TiO_2-Nanoparticles Catalyzed Synthesis of New Trifluoromethyl-4,5-dihydro-1,2,4-oxadiazoles and Trifluoromethyl-1,2,4-oxadiazoles

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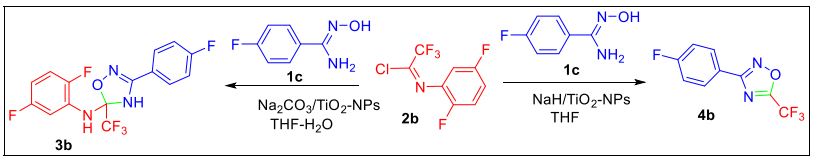

Synthesis of a new series of trifluoromethyl-4,5-dihydro-1,2,4-oxadiazoles and trifluoromethyl-1,2,4-oxadiazoles have been described by utilizing the reactions between amidoximes and trifluoroacetimidoyl chlorides. Trifluoromethyl-4,5-dihydro-1,2,4-oxadiazoles have been synthesized under mild conditions such as Na_2CO_3, THF-H_2O, and titanium dioxide nanoparticles as catalyst in good to excellent yields. Also, trifluoromethyl-1,2,4-oxadiazoles have been synthesized directly from reaction of amidoximes and trifluoroacetimidoyl chlorides in a one-pot manner in present of NaH, THF, and titanium dioxide nanoparticle as catalyst.

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INTRODUCTION

Heterocycles containing nitrogen–oxygen atoms are very important and attractive, because they form an important class of natural and non-natural compounds and many of them exhibit useful biological activities [1–4]. Oxadiazoles are the important class of heterocycles that apply widely as drugs in pharmaceuticals [5]. Among oxadiazoles, 1,2,4-oxadiazole derivatives have received much attention in medicinal chemistry, for example, prenoxdiazole, oxolamine, proxazole, and butalamine [6]. Compounds including 1,2,4-oxadiazole ring show an extensive biological properties such as HIV integrase inhibitors [7], antituberculostatic agents [8], and antikinetoplastid agents [9], muscarinic agonists [10,11], serotoninergic (5-HT3) antagonists [12], benzodiazepine receptor agonists [13], and dopamine ligands [14].

In the recent years, compounds containing trifluoromethyl group have gained a significant importance due to the biological actives and using as new materials. Today, these compounds are forehand in developments in the pharmaceutical and agrochemical industries [15–18].

Nowadays, metal oxide nanoparticles have drawn the attention of scientists, because of their extensive application in the development of new technologies in the areas of electronics, material sciences, catalyst, and medicine at the nanoscale [19–21]. As an efficient and versatile catalyst, TiO_2-nano-structured has been the focus of considerable research interests in recent years. Its small size and large specific surface area allow for certain unique and unusual physicochemical properties [22,23]. In addition, the use of carbonaceous nanomaterials to support TiO_2 has attracted much attention because of their unique structural and electrical properties [24].

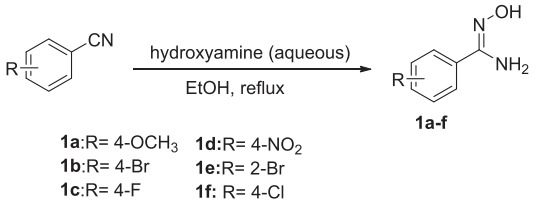
In continuing our efforts toward the development of new methods for the efficient synthesis of trifluoromethylated organic compounds [25–28], in the present paper, the reactions of trifluoroacetimidoyl chlorides and amidoximes are reported. Aided by these compounds, we report a high-yielding one-pot synthesis of trifluoromethyl-4,5-dihydro-1,2,4-oxadiazoles **3** and trifluoromethyl-1,2,4-oxadiazoles **4** by condensing trifluoroacetimidoyl chlorides and amidoximes in a two different conditions.

Trifluoroacetimidoyl chlorides are active substrate in nucleophilic reactions. Reaction of these compounds with N,N-binucleophiles and N,O-binucleophiles results to synthesis of important tifluoromethylated heterocycles such as (trifluoromethyl)benzotriazole and (trifluoromethyl) benzotriazine. Therefore, in these investigation, we were interested to the synthesis of trifluoromethyl-4,5-dihydro-1,2,4-oxadiazoles **3** from reaction of trifluoroacetimidoyl chlorides and amidoximes in the presence of sodium carbonate and titanium dioxide nanoparticles (TiO_2-NPs) as catalyst (Scheme 3).

