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A new and efficient method for the synthesis of 2-N-(aryl)-1,3,4-oxadiazole-2,5-diamine derivatives

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Abstract We report a series of cyclic analogues of 2,5-diamino-1,3,4-oxadiazoles which were prepared in a simple and general protocol. This method involves easy cyclisation of N-(aryl)-1,2-hydrazinedicarboxamides and mediated by tosylchloride/pyridine in ethanol (solvent) under a reflux condition (79–80 °C), over a time period of 20 h. We prepared different examples in a higher range of yields (80–98 %) by using this protocol.

Keywords Cyclisation · Heterocycles · Heteroatom · Synthesis · Diamino oxadiazoles · Reaction mechanism

Introduction

Heterocyclic compounds represent a huge family of biologically active organic molecules which have attracted the supreme attention of chemists throughout the world [1–3]. A majority of marketed drugs have included heterocyclic entities, highlighting their key roles in medicinal chemistry. In specific, the improvement of an efficient and practical synthesis of 2,5-disubstituted-1,3,4-oxadiazoles is an

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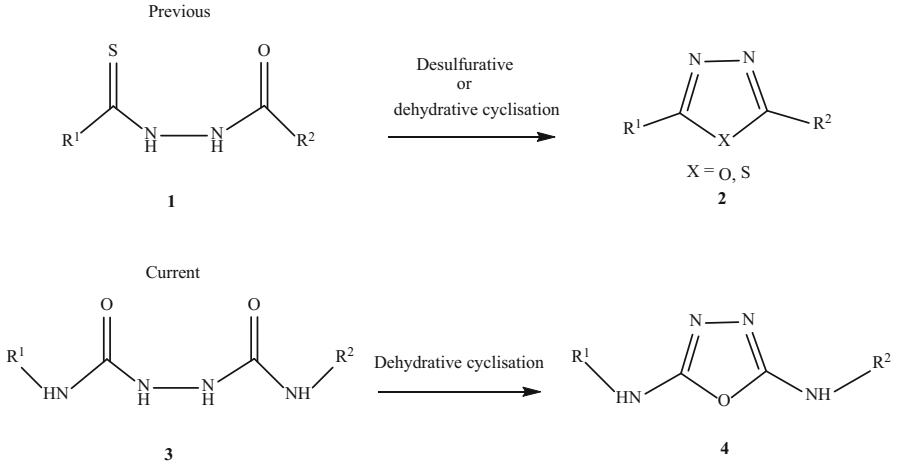
active subject of current organic research. In the course of our research, we became interested in 1,3,4-oxadiazoles as they are rousing and versatile building blocks with a wide range of biological activities, including the following: antibacterial, antiviral, anti-inflammatory, antitubercular, antipyretic, anticancer, central nervous system depressant, antischistosomal, diuretic, analgesic, anticonvulsive and antiemetic properties in the literature [4, 5]. The well-known use of 1,3,4-oxadiazole derivatives as a scaffold in modern medicinal chemistry [6], as verified by these specimens, establishes this moiety as a member of the prosperous structures course. Nevertheless, apart from their common use, procedures based on dehydrative cyclisation (Scheme 1) of semicarbazides are often used and remarkably involve tough reagents such as concentrated sulfuric acid [7, 8] or phosphoryl chloride ($POCl_3$) [9]. On the other hand, reagents that primarily initiate one carbonyl group for backing cyclization have been used. The outcomes of these particular reagents, including Burgess-type [10, 11] reagents and phosphonium salts, in inflexible byproduct materialization, conversely, have generally been limited to usage in solid-phase synthetic strategies. Recently, the Boger group [12, 13] reported an exciting method to synthesize 2-amino-[1,3,4]-oxadiazoles via the dehydrative cyclisation of a semicarbazide substrates mediated by tosyl chloride and a base at conventional room temperature [14, 15]. We have been paying attention to this methodology due to the low price of reagents and mild reaction conditions. Typically, 2,5-diamino-[1,3,4]oxadiazole derivatives are prepared by cyclization of the corresponding acyclic hydrazine-1,2-dicarboxamide substrates, semicarbazides and thiosemicarbazides [16]. We have a current interest in the development of novel strategies to access functionalized oxadiazoles. In an effort to chemically sew up these biologically active heterocycles, we sought to develop a synthesis of 2,5-diamino substituted-[1,3,4]-oxadiazoles as a major skeleton. Experimental charts for cyclisation reactions are shown in the supporting information, S1–S11, and are explained in the experimental section.



