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A facile and straightforward synthesis of 1,2,3-thiadiazoles from α-enolicdithioesters via nitrosation/reduction/diazotization/cyclization cascade in one-pot

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ABSTRACT

An operationally simple, economical, and straightforward synthesis of diverse 4,5-disubstituted 1,2,3-thiadiazoles from α-enolicdithioesters has been achieved via nitrosation/reduction/diazotization/cyclization sequence in one-pot through the formation of cascade 1–2 (N–S) and 3–4 (C–N) bonds. Importantly, this is the first straightforward entry to highly functionalized 1,2,3-thiadiazoles from dithioesters.

The key goal in modern organic synthesis is to design and develop new synthetic strategies by improving resource efficiency that provides maximum structural diversity with economies of step, atom, labor, and cost for the rapid generation of function-oriented molecules. Cascade processes that incorporate multiple bond-forming events carried out in one-pot have come into play, and are of paramount interest in organic synthesis.[1] The synthesis of heterocycles has always been a key aspect, and increasingly attracted the synthetic pursuit of chemists because they are a vital part of new drug discovery and indispensable materials in the implementation of any industrial evolution.[2]

Among the five-member *N,S*-heterocyclic frameworks, 1,2,3-thiadiazoles[3] are versatile privileged scaffolds present in many bioactive natural products and pharmaceuticals[4,5] exhibiting diverse applications in medicine[6] and agriculture.[7] Furthermore, 1,2,3-thiadiazoles are not only useful intermediates to construct several important bioactive compounds,[8] but also utilized as key precursors[9a] for the synthesis of dendrimers,[9b,c] tetrathiafulvalenes,[9d,e] 2-benzofuran thiolates,[9f] amides of 1-adamantylthioacetic acids,[9g] and 1,1-dialkylindolium-2-thiolates.[9h] In addition, thiadiazole can act as the bio-isosteric replacement of the thiazole moiety, so it acts like third and fourth generation cephalosporins.

Among many strategies toward substituted 1,2,3-thiadiazoles,[10] Hurd–Mori synthesis,[10a] Pechmann synthesis,[10b,c] and Wolff synthesis[10d] are the most favorite and frequently utilized protocols. Some applications of the Hurd–Mori reaction[11] and the Wolff synthesis[12] are reported. Recently, Kumar et al.[13] synthesized 1,2,3-thiadiazoles using ionic liquid-supported sulfonyl hydrazine. However, the paucity of efficient one-pot synthetic method to access 1,2,3-thiadiazoles, and significant limitations of the existing methods such as poor availability of the starting materials, lack of adequate derivatization, and harsh reaction conditions prompted us to develop a more general and viable route with operational simplicity. Consequently, herein we report a simple, economical, and straightforward method for the synthesis of diverse 1,2,3-thiadiazoles from α-enolicdithioesters via nitrosation/reduction/diazotization/cyclization sequence in one-pot (Scheme 1).

α-Enolicdithioesters are not commercially accessible and were synthesized in good yields by the reported procedure.[14a] They are valuable synthetic targets in organic synthesis due to their versatile reactivity as well as powerful intermediates in the functionalization of various heterocycles.[14] Very recently, we reported the synthesis of 4,5-disubstituted 1,2,3-thiadiazoles by treatment of α-enolicdithioesters with tosyl azide in the presence of triethyl

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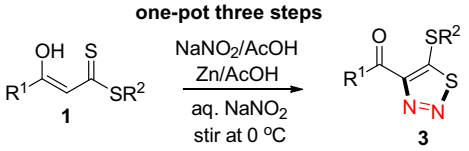


1a: R^1= C_6H_5, R^2=CH_3; **1b**: R^1=4-MeC_6H_4, R^2=CH_3
1c: R^1=2-ClC_6H_4, R^2=CH_3; **1d**: R^1=4-$CF_3C_6H_4$, R^2=CH_3
1e: R^1=thienyl, R^2=CH_3; **1f**: R^1=C_6H_5, R^2=allyl
1g: R^1=C_6H_5, R^2=methallyl; **1h**: R^1=4-MeC_6H_4, R^2=methallyl
1i: R^1=furyl, R^2=methallyl; **1j**: R^1=C_6H_5, R^2=benzyl
1k: R^1=4-MeC_6H_4, R^2=benzyl; **1l**: R^1=furyl, R^2=benzyl