RESULTS AND DISCUSSION

The necessary amidoximes **1** were readily synthesized according to a standard literature protocol in one-pot way [29]. The reaction of carbonitrile with aqueous hydroxylamine solution in ethanol under reflux conditions provided the desired amidoximes **2** (Scheme 1).

Scheme 1. Synthesized of amidoximes.

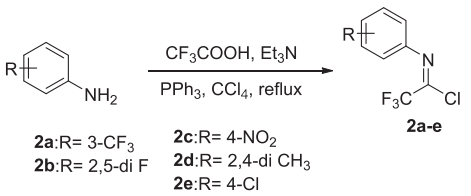


The required trifluoroacetimidoyl chlorides **2** were prepared by reaction mixture of a primary aromatic amine and trifluoroacetic acid in carbon tetrachloride in the presence of triethylamine and triphenylphosphine under reflux conditions according to known literature reported procedures [30,31], as depicted in Scheme 2.

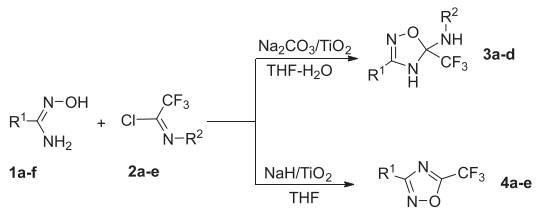
We also expected that the reaction of amidoximes **1** and trifluoroacetimidoyl chlorides **2** at the present of NaH, THF, and TiO_2-NPs could lead to the formation of trifluoromethyl-1,2,4-oxadiazoles **3**, but when the reaction was carried out in these conditions (NaH as base, THF solvent and TiO_2-NPs catalyst), no appreciable amounts of **3** were obtained, only trifluoromethyl-1,2,4-oxadiazoles **4** were detected (Scheme 3).

Subsequently, in order to obtain optimum conditions, we investigated the reaction of amidoximes **1a** and **1b** with trifluoroacetimidoyl chlorides **2a** and **2b**. The results are given in Table 1. Unfortunately, the reaction of amidoximes **1a** with trifluoroacetimidoyl chloride **2a** did not produce the expected **3a** or **4a**, and from these reaction, hydrolyzed product **5a** was isolated (Scheme 4 and Table 1) [32–34]. In fact, compared with previous our works [25–28], trifluoroacetimidoyl chloride could be converted to hydrolyzed product at some condition as main or by products.

Scheme 2. Synthesized of trifluoroacetimidoyl chlorides.



Scheme 3. Synthesis of trifluoromethyl-1,2,4-oxadiazoles types.



Interestingly, during these studies, we found that *changing reaction conditions* could result to synthesis of 3-(4-bromophenyl)-N-(2,5-difluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2,4-oxadiazol-5-amine **3a**, which with elimination of aniline molecule afford 3-phenyl-5-(trifluoromethyl)-1,2,4-oxadiazole **4a** in good yields so we could have different products depending on the conditions (**3a** or **4a**).

The optimum conditions without any catalyst were obtained with 0.5 mmol of amidoxime (**1**) and 1 mmol of trifluoroacetimidoyl chloride (**2**) in THF-H_2O in the presence of Na_2CO_3 as the base at room temperature for 20 min (entry 8 in Table 1). Alternatively, we also found that the yield and time could be substantially improved when the reaction was carried out in TiO_2-NPs as catalyst (entry 9 in Table 1). With the optimized conditions established, various (trifluoromethyl)-4,5-dihydro-1,2,4-oxadiazol-5-amine (**3a–d**) prepared from amidoximes **1a–d** with Na_2CO_3 were subjected to the reaction with trifluoroacetimidoyl chloride under mild conditions in order to explore the scope and generality of the reaction (Table 2). Changing the conditions (solvent and base) CH_3CN in THF instead of Na_2CO_3 in THF-H_2O resulted to synthesis of trifluoromethyl-1,2,4-oxadiazoles **4a** (entry 14 in Table 1) in good yields. After the optimal reaction, conditions were established, we continued to explore the generality of the protocol. The outcomes were listed in Table 2.