Scheme 1 Dithiocarbazate using for cyclisation of [1,3,4]-oxadiazole (**1**) and hydrazine-1,2-dicarboxamide (**3**)

Experimental

All commercially available reagents and solvents were obtained from the commercial suppliers and used without further purification. All these cyclization reactions were conducted in a 50-mL round-bottomed Pyrex glass flask under N_2 atmosphere with continuous and constant stirring speed at 900 rpm. Thin layer chromatography (TLC) was implemented on silica gel plates. Flash column chromatography was performed using 300–400 mesh silica gel. Visualization via TLC was achieved by illumination under an ultraviolet (UV) lamp (254 nm). Nuclear magnetic resonance (NMR) spectra were recorded on a 400-MHz spectrometer for ^{1}HNMR and 100 MHz for ^{13}C NMR in deuterated dichloro dimethyl silane (DMSO-d_6) or deuterated chloroform ($CDCl_3$) at room temperature; tetramethylsilane (TMS) served as an internal standard. High-resolution mass spectrometry (HRMS) was recorded. Some substrates were prepared according to the known experimental procedures [17–32] with petty modification.

General procedure for intramolecular cyclisation

We mixed hydrazine-1,2-dicarboxamide (17.3 mmol, 2.045 equiv), 4-methylbenzenesulfonyl chloride (10.7 mmol, 1.0 equiv), pyridine (36.45 mmol, 2.10 equiv) in ethanol (20 mL) under a nitrogen atmosphere in a 50-mL round bottom flask which was well purged by nitrogen with a neat and clean condenser and magnetic stir bar (900 rpm). The reactor was well bottomed by oil bath. The reaction mixture was then heated at the required reflux temperature (79–80 °C) until the required time (20 h) to complete the reaction. TLC was checked until the absence of starting substrates hydrazine-1 and 2-dicarboxamide derivatives in the product [TLC, mobile phase ethyl acetate (EtOAc) (5): *n*-Hexane (5)], and also until the reaction was adjudicated complete by liquid chromatography-mass spectrometry (LC–MS) analysis, after which the reaction mixture was allowed to cool to room temperature. EtOAc (10 mL) and brine solution (10 mL) were added to the mixture, which was vigorously stirred for 5 min; then, the aqueous layer was removed. The removed aqueous layer was again extracted with EtOAc (10 mL), and then the combined organic layers were flushed with *n*-octane (2 × 25 mL) and the material was concentrated to a yellowish slurry. The material was dissolved in 10 mL of ethanol (EtOH) and filtered. We then added 15 mL of diethyl ether to this mixture and stirred for 15 min at room temperature; a thin slurry was obtained. The slurry was filtered to produce 1.75 g of glittery white powder (85.3 % yield). The products were characterized by ^{1}H, ^{13}C NMR, and HRMS.

^{1}H NMR, ^{13} C NMR, MASS (m/z) spectra data for some selected compounds

2-N-(4-Methoxyphenyl)-1,3,4-oxadiazole-2,5-diamine **(4b):** White semisolid, m.p. 238-240 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 3.7 (s, 3H, 1 × OCH_3), 5.2 (brs, 3H, 3 × Ar–NH), 6.60-7.00 (m, 4H, 4 × Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.1,115.01, 115.03, 122.01, 122.03, 132.01, 153.30, 169.02, 169.04; HRMS (ESI) calcd for $[C_9H_{11}N_4O_2]^{+}$: 207.0877. Found: 207.0868.

2-N-(4-Methyphenyl)-1,3,4-oxadiazole-2,5-diamine **(4c):** Solid, m.p. 240-241 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.3 (s, 3H, 1 × CH_3), 5.0 (brs, 3H, 3 × Ar–NH), 7.40 (m, 4H, 4 × Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.02, 120.0, 120.01, 130.05, 131.00, 135.00, 153.3, 168.01, 169.03; HRMS (ESI) calcd for $[C_9H_{11}N_4O]^+$: 191.0927. Found: 191.037.

