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A convenient, facile and novel procedure for synthesis 2-amino-5-aryl-1,3,4-oxadiazoles derivatives

Kinjal D. Patel, Rajesh H. Vekariya and Hitesh D. Patel*

Department of Chemistry, School of Sciences, Gujarat University, Ahmedabad, Gujarat, India.

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Abstract: A convenient and efficient procedure for the synthesis of substituted 2-amino-5-aryl-1,3,4-oxadiazoles has been achieved by the reaction between isothiocynate, hydrazine hydrate and acid chloride in which cylodesulfurisation was carried out by Lugol's reagent (I_2/KI) in the presence of sodium hydroxide. All synthesised compounds were characterised by IR, Mass, ^{1}H-NMR, ^{13}C-NMR and elemental analysis.

Keywords: Cylodesulfurisation, Efficient synthesis, High yield, Lugol's reagent (I_2/KI), Oxadiazole.

Introduction

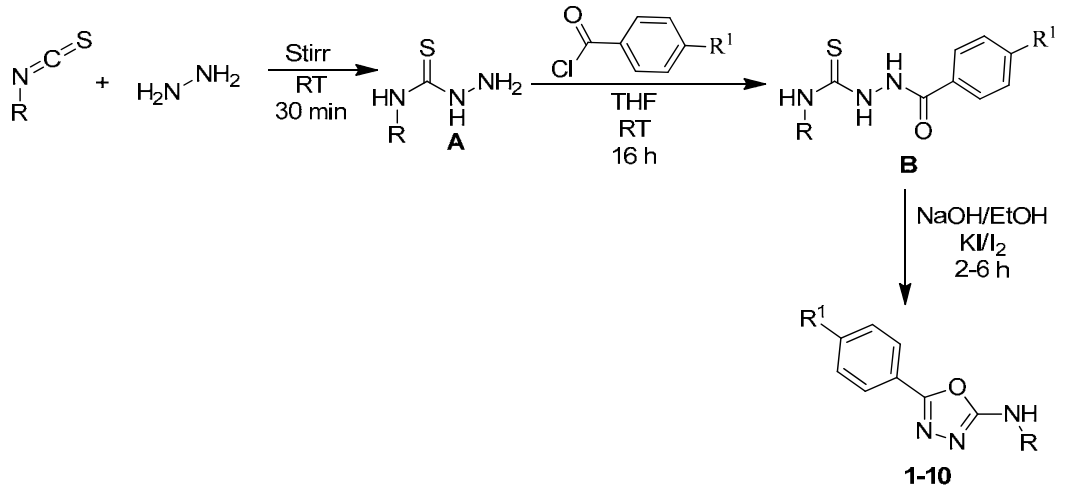
1,3,4-oxadiazole moiety shows wide applications in the field of pharmacologic field. 2-Amino-5-aryl-1,3,4-oxadiazole derivatives report various biological activities likeanti-tuberculosis [1]. Antimicrobial [2], anticancer [3]. In addition, they also have applications in the field of material science and organic electronics [4-6]. Previously, substituted 2-amino-1,3,4-oxadiazole was synthesized by using various catalysts like, iodine and potassium carbonate, [7] benzotriazole-1-yl-oxy-tris-(dimethylamino) phosphonium hexafluoro phosphate (BOP) and 1,8-diazabicycloundec-7-ene (DBU), [8] *o*-iodoxybenzoic acid (IBX), [9] resin bounded reagents like PS-carbodiimide, P-propylamine, PS-bemp, [10] *N*,*N*-diisopropylethylamine (DIEA) with various coupling agents like *N*,*N*'-diisopropylcarbodiimide (DIC), *N*,*N*'-dicyclohexylcarbodiimide (DCC), *N*,*N*'-carbonyldiimidazole (CDI), O-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluroniumtetrafluoroborate (TBTU), [11] tosyl chloride and pyridine, [12] 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) [13], N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDCI), [14] ferrous chloride or bromide and sodium acetate in acetic acid [15] and electrolysis method using $LiClO_4$ using various solvents [16]. We have reported one review article on the synthesis of 1,3,4-oxadiazole derivatives by using various methodologies. [17] One of the most common protocols involves the cyclization of 2-acyl-hydrazine carbothioamide in the presence of a cyclization catalyst to result in oxadiazole. However, most of these methods are having some limitations like longer reaction time, lower yields of the product, expensive catalysts and difficult work-up process. Thus, we have reported here an efficient protocol for the preparation of 2-amino-1,3,4-oxadiazole derivatives via three step synthesis. Here, we have used Lugol's reagent (I_2/KI) as an efficient catalysts for the synthesis of 2-amino-1,3,4-oxadiazole derivatives in excellent yields.