As mentioned in Table 2, when we used NaH as the base in THF at room temperature in the presence of TiO_2-NPs as the catalyst after 1 h, it resulted to **4a–e** products, and when we applied Na_2CO_3 as the base in THF-H_2O at room temperature in the presence of TiO_2-NPs, catalyst at 5 min produced **3a–d** products. Using TiO_2-NPs in both conditions decreased the reaction time with the higher yield.

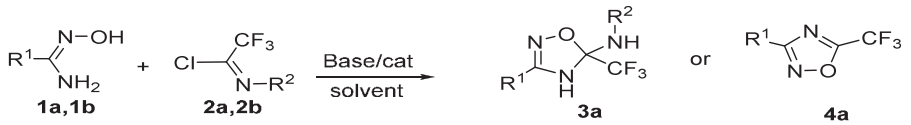
The reaction is suggested to be proceeding via the initial activation of imidoyl by TiO_2-NPs to produce of TiO_2-imidoyl complex. Then, this activated complex is attacked by the nucleophilic amidoxime to replace the chlorine atom by oxygen. Subsequent attack of the –NH anion on the imino group generates the cyclic intermediate 3-(4-aryl)-N-(aryl)-5-(trifluoromethyl)-4,5-dihydro-1,2,4-oxadiazol-5-amine **3**, which with eliminating of aryl amine result to 3-(4-aryl)-5-(trifluoromethyl)-1,2,4-oxadiazole **4** (Scheme 5).

CONCLUSION

In summary, we have presented a new protocol for the synthesis of trifluoromethyl-4,5-dihydro-1,2,4-oxadiazoles and trifluoromethyl-1,2,4-oxadiazoles using TiO_2-NPs as a catalyst. The product produced from reaction of

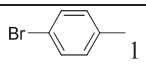
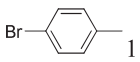
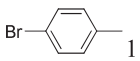
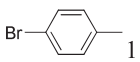
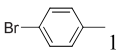
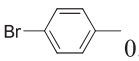
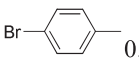
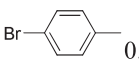
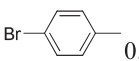
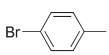
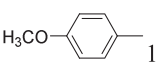
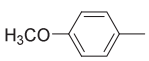
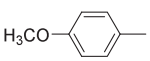
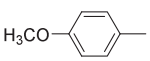
Table 1

Screening optimal conditions.



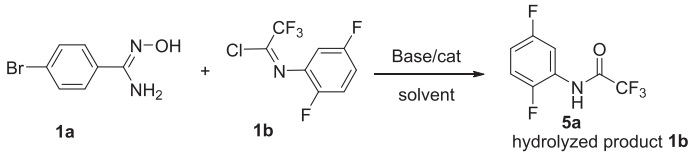
3a: 1b: R^1= 4-Br, 2b: R^2= 2,5-di F

4a: 1a: R^1= 4-OCH_3, 2a: R^2= 3-CF_3

Entry	R^1/ mmol	R^2/ mmol	Base	Cat (%mol)	Solvent	Conditions	Yield (%)
1	 1	2,5 di F/ 1	K_2CO_3	-	CH_3CN	r.t, 4 h	0
2	 1	2,5 di F/ 1	K_2CO_3	-	CH_3CN	Reflux,1 h	0
3	 1	2,5 di F/ 1	K_2CO_3	-	THF	r.t, 2 h	0
4	 1	2,5 di F/ 1	Na_2CO_3	-	THF-DMF	50, 1 h	0
5	 1	2,5 di F/ 1	Et_3N	-	toluene	r.t, 5 h	0
6	 0.5	2,5 di F/ 1	Et_3N	-	toluene	r.t, 18 h	3a (25)
7	 0.5	2,5 di F/ 1	Et_3N	-	THF	r.t, 18 h	3a (32)
8	 0.5	2,5 di F/ 1	Na_2CO_3	-	THF-H_2O	r.t, 20 min	3a (67)
9	 0.5	2,5 di F/ 1	Na_2CO_3	TiO_2(5)	THF- H_2O	r.t, 5 min	3a (88)
10	 0.5	2,5 di F/ 1	Na_2CO_3	TiO_2(10)	THF-H_2O	r.t, 5 min	3a (88)
11	 1	3-CF_3 /1	NaH	-	THF	r.t, 8 h	4a (20)
12	 0.5	3-CF_3 /1	NaH	-	THF	r.t, 8 h	4a (43)
13		3-CF_3 /1	NaH	TiO_2(5)	THF	r.t, 1 h	4a (78)
14	0.5  0.5	3-CF_3 /1	NaH	TiO_2(5)	CH_3CN	r.t, 1 h	4a (80)

-, The reaction proceeded in the absence of any catalyst.