2-N-(phenyl)-1,3,4-oxadiazole-2,5-diamine **(4d):** Yellow semisolid, m.p. 235–240 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.0 (brs, 3H, 3 × Ar–NH), 7.0–7.5 (m, 5H, 5 × ArH).^{13}C NMR (100 MHz, DMSO-d_6) δ 116.01, 117.00, 129.0, 137.50, 168.0, 168.01; HRMS (ESI) calcd for $[C_8H_9N_4O]^+$: 177.0771. Found: 177.0740.

2-N-(2-methoxyphenyl)-1,3,4-oxadiazole-2,5-diamine **(4e):** White solid, m.p. 270–272 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.8 (s, 3H, 1 × OCH_3), 5.45 (brs, 3H, 3 × Ar–NH), 7.680 (m, 4H, 4 × Ar–H); HRMS (ESI) calcd for $[C_9H_{11}N_4O_2]^+$: 207.0859. Found: 207.0865.

2-N-(2,6-dimethoxyphenyl)-1,3,4-oxadiazole-2,5-diamine **(4f):** White, shiny solid, m.p. 242 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 3.8 (s, 3H, 1 × OCH_3), 3.90 (s, 3H, 1 × OCH_3), 5.50 (brs, 3H, 3 × Ar–NH), 7.50 (m, 3H, 3 × Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.01, 55.02, 105.01, 105.02, 130.05, 146.0, 146.01, 169.01, 169.03; HRMS (ESI) calcd for $[C_{10}H_{13}N_4O_3]^+$: 237.091. Found: 237.100.

2-N-(3-chlorophenyl)-1, 3, 4-oxadiazole-2, 5-diamine **(4g):** Pale yellow solid, m.p. 270–271 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 5.00 (brs, 3H, 3 × Ar–NH), 7.40 (m, 3H, 3 × Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.70, 116.00, 121.90, 129.00, 135.00, 143.00,169.00, 169.02; HRMS (ESI) calcd for $[C_8H_8ClN_4O]^+$: 211.6209. Found: 211.6219.

2-N-(4-bromoophenyl)-1, 3, 4-oxadiazole-2, 5-diamine **(4 h):** White solid, m.p. 240-245 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.50 (brs, 3H, 3 × Ar–NH), 7.40 (m, 4H, 4 × Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 114.90, 117.80, 117.90, 129.00, 129.02, 143.01, 169.01, 169.02; HRMS (ESI) calcd for $[C_8H_8BrN_4O]^+$: 256.0711. Found: 256.0658.

2-N-(4-fluorophenyl)-1,3,4-oxadiazole-2,5-diamine **(4i):** Pale yellow solid, m.p. 265–269 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 5.00 (brs, 3H, 3 × Ar–NH), 7.70–7.80 (m, 3H, 3 × Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11,700, 118.00, 123.91, 124.00, 141.80, 155.00, 169.00, 169.01; HRMS (ESI) calcd for $[C_8H_8FN_4O]^+$: 195.0456. Found: 195.0438.

2-N-(4-nitroophenyl)-1,3,4-oxadiazole-2,5-diamine **(4j):** Shiny white powder, m.p. 276 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.40 (brs, 3H, 3 × Ar–NH), 7.60–7.80 (m, 3H, 3 × Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 119.01, 119.04, 124.40, 124.50, 137.00, 145.00, 170.00, 170.02; HRMS (ESI) calcd for $[C_8H_8N_5O_3]^+$: 222.0681. Found: 222.0701.

2-N-[4-(N,N-Dimethyl)phenyl]-1,3,4-oxadiazole-2,5-diamine **(4k):** Semisolid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.8 (s, 6H, 2 × NCH_3), 5.40 (brs, 3H, 3 × Ar–NH),

Table 1 Optimization of reaction conditions for the synthesis of 2,5-diamine-[1,3,4]-oxadiazole (**4a–p**)