Results and discussion

By taking clues from previously reported protocols, and recent developments, we describe synthesis of the 2-amino-5-aryl-1,3,4-oxadiazoles in high yield that does not require any chromatographic purification of the products. The procedure does not require an anhydrous

*Corresponding author. Tel: +91-079-26300969, Fax: +91-079-2630854, E-mail: drhiteshpatel1@gmail.com

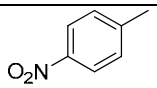
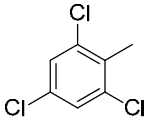
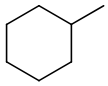
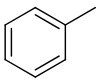
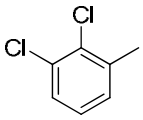
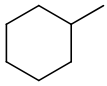
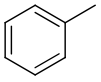
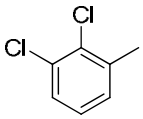
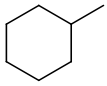
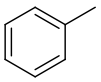
solvent and inert gas atmosphere. We establish our methodology utilizing commercially available acid chlorides (1 equiv.), hydrazine hydrate (3 equiv., 80 %) and various isothiocynates (1 equiv.) **(**Scheme**1)**. Here, we describe a general protocol where R group represent a broad spectrum of aliphatic and aromatic substituent as shown in (Table **1**).



Scheme 1: Synthetic strategy for the preparation of 2-amino-5-aryl-1,3,4-oxadiazole derivatives.

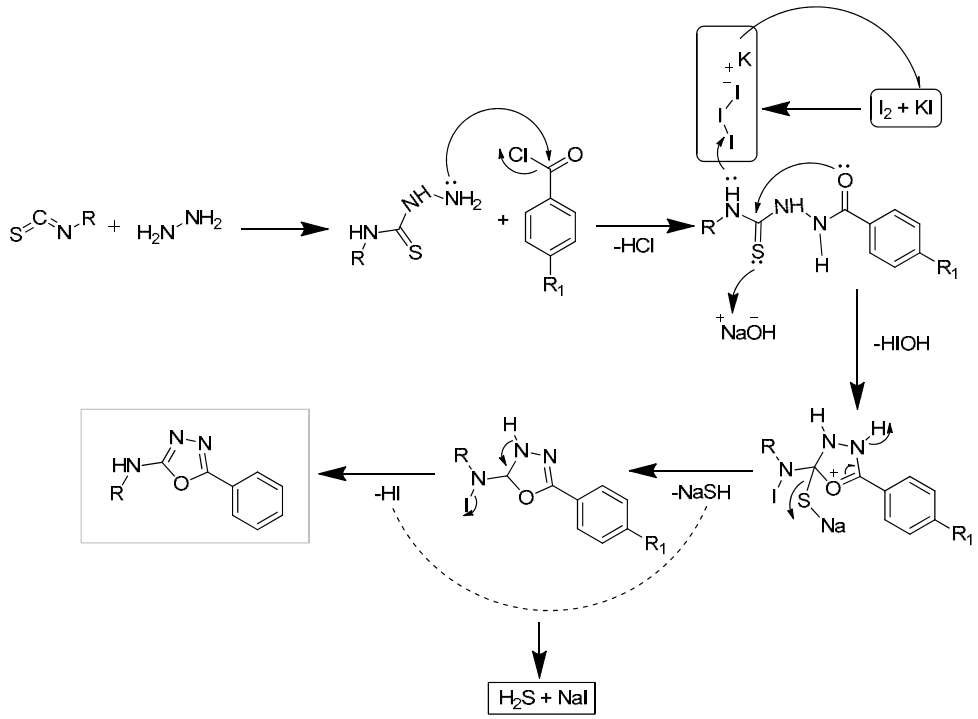
The isolated yields of the products varied depending on the substituent present on acid chlorides and isothiocynate. The results of our method showed that compounds containing electron-rich substituent tend to lead high yield of the products as compared to compounds with electron withdrawing groups **(Table 1)**.

