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Research Article

OXIDATIVE CYCLISATION BASED ONE-POT SYNTHESIS OF 1, 3, 4 OXADIAZOLE DERIVATIVES USING Me_4NBR/OXONE

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ABSTRACT

One-pot syhthesis of 1, 3,4 oxadiazole is described. This protocol significantly involves to synthesize 1, 3, 4 oxadiazole motif through oxidative cyclization with the assistance of Me_4NBr and oxone mixture. This one-pot procedure is an efficient method and is able to tolerate wide range of functional groups.

Keywords: 1, 3,4-oxadiazole, Tetramethylammonium bromide, Oxone, Aromatic Aldehyde

1. INTRODUCTION

Hetero aromatic system is an important pharmacore of any active drug molecule. It plays a significant role in modern medicinal chemistry and drug discovery since it provides similarity with respect to the biologically active compounds present in our body for instance nucleic acids, hormones, neurotransmitters etc. Among all hetrocycles, oxadiazole is an important structural motif of many paharmectical ingredients. In particular, the derivatives 1,3,4 oxadiazole have extensively studied in the past few decades due its thermal stability and immense applicability[1]. Among all other isomeric motif, 1,3,4 oxadiazoles exhibits wide range of biological application including antibacterial [2], antitubercular [3], vasodialatory [4], antifungal [5], cytotoxic [6], anti-inflammatory and analgesic [7, 8] hypolipidemic [9] anticancer [10] , ulcerogenic [11], pesticidal [12] , anti-peripheral vasomotility [13], CNS stimulant, anti-inflammatory, hypotensive [14], insecticidal [15], bactericidal [16], analgesic, anticonvulsive, antiemetic, diuretic [17], hypoglycemic [18], muscle relaxant [19], herbicidal [20, 21] and fungicidal activity [22, 23].

In the view of literature, several methods for the preparation of 1,3,4-oxadiazole derivatives and its fused ring systems have been briefly described. Most popularly, the construction of 1,3,4-oxadiazole is employing an acid hydrazide reaction with carbondisulphide and potassium hydroxide [23].

However, conventionally, in order to access 1,3,4 oxadiazoles, several cyclodehydrating agent such as phosphorus oxychloride, polyphosphoric acid, acetic anhydride etc. have been suceesfully used [24-29]. In addition, oxidative cyclisation is one of most emerging route to synthesis 1,3,4 oxadiazole derivatives. Recently, Sowjanya *et al* [30] and Srivastava *et al* [31] have reported the oxidative cyclisation of aryl aldehyde with semicarbazide using bromine in acetic acid. However this protocol suffers from the disadvantages such as the requirement of stiochiometric amount of reagents and the employment of hazardous materials or metal reagents. Further the intermediate hydrazone needs to be isolated and then purified prior to oxidative cyclization. Thus, it is highly desirable to find a new reagent which should be non-toxic and metal-free. Furthermore, one-pot protocol is more convenient since it avoids the unnecessary work up and purification of the intermediate. Although considerable attention has been paid to synthesis of 1,3,4 oxadiazole using various reagent, the utilisation of Me_4NBr/oxone for constructing 1,3,4 oxadiazole has not yet been reported in the literature.

As a continuation of the reaserch work in on oxidative cyclisation, we are herein report a oxidative cyclisation based one-pot synthesis of 2,5 disubstituted ,1,3,4 oxadiazole derivatives using Me_4NBr/oxone.

2. EXPERIMENTAL

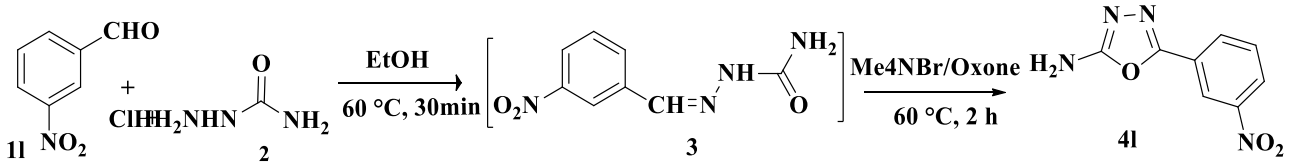
All reagents were purchased from commercial suppliers and were used without purification. Melting points were determined in Buchi B-545 melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance and Varian 400 & 300 NMR MHz spectrometers in DMSO-d_6 & $CDCl_3$ solution using TMS as an internal reference and ^{13}C NMR spectra were recorded on 100 & 75 MHz. Mass spectra were recorded on GC-MS using 230-400 mesh silica gel.