Scheme 4. Conditions reaction for Hydrolyze **1b.**



Base: K_2CO_3, solvent: CH_3CN, Condition: r.t
Base: K_2CO_3, solvent: CH_3CN, Condition: Reflux
Base: K_2CO_3, solvent: THF, Condition: r.t
Base: Na_2CO_3, solvent: THF-DMF, Condition: 50 ^{0}C
Base: Et_3N, solvent: toluene, Condition: 50 ^{0}C

amidoximes with trifluoroacetimidoyl chlorides at the room temperature and in the present TiO_2-NPs depend on solvent and base used. When this reaction was carried out with Na_2CO_3 as the base and THF-H_2O as solvent, trifluoromethyl-4,5-dihydro-1,2,4-oxadiazoles was synthesized in good yields, and when the reaction occurred in THF using NaH base, resulted to trifluoromethyl-1,2,4-oxadiazoles. In conclusion, the chemistry developed here is very versatile and accommodates various functional groups. Also, the synthesized heterocycles are of potential utility as new pharmacophores and scaffolds for drug discovery.

EXPERIMENTAL SECTION

General information. Melting points were determined using a Melt-Tem II melting point apparatus and are uncorrected. IR spectra were recorded on Matson-1000 FT-IR spectrometer. All of the NMR spectra were recorded on a Bruker model DRX-400 AVANCE (^{1}H: 400, ^{13}C: 100, F: 376 MHz) NMR spectrometer. Chemical shifts of ^{1}H and ^{13}C NMR are reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference in DMSO-d_6 or $CDCl_3$ as a solvent and ^{19}F NMR are reported in ppm from $CFCl_3$ as an internal standard in DMSO-d_6 or $CDCl_3$ as solvent. Coupling constants (J) are reported in Hertz (Hz), and spin multiplicities are presented by the following symbols: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Element analyses (CHN) were performed with a EUROVECTOR EuroEA3000 CHNSO analyzer.

General procedure for the synthesis of compounds 3a–d. To a stirred solution of the corresponding amidoxime **1a–f** (0.5 mmol), Na_2CO_3(0.6 mmol) and titanium dioxide (5% mmol) as catalyst in THF, H_2O 1:1 (5 mL) was added mixture of acetimidoyl chloride **2a–e** (1 mmol) in 5 ml THF and the resulting solution was stirred for 5 min. The mixture was stirred until substrate was consumed (the progress of the reaction was monitored by TLC for disappearance of substrate). After that time, the reaction was diluted with H_2O and extracted with EtOAc (3×). The organic layer was dried ($MgSO_4$) and residual solvent was removed by evaporation to give the products.

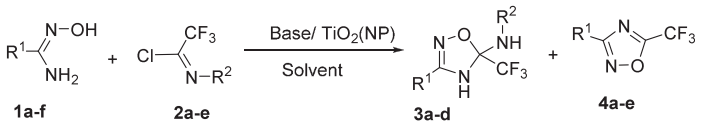
3-(4-Bromophenyl)-N-(2,5-difluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2,4-oxadiazol-5-amine (3a). White solid; 92% yield, m.p. 93–95°C. IR (KBr, cm^{-1}): 3464, 3354, 1711. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 (d, J = 8.4 Hz, NH), 7.85 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.19 (m, NH and 1H), 7.01 (ddd, J = 9.5, 6.5, 3.2 Hz, 1H), 6.90 (ddd, J = 12.1, 8.5, 3.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.54 (d, J = 253.6 Hz, C–F), 147.88 (d, J = 253.7 Hz, C–F), 147.14, 132.66, 131.17 (2C), 129.28, 128.30 (2C), 124.96 (q, J = 266.0 Hz, C–$\underline{C}F_3$), 124.39, 115.90 (dd, J = 23.1, 9.4 Hz), 110.48 (dd, J = 24.0, 7.5 Hz), 108.64 (dd, 25.8, 6.0 Hz), 103.24 (q, J = 32.7 Hz, $\underline{C}$–CF_3). ^{19}F NMR (376 MHz, DMSO-d_6): δ = −73.41 (s, 3F). *Anal*. *Calcd*. For $C_{15}H_9BrF_5N_3O$ (422.15): C, 42.68; H, 2.15; N, 9.95. Found: C, 42.33; H, 2.02; N, 9.74%.