Table 1: One-pot solvent free synthesis of substituted 2-amino-5-aryl-1,3,4-oxadoazoles.

Entry	R	R^1	Time (hr)	%Yield
1		H	1.5	75
2		H	1.25	82
3		$-NO_2$	1.25	72
4		$-NO_2$	1.5	78
5		$-NO_2$	1.5	70
6		-Cl	1.25	78
7		-Cl	1.25	82
8		-Cl	1.5	86
9		$-OCH_3$	2	71
10		$-OCH_3$	2	64

We have also describe the proposed reaction mechanism (Scheme**2**).Thiosemicarbazide was yield from isothiocynate and hydrazine hydrate which would be further cyclised which is catalysed by I_2/KI (Lugol's reagent)to form 2-amino-1,3,4-oxadiazole derivative. Here, I_2/KI plays an important role to hold electrons of nitrogen to not interfere in cyclisation with oxygen. Sodium hydroxidetries to pull electrons of sulphur (C=S) which allow oxygen to share lone pair of

electrons to deficient carbon. After transfer of electrons and removal of by-products, desired product was formed. Sodium hydrosulphide and hydroiodic acid react to form sodium iodide and hydrogen sulphide (tested by lead acetate paper).



Scheme 2: Proposed reaction mechanism.

Experimental

Melting points are uncorrected and were determined in automatic melting point apparatus named Optimelt MPA 100. TLC was run on Aluminum pre-coated ready-made thin layer chromatography (TLC) silica gel 60 F_{254} plate (Merck, Germany) and visualization were done using iodine or UV light. IR Spectra (V max in cm^{-1}) were recorded on a Perkin- Elmer FT-IR 377 spectrophotometer using KBr. Proton NMR spectra were recorded on Bruker AV 400 MHz spectrometer using DMSO as solvent and TMS as the internal reference and Carbon NMR spectra were recorded on Bruker AV 100 MHz spectrometer using DMSO as solvent. Mass spectra were recorded at Advion expression CMS, USA, Acetone is used as mobile phase, electron spray ionization (ESI) is used as ion source. Elemental analysis was performed on a CHN elemental analyzer.

General Procedure

Synthesis of A [18]

Add hydrazine hydrate (3.0 equi.) in to the mixture ofisothiocynate (1.0 equi.) and methanol (5 mL). Let the reaction stir at room temperature for 30 min. check TLC upto the completion of reaction. Filter the precipitates and recrystallized in methanol.

Synthesis of B [19]

Dissolve 1.0 equiv. of ***A***in 10 mL THF, add 1.0 equiv. acid chloride drop wise in to it and allow to stir for 16 h at room temperature. After completion of the reaction neutralise reaction mixture by sodium bicarbonate and recrystallize it with methanol.

Synthesis of 1-14 [20]

B (1 mol) in (6 ml)ethanol was added to a solution of (5 N) NaOH with coolingand stirring. To this clear solution was added a solution ofKI/I_2(Lugol's reagent) until a permanent tinge colour of iodine persisted at roomtemperature. The mixture was immediately refluxed, and moreKI/I_2 solution was added until the permanent tinge colour of iodineremained at the higher temperature. The solution wasthen refluxed until the TLC proves completion of reaction, after completion of the reaction solution was then cooled and poured into ice-cold water. The solid that separatedwas

collected by filtration and was then washed withdistilled water, with dilute thiosulfate solution, and again withdistilled water before being dried. The crude compounds wererecrystallized from ethanol.