Entry	Reagent (equiv)	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	
					4a	5
1	DCC	THF	70	12	15	>4
2	EDC.HCl	THF	70	12	20	>6
3	TsCl/pyridine	THF	70	24	70	0
4	TsCl/TEA	THF	70	24	50	>4
5	TsCl/pyridine (1.0/2.1)	EtOH	79	20	98	0
6	TsCl/TEA (1.0/2.1)	EtOH	80	24	60	>4
7	TMSCl	DCE	60	24	80	>5
8	TsCl	EtOH	80	20	23	5
9	TsCl/pyridine (1.0/2.1)	Toluene	110	20	12	>5
10	TsCl/pyridine (1.0/2.1)	THF	70	20	65	>4
11	TsCl/pyridine (1.0/2.1)	MeOH	60	20	70	>5
12	TsCl/K_2CO_3 (1.0/2.1)	DCE	60	20	10	>6
13	DCC/pyridine (1.0/2.1)	DMSO	80	20	19	>5
14	TsCl/pyridine (1.0/2.1)	$CHCl_3$	80	20	10	>5
15	BF_3.etherate	EtOH	80	20	0	
16	No Reagent	EtOH	80	20	0	
17	TsCl/pyridine (2.0/4.5)	EtOH	80	20	70	15
18	TsCl/pyridine (2.3/5.0)	EtOH	80	20	65	17
19	TsCl/pyridine (3.0/6.0)	EtOH	80	20	50	>20
20	TsCl/pyridine (4.0/7.0)	DMF	140	5	0	75

[a] Conversion rate and isolated yields were based on a GC monitoring

7.4 (d, *J* 8.1 2H, 2 × Ar–H), 7.8 (d, *J* 8.3, 2H, 2 × ArH); ^{13}CNMR (100 MHz, DMSO-d_6) δ 40.00,40.01,113.00, 113.03, 119.0, 119.04, 144.91, 145.70, 168.02, 168.04; HRMS (ESI) calcd for $[C_{10}H_{14}N_5O]^+$: 220.0203. Found: 220.0303.

2-N-[4-hydroxyphenyl]-1,3,4-oxadiazole-2,5-diamine **(4 l):** White powder, m.p. 278 °C. HRMS (ESI) calcd for $[C_8H_9N_4O_2]^{+:}$ 193.1430. Found: 193.1406.

2-N-[3,5-dimethylphenyl]-1,3,4-oxadiazole-2,5-diamine **(4m):** Semisolid. HRMS (ESI) calcd for $[C_{10}H_{13}N_4O]^+$: 205.3016. Found: 204.3028.

2-N-(2-methylphenyl)-1,3,4-oxadiazole-2,5-diamine **(4n):** White solid, m.p. 280–281 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 2.3 (s, 3H, 1 × $ArCH_3$), 5.50 (brs, 3H, 3 × Ar–NH), 7.4–7.6 (m, 4H, 4 × Ar–H); HRMS (ESI) calcd for $[C_9H_{11}N_4O]^+$: 191.0911. Found: 191.0919.

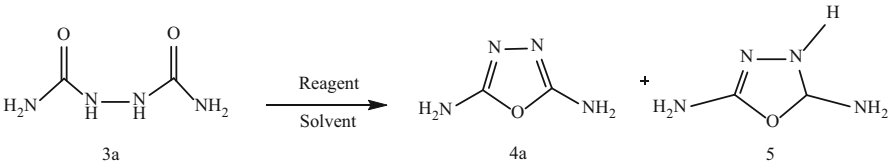
2-N-(2-chlorophenyl)-1,3,4-oxadiazole-2,5-diamine **(4o):** White solid, m.p. 269–273 °C. HRMS (ESI) calcd for $[C_8H_8ClN_4O]^+$: 211.0124. Found: 211.0113.

2-N-(2-fluorophenyl)-1,3,4-oxadiazole-2,5-diamine **(4p):** Semisolid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.50 (brs, 3H, J 7.8, 3 × Ar–NH), 7.25-7.75 (m, 4H, 4 × Ar–H); HRMS (ESI) calcd for $[C_8H_8FN_4O]^+$ 195.1703. Found: 195.1806.

