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Microwave assisted one pot synthesis of some novel 2,5-disubstituted 1,3,4-oxadiazoles as antifungal agents

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ABSTRACT

Sodium bisulfite has been reported first time for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole using microwave and conventional method in ethanol–water. The yields obtained are in the range of 90–95% using microwave and 87–91% using conventional method. All the synthesized compounds (**8a**–**8s**) are novel and were evaluated for their in vitro antifungal activity. SAR for the series has been developed by comparing their MIC values with miconazole and fluconazole. Some of the compounds from the series like **8k** was equipotent with miconazole against *Candida albicans* and *Fusarium oxysporum*. Also compound **8n** was equipotent with miconazole against *F. oxysporum*.

1,3,4-Oxadiazoles are a class of heterocycles, which have attracted significant interest in medicinal chemistry.[1] Among the 1,3,4-oxadiazoles, 2,5-unsymmetrical disubstituted derivatives have attracted considerable attention because of their biological importance.[2] The 1,3,4-oxadiazole-ring system has been identified as the main core of many bioactive molecules. Compounds containing these aromatic five-membered heterocycles have been shown to exert antiinflammatory,[3] antimicrobial,[4] anticonvulsant, and hypoglycemic activities.[5]

Several synthetic methods have been reported for the preparation of 1,3,4-oxadiazoles. One of the popular methods involves cyclization of diacylhydrazines prepared from the reaction of acyl chlorides and hydrazine. Several cyclodehydrating agents such as BF_3–OEt_2,[6] 1,1,1,3,3,3-hexamethydisilazane,[2] triflic anhydride,[7] phosphorus pentoxide,[8] polyphosphoric acid,[9] thionyl chloride,[10] phosphorus oxychloride,[11] and sulfuric acid[12] have been used.

One-pot syntheses of 1,3,4-oxadiazoles from hydrazine with carboxylic acids have also been reported.[13] Another synthetic route for the preparation of these compounds is via acylation of tetrazoles.[14] 1,3,4-Oxadiazoles have also been prepared by oxidation of acyl hydrazones with different oxidizing agents.[15–17] Reaction of acyl hydrazides with orthoesters in the presence of an acidic catalyst,[18] and solid phase synthesis of oxadiazoles[19] are other approaches for the synthesis of this group of compounds. Recently CAN has been reported for one pot synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from hydrazides and substituted aromatic aldehydes.[20]

However, many of these methods suffer from drawbacks such as long reaction times,[21] unsatisfactory yields, special care in handling and storing the reagents, undesired side products in reaction with harsh reagents,[22] using heavy metal oxidants,[23] cumbersome product isolation procedure and environmental pollution. Therefore, a need still exists for further development of versatile and milder reaction conditions.

Sodium bisulfite ($NaHSO_3$) is important reagent in organic transformation. We have reported $NaHSO_3$ in C–C bond forming reaction.[24] In the present work utility of sodium bisulfite in synthesis of some novel 2,5-disubstituted 1,3,4-oxadiazoles using microwave (Microsynth microwave lab station-Ethosi Milestone) and conventional method has been demonstrated.

1,2,3-Triazole and its derivatives are important heterocycles with different activities like potent antineoplastic,[25] antimicrobial,[26–28] analgesic,[29] antiinflammatory, local anesthetic,[30] anticonvulsant,[31] antimalarial,[32] anti HIV agents.[33] Some 1,2,3-triazole derivatives were used as DNA cleaving agents[34] and potassium channel activators,[35] cannabinoid CB1 receptor antagonists[36] and antitubercular agents.[37]

Considering the biological significance of 1,3,4-oxadiazole and 1,2,3-triazole and in continuation of our work on synthesis of pharmacologically significant heterocycles,[38] a novel series of 1,3,4-oxadiazole has been synthesized by one pot reaction of

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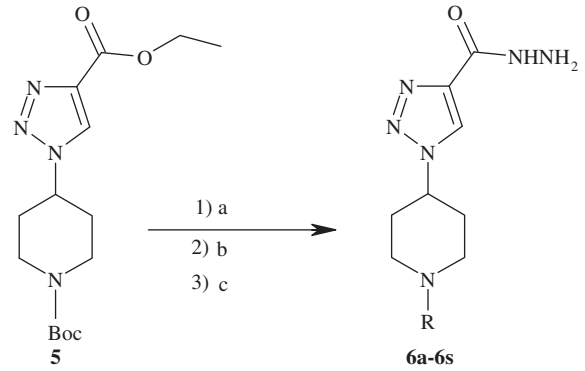
hydrazide, aromatic aldehyde in ethanol: water using sodium bisulfite as a catalyst. The synthesized compounds are novel and evaluated for in vitro antifungal activity.

