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Microwave promoted one-pot synthesis of 2-aryl substituted 1,3,4-oxadiazoles and 1,2,4-oxadiazole derivatives using Al^{3+}-K10 clay as a heterogeneous catalyst

Dhanusu Suresh,[a] Kuppusamy Kanagaraj,[a] and Kasi Pitchumani*[a,b]

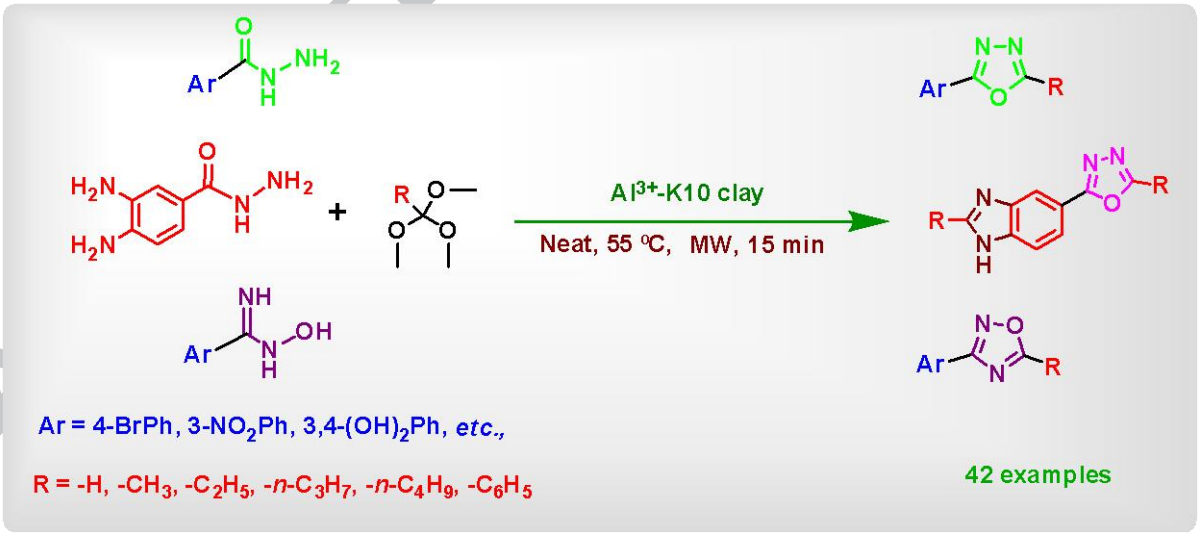
[a]*School of Chemistry, Madurai Kamaraj University, Madurai 625012, India*

[b]*Centre for Green Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625012, India*

E-mail : pit12399@yahoo.com

Abstract

An efficient, inexpensive method is developed for the one-pot synthesis of 2-aryl substituted 1,3,4-oxadiazoles and 1,2,4-oxadiazoles starting from acid hydrazides and trimethyl orthoformate under solvent-free, microwave conditions using a reusable Al^{3+}-K10 montmorillonite clay as heterogeneous catalyst. The novelty of the present study lies in the synthesis of oxadiazole and benzimidazole moieties in a one-pot process in high yield from easily available precursors and catalysts under mild conditions.



Keywords: K10-Montmorillonite; 1,3,4-oxadiazoles; 1,2,4-oxadiazoles; one-pot solvent-free synthesis; Green Protocol.

Heterocyclic compounds are very important class of organic compounds and in particular oxadiazole derivatives receive much attention because of their applications in drug discovery.[1a-c] Often, these molecules are used as pharmacophores due to their metabolic stability, ability to bind with target peptides and can be engaged in hydrogen bond formation.[2] They have activities like anti-fungal, antimicrobial,[3] anti-hypertensive[4] and antituberculosis.[5] They are also useful as inhibitors of bacterial phenylalanyl-tRNA synthetase,[6] human neutrophil elastase,[7] antagonists,[8,9] y-secretase inhibitor,[10] antikinetoplastid activity,[11] cancer cell proliferation[12] and orientation in the γ-aminobutyric acid binding site.[9] In addition, they are known as inhibitors of cathepsin K,[13] and found as astrocyte differentiation enhancement in rat fetal neural stem cells.[14]