Results and discussion

Initially N,N'-(aryl substituted)hydrazine-1,2-dicarboxamide (3a) was chosen as a model substrate for the optimization of dehydrative-cyclisation environs. As depicted in Table 1 (Scheme 2), a range of selected reagent systems were evaluated as careful cyclisation conditions in the presence of different solvents. Our results indicate that the catalyst systems, such as N,N'-dicyclohexylcarbodiimide (DCC), 3-(ethyliminomethyleneamino)-N,N-dimethylpropan-1-amine (EDC.HCl), trimethylsilylchloride (TMSCl), boron trifluoride ethyl etherate (BF_3.etherate) and p-toluenesulfonyl chloride (TsCl) all have the capacity to catalyze the dehydrative cyclisation process quite efficiently at 1.0 equivalents. Among the various dehydrating conditions, DCC and EDC.HCl were found to be least effective for the cyclisation of hydrazodicaboxamides under these conditions (Table 1, entries **1** and **2**). It is worth mentioning that, along with cyclized 1,3,4-oxadiazole **(4a)**, the product 2,3-dihydro-[1,3,4]-oxadiazole-2,5-diamine (5) from 3a regularly looked as a side product in many of these reactions. Reports in the literature suggest compound **4a** is quite commonly the preferred product in the presence of week basic conditions. Among these twenty various (Table 1) selected reagent systems tested, TsCl-pyridine/EtOH appeared the most effective in producing **4a** in higher yields. Thus, we established TsCl as the prominent reagent of choice based on its efficiency, cost effectiveness, and environmentally benign nature. We then continued to further optimize the reagent loading and solvent screening for the dehydrative cyclisation reaction. On increasing the amount of TsCl-pyridine (in equivalents) from 2.0/4.5 to 4.0/7.0 led to a slight decrease in the yield of **4a**, and an increase in the yield of compound 5 (Table 1, entries **17-20**, Scheme 2). On the other hand, when the amount of reagent system was reduced to 1.0/2.1 (TsCl-pyridine), compound 4a formed exclusively (98 %) without any discovery of compound 5 under these conditions (Table 1, entry 5). Moreover, in the absence of tosylchloride-pyridine/EtOH, the formation of **4a** did not take place at all (Table 1, entry 15, Scheme 2). This suggests the presence of the basic condition such as tosylchloride/pyridine was essential for the dehydrative cyclisation of 3a to takes place.

With the superlative reagent system picked, we subsequently investigated the effect of solvents on dehydrative cyclisation of **3a**. It was discovered that a change in solvent has an intensive impact on the reaction outcome. A cleaner conversion of 3a to 4a was observed in ethanol, affording **4a** at a 98-% yield, however, the required reaction time took 20 h (Table 1, **entry 5,** Scheme 2). The desired cyclisation reaction rate seems to be quite lethargic in nonpolar solvent, such as toluene. Use of organic solvents (tetrahydrofuran, methanol and ethanol) mainly resulted in the formation of compound 4a after a significantly longer time (Table 1, entries **5, 10 and 11**). The commonly presented oxygen (the second most highly electronegative element in the periodic table) in ethanol, methanol and tetrahydrofuran could



Scheme 2 Cyclization of hydrazine-1,2-dicarboxamide for various conditions

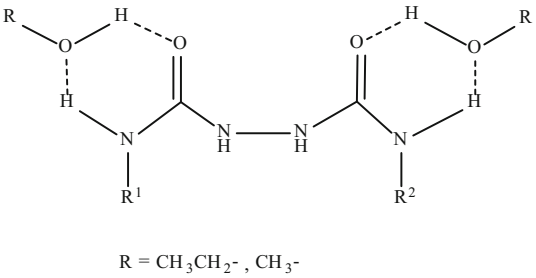


Fig. 1 Formation of cyclic, six-membered rings through intermolecular hydrogen bonding

increase the viscosity of the reaction mixture by forming strong interactions with the terminal amines of substrates through intermolecular hydrogen bonds to avoid any unwanted reaction centers, which results in the retention of terminal amino groups in the final product (Fig. 1). Something interesting, an exclusive formation of 5 was observed in DMF just after 5 h of reflux (Table 1, **entry 20**, Scheme 2). Reducing the reaction temperature results in slowing of the reaction rate along with a negotiated yield. Thus, after broad investigation, we concluded the best yield of 4a (98 %) was obtained with TsCl-pyridine (1.0-2.1 equivalents)/ethanol 80 °C under reflux (Table 1, **entry 5**, Scheme 2). These conditions were found to be superior compared to conventional microwave irradiative cyclizations [33, 34]. Next, in order to demonstrate the substrate choice and functional group acceptance, we selected sixteen disubstituted-1,3,4-oxadiazoles (4a–p) in this present study (1-NMR and ^{13}CNMR analyses were conducted for selected compounds and presented in the supporting information **S1–S11**).