Scheme 1. Synthesis of 1,2,3-thiadiazoles **3**.

amine (TEA).[15] The importance of 1,2,3-thiadiazole scaffolds in medicinal and material-based applications prompted us to construct this skeleton directly from dithioester in an atom- and step-economical manner. We envisioned to introduce diazo functional group at α-position of dithioester and further transform it directly to 1,2,3-thiadiazole via Wolff cyclization. In this perspective, we hypothesized that first nitrosation would lead to the corresponding oxime, which upon reduction should give amine followed by diazotization that could produce the diazo group. So, in continuation of our ongoing research regarding the synthetic utility of α-enolicdithioesters for the synthesis of various heterocyclic systems,[16,17] we report herein a simple, straightforward, and economical synthesis of 1,2,3-thiadiazoles from α-enolicdithioesters (Scheme 1).[18]

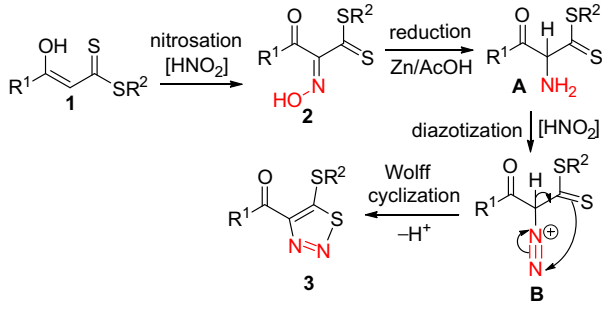
To optimize the reaction conditions for the synthesis of 1,2,3-thiadiazoles, methyl-3-hydroxy-3-phenyl-prop-2-enedithioate **1a** was taken as model substrate. Initially, the solution of **1a** (1 mmol) in 5 ml of dichloromethane (DCM) was treated with aq $NaNO_2$ (2 ml) followed by slow addition of zinc powder (1 equiv). The reaction mixture was stirred at 0 °C for 3 h. The work-up of the reaction provided **3a** in 20% yield characterized as 4-benzoyl-5-thiomethyl 1,2,3-thiadiazole with the help of satisfactory spectral (IR, ^1H & ^{13}C NMR, mass) studies and comparison with the reported one.[15] Encouraged by the above result, the effects of various parameters such as solvent, sodium nitrite loading, acetic acid, and the amount of zinc were examined on the model substrate **1a**. Screening of loading of $NaNO_2$ and zinc showed 3 equiv of $NaNO_2$ (1 ml) and 3 equiv of zinc afforded the maximum yield of the desired product in minimum time. Next, screening of various solvents such as $CHCl_3$, acetone, MeOH, and EtOH showed that the reaction mixture is not fairly soluble at 0 °C; however DCM was found to be the best among all. To get rid of the solubility problem, 1 ml of methanol was added in DCM, which resolved the solubility problem. Addition of methanol not only made the reaction clean, but reduced the reaction time also. So, the best solvent system was found to be a mixture of DCM and MeOH in 5:1 ratio. Thus, the best reaction conditions for the synthesis of **3a** was found to be **1a** (1 mmol), 6 ml of DCM+MeOH (5:1), 1 ml of AcOH, aqueous $NaNO_2$ (3 equiv, 1 ml), and zinc powder (3 equiv) at 0 °C.

With the optimized conditions in hand, we investigated the scope and versatility of our newly developed protocol utilizing various dithioesters **1a–l** (Table 1). Notably, the protocol tolerated well a wide range of substituents such as aryl and hetaryl groups at R^1 and alkyl, allyl, methallyl, and benzyl substituents at R^2 of our precursor moiety **1**. It was observed that dithioester bearing electron-donating group at R^1 (**1b**) reacted smoothly and afforded the desired product in higher yield than those containing the electron-withdrawing group (**1d**). Even electron-rich heteroaromatic groups such as 2-thienyl and 2-furyl at R^1 (**1e**, **1i**, and **1l**) were also

Table 1
Synthesis of 1,2,3-thiadiazole derivatives **3**[a]

