Research Article

KF/Al_2O_3 Mediated Synthesis of N-arylamines and their Antifungal Activity

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ABSTRACT

KF/Al_2O_3 (basic) was used to prepare a number of N-arylamines by N-arylation of primary/secondary amines with activated aryl halides at room temperature. All the new compounds have been characterized by their spectral and micro analytical data. Compounds were examined for their antifungal activity against Candida albicans and Saccharomyces cerevisiae. Some of the synthesized compounds showed significant anti-fungal activity.

Keywords: Activated aryl halides, Antifungal activity, KF/Al_2O_3 (basic), N-arylation, Primary/Secondary amines,

INTRODUCTION

Synthesis of N-arylated compounds has received attention worldwide due to their structural motifs which are present in a number of molecules with several applications. N-arylated compounds are distinctive structures in medicinal chemistry. Thus N-arylation is an important reaction since the outcome N-arylated product plays a very important role in pharmaceuticals, natural products and biologically active compounds.[1-6]

The standard method to prepare these moieties is either by using traditional Ullmann type coupling[7-8] as well as the reaction of amines with aryl bismuth, aryl silane and aryl lead reagents.[9-11] However, these reactions suffer from various drawbacks such as high temperature, harsh reaction condition, longer time for completion and stoichiometric quantity of copper, which prevented the use of Ullmann coupling reaction from achieving its potency for a long time and limited their applications. A progress has been made by Buchwald and co workers who revealed that N-arylation of amines with activated aryl halides using copper as a catalyst could be accomplished in good yields in the presence of ligand under mild conditions.[12-18] N-arylation using copper salts, protic solvents and in the absence of base[19-21] has been reported recently. Chan[22] and Lam[23-24] reported the copper-mediated N-arylation using copper (II) acetate and boronic acids. Chiang et al. introduced the C-N cross-coupling reactions with aryl boronic acids using a polymer supported copper catalyst.[25] Collman enhanced the method using catalytic amount of $[Cu(OH)TMEDA]_2Cl_2$, in absence of the base at room temperature.[26-27] However the transition metal used leaves traces of it in the reaction product which creates a problem for drug synthesis. Also ligand and solvent free system would represent a major advance as the inconvenience during workup can be overcome.

Due to increasing environmental and financial problems, the chemical industry altogether has started researching various ways of developing the cleanliness and abundance of many synthetic methods. One such access is the relevance of solid support method. Solid-supported technology has been in use for decades, and has found to be useful for a large range of transformations which are very important to chemists. The advantages of solid support method have been well illustrated in the recent literature: excess reagents and reaction impurities can be easily removed by washing of the solid-phase and large number of compounds can be prepared by using this methodology. Thus this methodology has become a key constituent of a medicinal chemist's armory. Recently we have developed a simple and time effective method for N-arylation.[28]

We report herein the synthesis of N-arylamines by the arylation of primary/secondary amines with activated aryl halides by using KF on basic Al_2O_3as the solid support at room temperature. Basic alumina coated with potassium fluoride (KF/ Al_2O_3), has replaced many organic bases in number of reactions.[29] The KF/ Al_2O_3 possesses a number of advantages. The product can be easily removed by filtration, avoiding tedious workups and decreasing solvent waste concern. In addition, the product is not bounded covalently to the solid support, the reactions can be easily monitored and analysis can be achieved by using thin layer chromatography.

MATERIALS AND METHODS

The melting points were determined using capillary tube and are uncorrected. The FTIR spectra were recorded on Spectrum One Perkin Elmer (US). The ^1H NMR spectra were recorded on a Bruker AVANCE (300 MHz) spectrometer (with TMS as internal reference). ^{13}C NMR spectra were recorded on Bruker AVANCE (75MHz) spectrometer. Mass spectra were recorded on API-3000 MD-series (US). Elemental analyses were carried out in EA 3000, Euro Vector, Italy. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (200mesh).

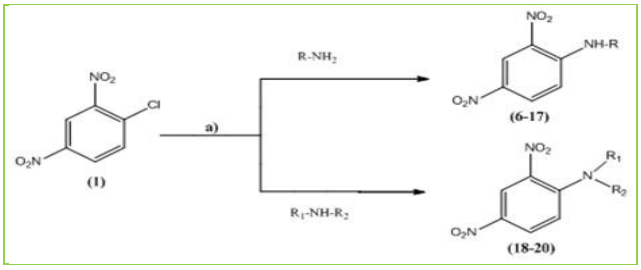
General procedure for the preparation of compounds (6-39)

To a mixture of dry KF (0.3g) and basic Al_2O_3 (0.5g) as solid support add primary/secondary amines (0.005M) and stir it well. Now add activated aryl halide (0.005M) at room temperature with continuous stirring. After completion of reaction (Thin layer chromatography) the solid was extracted with chloroform and filtered. The chloroform extract was distilled and residue purified by crystallization/column chromatography.