Synthesis of 1,3,4-oxadiazoles has been reported by the cyclization of acid hydrazides under strong acid conditions.[15] This heterocyclic compound has also been synthesized from diacylhydrazines, semicarbazide and thiocarbzide in the presence of dehydrating agents such as phosphorusoxychloride,[16] (O-benzotiazol-1-yl)-N,N,N',N'-tetramethyluranium tetrafluoroborate) TBTU,[17] molecular iodine,[18] and polymer supported reagents.[19-21] 1,3,4-Oxadiazoles was also synthesized in high temperature/high pressure in continuous flow method[22] and the reaction between (N-isocyamino)triphenylphosphorane with acid derivatives.[23] On the other hand, the reaction between acid hydrazides and orthoesters resulted in the formation of 1,3,4-oxadiazoles under harsh condition, use of excess orthoformate and longer reaction time[24-25.] This strategy was modified by use of catalyst such as BF_3.EtO,[26] orthophosphoric acid,[15] silica sulphuric acid,[27] acetic acid[28] and solid supported Nafion ®NR50.[29a] These reported methods suffer from any one or more of the following drawbacks like expensive homogeneous catalysts, requires strong acidic conditions, long reaction times, low yields of the products, tedious work-up procedure, and the reagents are toxic in nature. With a view to develop environmentally benign protocols,[29b-

[h] the present study aims to develop a facile one-pot synthesis of 1,3,4-oxadiazole and 1,2,4-oxadiazole derivatives from acidhydrazide with orthoesters and also from amidoxime with orthoesters using Al^{3+}-K10 clay as a heterogeneous catalyst under solvent-free, microwave conditions.

The reaction conditions were optimized in the one-pot synthesis of 2-(4-methoxyphenyl)-1,3,4-oxadiazole (**3i**) using 4-methoxybenzhydrazide (**1i**) and trimethylorthoformate (**2a**) as substrates. The observed results are presented in Table 1. Control experiments showed the absence of product (Table 1, entries 1 and 2) under thermal and MW heating indicating the requirement of a catalyst to promote this transformation. On the other hand, catalysts like $AlCl_3$, Al_2O_3, CuCl and $TiCl_4$ (Table 1, entries 3-6) resulted in 56, 39, 29 and 67 % yield of **3i** under MW irradiation at 55 ^oC in 15 min. In addition, Cu^{2+}, Zn^{2+} and Ti^{4+}-exchanged K10 clays resulted 71, 83 and 90 % yields respectively (Table 1, entries 7-9) under MW irradiation in 15 min. On the other hand Al^{3+}-K10 clay showed 65 % yield in toluene at 55 ^oC in 2.5 h while the same catalyst yielded 90 % of the product **3i** under neat conditions by heating at 55 ^oC in 45 min. Further, when the reaction was carried out at room temperature with Al^{3+}-K10 clay as catalysts yields 17 % of the desired product (**3i**) (Table 1, entry 10). Increase in temperature from 40 and 55 ^oC under MW conditions accelerates the reaction and further increase the temperature to 100 ^oC under MW condition no significant increase in yield (Table 1, entries 13-15). Also, it is interesting to note that Al^{3+}-K10 clay exhibited 96 % of the product **3i** under MW irradiation at 55 ^oC in 15 min (Table 1, entry 14). It was observed that Al^{3+}-K10 catalyst under MW irradiation at 55 ^oC for 15 min with various organic solvents exhibited in lower yields of the product **3i** (Table 1, entries 13-18). This gives an additional advantage to the present protocol where it does not require any solvent, reaction gets completed in a short span of time and non-conventional energy source namely MW irradiation is used as an alternative source. On the other hand, a

three dimensional porous aluminosilicate namely HY zeolite yielded 64 % of the desired product **3i** under identical reaction conditions with MW. Further reducing the loading of **2a** from 3 equiv. to 1.5 equiv. lowered the yield from 96 to 49 % respectively. In addition, the catalyst loading also influenced the yield of the product. For example, use of 25 and 50 mg of Al^{3+}-K10 catalyst resulted in 24 and 62 % yields whereas 75 mg showed 96 % yield under the same conditions.