2.1. Typical procedure for the synthesis of 1,3,4 oxadiazole derivatives:

A mixture of hydrazine carboxamide hydrochloride **2** (4 mmol), aldehyde **1a-1l** (6 mmol) in absolute ethanol were heated at 60°C for 30 min. The reaction was monitored by TLC (8:2, Ethylacetate: Hexane). The formation of benzylidene (**3a**) was checked by TLC and the reaction mixture was cooled to room temperature. Oxone (1.5 mmol) was added to the mixture at room temperature followed by tetra methyl ammonium bromide (0.2 mmol) and the resulting mixture was heated at 60°C for another 5 h. The mixture was cooled to room temperature and extracted with dichloromethane (2 x 25 mL), dried over anhydrous sodium sulphate and concentrated to obtain a residue which was purified by recrystallization using ethanol /ethyl acetate as eluent to furnish the desired compound **4a-al.**

3. RESULTS AND DISCUSSION

To execute the task, the model substrate **1l** was treated with hydrazinecarboxamide hydrochloride **2** in ethanol at 60°C for 6 hr. The obtained hydrazone was directely subjected to oxidative cyclization to furnish oxadiazole **1c**. The compound **4l** was purified and confirmed by NMR and LCMS. In order to setup the optimum condition, several reactions were screened by changing various solvents and reagents as shown in the table 1. Polar aprotic solvent such as EtOAc, THF, DMF, DMSO did not improve the yield and in some cases failed to give required compound whereas polar solvent like EtOH, MeOH and IPA gave good to moderate yield. Alternate to the NMe_4Br, the use other reagent such as of $^nBu_4NBr$, NBS and KI did not improve the yield. Quick screening revealed that the combination of stiochiomentric amount of NMe_4Br/oxone was found to be suitable reagent setup to deliver 1,3,4-oxadiazole derivatives.



Scheme 1: Oxidative cyclisation of m-nitro benzaldehyde with hydrazide

[a]1 equiv. of reagent was used. [b]1.5 equiv. of oxidant was used. [c]Isolated yield. [d]20mol% of reagent and 1.5 equiv. of oxidant were used

Table 1.Optimization of oxidative cyclization of 1l and 2

Entry	Reagent/oxidant[b]	Solvent[b]	Temp (°C)	Time (h)	Yield (%)[c]
1	KI/oxone	EtOAc	RT	12	No reaction
2	KI/oxone	DMF	60°C	12	5
3	KI/oxone	THF	RT	12	No reaction
4	KI/oxone	DMSO	60°C	12	10
5	NBS/oxone	DMF	60°C	12	10
6	NBS/oxone	DMF	RT	12	No reaction
7	NBS/oxone	THF	60°C	12	No reaction
8	NBS/oxone	DMSO	60°C	12	12
9	KI/oxone	EtOH	60°C	12	No reaction
10	KI/oxone	IPA	60°C	12	15
11	NBS/oxone	MeOH	60°C	5	15
12	NBS/oxone	EtOH	60°C	5	20
13	$^nBu_4NBr$/oxone	EtOH	60°C	5	60
15[d]	Me_4NBr/ oxone	EtOH	60°C	5	82