The activated halides 1-chloro-2,4-dinitrobenzene (**1**)[30], 2-chloro-1,3-dinitro-5-(trifluoromethyl) benzene (**2**)[31], 2-chloro-3-nitropyridine (**3**)[32], 2-chlorobenzoxazole (**4**)[33], 2-chlorobenzothiazole (**5**)[34] have been synthesized as per the literature procedure.

Antifungal activity

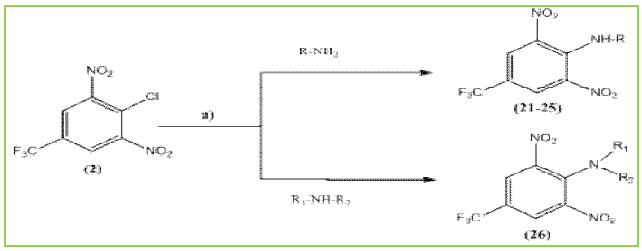
The antifungal activity of the synthesized compounds was tested against *Candida albicans* and *Saccharomyces cerevisiae* using nutrient agar medium (Hi-Media Laboratories, India).The results are summarized in Table 6.The medium is prepared by dissolving 3.39 g of the commercially available Muller Hinton Agar Medium (HiMedia) in 100 ml of distilled water. The dissolved medium was autoclaved at 15 lbs pressure at 121°C for 15 minutes. The autoclaved medium was mixed well and poured onto 100 mm petriplates (25-30 ml/plate) while still molten. 100 ml of nutrient broth was prepared by dissolving 1.3 g of commercially available nutrient medium (HiMedia) in 100 ml distilled water and boiled to dissolve the medium completely. The medium was dispensed as desired and sterilized by autoclaving at 15 lbs pressure (121°C) for 15 minutes. Petri plates containing 20 ml Muller Hinton medium were seeded with 24hr culture of bacterial strains. Wells were cut and 20µl of the compounds (in DMSO) were added. The plates were incubated at 37^0C for 24 hours for antifungal activity. Amphoterin is used as standard.



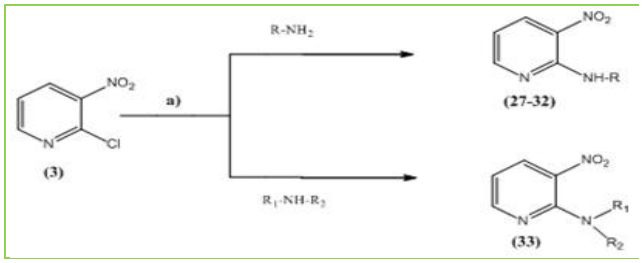
Scheme 1: Synthesis of N-arylamines (**6-20**) by N-arylation of amines with 2,4-dinitrochlorobenzenene (**1**). Reaction conditions: a) KF/Al_2O_3 at room temperature.

RESULTS AND DISCUSSION

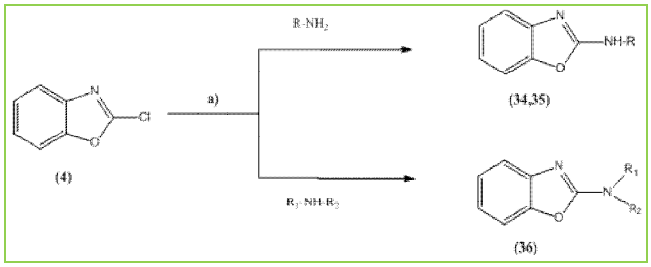
To assess the efficiency and scope of our method, different amines were N-arylated with different activated arylhalides. Initially the C-N bond formation was tested for a number of different primary/secondary amines (0.005M)with different activated aryl halides (0.005M) in presence of KF/Al_2O_3 at room temperature (Schemes 1 and 2) (table 1, 2). The reactivity of arylhalides was greatly improved by electron withdrawing groups such as NO_2, CF_3 either ortho/para or both to the aryl halides compound **1** and **2**. After that we carried out the reaction of different primary/secondary amines (0.005M) with different hetero aryl halides (0.005M) compound **3, 4** and **5** under same conditions(Schemes 3, 4 and 5) (table 3, 4, 5). Good yields of the N-arylated compounds were produced. The N-arylation was also selective; phenolic –OH group (table 1, compound **12**) and alcoholic –OH group (table 4, compound **34**) remained unaffected.