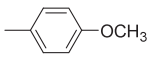
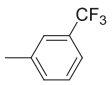
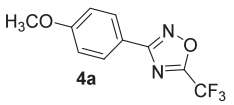
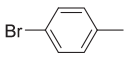
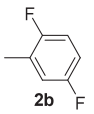
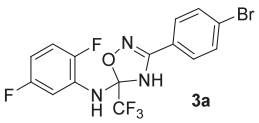
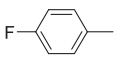
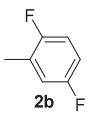
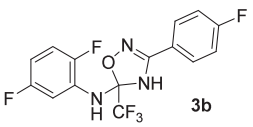
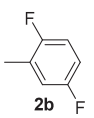
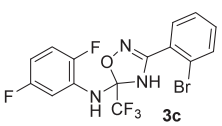
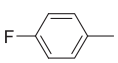
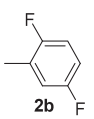
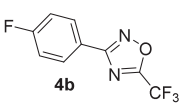
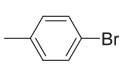
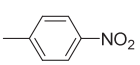
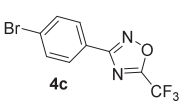
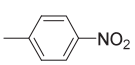
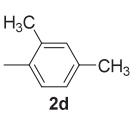
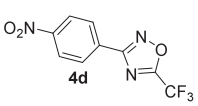
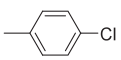
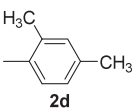
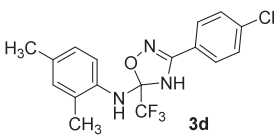
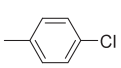
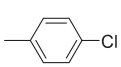
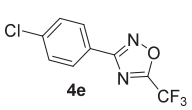
N-(2,5-difluorophenyl)-3-(4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2,4-oxadiazol-5-amine (3b). White solid; 90% yield, m.p. 84–86°C. IR (KBr, cm^{-1}): 3503, 3362, 1732. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.10–8.12 (m, NH and 1H), 6.82–7.76 (m, NH and 4H), 6.49 (m, 1H), 6.24(m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.33(d, J = 251.8 Hz, C–F), 159.03 (d, J = 251.8 Hz, C–F), 153.11 (d, J = 251.9 Hz, C–F), 149.98, 130.11, 128.85, 128.73, 126.32, 123.80 (q, J = 268.1 Hz, C–$\underline{C}F_3$), 116.82 (dd, J = 20.0, 7.6 Hz), 115.36, 115.07, 110.38 (dd, J = 24.0, 7.5 Hz), 108.71 (dd, J = 20.0, 7.6 Hz), 102.45 (q, J = 26.7 Hz, $\underline{C}$–CF_3). ^{19}F NMR (376 MHz, DMSO-d_6): δ = −69.60 (s, 3F), −109.62 (m, 1F), −118.98 (m, 1F), −130.78 (m, 1F). *Anal*. *Calcd*. For $C_{15}H_9F_6N_3O$ (361.25): C, 49.87; H, 2.51; N, 11.63. Found: C, 49.84; H, 2.46; N, 11.59%.

3-(2-Bromophenyl)-N-(2,5-difluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2,4-oxadiazol-5-amine (3c). Cream solid; 88% yield, m.p. 92–95°C. IR (KBr, cm^{-1}): 3480, 3334, 1685. ^{1}H NMR (400 MHz, DMSO-d_6):

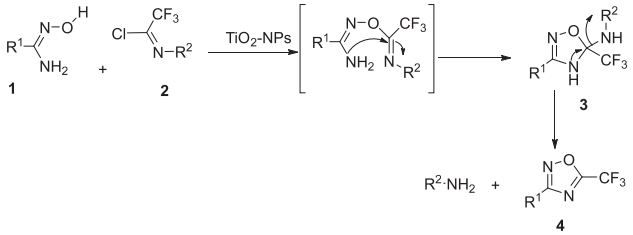
Table 2

One-pot synthesis of trifluoromethyl-4,5-dihydro-1,2,4-oxadiazoles and trifluoromethyl-1,2,4-oxadiazoles in the presence of TiO_2-NPs.