The ester compound **5** was prepared from commercially available *N*-boc piperidone as described in our previously reported method (Scheme 1).[38d,e] Starting hydrazide compound has been prepared from ester compound **5** using hydrazine hydrate in methanol and further deprotection using trifluoroacetic acid. Deprotected hydrazide compound on alkylation or acylation in presence of triethylamine in tetrahydrofuran gave compounds **6a–6s** (Scheme 2).Corresponding hydrazide compounds and aromatic aldehydes were heated at 100 °C in ethanol–water (1:2) using 20 mol % $NaHSO_3$ to get the target compounds **8a–8s** (Scheme 3).

$NaHSO_3$ promotes the reaction of hydrazide with aromatic aldehyde with elimination of water molecule followed by cyclization to form substituted 1,3,4-oxadiazole.

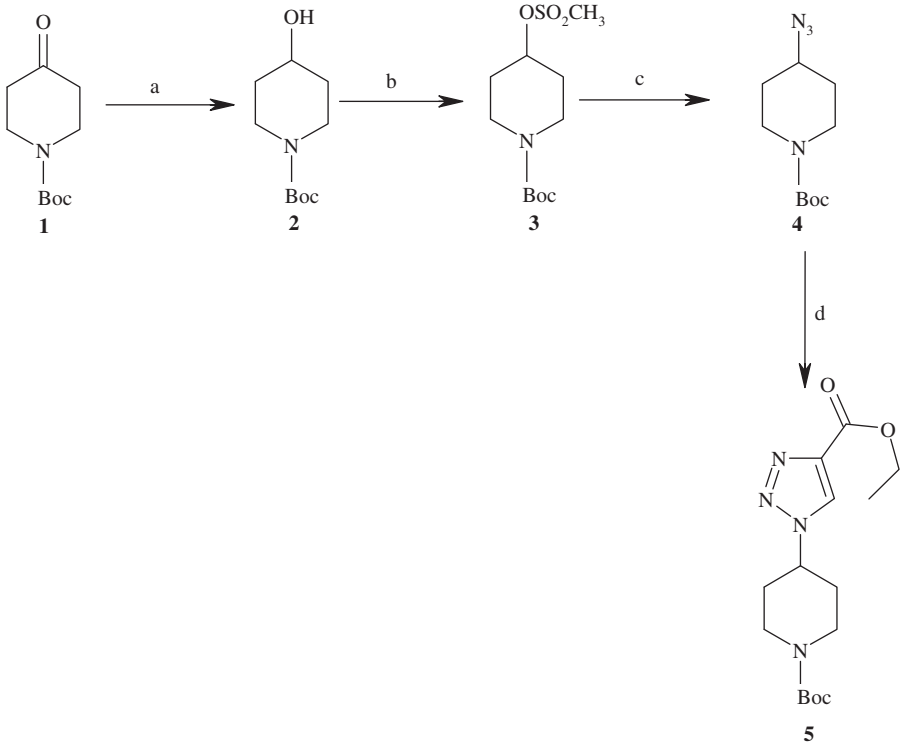
Catalytic property of $NaHSO_3$ has been studied considering synthesis of (**8a**). Effect of various solvents like *THF*, acetonitrile, ethanol have also been studied. Among the results obtained, use of 20-mol % $NaHSO_3$ in ethanol–water gave the better yield (95% and 91% using microwave and conventional method, respectively) for the synthesis of **8a** (Table 1). The use of environmental benign solvent such as water has got very much importance in 'Green Chemistry'. To study this aspect, the reaction was carried out for synthesis of **8a** using 20-mol % $NaHSO_3$ and corresponding substrates in water. The reaction was found to be sluggish and it may be due to the less solubility of substrates. To avoid this problem, the ethanol–water (1:2; v/v) solvent was used and found to be effective for synthesis of **8a**. The synthetic procedure was extended for synthesis of all the compounds **8a–8s** using different hydrazides, and aromatic aldehydes. Results are summarized in Table 2. The yields were obtained in the range of 87–91%. All synthesized derivatives were characterized using mass and ^1H NMR.