Table 1

After optimizing the catalyst loading, time, heating method and catalyst for the synthesis of 2-substituted 1,3,4-oxadiazole in very high yield, we extended this protocol for the synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles starting from the corresponding acid hydrazides with **2a** or trimethyl orthoacetate (**2b**). The observed results are summarized in Table 2.

Table 2

Reasonably high yields (85-96 %) were observed with acid hydrazides containing electron withdrawing or electron donating substituents. Interestingly, acid hydrazide with disubstituted groups also resulted in high yields with **2a** (Table 2, entries 10-12). Increasing the size of the acid hydrazide showed no influence on yield (Table 2, entry 7). On the other hand, replacing **2a** by **2b** exhibited high yields with various substituted acid hydrazides and

the observed results are given in Table 2.[37] These experiments have clearly shown that the process is highly efficient and clean as the observed product only is 2,5-disubstituted 1,3,4-oxadiazole in high yields.

The efficiency of this protocol was further extended to synthesize another set of 2,5-disubstituted 1,3,4-oxadiazole derivatives. Various substituted acid hydrazides were treated with **2b**, triethyl orthopropionate (**2c**), trimethyl orthobutyrate (**2d**), triethyl orthovalerate (**2e**) and triethyl orthobenzoate (**2f**) under the optimized reaction conditions resulting in the corresponding 2,5-disubstituted 1,3,4-oxadiazole (**3u-ad**) derivatives in high yields. The observed results are presented in Table 3.[37]

Table 3

These interesting results have prompted us to construct oxadiazole and benzimidazole in the same molecule through one-pot synthesis starting from acid hydrazide containing 1,2-diamino groups with excess trimethyl orthoesters (**2a-f**) under the optimized conditions. The observed results are given in Table 4.[37] It is evident from this table that this methodology can be easily applied to synthesize various heterocycles containing oxadiazole and benzimidazole moieties (**4a-f**) simultaneously in high yields (~ 90 %).

Table 4

To ascertain the formation of oxadiazole, structure of **4c** (Table 4) was solved by single crystal X-ray diffraction (Figure S4) which confirms the presence of benzimidazole and oxadiazole moieties in the synthesized molecule. These examples clearly illustrate that use of

Al^{3+}-K10 clay can be conveniently used as a green solid acid catalyst, for the construction of nitrogen heterocycles in high yields.

After having demonstrated the catalytic activity of Al^{3+}-K10 as superior catalyst for the synthesis of 1,3,4-oxadiazoles, we are prompted to explore the synthesis of isomeric 1,2,4-oxadiazoles. To our surprise, the optimized reaction conditions allowed us to synthesize a series of 3-substituted 1,2,4-oxadiazoles (**6a-f**) were synthesized starting from substituted amidoximes (**5a-f**) and **2a** in the presence of Al^{3+}-K10 clay as catalysts in high yields. The observed results are given in Table 5.[38]

Table 5

The data clearly show that the present methodology leads to the synthesis of various 3-substituted 1,2,4-oxadiazoles containing various functional groups and presence of electron donating/electron withdrawing substituents have no influence on the yield of the products. In addition, this procedure allows to synthesize 1,2,4-oxadiazole moiety bearing heterocyclic unit such as substituted pyridyl in the 3rd position demonstrating that this protocol can be utilized for the facile construction of various 1,2,4-oxadiazoles using an environmentally benign catalyst in high yields.

Reusability experiments were performed between acid hydrazide and trimethyl orthoformate as substrates using Al^{3+}-K10 clay as catalyst and it was observed that the catalyst can be used atleast five times with only a slight decrease in yield (Table 6) which can be attributed to loss of catalyst while recycling.