N-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazol-2-amine **(1)***:* Orange powder (MeOH); mp 192 ^{o}C; ^{1}H NMR (DMSO-d6, 400MHz) δ = 8.235-8.263 (2H, dd, J=2.5 Hz), 7.786-7.809 (2H, d, J=2.1 Hz), 7.843-7.866 (1H, d, J=2.1 Hz), 7.676-7.590 (2H, dt, J=7.8 Hz), 7.920-7.957 (2H, dd, J=3.3 Hz), 7.504-7.551 (2H, dd, J=7.5 Hz), 10.841 (1H, s, -NH); ^{13}C NMR (DMSO, 100 MHz): 184.53, 168.77, 164.18, 149.37, 137.86, 129.08, 128.45, 128.15, 123.71, 112.58; IR (KBr) in cm^{-1}: 1120, 1590, 1360, 1500, 1660, 2960; ESI-MS (m/z) M^{+} 282.25 [14%], base peak 117.1 [100%]; Anal. Calcd. For $C_{14}H_{10}N_4O_3$: C, 59.78; H, 3.37; N, 19.66. Found: C, 59.57; H, 3.57; N, 19.85.

N-(2,4,6-trichlorophenyl)- 5-Phenyl-1,3,4-oxadiazol-2-amine (**2**): White powder (MeOH); mp 175 ^{o}C; ^{1}H NMR (DMSO-d6, 400MHz) δ = 7.697 (2H, s), 7.515-7.552 (1H, t, J=3.3 Hz), 7.591-7.628 (2H, t, J=3.3 Hz), 7.919-7.940 (2H, dd, J=1.9 Hz), 10.538 (1H, s, -NH); ^{13}C NMR (DMSO, 100 MHz): 181.02, 165.83, 135.08, 135.86, 135.23, 132.52, 131.85, 128.49, 127.78, 128.15, 127.44; IR (KBr) in cm^{-1}: 1178, 1629, 1288, 592, 688, 1213, 1026, 1630, 1900, 3005; ESI-MS (m/z) $[M^{-2}]^{+}$336.3 [9%], base peak 116.9 [100%]; Anal. Calcd. For$C_{14}H_8Cl_3N_3O$: C, 49.67; H, 2.27; N, 12.44.Found:C, 49.37; H, 2.37; N, 12.34.

N-Cyclohexyl-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (**3**)*:*Brownish yellow powder (MeOH); mp 275 ^{o}C, ^{1}H NMR (DMSO-d6, 400 MHz) δ = 8.390-8.412 (2H, d, J=0.3 Hz), 8.154-8.176 (2H, d, J=3.9 Hz), 2.498 (1H, m), 1.882 (2H, m), 1.744 (2H, m), 1.48 (1H, m), 11.053 (1H, s, -NH); ^{13}C NMR (DMSO, 100 MHz): 164.22, 162.03, 149.43, 137.86, 129.03, 123.77, 49.25, 32.21, 31.57, 30.29, 25.02, 24.52;IR (KBr) in cm^{-1}: 1108, 1181.8, 1014, 1300.9, 1319.2, 2853, 1347, 3208, 1270.5, 1900, 3030, 2928, 1580, 770, 713, 644, 618; ESI-MS (m/z) M^{+} and Base peak 288.30 [100%]. Anal. Calcd. For$C_{14}H_{16}N_4O_3$: C, 58.35; H, 5.62; N, 19.51. Found: C, 58.32; H, 5.59; N, 19.43.

5-(4-Nitrophenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**4**)*:* Light yellow powder (Dilute MeOH); mp 266 ^{o}C; ^{1}H NMR (DMSO-d6, 400MHz) δ = 8.411-8.389 (2H, d, J=2.0 Hz), 8.181-8.159 (2H, d, J=2.0 Hz), 6.58-6.60 (2H, t, J=1.8 Hz), 7.731-7.780 (2H, d, J=7.3 Hz), 5.81 (1H, m) 9.166 (1H, s, -NH). IR (KBr) in cm^{-1}: 1108.5, 1127.8, 1314.3, 1346.9, 1613, 1590, 3199.2, 1013.9, 1935, 3037, 1513.5, 1301, 1319.3,1346.9, 770, 712; ESI-MS (m/z) M^{+} 282.25 [14%], base peak 117.1 [100%]; Anal. Calcd. For$C_{14}H_{10}N_4O_3$: C, 59.69; H, 3.47; N, 19.92. Found:C, 59.57; H, 3.57; N, 19.85.