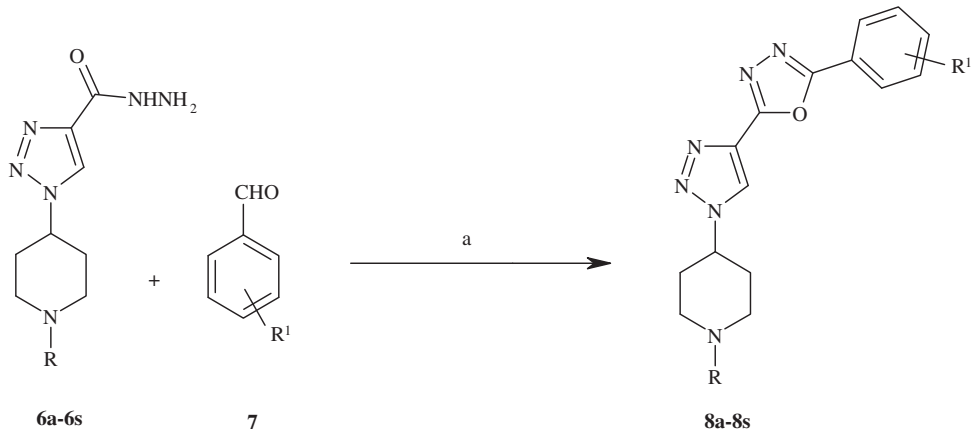
Scheme 2. Synthesis of hydrazide compounds (**6a–6s**) from compound **5**. (a) Hydrazine hydrate**,** methanol, reflux, 8 h; (b) TFA, dichloromethane, rt, 16 h; (c) triethylamine, R-X or RCOX, tetrahydrofuran, 0–5 °C to rt, 2.5 h.

All the synthesized compounds were screened for in vitro antifungal activity. The antifungal activity was evaluated against different fungal strains such as *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus, Aspergillus niger*, and *Cryptococcus neoformans*. Minimum inhibitory concentration (MIC) values were determined using standard agar method.[39] Miconazole and Fluconazole were used as a standard for the comparison of antifungal activity. Dimethyl sulfoxide was used as solvent control. MIC values of the tested compounds are presented in Table 3.

Many of newly synthesized compounds were found to show good antifungal activity. From the antifungal activity data (Table 3), it is observed that compound **8k** and **8n** are the most active among all tested compounds against most of the tested organisms. N-Protected compound with phenyl substituents at 5 position (**8a**) shows very less antifungal activity comparable to miconazole and fluconazole. Deprotected compound **8b** shows significant rise in activity



Scheme 1. Synthesis of compound **5** from *N*-Boc piperidone. (a) $NaBH_4$**,** ethanol, rt, 2 h; (b) methanesulfonyl chloride, triethylamine, dichloromethane; (c) NaN_3, DMF, 80 °C, 8 h; (d) ethyl propiolate, CuI, acetonitrile, rt, 12 h; (e) TFA, dichloromethane, rt, 14 h; (f) triethylamine, R-X or RCOX, tetrahydrofuran, 0–5 °C to rt, 2 h.



Scheme 3. Synthesis of 2-substituted phenyl-5-(1-(substituted piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)-1,3,4-oxadiazole. (a) Sodium bisulfite (20 mol %), ethanol–water (1:2), 100 °C, 9–10.5 h using conventional method and 10–15 min using microwave.

Table 1
Optimization of reaction conditions and the quantity of $NaHSO_3$ for the synthesis *tert*-butyl 4-(4-(5-phenyl-1,3,4-oxadiazol-2-yl)-1*H*-1,2,3-triazol-1-yl)piperidine-1-carboxylate (**8a**)

Solvent	Mol of $NaHSO_3$	Microwave		Conventional	
		Reaction time (min)	Yield[a] (%)	Reaction time (h)	Yield[a] (%)
THF	20	30	72	20	68
Acetonitrile	20	30	75	18	74
Dichloromethane	20	40	70	14	70
Ethanol	20	10	95	09	91
Ethanol–water (1:2)	20	10	95	09	91
Ethanol–water (1:2)	10	20	88	12	79
Ethanol–water (1:2)	5	30	76	15	72