Product	R^1	R^2	Time (h)	Yield[b] (%)	mp (°C)
3a	C_6H_5	Methyl	4	61	109–111[15]
3b	4-MeC_6H_4	Methyl	3	78	165–167[15]
3c	2-ClC_6H_4	Methyl	4	65	99–101[15]
3d	4-$CF_3C_6H_4$	Methyl	6	48	132–134[15]
3e	2-Thienyl	Methyl	4	60	172–174[15]
3f	C_6H_5	Allyl	4	65	Liquid[15]
3g	C_6H_5	Methallyl	5	68	Liquid
3h	4-MeC_6H_4	Methallyl	4	73	77–79
3i	2-Furyl	Methallyl	6	53	87–89
3j	C_6H_5	Benzyl	5	60	134–136[15]
3k	4-MeC_6H_4	Benzyl	5	70	143–146
3l	2-Furyl	Benzyl	6	55	132–134

[a] Reaction conditions: α-Enolicdithioesters 1 (1 mmol), aq $NaNO_2$ (3 equiv, 1 ml), AcOH (1 ml), DCM (5 ml), MeOH (1 ml), Zn (3 equiv), and aq $NaNO_2$ (1 equiv, 1 ml) at 0 °C.
[b] Yield of isolated products.



Scheme 2. Tentative mechanism for the formation of 1,2,3-thiadiazoles **3**.

suitable for this transformation giving the desired products in good yields (Table 1, **3e**, **3i,** and **3l**). Since the reaction is completed in a three-step one-pot fashion, the final yield of the desired product was considered to be good. In all the reactions the conversion of dithioesters **1** are nearly 100%. The structures of all the synthesized 1,2,3-thiadiazoles **3** were confirmed by their spectral (IR, ^1H & ^{13}C NMR and mass) studies and comparison with the reported ones.[15]

To rationalize the reaction outcome, based on our experimental results, we propose a tentative mechanism as shown in Scheme 2. First, α-enolicdithioester **1** upon nitrosation forms oxime **2**, which was subjected to Zn/AcOH reduction to give amine intermediate **A**. Subsequent diazotization of intermediate **A** produces α-diazo dithioester **B**, which undergoes Wolff-type cyclization that is a nucleophilic attack of the thiocarbonyl sulfur to diazo group followed by deprotonation to give the desired 1,2,3-thiadiazoles **3**.

In summary we have developed a simple and straightforward approach for the synthesis of 1,2,3-thiadiazoles from dithioesters in one-pot under mild and rapid reaction conditions. The present protocol not only serves as a step-economical alternative to existing methods but also allows direct construction of 1,2,3-thiadiazoles via the formation of cascade C–N/N–N/N–S bonds. Importantly, the presence of aroyl and alkylthio groups at 4- and 5-positions makes these molecules excellent entrants as precursors for further synthetic renovations to meet the need for diverse useful purposes.