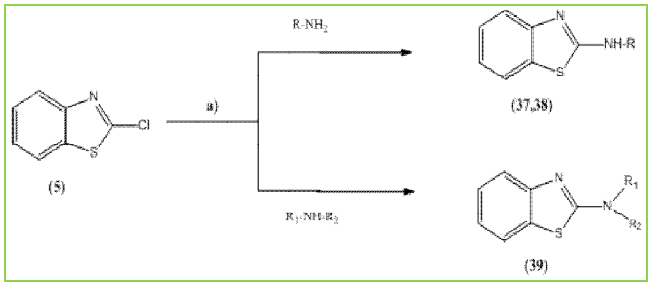
Scheme 2: Synthesis of N-arylamines (**21-26**) by N-arylation of amines with 2-chloro-1,3-dinitro-5-(trifluoromethyl) benzene (**2**). Reaction conditions: a) KF/Al_2O_3 at room temperature.



Scheme 3: Synthesis of N-arylamines (**27-33**) by N-arylation of amines with 2-chloro-3-nitropyridine (**3**). Reaction conditions: a) KF/Al_2O_3 at room temperature.



Scheme 4: Synthesis of N-arylamines (**34-36**) by N-arylation of amines with 2-chlorobenzoxazole (**4**). Reaction conditions: a) KF/Al_2O_3 at room temperature.



Scheme 5: Synthesis of N-arylamines (**37-39**) by N-arylation of amines with 2-chlorobenzothiazole (**5**). Reaction conditions: a) KF/Al_2O_3 at room temperature.

Table 1: Synthesis of N-arylamines (6-20) by N-arylation of amines with 2,4-dinitrochlorobenzenene (1) in presence of KF/Al_2O_3 at room temperature.

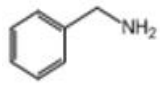
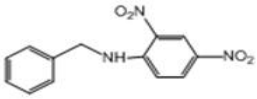
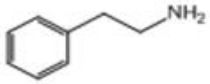
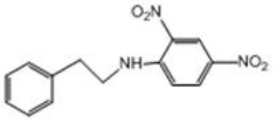
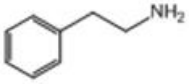
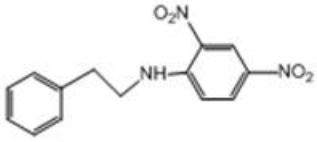
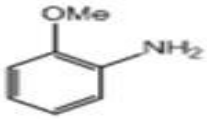
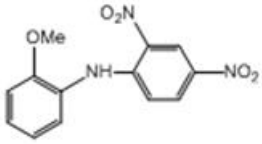
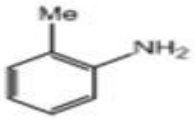
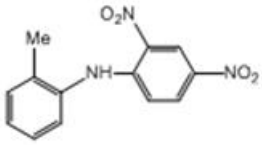
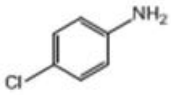
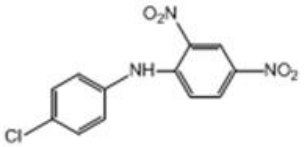
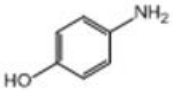
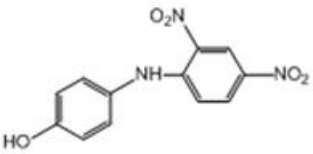
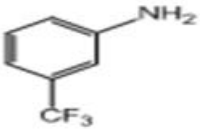
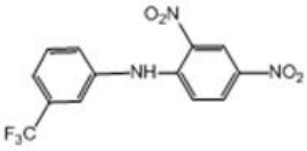
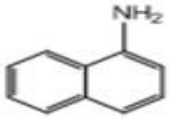
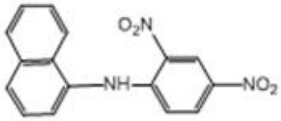
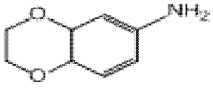
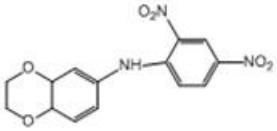
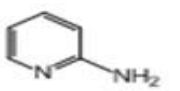
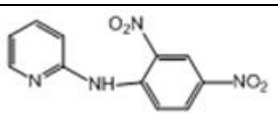
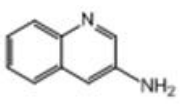
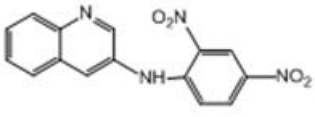
Amine	Product	Time (min)	M.P.[a] (^{0}C)	Yield[b] (%)
		5	115-118[35]	81
		5	155[36]	88
		5	142	82
		8	165-166[37]	78
		7	128-129[38]	80
		5	165-166[39]	85
		6	196[40]	77
		5	125[41]	79
		6	192[42]	83
		6	165	87
		8	155[37]	79
		8	172	80