Entry	R^1	R^2	Base/ solvent	Products	Time	Yield (%)
1	 1a	 2a	NaH/THF	 4a	1 h	88
2	 1b	 2b	Na_2CO_3/THF-H_2O	 3a	5 min	92
3	 1c	 2b	Na_2CO_3/THF-H_2O	 3b	5 min	90
4	 1e	 2b	Na_2CO_3/THF-H_2O	 3c	5 min	88
5	 1c	 2b	NaH/THF	 4b	1 h	90
6	 1b	 2c	NaH/THF	 4c	1 h	85
7	 1d	 2d	NaH/THF	 4d	1 h	80
8	 1f	 2d	Na_2CO_3/THF-H_2O	 3d	5 min	87
9	 1f	 1e	NaH/THF	 4e	1 h	89

Scheme 5. Proposed mechanism for synthesis of trifluoromethyl-4,5-dihydro-1,2,4-oxadiazoles and trifluoromethyl-1,2,4-oxadiazoles.



δ = 7.92 (m, NH and 1H), 7.69–7.55 (m, 3H), 6.97 (ddd, *J* = 11.1, 8.9, 5.2 Hz, 1H), 6.52 (ddd, *J* = 10.5, 7.3, 3.1 Hz, 1H), 6.25 (tt, *J* = 8.6, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.95, 158.76 (d, *J* = 236.1 Hz), 146.85 (d, *J* = 230.8 Hz), 134.29, 133.54, 132.31 (2C), 128.32, 125.63, 125.19 (q, *J* = 268.7 Hz, C–$\underline{C}F_3$), 121.25, 115.35 (dd, *J* = 20.9, 10.9 Hz), 105.40 (q, *J* = 26.2 Hz, $\underline{C}$–CF_3), 101.91 (dd, *J* = 27.2, 4.9 Hz), 100.85 (dd, *J* = 24.5, 7.1 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ = −73.45 (s, 3F). *Anal*. *Calcd*. For $C_{15}H_9BrF_5N_3O$ (422.15): C, 42.68; H, 2.15; N, 9.95. Found: C, 42.21; H, 1.83; N, 9.54%.

3-(4-Chlorophenyl)-N-(2,4-dimethylphenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2,4-oxadiazol-5-amine (3d). White solid; 87% yield, m.p. 124–130°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75–7.53 (m, 4H), 6.93–6.86 (m, 2H), 6.80 (s, 1H, NH), 6.76 (dd, *J* = 7.8, 1.9 Hz, 1H), 2.32 (s, 3H, CH_3), 2.24 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.00, 141.09, 136.29, 133.21, 131.00, 130.88, 128.96 (2C), 128.44 (2C), 127.51, 124.68, 122.73 (q, *J* = 268.4 Hz, C–$\underline{C}F_3$), 120.86, 102.45 (q, *J* = 26.7 Hz, $\underline{C}$–CF_3), 20.84 (CH_3), 17.62 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −73.42 (s, 3F). *Anal*. *Calcd*. For $C_{17}H_{15}ClF_3N_3O$ (369.77): C, 55.22; H, 4.09; N, 11.36. Found: C, 55.18; H, 3.96; N, 11.08%.

General procedure for the synthesis of compounds 4a–e. To the stirred solution of the amidoximes **1a–f** (0.5 mmol), NaH (2 mmol) and titanium dioxide (5% mmol) as catalyst in THF (10 ml) was added mixture of acetimidoyl chlorides **2a–e** (1 mmol) in 5 ml THF and the resulting solution was stirred for 1 h. The mixture was stirred at room temperature appropriate time and then filtered. After removing the solvent under reduced pressure, the crude product was purified by preparative thin-layer chromatography on silica gel [eluent: n-hexane/EtOAC] to give the products.

3-(4-Methoxyphenyl)-5-(trifluoromethyl)-1,2,4-oxadiazole (4a). The product was purified by Plate Chromatography (n-hexane/EtOAc, 6:1) to give product as a yellow oil; 88%yeild. IR (neat, cm^{-1}): 3020, 2959, 1718, 1678. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.75–7.66 (m, 2H), 7.06–6.79 (m, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.69 (q, *J* = 32.4 Hz, $\underline{C}$–CF_3), 167.04, 159.74, 127.07 (2C), 123.93, 115.71 (q, *J* = 267.3 Hz, C–$\underline{C}F_3$), 113.50(2C), 55.04. ^{19}F NMR (376 MHz, DMSO-d_6): δ = −77.46 (s, 3F). *Anal*. *Calcd*. For $C_{10}H_7F_3N_2O_2$ (244.17): C, 49.19; H, 2.89; N, 11.47. Found: C, 48.91; H, 2.88; N, 11.44%.