[a] Yields refer to the isolated pure products.

compared to **8a**. Substitution of methyl group (**8c**) on piperidine nitrogen increases the antifungal activity compared with unsubstituted nitrogen (**8b**). Substitution of ethyl group (**8d**) on nitrogen further enhance activity against *C. albicans* and *F. oxysporum* whereas there is no effect on activity against *A. niger* and *A.* flavus and as evidenced by same MIC. Introduction of mesyl group on nitrogen (**8e**) increases the antifungal activity by 2–3-fold compared with unsubstituted piperidine against all tested organisms. Introduction of benzoyl group on nitrogen (**3f**) shows significant loss of activity compared with unsubstituted nitrogen. No activity was reported up to 200 μg/mL against *C. albicans*. Introduction of Cl group at *p* position of Phenyl of benzoyl (**8g**) shows slight increase in the antifungal activity compared with unsubstituted benzoyl.

Introduction of –Cl group on 5 phenyl (**8h–8k**) shows increase in activity against all tested organisms except *C. neoformans* compared to compounds with unsubstituted 5 phenyl group.

Table 2
Experimental data of the synthesized compounds **8a–8s**

Entry	R	R_1	Microwave		Conventional		Molecular formula/molecular weight
			Time (min)	Yield[a]	Time (h)	Yield[a]	
8a	–Boc	–H	10	95	09	91	$C_{20}H_{24}N_6O_3$ 396
8b	–H	–H	10	91	09	88	$C_{15}H_{16}N_6O$ 296
8c	$-CH_3$	–H	12	94	9.5	91	$C_{16}H_{18}N_6O$ 310
8d	$-CH_2CH_3$	–H	15	91	10	87	$C_{17}H_{20}N_6O$ 324
8e	$-SO_2CH_3$	–H	12	95	09	91	$C_{16}H_{18}N_6O_{8s}$ 374
8f	$-COC_6H_5$	–H	12	90	9.5	88	$C_{22}H_{20}N_6O_2$ 400
8g	$-COC_6H_5$, 4 Cl	–H	12	94	9.5	90	$C_{22}H_{19}$ Cl N_6O_2 434
8h	$-CH_3$	–Cl	10	94	09	89	$C_{16}H_{17}$ Cl N_6O 344
8i	$-CH_2CH_3$	–Cl	15	92	10	87	$C_{17}H_{19}$ Cl N_6O 358
8j	$-COCH_3$	–Cl	10	92	9.5	88	$C_{17}H_{17}$ Cl N_6O_2 372
8k	$-SO_2CH_3$	–Cl	10	94	9	90	$C_{16}H_{17}$ Cl N_6O_{8s} 408
8l	$-CH_3$	–OH	15	95	10	89	$C_{16}H_{18}$ N_6O_2 327
8m	$-CH_2CH_3$	–OH	15	92	10	87	$C_{17}H_{20}N_6O_2$ 341
8n	$-SO_2CH_3$	–OH	15	95	10	90	$C_{16}H_{18}N_6O_4S$

Table 2 (*continued*)

Entry	R	R_1	Microwave		Conventional		Molecular formula/molecular weight
			Time (min)	Yield[a]	Time (h)	Yield[a]	
8o	$-CH_3$	$-OCH_3$	15	92	10	89	390 $C_{17}H_{20}N_6O_2$
8p	$-CH_2CH_3$	$-OCH_3$	15	90	10.5	88	340 $C_{18}H_{19}ClN_6O_2$
8q	$-SO_2CH_3$	$-NO_2$	15	95	10	90	354 $C_{16}H_{17}N_7O_5S$
8r	$-COCH_3$	$-CH_3$	15	92	10	89	419 $C_{18}H_{20}N_6O_2$
8s	$-COC_6H_5$	$-CH_3$	15	92	10	87	352 $C_{23}H_{22}N_6O_2$
							414

[a] Yields refer to the isolated pure products.

