steric factor imparted by *ortho*-disubstituted substrates in any one of the aryl rings of thiosemicarbazone. Due to the steric factor it adopts a *syn-syn* conformation as opposed to *syn-anti* conformation and thereby bringing the sulfur atom of thiocarbonyl to the proximity of imine C–H bond for oxidative cyclization (C–S bond formation).[18b] The oxidative cyclization of *N*-arylidenearoylhydrazide leading to 1,3,4-oxadiazoles via imine C–H bond oxidation have been achieved under a metal free (using I_2) condition by our group.[18c] On the other hand, DDQ has been used for the C–S bond formation during the synthesis of cephalosporins from 3-thiocarbonylhydrazone.[19a] Further, DDQ has been used for synthesis of thiadiazole from azomethene derivatives or thiosemicarbazones.[19b,c] Taking cues from the aforementioned reports we reasoned that a DDQ mediated oxidative cyclization of thiosemicarbazone involving its imine C–H bond may provide either an aminothiadiazole (through C–S bond formation) or a triazole-3-thione (through C–N bond formation).

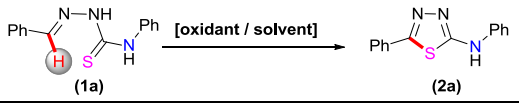


Scheme 2. Selective formation of C–O, C–N and C–S bonds *via* imine C–H bond functionalization.

Results and discussion

With this inspiration in mind, an initial reaction was attempted by treating thiosemicarbazone (**1a)** with DDQ (1 equiv.) in $CHCl_3$ at room temperature. A product formation (53% yield) was observed after 1 h and detailed spectroscopic analysis (^{1}H NMR, ^{13}C NMR, IR, HRMS) of the isolated product revealed its structure to be *N*,5-diphenyl-1,3,4-thiadiazol-2-amine (**2a**). In compound (**2a**) the –NH proton signals in its ^{1}H NMR was observed at ~10.5 ppm and the C_2 and C_5 carbons of the thiadiazole skeleton appear respectively at 164 and 156 ppm in its ^{13}C NMR. This observation is in sharp contrast to our recent result on Cu catalyzed C–N bond formation from thiosemicarbazones.[18b] The isomeric product i.e 4,5-diphenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (Scheme 2, equation II) obtained from thiosemicarbazones[18b] showed NH proton signal above 14 ppm in the same solvent (DMDO-d_6) and C_3 and C_5 carbons signals in the 1,2,4-triazole skeleton around 168 and 150 ppm respectively. To investigate the optimal reaction conditions, we began our studies using thiosemicarbazone (**1a**) as the model substrate (Table 1). The precursor thiosemicarbazones (**1a-1x**) are not commercially available, and were prepared according to the reported methods.[20]

Table 1. Optimization of reaction conditions[a,b]