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18. *General procedure for the synthesis of 1,2,3-thiadiazoles* ***3****:* 1.0 mmol of α-enolicdithioester **1** was dissolved in 6 ml of DCM + MeOH (5:1) and set the reaction on an ice-bath. Then 1 ml of glacial acetic acid was added followed by drop-wise addition of aqueous $NaNO_2$ (3 equiv, 1 ml). Reaction mixture was stirred at 0 °C for 30–60 min. After complete conversion of dithioester to oxime (monitored by TLC), zinc dust (3 equiv) was added in small portions over a period of 30 min and stirring was continued till the complete consumption of oxime. Finally, aqueous $NaNO_2$ (1 equiv, 1 ml) was added and continued stirring for further 30–40 min. Then reaction mixture was quenched with K_2CO_3 followed by the addition of 20 ml of water. The mixture was extracted with DCM (3 × 20 ml), washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue thus obtained was purified by column chromatography over silica gel using ethyl acetate/hexane (5: 95) as eluent to give the pure product. *Data of some selected compounds: 4-Benzoyl-5-methylsulfanyl-1,2,3-thiadiazole (****3a****):* White solid; mp 109–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, J = 7.2 Hz, 2H, ArH), 7.63–7.49 (m, 3H, ArH), 2.69 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.6, 170.3, 153.0, 136.9, 133.0, 130.5, 128.2, 21.7. IR (KBr, cm^{-1}): 3064, 2906, 1621, 1559, 1543, 1424, 1381, 1207, 1056. HRMS (ESI$^+$): calcd for $C_{10}H_8N_2OS_2$ [M+H]$^+$ 237.0151, found 237.0156. *4-Benzoyl-5-(2-methylallylsulfanyl)-1,2,3-thiadiazole (****3g****):* Yellow viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, J = 7.2 Hz, 2H, ArH), 7.60–7.48 (m, 3H, ArH), 5.22 (s, 1H, =CH_2), 5.12 (s, 1H, =CH_2), 3.70 (s, 2H, SCH_2), 1.89 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.6, 167.2, 153.9, 137.4, 136.9, 133.0, 130.6, 128.2, 117.3, 45.4, 21.2. HRMS (ESI$^+$): calcd for $C_{13}H_{12}N_2OS_2$ [M+Na]$^+$ 299.0283, found 299.0286. *[5-(2-Methylallylsulfanyl)-4-(4-methylbenzoyl]-1,2,3-thiadiazole (****3h****):* White solid; mp 77–79 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (d, J = 8.1 Hz, 2H, ArH), 7.31 (d, J = 7.8 Hz, 2H, ArH), 5.22 (s, 1H, =CH), 5.12 (s, 1H, =CH), 3.70 (s, 2H, SCH_2), 2.44 (s, 3H, $ArCH_3$), 1.89 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.3, 166.9, 154.2, 144.1, 137.6, 134.4, 130.8, 129.0, 117.3, 45.5, 21.6, 21.2. IR (KBr, cm^{-1}): 2927, 1603, 1412, 1388, 1273, 1226, 1176, 878, 757. HRMS (ESI$^+$): calcd for $C_{14}H_{14}N_2OS_2$ [M+H]$^+$ 291.0620, found 291.0627. *4-(2-Furoyl)-5-(2-methylallylsulfanyl)-1,2,3-thiadiazole (****3i****):* White solid; mp 87–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, J = 3.3 Hz, 1H, ArH), 7.77 (s, 1H, ArH), 6.64 (d, J = 1.8 Hz, 1H, ArH), 5.22 (s, 1H, =CH_2), 5.12 (s, 1H, =CH_2), 3.70 (s, 2H, SCH_2), 1.89 (s, 3H, CH_3). ^{13}C NMR

(75 MHz, $CDCl_3$): δ 172.0, 166.3, 151.1, 148.0, 137.5, 122.7, 117.3, 117.2, 112.5, 45.5, 21.2. IR (KBr, cm^{-1}): 3126, 3107, 2913, 1627, 1465, 1429, 1278, 1028, 922, 859, 767. HRMS (ESI^+): calcd for $C_{11}H_{10}N_2O_2S_2$ $[M+H]^+$ 267.0256, found 267.0261. *5-benzylsulfanyl-4-(4-methylbenzoyl)-1,2,3-thiadiazole (3k):* White solid; mp 143–146 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 7.8 Hz, 2H, ArH), 7.43–7.28 (m, 7H, ArH), 4.24 (s, 2H, SCH_2), 2.42 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.1, 166.7, 153.6, 144.0, 134.3, 133.7, 130.8, 130.7, 129.0, 128.9, 128.4, 42.7, 21.6. IR (KBr, cm^{-1}): 3073, 2914, 1619, 1599, 1412, 1389, 1274, 1181, 879, 709. HRMS (ESI^+): calcd for $C_{17}H_{14}N_2OS_2$ $[M+H]^+$ 327.0620, found 327.0626. *5-Benzylsulfanyl-4-(2-furoyl)-1,2,3-thiadiazole (**3l**):* White solid; mp 132–134 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, J = 3 Hz, 1H, ArH), 7.77 (d, J = 6.6 Hz, 1H, ArH), 7.45–7.34 (m, 5H, ArH), 6.63 (s, 1H, ArH), 4.26 (s, 2H, SCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 166.1, 152.0, 151.0, 148.1, 133.6, 129.1, 129.0, 128.5, 123.0, 112.5, 42.8. IR (KBr, cm^{-1}): 3115, 2918, 1621, 1461, 1418, 1269, 1024, 855, 778. HRMS (ESI^+): calcd for $C_{14}H_{10}N_2O_2S_2$ $[M+H]^+$ 303.0256, found 303.0265.