Table 6

Scheme 1

To test that the methodology does not affect the integrity of stereogenic centers, Boc protected *L*-proline was used to prepare the hydrazide, which was treated with trimethyl orthoformate to give 2-substituted-1,3-4,-oxadiazole (Scheme 1). Specific Optical Rotation results confirmed that this methodology does not affect the integrity of stereogenic center. SFC chiral purity report also confirmed the formation of a single stereoisomer.

Based on the reported literature reports,[15, 17, 18, 20, 21, 24-29, 36] a plausible mechanism is proposed for the formation of 1,3,4-oxadiazoles (Scheme 2). Initially Al^{3+} binds to the oxygen atoms in trialkyl orthoester and forms reactive intermediate (I) which readily loses an alcohol molecule. When electron rich nitrogen from hydrazide approaches the electron deficient carbon center, intramolecular cyclization is facilitated, leading to loss of another molecule of alcohol. Subsequent elimination of hydrogen and O-alkyl group from the cyclic intermediate (II) leads to aromatization and release of the heterocyclic 1,3,4-oxadiazole.

Scheme 2

A similar route is also proposed to rationalize the formation of 1,2,4-oxadiazoles (scheme 3).

Scheme 3

Data on the reaction conditions, as well as the activity and efficiency of the different catalysts reported in literature for the synthesis of 2-substituted 1,3,4-oxadiazoles and 1,2,4-oxadiazole derivatives are given in Table 7. These reported catalytic systems have their own advantages and disadvantages. These catalytic systems involve hazadous Lewis acid catalysts and some of them transition-metal-mediated catalytic processes, and the catalysts are not easy to recover by simple filtration. Taking all these into account, the use of Al^{3+}-K10 clay as catalyst which not only generates less waste but also has several advantages, which includes insolubility in water / organic solvent, good catalytic activity and high thermal stability. It is also nontoxic, environmentally benign, milder, cheap and exhibit wider substrate scope with higher selectivity and improved product yields. Al^{3+}-K10 clay catalyst can also be easily recovered by simple filtration and reused for many times without significant change of its activity. The catalyst is commercially available and easy to prepare and handle. It is evident that the present system enjoys many advantages like reusability without much decrease in the yield, use of green solid acid catalyst and a non-conventional energy source namely MW, and requires no additional solvent for the synthesis of the heterocyclic compounds.

Table 7

In summary, we have developed a novel protocol for the one-pot solvent-free synthesis of 2-substituted 1,3,4- and 1,2,4-oxadiazole derivatives using a reusable, non toxic, cheap, metal-exchanged clay (Al^{3+}-K10 clay) as the heterogeneous catalyst. The present methodology can also be successfully applied for the synthesis of heterocyclic compounds bearing oxadiazole and benzimidazole moieties simultaneously in a one-pot synthesis.

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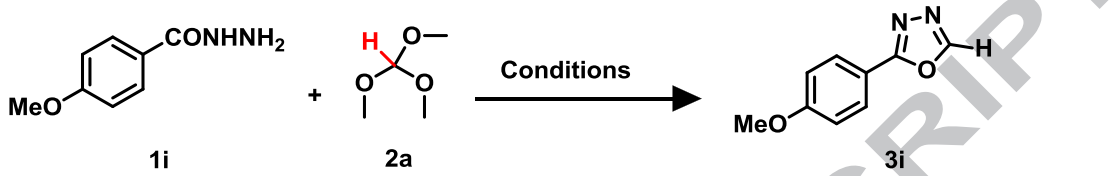
37. **General procedure for the synthesis of 1,3,4-oxadiazole derivatives :** *A 5 mL microwave vial was charged with acidhydrazide (100 mg, 1 equiv.), trimethyl orthoester (2 equiv.) and Al^{3+}-K10 clay (75 mg). The resulting mixture was kept under microwave irradiation maintaining the temperature at 55 ^{0}C for 15 min (Microwave irradiations were performed on CEM-discover model No. 908010). The reaction was monitored by TLC. After completion of the reaction, reaction mixture was diluted with ethyl acetate stirred well, filtered, washed well with ethyl acetate. Filtrate was evaporated under reduced pressure to obtain highly pure product. In some cases, products were purified by column chromatography using 60-120 mesh silica with 20-100 % ethyl acetate in petroleum ether as eluents. The catalyst recovered by filtration was reused for consecutive runs.*