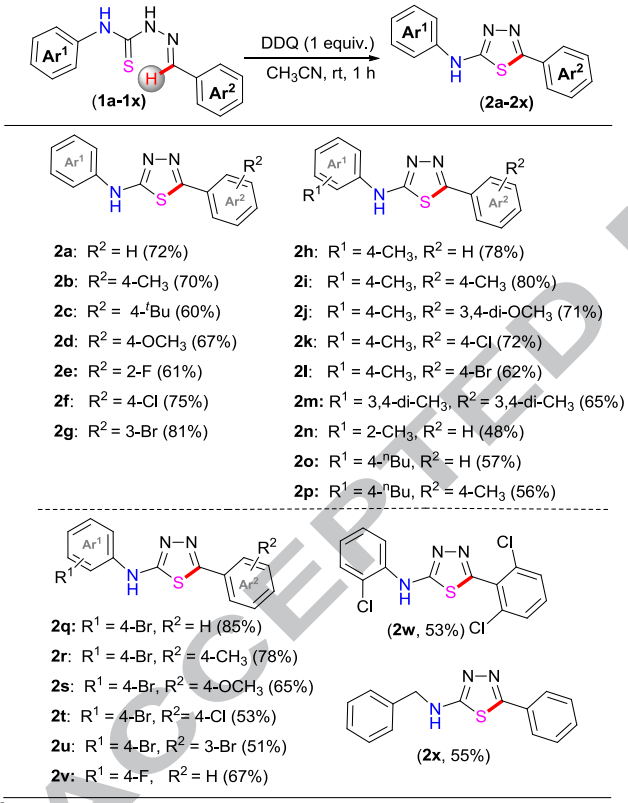


Entry	Oxidant	Solvent	Yield (%)
1	DDQ	$CHCl_3$	53
2	DDQ	CCl_4	75
3	DDQ	CH_3CN	72
4	DDQ	THF	51
5	DDQ	1,4-dioxane	45
6	DDQ	DMF	47
7	DDQ	Toluene	43
8	I_2	CH_3CN	50
9	DIB	CH_3CN	10
10	TEMPO	CH_3CN	00
11	TBHP (in dec)	CH_3CN	57
12	chloranil	CH_3CN	60
13	DDQ[c]	CH_3CN	73
14	DDQ[d]	CH_3CN	35

[a]Reaction conditions: (**1a**) (0.5 mmol), oxidant (0.5 mmol), and solvent (2 mL) at room temperature for 1 h. [b]Isolated yield. [c]0.75 mmol of DDQ was used. [d] 0.25 mmol of DDQ was used.

Encouraged by this selective C–S bond forming process, further optimizations were carried out to attain an optimum yield of the product. Various solvents such as CCl_4 (75%), CH_3CN (72%), THF (51%), 1,4-dioxane (45%), DMF (47%) and toluene (43%) (Table 1, entries 2-7) were screened, from which CCl_4 (Table 1, entry 2) was found to be the most efficient medium. Due to the toxicity and safety issues of chlorinated solvent CCl_4 was avoided and CH_3CN (Table 1, entry 3) was chosen as the reaction medium, albeit in little lower yield than CCl_4 (Table 1, entry 2). A variety of other nonmetallic oxidants such as I_2, DIB, TEMPO, TBHP (in decane) and chloranil (Table 1, entries 8-12) were examined, DDQ (Table 1, entry 3) was found to be the most effective for this transformation. Higher percentage loading of DDQ (1.5 equiv.) neither increased the yield nor reduced the reaction time (Table 1, entry 13). However, a significant decrease in the yield was observed by reducing the amount of DDQ (0.5 equiv.) (Table 1, entry 14). Thus, the optimized reaction conditions for the oxidative intramolecular C–S bond formation of (**1a**) (0.5 mmol) was achieved using DDQ (0.5 mmol) in CH_3CN (2 mL) at room temperature for 1 h.

Scheme 3. Substrate scope of 2-amino-substituted-1,3,4-thiadiazoles.[a,b]

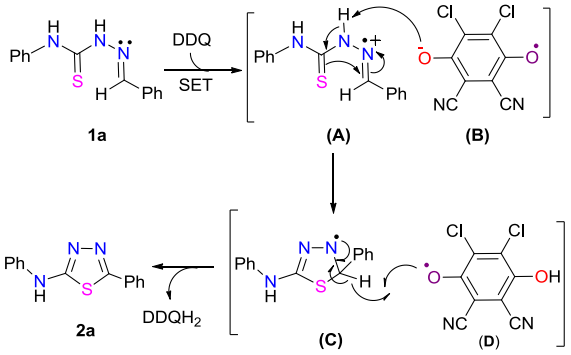


[a]Reaction conditions: **1** (0.5 mmol), DDQ (0.5 mmol), CH_3CN (2 mL), rt, 1 h. [b]Isolated yields.