Table 1: Synthesis of N-arylamines (6-20) by N-arylation of amines with 2,4-dinitrochlorobenzenene (1) in presence of KF/Al_2O_3 at room temperature. (Continued.....)

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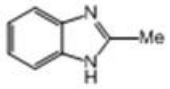
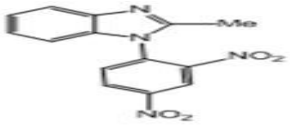
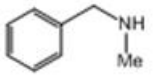
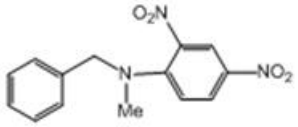
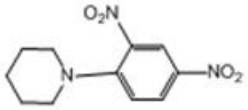
		8	181-182[43]	78
		5	139-140[44]	83
		5	155-156[45]	86

[a]References, [b]Isolated yield

Table 2: Synthesis of N-arylamines (21-26) by N-arylation of amines with 2-chloro-1,3-dinitro-5-(trifluoromethyl) benzene (2) in presence of KF/Al_2O_3 at room temperature.

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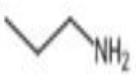
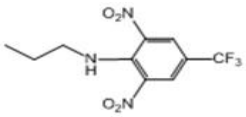
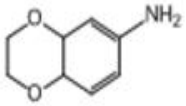
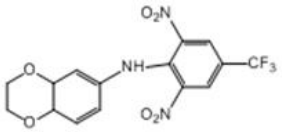
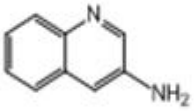
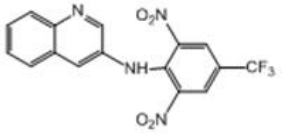
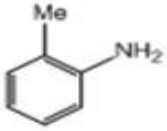
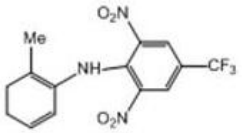
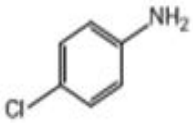
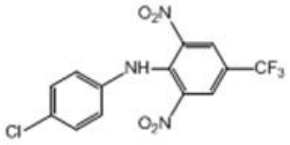
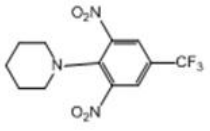
		5	61-62[46]	82
		7	140	80
		7	150	81
		8	124-126[47]	79
		5	102-103[48]	83
		5	106-108[49]	82

[a]References, [b]Isolated yield

Table 3: Synthesis of N-arylamines (**27-33**) by N-arylation of amines with 2-chloro-3-nitropyridine (**3**) in presence of KF/Al_2O_3 at room temperature.

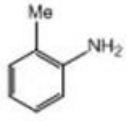
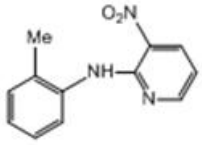
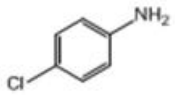
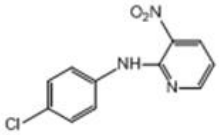
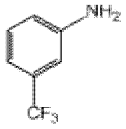
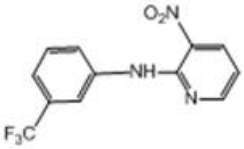
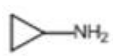
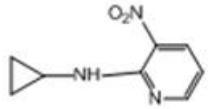
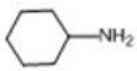
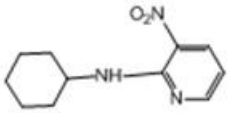
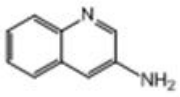
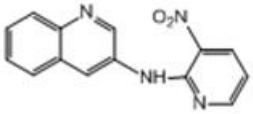
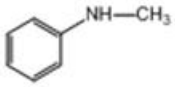
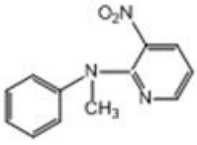
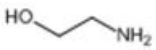
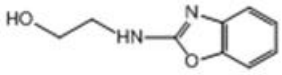
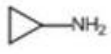
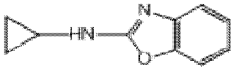
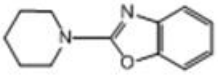
Amine	Product	Time (min)	M.P.[a] (^{0}C)	Yield[b] (%)
		6	124-126[50]	82