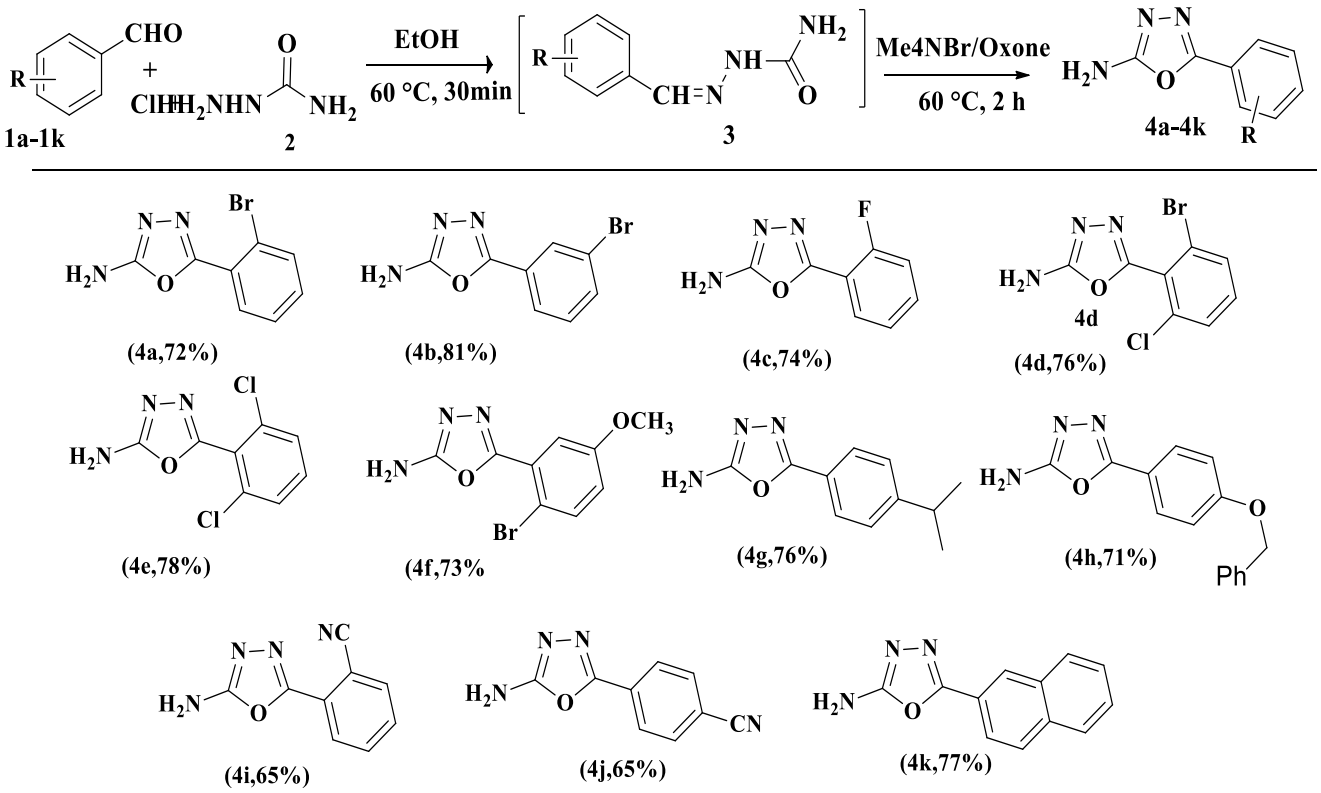


Fig. 2: One-pot oxidative cyclization of 4a-4k

In order to apply this strategy, aldehyde bearing electron withdrawing and electron donating functional groups were subjected to the optimised conditions. Bromo, chloro, fluoro substituted aldehyde **1b-1f** underwent iodination smoothly to deliver the corresponding 1,3,4 triazole, **2b-2e** in high yield (table 2). Similarly, alkyl and alkoxy and benzyloxy substituted aldehyde gave the desired products **2f-2h**. Nitrile and napthayl aldehyde also delivered the desired products **2i-2k.**

3.1. Analytical data for selected compounds

5-(2-Bromophenyl)-1,3,4-Oxadiazole-2-aime (4a)*:** White solid, 0.7g (yield 72%), m.p. 105-110°C; ***IR (Neat): 3462.8, 1653.9, 1586.0, 1412.5, 1342.6, 1275.0, 1214.7, 1151.6, 1023.1739.1, 621.8, 471.3; ***^{1}H NMR (400 MHZ CDCl$_3$)*** ppm: 6.57 (s, 2H), 7.35-7.39 (m, 1H), 7.60-7.62 (m, 1H), 8.15-8.18 (m, 2H); ***^{13}C NMR (100 MHZ CDCl$_3$)*** ppm: 123.1, 127.8, 128.2, 131.1, 133.3, 133.8, 137.8, 156.9; ***UPLCMS***: 212[M+1].