38. General procedure for the synthesis of 1,2,4-oxadiazole : *A 5 mL microwave vial was charged with amidoxime (100 mg, 1 equiv.), trimethyl orthoester (0.2 ml, 3 equiv.) and Al^{3+}-K10 clay (75 mg). The above procedures were followed to obtain products in high purity. Microwave irradiations were performed on CEM-discover model No. 908010.*

Tables

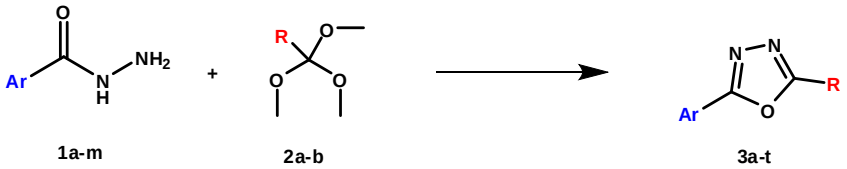
Table 1. Optimization of reaction conditions in the one-pot synthesis of 2-(4-methoxyphenyl)-1,3,4-oxadiazole.[a]



S.No	Catalyst	Solvent	Temp (^{0}C)	Time (min)	Yield[b] (%)
1	-	Toluene	55	150	-
2	-	-	55, MW	15	-
3	$AlCl_3$	-	55, MW	15	56
4	Al_2O_3	Neat	55, MW	15	39
5	CuCl	-	55, MW	15	29
6	$TiCl_4$	-	55, MW	15	67
7	Cu^{2+}-K10	-	55, MW	15	71
8	Zn^{2+}-K10	-	55, MW	15	83
9	Ti^{4+}-K10	-	55, MW	15	90
10	Al^{3+}-K10	-	RT	300	17
11[c]	Al^{3+}-K10	Toluene	55	150	65
12	Al^{3+}-K10	-	55	45	90
13	Al^{3+}-K10	-	40, MW	15	63
14	Al^{3+}-K10	-	55, MW	15	96
15	Al^{3+}-K10	-	100, MW	15	96
16[c]	Al^{3+}-K10	Toluene	55, MW	15	61
17	Al^{3+}-K10	CAN	55, MW	15	46
18	Al^{3+}-K10	THF	55, MW	15	33
19	Al^{3+}-K10	1,4-Dioxane	55, MW	15	29
20	Al^{3+}-K10	Methanol	55, MW	15	61
21	Al^{3+}-K10	DMF	55, MW	15	27
22	HY	-	55, MW	15	64
23[c]	Al^{3+}-K10	-	55 MW	15	49
24[d]	Al^{3+}-K10	-	55 MW	15	24, 62
25	K10	-	55 MW	15	12

[a]Reaction conditions: 4-Methoxybenzhydrazide **1i** (100 mg, 1.0 equiv.), trimethyl orthoformate **2a** (3.0 equiv.), Al^{3+}-K10 clay (75 mg), solvent (1 ml used for entries 1, 4, 10, 13-18), 55 ^{0}C. [b]Isolated yield. [c]Yield of the product with 1.5 equiv. of trimethyl orthoformate is used. [d]Yield of the reaction carried out with 25 and 50 mg of catalyst respectively.