N-(2,3-Dichlorophenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (**5**)*:*Light yellow powder (MeOH); mp 250 ^{o}C; ^{1}H NMR (DMSO-d6, 400MHz) δ = 8.154-8.172 (2 H, d, J=1.6 Hz), 8.387-8.405 (2H, d, J=1.6 Hz), 11.033 (1H, s, -NH), 7.222-7.243 (1 H, dd, J=1.8 Hz), 7.324-7.316 (1H, d, J=0.9 Hz), 7.693-7.628 (1H, d, J=2.7 Hz); ^{13}C NMR (DMSO, 100MHz): 169.82, 164.22, 149.42, 137.86, 133.73, 129.03, 128.19, 123.75, 122.90, 118.19, 117.96, 111.92; IR (KBr) in cm^{-1}: 1108.5, 1127.7, 1013, 1300, 1319, 1613.2, 1595, 3199.6, 1184, 1050, 1935.6, 3037.3, 1513.6, 1300.5, 1319.4, 1346.7, 909.7, 712.5, 547.9, 619.4, 640.8; ESI-MS (m/z) M^{+} 351.14 [2.63%] base peak 78.8 [100%]; Anal. Calcd. For $C_{14}H_8Cl_2N_4O_3$: C, 47.99; H, 2.20; N, 15.86. Found:C, 47.89; H, 2.30; N, 15.96.

5-(4-Chlorophenyl)-N-cyclohexyl-1,3,4-oxadiazol-2-amine (**6**)*:* White powder (MeOH); mp 287 ^{o}C; ^{1}H NMR (DMSO-d6, 400MHz) δ = 7.949-7.930 (2H, d, J=1.7 Hz), 7.630-7.612 (2H, d, J=1.6 Hz), 1.091 (1H, m), 1.102 (2H, m), 1.109 (2H, m), 1.127 (1H, m), 10.650 (1H, s, -NH); ^{13}C NMR (DMSO, 100MHz): 170.04, 164.84, 136.80, 131.12, 129.55, 129.37,25.02, 49.25, 30.29, 31.57, 32.21, 24.52; IR (KBr) in cm^{-1}: 1100, 1263, 1562, 1020, 1597, 3014, 1465, 650, 720, 520; ESI-MS (m/z) M^{+} 277.10 [8.33%], base peak 309.1 [100%]; Anal. Calcd. For $C_{14}H_{16}ClN_3O$:C, 60.69; H, 5.71; N, 15.08. Found: C, 60.54; H, 5.81; N, 15.13.

5-(4-Chlorophenyl)-N-phenyl-1,3,4-oxadiazol-2-amine **(7)***:*White powder (MeOH); mp 285 ^{o}C; ^{1}H NMR (DMSO-d6, 400MHz) δ = 7.953-7.949 (2H, d, J=0.4 Hz), 7.636-7.715 (2H, d, J=6.9 Hz), 7.423-7.461 (1H, t, J=3.4 Hz), 6.535-6.736 (2H, dd, J=6.3 Hz), 8.021-8.046 (2H, d, J=2.3 Hz), 10.672 (1 H, s, -NH); ^{13}C NMR (DMSO, 100MHz): 169.62, 164.79, 136.76, 131.13, 129.36, 128.68, 124.22, 118.96, 117.36;IR (KBr) in cm^{-1}: 1090, 1125.9, 1265.3, 1600, 3188.6, 1011.4, 1172.3, 1915.9, 1787.9, 3011.9, 687, 725, 660.8, 625.2, 545.2, 837.4; ESI-MS (m/z) M^{+} 271.7 [11%], base peak 117.1 [100%]; Anal. Calcd. For $C_{14}H_{10}ClN_3O$: C, 61.90%; H, 3.70; N, 15.47. Found: C, 61.89; H, 3.71; N, 15.47.