After possessing all the wanted hydrazodicaboxamides in our hands, we set out to explore the opportunity of our cyclisation methodology in detail. A significant substitution effect was observed on the reactivity of substrates towards the cyclisation protocol (Table 2; Scheme 3). In general, the electron-donating groups facilitated the reaction (80–90 %), while the electron-withdrawing [30–33] substituents declined the reactivity of N-(ortho or meta or para substituted aryl rings)-hydrazine-1, 2-dicarboxamide towards this reaction (10–20 %). Higher temperatures (100–110 °C) and longer reaction times were required to promote this cyclisation reaction of hydrazodicabonamides bearing electron-withdrawing groups (Table 2, entries **3g-3k, 3o, and 3p**). In the cases of aryl-hydrazodicabonamides having electron-donating substituents [31–34], enhanced yields were

Table 2 Cyclisation of N-(aryl)-1, 2-hydrazinedicarboxamides to 2-N-(aryl)-1, 3, 4-oxadiazole-2, 5-diamine

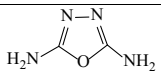
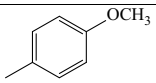
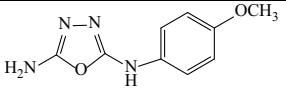
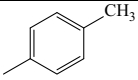
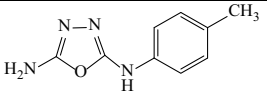
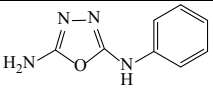
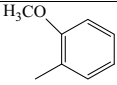
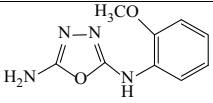
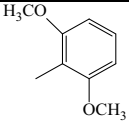
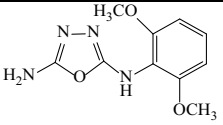
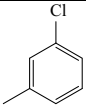
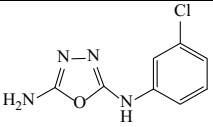
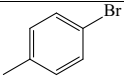
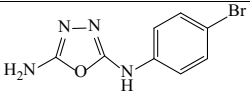
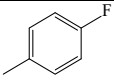
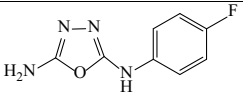
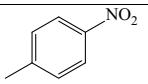
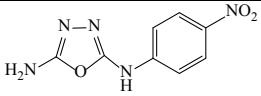
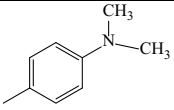
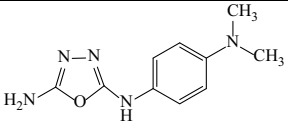
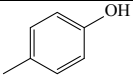
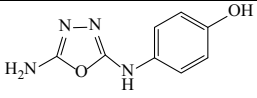
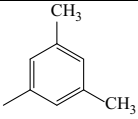
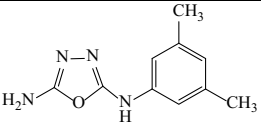
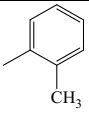
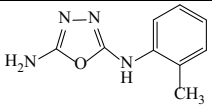
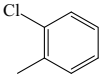
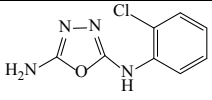
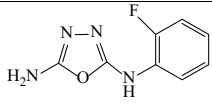
Entry	R^1	R^2	Product	Conversion[a] (%)	Yield (%)[b]
3a	H	H	 **4a**	93	90
3b	H		 **4b**	99	98
3c	H		 **4c**	97	91
3d	H		 **4d**	96	90
3e	H		 **4e**	97	92
3f	H		 **4f**	90	86
3g	H		 **4g**	80	77
3h	H		 **4h**	87	83
3i	H		 **4i**	89	80

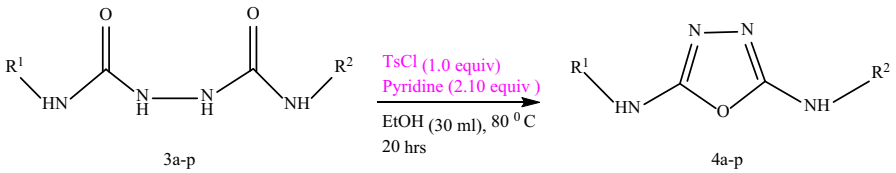
Table 2 continued

Entry	R^1	R^2	Product	Conversion[a] (%)	Yield (%)[b]
3j	H		 **4j**	96	89
3k	H		 **4k**	98	89
3l	H		 **4l**	97	94
3m	H		 **4m**	99	97
3n	H		 **4n**	94	90
3o	H		 **4o**	87	80
3p	H		 **4p**	86	80