Table 2. One-pot synthesis of 2,5-disubstituted 1,3,4-oxadiazole using Al^{3+}-K10 clay as heterogeneous catalyst.[a]

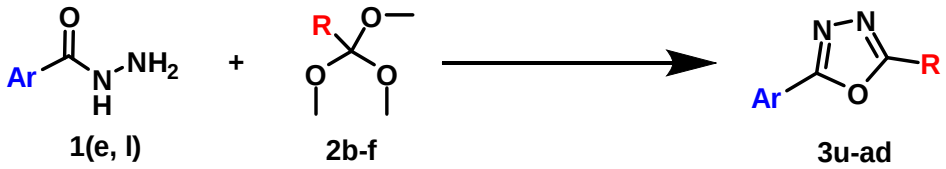


1a-m 2a-b 3a-t

Entry	Ar	R	Product	Yield[b] (%)
1	2-F-C_6H_4-	H	3a	92
2	4-F-C_6H_4-	H	3b	94
3	3-Cl-C_6H_4-	H	3c	89
4	4-Br-C_6H_4-	H	3d	93
5[c]	3-NO_2-C_6H_4-	H	3e	92
6	3-CF_3-C_6H_4-	H	3f	90
7	4-CH_3CONH-C_6H_4-	H	3g	91
8	3-CH_3O-C_6H_4-	H	3h	93
9	4-CH_3O-C_6H_4-	H	3i	96
10	2,4-Cl_2-C_6H_3-	H	3j	93
11	2,5-Cl_2-C_6H_3-	H	3k	91
12[c]	3,5-$(OH)_2$-C_6H_3-	H	3l	93
13	2-F-C_6H_4-	CH_3	3m	92
14	4-F-C_6H_4-	CH_3	3n	94
15	3-Cl-C_6H_4-	CH_3	3o	91
16	3-CF_3-C6H_4-	CH_3	3p	90
17	4-CF_3-C_6H_4-	CH_3	3q	92
18	3-CH_3O-C_6H_4-	CH_3	3r	92
19	4-CH_3O-C_6H_4-	CH_3	3s	94
20	2,5-Cl_2-C_6H_3-	CH_3	3t	90

[a]Reaction conditions: Acid hydrazide (**1a-m**) (100 mg,1 equiv.), trimethyl orthoformate (**2a**) or trimethyl orthoacetate (**2b**) (3.0 equiv.), Al^{3+}-K10 clay (75 mg), 55 ^{0}C, and MW, 15 min. [b]Isolated yield. [c]Reaction carried with excess of **2a**.

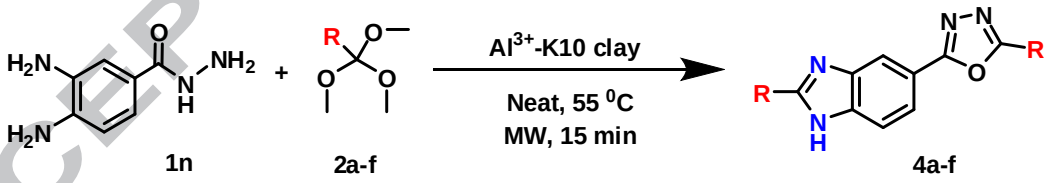
Table 3. One-pot synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives.[a]



Run	Ar	R	Product	Yield[b] (%)
1	3-$NO_2C_6H_4$- (**1e**)	-CH_3	3u	93
2	**1e**	-C_2H_5	3v	93
3	**1e**	-*n*-C_3H_7	3w	91
4	**1e**	- *n*-C_4H_9	3x	90
5	**1e**	-C_6H_5	3y	90
6	3,5-$(OH)_2$-C_6H_3- (**1l**)	-CH_3	3z	90
7	**1l**	-C_2H_5	3aa	91
8	**1l**	-*n*-C_3H_7	3ab	90
9	**1l**	-*n*-C_4H_9	3ac	91
10	**1l**	-C_6H_5	3ad	88

[a]Reaction conditions: Acid hydrazide (**1e, 1l**) (100 mg,1 equiv.), orthoester (**2b-f**) (5.0 equiv.), Al^{3+}-K10 clay (75 mg), 55 ^{0}C, and MW, 15 min. [b]Isolated yield.