5-(4-Chlorophenyl)-N-(2,3-dichlorophenyl)-1,3,4-oxadiazol-2-amine (**8**)*:*White powder (Dilute MeOH); mp 231 ^{o}C; ^{1}H NMR (DMSO-d6, 400MHz) δ = 7.929-7.950 (2H, d, J=1.9 Hz), 7.636-7.614 (2H, d, J=2.0 Hz), 7.164-7.186 (1 H, dd, J=1.8 Hz), 7.28-7.24 (1H,

d, J=3.6 Hz), 7.63-7.60 (1H, d, J=2.7 Hz), 10.666 (1H, s, -NH); ^{13}C NMR (DMSO):164.82, 161.94, 136.79, 131.88, 131.13, 129.55,129.37, 128.66, 128.25, 122.940, 118.27;IR (KBr) in cm^{-1}: 1091, 1055, 1564, 160, 1290, 1396, 1265, 1174, 1010, 1492, 1464, 3009, 844, 742, 663; ESI-MS (m/z) M^+ 340.5 [6.25%], base peak 135.2 [100%]; Anal. Calcd. For $C_{14}H_8Cl_3N_3O$: C, 49.37; H, 2.37; N, 12.34.Found: C, 49.37; H, 2.37; N, 12.34.

N-Cyclohexyl-5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine (**9**): White Powder (MeOH); mp 221 ^{o}C; ^{1}H NMR (DMSO-d6, 400MHz) δ = 7.901-7.923 (2H, d, J=2.0 Hz), 7.049-7.071 (2H, d, J=2.0 Hz), 3.838 (3H, s), 2.728 (1H, m), 2.515 (2H, m), 2.533 (2H, m), 2.610 (1H, m), 10.322 (1H, s, -NH); ^{13}C NMR (DMSO): 165.35, 161.94, 129.72, 129.34, 124.73, 113.65, 55.36, 52.55, 31.80, 31.59, 25.04; IR (KBr) in cm^{-1}: 1107.9, 1025.9, 1176.8, 1308.7, 1630, 3211.3, 1253.2, 2846.4, 3000, 779.1, 750.5, 657.2, 625.8, 606.9, 1439, 1469.8. ESI-MS (m/z) M^+ and base peak 273.4 [100%]; Anal. Calcd. For $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37.Found: C, 65.91; H, 7.01; N, 15.37.

5-(4-Methoxyphenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**10**)*:*White powder (MeOH); mp 222 ^{o}C; ^{1}H NMR (DMSO-d6, 400MHz) δ = 7.920-7.898 (2H, d, J=2.0 Hz), 7.044-7.066 (2H, d, J=2.0 Hz), 6.627-6.592 (1H, d, J=5.1 Hz), 6.541-6.455 (2H, d, J=3.4 Hz), 8.897-8.919 (2H, d, J=4.7 Hz), 3.833 (3H, s), 10.317 (1H, s, -NH); ^{13}C NMR (DMSO, 100 MHz):165.35, 161.94, 129.73, 129.31, 124.72, 113.68, 55.36; IR (KBr) in cm^{-1}: 1109, 1176, 1307, 1600, 1562, 1260, 1026, 1516, 1467, 1440, 3012, 694, 750, 657, 607. ESI-MS (m/z) M^+ 267.3 [3%], base peak 135.2 [100%]; Anal. Calcd. For $C_{15}H_{13}N_3O_2$: C, 67.55; H, 4.75; N, 15.72.Found: C, 67.40; H, 4.90; N, 15.72.

Conclusion

In conclusion, we have demonstrated here a convenient and straightforward procedure for the preparation of substituted 2-amino-5-aryl-1,3,4-oxadiazoles utilizing Lugol's reagent (I_2/KI) as a catalyst under mild reaction conditions. Simple reaction conditions, easy work-up procedure, good product yields are the added features of this protocol.

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