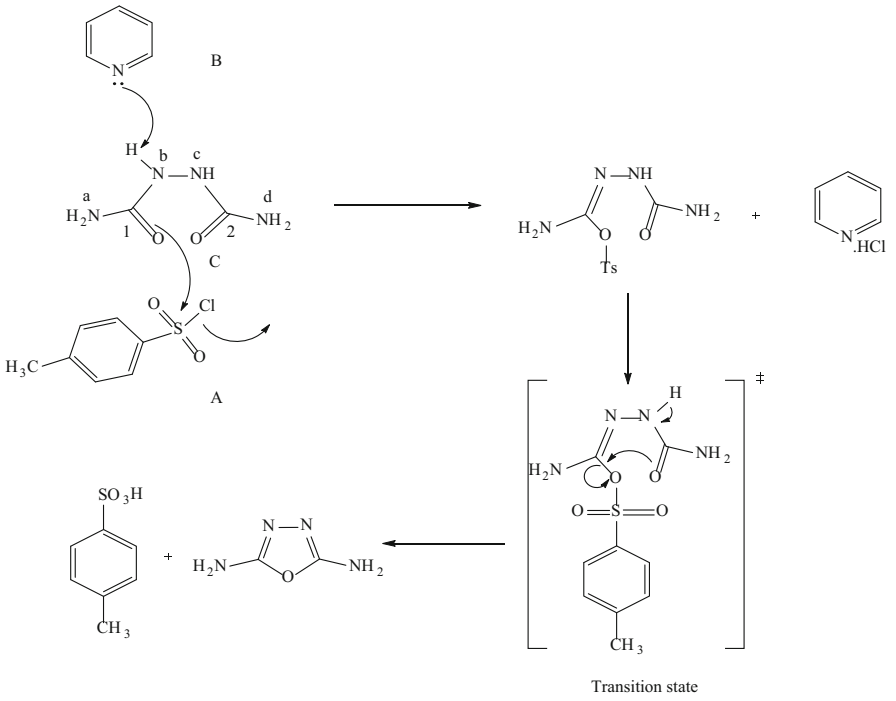
[a,b] Conversion rate and isolated yields were based on the GC monitoring

about 90–98 %, rather a loss in yield with the formation of minor amounts of product 2, 3-dihydro-1, 3, 4-oxadiazole-2, 5-diamine (5) was observed.

Consistent with previous reports [35], we propose the mechanism (Scheme 4) for the formation of 2,5-diamino-[1,3,4]-oxadiazole to be similar to the H.Gehlen



Scheme 3 Synthesis of 2-N-(aryl)-1,3,4-oxadiazole-2,5-diamine



Scheme 4 A plausible mechanism for the formation of 2,5-diamino-1,3,4-oxadiazole (4a)

cyclisation reaction [36]. Initially, pyridine (B) attacks one of the acidic protons of nitrogen (b) in hydrazine-1,2-dicarboxamide (C) followed by a migration of double-bond electrons of carbonyl oxygen (1) C (see Scheme 4) on to the tosyl cation (A) resulting in the formation of tosylated-hydrazine-1,2-dicarboxamide and pyridinium salt of hydrogen chloride (Scheme 4). This was further cyclised by the removal of an acidic proton from nitrogen (c), an internal attack of double-bonded electrons of a second carbonyl oxygen (2) in C (Scheme 4) onto the first carbonyl carbon in C (Scheme 4) and thereafter the removal of p-toluenesulfonic acid takes place, respectively, which resulted in the desired product 2, 5-diamino-[1,3,4]-oxadiazole via a transition state (Scheme 4).

In summary, we reported one-pot synthesis of 2,5-disubstituted analogues to cyclic 2,5-diamino-[1,3,4]-oxadiazoles from simple and readily available inputs

under mild reaction conditions. The flexibility of one-pot cyclic reactions provided a series of new organic molecules in good yields, considering their molecular difficulty, in approximately 20-24 h under smooth conditions. This procedure can be extended to prepare other amines, making it a very useful methodology.

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