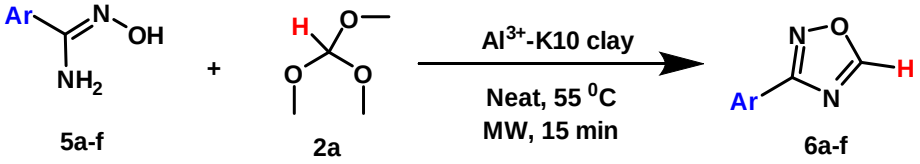
Table 4. One-pot synthesis of 2,5-disubstituted 1,3,4-oxadiazole-2-yl)1*H*-benzo[*d*]imidazole derivatives.[a]



Run	R	Product	Yield[b] (%)
1	-H(**2a**)	4a	92
2	-CH_3(**2b**)	4b	92
3	-C_2H_5(**2c**)	4c	90
4	-*n*-C_3H_7(**2c**)	4d	91
5	-*n*-C_4H_9(**2d**)	4e	90
6	-C_6H_5(**2e**)	4f	89

[a]Reaction conditions: 3,4-Diaminobenzhydrazide (**1n**) (100 mg, 1equiv.), orthoester (**2a-f**) (5.0 equiv.), Al^{3+}-K10 clay (75 mg), 55 ^{0}C, and MW, 15 min. [b]Isolated yield.

Table 5. One-pot synthesis of 3-substituted 1,2,4-oxadiazole.[a]



Entry	Ar	Product	Yield[b] (%)
1	4-Br-C_6H_4-	**6a**	92
2	4-OH-C_6H_4-	**6b**	91
3	4-$CH_3CONHC_6H_4$-	**6c**	94
4	2-Cl-6-pyridyl-	**6d**	93
5	2-Br-3-pyridyl-	**6e**	92
6	3-Cl-4-CH_3-C_6H_3-	**6f**	92

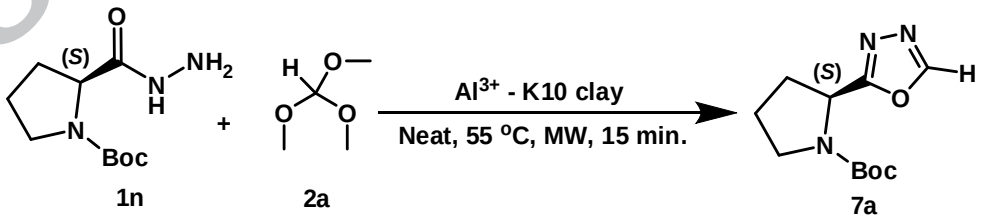
[a]Reaction conditions: Amidoxime (**5a-f**) (100 mg, 1eqiv.), **2a** (3.0 equiv.), Al^{3+}-K10 clay (75 mg), 55 ^{0}C, MW and 15 min. [b]Isolated yield.

Table 6. Reusability of Al^{3+}-K10 clay in one-pot synthesis of 2-(4-methoxyphenyl)-1,3,4-oxadiazole.