Table 3
Antifungal activity of the synthesized compouunds

Compound	MIC values (μg/mL)[a,b]				
	C. albicans	*F. oxysporum*	*A. flavus*	*A. niger*	*C. neoformans*
8a	100 ± 2.88	125 ± 0.577	100 ± 2.886	150 ± 2.886	a
8b	80 ± 1.443	85 ± 0.2.886	90 ± 0.577	125 ± 2.886	150 ± 2.886
8c	70 ± 2.886	70 ± 1.443	60 ± 0.577	80 ± 1.443	90 ± 2.886
8d	55 ± 2.886	50 ± 1.443	60 ± 1.443	80 ± 2.500	80 ± 2.500
8e	35 ± 1.443	40 ± 0.2.886	45 ± 0.577	40 ± 2.886	55 ± 2.886
8f	a	100 ± 2.500	150 ± 1.154	175 ± 1.443	a
8g	150 ± 2.886	90 ± 2.500	90 ± 1.443	100 ± 1.154	a
8h	55 ± 1.443	50 ± 1.154	40 ± 1.154	45 ± 2.500	150 ± 2.886
8i	40 ± 1.154	35 ± 2.500	25 ± 2.886	50 ± 1.154	50 ± 1.154
8j	35 ± 1.443	30 ± 2.500	20 ± 0.577	25 ± 1.443	a
8k	25 ± 1.154	25 ± 1.443	15 ± 1.443	20 ± 2.500	50 ± 2.500
8l	40 ± 1.443	35 ± 2.500	25 ± 1.443	35 ± 2.886	a
8m	35 ± 1.443	35 ± 1.154	20 ± 1.154	20 ± 2.500	60 ± 2.886
8n	30 ± 2.886	25 ± 2.500	15 ± 2.886	15 ± 2.886	100 ± 1.443
8o	60 ± 2.886	65 ± 1.443	50 ± 2.886	70 ± 2.500	80 ± 2.500
8p	50 ± 1.154	60 ± 1.443	50 ± 1.443	75 ± 2.886	100 ± 2.886
8q	40 ± 1.154	55 ± 1.154	50 ± 2.886	70 ± 2.500	90 ± 1.443
8r	45 ± 1.154	40 ± 1.154	35 ± 2.500	40 ± 2.886	a
8s	a	100 ± 2.500	150 ± 1.154	a	a
Miconazole	25 ± 2.886	25 ± 1.443	12.5 ± 1.443	12.5 ± 1.443	25 ± 2.886
Fluconazole	5 ± 2.500	5 ± 1.154	5 ± 1.154	10 ± 2.500	5 ± 2.500

[a] No activity was observed up to 200 μg/mL.
[b] Values are the average of three readings ± standard deviation.

Compound **8k** with methyl sulfone group on piperidine nitrogen and –Cl group on 5 phenyl substituents shows better activity. Compound **8k** was equipotent with miconazole against *F. oxysporum* and *C. albicans*.

Introduction of –OH group on 5 phenyl (**8l**–**8n**) shows increase in activity against all tested organisms except *C. neoformans* compared to compounds with unsubstituted 5 phenyl group. Compound **8n** with methyl sulfone group on piperidine nitrogen and –OH group on 5 phenyl substituents shows better activity. Compound **8n** was equipotent with miconazole against *F. oxysporum* Activity of **8n** was comparable with miconazole against*C. albicans, A. flavus,* and *A. niger*.

Introduction of $-OCH_3$ group on 5 phenyl (**8o**–**8p**) shows increase in activity against all tested organisms except *C. neoformans* compared to compounds with unsubstituted 5 phenyl group.

Introduction of $-NO_2$ group on 5 phenyl (**8q**) shows decrease in activity against all tested organisms except *A. niger* compared to compounds with unsubstituted 5 phenyl group.

Introduction of CH_3 group on 5 phenyl (**8r**) shows decrease in activity against *C. albicans, A. flavus* and *A. niger* compared to compound with Cl substituted 5 phenyl group (**8j**). Compound from same series with benzoyl group on piperidine nitrogen (**8s**) shows very less antifungal activity.

From activity it is observed that introduction of mesyl on piperidine nitrogen along with introduction of chloro and hydroxyl group on phenyl serves as an important arrangement to give the most active compounds from series.

In conclusion, we have first time demonstrated use of sodium bisulfite for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole from hydrazides and aromatic aldehydes using conventional as well as microwave synthesis in good yield. Also all the synthesized compounds are novel with 1,2,3-triazolo piperidine scaffold. All the synthesized compounds were tested for in vitro antifungal activity. Based on the activity data, SAR for the series has been developed. From the series **8k** and **8n** can serve as an important pharmacophore for the design and development of new lead as antifungal agent.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.10.120.

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