Having achieved the optimal reaction conditions, we next examined the scope and generality of this intramolecular C–S bond formation using various thiosemicarbazones (Scheme 3). Initially, the effects of various substituents on the aryl ring (**Ar**^{2}) were screened. Various substituents such as 4-CH_3 (**1b**), 4-^{t}Bu (**1c**), 4-OCH_3 (**1d**), 2-F (**1e**), 4-Cl (**1f**) and 3-Br (**1g**) on the aryl ring (**Ar**^{2}) of thiosemicarbazones were all reacted smoothly under the optimized reaction condition affording their corresponding 1,3,4-thiadiazoles (**2b**), (**2c**), (**2d**), (**2e**), (**2f**) and (**2g**) respectively in the yield ranging from 61% to 81% (Scheme 3). Subsequently, the effects of various substituents on both the aryl rings (**Ar**^{1} and **Ar**^{2}) of thiosemicarbazones (Scheme 3) were examined. When electron-donating substituents such as 4-CH_3 is fixed on the aryl ring (**Ar**^{1}) and the substituents on the other aryl ring (**Ar**^{2}) were varied from electron-neutral –H (**1h**) and electron-donating such as 4-CH_3 (**1i**) and 3,4-diOCH_3 (**1j**) and electron-withdrawing substituents such as 4-Cl (**1k**) and 4-Br (**1l**) all afforded their respective 1,3,4-thiadiazoles (**2h**) (78%), (**2i**) (80%), (**2j**) (71%), (**2k**) (72%) and (**2l**) (62%) respectively. Substitution on the aryl ring (**Ar**^{1}) with electron-donating groups such as 3,4-diCH_3 (**1m**), 2-CH_3 (**1n**), and 4-^{n}Bu (**1o-1p**) while the other ring (**Ar**^{2}) with 3,4-diCH_3 (**1m**), electron neutral –H (**1n-1o**) and 4-CH_3 (**1p**) yielded their respective thiadiazoles (**2m**), (**2n**), (**2o**) and (**2p**) in 65%, 48%, 57% and 56% yields respectively.

Similarly, the presence of a moderately electron withdrawing substituent such as 4-Br (**1q**), on aryl ring (**Ar**^{1}) while the other aryl ring (**Ar**^{2}) having no substituent -H (**1q**) or substituents such as 4- CH_3 (**1r**), 4-OCH_3 (**1s**), 4-Cl (**1t**) and 3-Br (**1u**) gave moderate to high yields of their corresponding products (**2q**) (85%), (**2r**) (78%), (**2s**) (65%), (**2t**) (53%) and (**2u**) (51%) (Scheme 3). The presence of 4-F (**1v**) on aryl ring (**Ar**^{1}) and other ring (**Ar**^{2}) having an electron neutral -H gave product (**2v**) in modest yield (67%) as compared to its corresponding substrate (**2q**). Moreover, incorporation of an electron withdrawing substituent at *ortho* position of both the aryl rings (**Ar**^{1} and **Ar**^{2}) as in (**1w**) considerably lowered the product (**2w**) yield to 53%. As can been seen from Scheme 3 there is no correlation between the effects of substituents on any of the aryl rings and their product yields. Replacement of one of the aryl group (**Ar**^{1}) with an aliphatic group such as benzyl group (**1x**) provided the corresponding 1,3,4-thiadiazole (**2x**) in lower yield (55%) as compared to its corresponding diaryl substrate (**2a**).

Based on literature reports,[21] a plausible mechanism is proposed as shown in Scheme 4. A single electron transfer (SET) from the imine nitrogen to DDQ generates a nitrogen centered radical cation (**A**) and a DDQ radical anion (**B**). The DDQ radical anion (**B**) abstracts a hydrogen atom from the thioamidic nitrogen, this is then followed by an intramolecular nucleophilic attack of sulfur at the imine carbon to form a nitrogen centred radical (**C**) and a DDQ radical (**D**). The DDQ radical (**D**) then abstracts a proton from the intermediate (**C**) to form the desired 1,3,4-thiadiazole (**2a**) with the generation of $DDQH_2$.



Scheme 4. Proposed mechanism for the formation of 2-amino-1,3,4-thiadiazoles.

In summary, we have developed an effective oxidative intramolecular C–S bond formation to generate 2-amino-substituted-1,3,4-thiadiazoles from thiosemicarbazones using DDQ. This protocol represents an attractive route for a straight forward access to a diverse range of 2-amino-substituted-1,3,4-thiadiazole.We hope this clean procedure will be a valuable addition to the synthesis of substituted thiadiazoles.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.xxxxxx.