Run	1	2	3	4	5
Yield[b] (%)	93	91	88	84	81

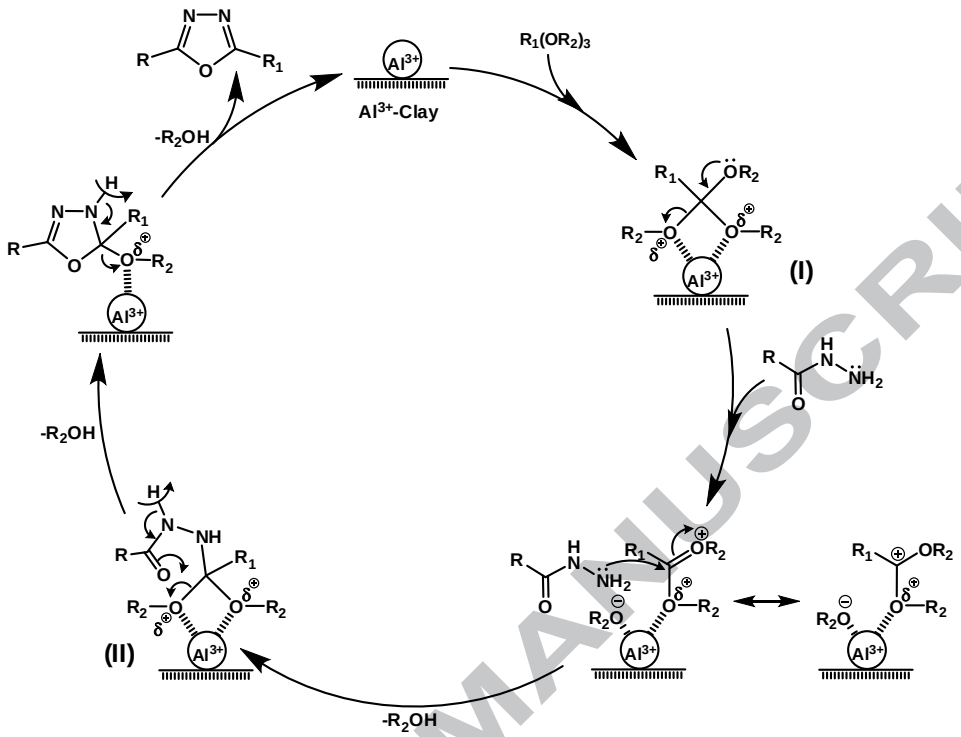
[a]Reaction conditions: 4-Methoxybenzhydrazide (**1i**) (100 mg, 1eqiv.), **2a** (3.0 equiv.), Al^{3+}-K10 clay (75 mg), 55 ^{0}C, and MW, 15 min. [b]Isolated yield.

Schemes

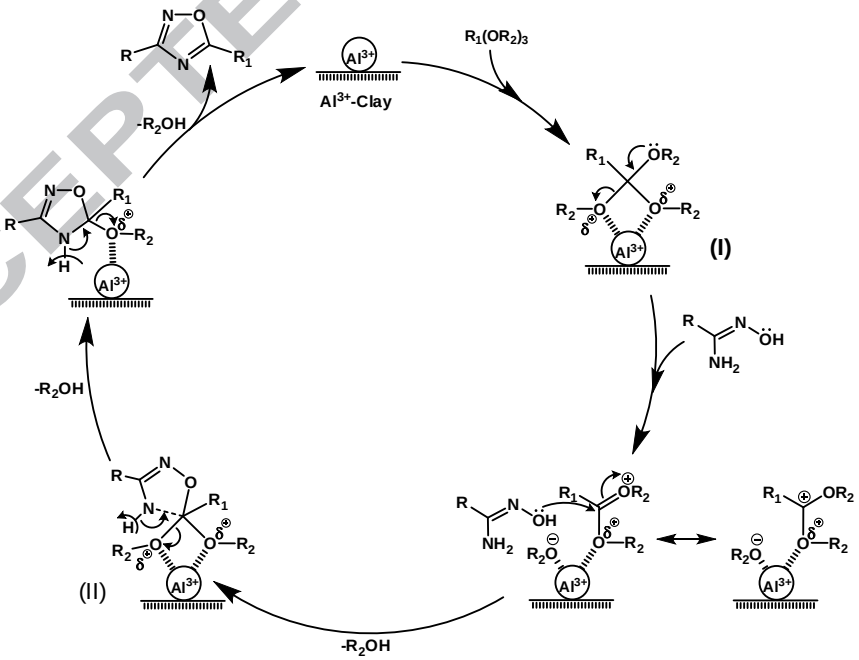


A name could not be generated for this structure.

Scheme 1. One-pot synthesis (*S*)-*tert*-butyl-2-(1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate.



Scheme 2. Proposed mechanism for the synthesis of 2-substituted 1,3,4-oxadiazoles.



Scheme 3. Proposed mechanism for the synthesis of 2-substituted 1,2,4-oxadiazoles.

Highlights

- Synthesis of 1,3,4- / 1,2,4-oxadiazoles using Al^{3+}-K10 clay as catalyst
- Recovery and reuse for atleast five times
- High yield under mild conditions from easily available precursors
- Use of MW as a non-conventional energy source
- Solvent-free condition