5-(5-Bromo-2-methoxypenyl)-1,3,4-Oxadiazole-2-amine (4f)*:** Pale yellow solid, 0.78g (yield 73%), m.p. 88-94°C. ***IR (Neat): 3128.4, 2835.3, 1409.9, 1509, 1113.6, 1679.4, 1020.2, 1260.1, 1044.9; ***^{1}H NMR (400 MHZ CDCl$_3$) ppm***: 3.8 (s, 3H), 7.16 (d, 1H, *J*=8.0 Hz), 7.29 (s, 2H), 7.66 (t, 1H, *J* = 7.20 Hz), 7.75 (d, 1H, *J*= 2.0 Hz). ***^{13}C NMR (100 MHZ CDCl$_3$)*** ppm: 56.6, 112.1, 115.3, 115.9, 131.5, 134.7, 155.0, 156.4, 160.4.

5-(4-Benzyloxyphenyl)-1,3,4-Oxadiazole-2-aime (4h)*:** Pale yellow solid, 0.75g (yield 71%), m.p, 88-94°C. ***IR (Neat): 3275.3, 3120, 1413.9, 1501.1, 1113.1, 1640.4, 1011.2, 1252.1, 1036.9; ***^{1}H NMR (400 MHZ CDCl$_3$) ppm***: 5.17 (s, 2H), 7.16 (d, 1H, *J*=8.0 Hz), 7.29 (s, 2H), 7.66 (t, 1H, *J* = 7.20 Hz), 7.75 (d, 1H, *J*= 2.0 Hz). ***^{13}C NMR (100 MHZ CDCl$_3$)*** ppm: 56.6, 112.1, 115.3, 115.9, 131.5, 134.7, 155.0, 156.4, 160.4.

4-(5-Amino-1,3,4-oxadiazol-2-yl)benzonitrile (4j)*;** Pale yellow solid, 0.48g (yield 65%), m.p. 97-99°C .^{1}H NMR (400 MHZ CDCl$_3$) ppm***: 7.49 (s, 2H), 7.93 (d, 2H, *J*=7.2 Hz), 7.90 (d, 2H, *J*=8.3 Hz). ***^{13}C NMR (100 MHZ CDCl$_3$)*** ppm: 112.7, 118.8, 125.9, 128.6, 133.7, 156.6, 164.9.

5-(Naphthalenyl-2-yl)-1,3,4-Oxadiazole-2-aime* (4k)** White solid, 0.65g (yield 77%), m.p. 105-110°C; ***IR (Neat): 3260.8, 3097.0 1650.0, 1592.4, 1543.1, 1463.4, 1283.2, 1196.4, 1049.0, 990.3, 767.1, 738.5,

650.8, 531.1; ***^{1}H NMR (400 MHZ CDCl$_3$)*** ppm: 7.16 (m, 1H), 7.38 (s, 2H), 7.64-7.74 (m, 3H), 7.97 (d, 1H, *J* = 7.2 Hz), 8.04 (d, 1H, *J* = 8.0 Hz), 8.09 (d, H, *J* = 8.0 Hz). ***^{13}C NMR (100 MHZ CDCl$_3$)*** ppm: 125.8, 126.2, 126.9, 128.1, 129.3, 131.4, 133.9, 137.5, 157.7, 164.0; ***UPLCMS***: 212[M+1].

5-(3-Nitropenyl)-1,3,4-Oxadiazole-2-aime (**4l**) Pale yellow solid, 0.67g (yield 82%), m.p. 120-130ºC, ***IR (Neat)***: 3409.6, 3091.0, 1519.0, 1509, 1116.3, 1663.8, 1040.3, 1268.1, 1044.9 ; ***^{1}H NMR (400 MHZ CDCl$_3$)*** ppm: 7.47 (s, 2H), 7.8.3 (t, 1H, *J*=8.0 Hz), 8.2 (d, 1H, *J*=7.8 Hz), 8.34 (d, 1H, *J* = 8.2 Hz), 8.4 (s, 1H). ***^{13}C NMR (100 MHZ CDCl$_3$)*** ppm: 119.8, 125.1, 126.2, 131.3, 131.6, 148.6, 156.2, 164.7.

4. CONCLUSION

In conclusion, one-pot synthesis of 1,3,4 oxadiazole derivatives was developed from the readily available aldehydes and hydrazinecarboxamide hydrochloride. Similarly, Our method to construct 1,3,4-oxadiazole moiety is based on oxidative cyclization which was successfully executed by Me_4NBr and oxone, Also, this condition is mild and thus displayed a wide functional group tolerance.

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