3-(4-Fluorophenyl)-5-(trifluoromethyl)-1,2,4-oxadiazole (4b). The product was purified by Plate Chromatography (n-hexane/EtOAc, 4:1) to give product as cream solid; 90% yield. m.p. 190°C dec. ^{1}H NMR (400 MHz, DMSO- d_6): δ = 7.87–7.78 (m, 2H), 7.28–7.18 (m, 2H).^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.15 (q, *J* = 31.5 Hz, $\underline{C}$–CF_3), 167.03, 163.01 (d, *J* = 245.2 Hz, C–F), 128.32, 128.24, 124.98, 115.71, 115.50, 116.33 (q, *J* = 286.3 Hz, C–$\underline{C}F_3$). ^{19}F NMR (376 MHz, DMSO-d_6): δ = −73.58 (s, 3F), −112.72 (m, 1F). *Anal*. *Calcd*. For $C_9H_4F_4N_2O$ (232.14): C, 46.57; H, 1.74; N, 12.07. Found: C, 46.56; H, 1.77; N, 12.12%.

3-(4-Bromophenyl)-5-(trifluoromethyl)-1,2,4-oxadiazole (4c). The product was purified by Plate Chromatography (n-hexane/EtOAc, 3:1) to give product as yellow solid; 85% yield. m.p. 230–235°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.17 (d, *J* = 8.7 Hz, 2H), 7.44 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.13, 140.05 (q, *J* = 32.2 Hz, $\underline{C}$–CF_3), 126.86, 125.33, 125.01(2C), 121.29(2C), 117.55 (q, *J* = 288.2 Hz, C–$\underline{C}F_3$).^{19}F NMR (376 MHz, DMSO-d_6): δ = −73.47(s, 3F).

3-(4-Nitrophenyl)-5-(trifluoromethyl)-1,2,4-oxadiazole (4d). The product was purified by Plate Chromatography (n-hexane/EtOAc, 4:1) to give product as cream solid; 80% yield. m.p. 56–60°C. IR (KBr, cm^{-1}): 3103, 1607, 1544. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.48–8.43 (m, 2H), 8.38–8.31 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.00 (q, *J* = 32.3 Hz, $\underline{C}$–CF_3), 167.13, 149.70, 130.15 (2C), 128.88 (2C), 124.67, 115.63 (q, *J* = 267.5 Hz, C–$\underline{C}F_3$). ^{19}F NMR (376 MHz, DMSO-d_6): δ = −72.36 (s, 3F). *Anal*. *Calcd*. For $C_9H_4F_3N_3O_3$ (259.14): C, 41.71; H, 1.56; N, 16.22. Found: C, 41.64; H, 1.42; N, 16.66%.

3-(4-Chlorophenyl)-5-(trifluoromethyl)-1,2,4-oxadiazole (4e). The product was purified by Plate Chromatography (n-hexane/EtOAc, 4:1) to give product as white solid; 89% yield. m.p. 256–260°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.81–7.76 (m, 2H), 7.47–7.43 (m, 2H). ^{13}C NMR

(100 MHz, DMSO-d_6) δ = 174.95 (q, J = 39.4 Hz, C–CF_3), 173.30, 128.26 (2C), 127.35 (2C), 126.31, 116.13 (q, J = 267.6 Hz, C–CF_3). ^{19}F NMR (376 MHz, DMSO-d_6): δ = −73.46 (s, 3F). *Anal*. *Calcd*. For $C_9H_4ClF_3N_2O$ (248.59): C, 43.48; H, 1.62; N, 11.27. Found: C, 43.38; H, 1.80; N, 11.20%.

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REFERENCES AND NOTES

[1] Swinbourne, J. F.; Hunt, H. J.; Klinkert, G. Adv Heterocycl Chem 1987, 23, 103.

[2] Pace, A.; Pierro, P. Org Biomol Chem 2009, 7, 4337.

[3] Maftei, C. V.; Fodor, E.; Jones, P. G.; Franz, M. H.; Kelter, G.; Fiebig, H.; Neda, I. Beilstein J Org Chem 2013, 9, 2202.

[4] Ledford, R. M.; Collett, M. S. D C An-tiviral Res 2005, 68, 135.

[5] Messer, W. S. Jr.; Abuh, Y. F.; Liu, Y.; Periyasamy, S.; Ngur, D. O.; Edgar, M. A. N.; El-Assadi, A. A.; Sbeih, S.; Dunbar, P. G.; Roknich, S.; Rho, T.; Ojo, Z. F.; Ojo, B.; Zhang, H.; Huzl, J. J.; Nagy, P. I. J Med Chem 1997, 40, 1230.

[6] Rudolph, J.; Theis, H.; Hanke, R.; Endermann, R.; Johannsen, L.; Geschke, F. U. J Med Chem 2001, 44, 619.

[7] Rajapakse, H. A.; Zhu, H.; Young, M. B.; Mott, B. T. Tetrahedron Lett 2006, 47, 4827.

[8] Vazquez, G. N.; Salinas, G. M. M.; Fajardo, Z. V. D.; Villarreal, J. V.; Soto, S. E.; Salazar, F. G.; Nunes, E. H.; Fernandez, S. S. Bioorg Med Chem 2007, 15, 5502.

[9] Cottrell, D. M.; Capers, J.; Salem, M. M.; Fradley, K. D. L.; Croft, S. L.; Werbovetz, K. A. Bioorg Med Chem 2004, 12, 2815.

[10] Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsorth, H. J.; Wyman, P. J Med Chem 1991, 34, 2726.

[11] Suzuki, T.; Uesaka, H.; Hamajima, H.; Ikami, T. Chem Pharm Bull 1999, 47, 876.

[12] Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. J Med Chem 1991, 34, 140.

[13] Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; Macleod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunders, J.; Swain, C. J.; Wong, E.; Springer, J. P. J Med Chem 1989, 32, 2282.

[14] Carroll, F. I.; Gray, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. J Med Chem 1993, 36, 2886.

[15] Ma, J. A.; Cahard, D. J. Fluorine Chem. 2007, 128, 975.

[16] Tomashenko, O. A.; Grushin, V. V. Chem Rev 2011, 111, 4475.

[17] Liang, T.; Neumann, C. N.; Ritter, T. Angew Chem Int Ed 2013, 52, 8214.

[18] Chen, P.; Liu, G. Synthesis 2013, 45, 2919.

[19] Andre, L. C R Chem 2004, 7, 103.

[20] Lim, C. W.; Lee, I. S. Nano Today 2010, 5, 412.

[21] Narayanan, K. B.; Sakthivel, N. Adv Colloid Interface Sci 2011, 169, 59.

[22] Pio, F. Catalysis Today 2000, 62, 51.

[23] Maldotti, A.; Molinari, A.; Amadeni, R. Chem Rev 2002, 102, 3811.

[24] Safari, J.; Gandomi-Ravandi, S. J Mol Struct 2014, 1065, 241.

[25] Darehkordi, A.; Javanmiri, M.; Ghazi, S.; Assar, S. J. Fluorine Chem. 2011, 132, 263.

[26] Darehkordi, A.; Rahmani, F.; Hashemi, V. Tetrahedron Lett 2013, 54, 4689.

[27] Rahmani, F.; Darehkordi, A.; Notash, B. J. Fluorine Chem. 2014, 166, 84.

[28] Darehkordi, A.; Rahmani, F. J Fluorine Chem 2016, 190, 41.

[29] Lin, C. C.; Hsieh, T. H.; Liao, P. Y.; Liao, Z. Y.; Chang, C. W.; Shih, Y. C.; Chien, T. C Organic lett 2014, 16, 892.

[30] Uneyama, K.; Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H. J Org Chem 1993, 58, 32.

[31] Moore, H. M.; Hughes, G.; Srinivasachar, K.; Fernandez, M.; Nguyen, N.; Schoon, D.; Tranne, A. J Org Chem 1985, 50, 4231.

[32] Salazar, J.; Lopez, S. E. O J Flu-orine Chem 2003, 124, 111.

[33] Lopez, S. E.; Perez, Y.; Restrepo, J.; Salazar, J.; Charris, J. J Fluorine Chem 2007, 128, 566.

[34] Kim, J. G.; Jang, D. O. Tetrahedron Lett 2010, 51, 683.