Table 3: Synthesis of N-arylamines (**27-33**) by N-arylation of amines with 2-chloro-3-nitropyridine (**3**) in presence of KF/Al_2O_3 at room temperature. (Continued.....)

Amine	Product	Time (min)	M.P.[a] (^{0}C)	Yield[b] (%)
		5	145-147[51]	85
		6	81-82[51]	78
		5	55	82
		5	40	81
		7	165	82
		5	73-74[52]	85

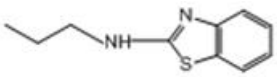
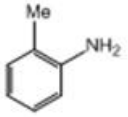
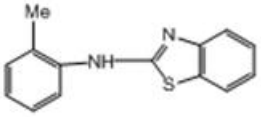
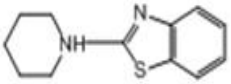
[a]References, [b]Isolated yield

Table 4: Synthesis of N-arylamines (**34-36**) by N-arylation of amines with 2-chlorobenzoxazole (**4**) in presence of KF/Al_2O_3 at room temperature.

Amine	Product	Time (min)	M.P.[a] (^{0}C)	Yield[b] (%)
		5	158-160[53]	78
		5	95-97[54]	80
		5	67-77[55]	82

[a]References, [b]Isolated yield

Table 5: Synthesis of N-arylamines (**37-39**) by N-arylation of amines with 2-chlorobenzothiazole (**5**) in presence of KF/Al_2O_3 at room temperature.

Amine	Product	Time (min)	M.P.[a] (^{0}C)	Yield[b] (%)
		5	79-80[56]	84
		7	121-123[57]	82
		5	90-91[58]	85

[a]References, [b]Isolated yield

Spectroscopic data of compounds (8, 15, 17, 22, 23, 30-32)

N-(4-chlorophenethyl)-2,4-dinitroaniline (8)

Yield 82%.mp: 142^{0}C. IR (KBr, cm-1):3360 (N-H stretching), 3088 (C-H stretching, Ar-H), 1330 (C-N stretching), 720 (C-Cl stretching). ^{1}H NMR (300MHz, $CDCl_3$) δ 9.09 (d, 1H, J=2.7Hz), 8.56 (s,-NH), 8.27 (dd, 1H, J=8.4Hz, J=2.4Hz), 7.33 (d, 2H, J=8.4 Hz), 7.22 (d, 2H, J=8.4 Hz), 6.93 (d, 1H, J=8.4Hz), 3.70 (q, 2H), 3.07 (t, 2H, J=6.9Hz, J=6.9Hz).^{13}C NMR (75MHz,$CDCl_3$)δ 148.0, 136.1, 135.6, 133.2, 130.5, 130.3, 129.9, 129.2, 124.2, 113.7, 44.6, 34.3. MS m/z (%): 321.79 (M+, 100). Anal. Calcd. For $C_{14}H_{12}N_3O_4Cl$: C, 52.27; H, 3.76; N, 13.06. Found: C, 52.24; H, 3.74; N, 13.05.

N-(2, 4-dinitrophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine (15)

Yield 87%.mp: 165^{0}C. IR (KBr, cm-1): 3340 (N-H stretching), 3102 (C-H stretching, Ar-H), 1341 (C-N stretching).^{1}H NMR (300MHz, $CDCl_3$) δ 9.83 (s, -NH), 9.18 (d, 1H, J=2.4Hz), 8.17 (dd, 1H, J=8.1Hz, J=2.4Hz), 7.11 (d, 1H, J=8.4Hz), 6.98 (d, 1H, J=8.4Hz), 6.83 (d, 1H, J=2.4Hz), 6.78 (dd, 1H, J=8.4Hz, J=2.4Hz), 4.32 (m, 4H).^{13}C NMR (75MHz, $CDCl_3$)δ 147.7, 144.5, 137.6, 137.0, 133.2, 131.5, 129.8, 124.0, 119.0, 116.1, 115.0, 113.2, 64.3. MS m/z (%): 316.94 (M+, 100). Anal. Calcd. For $C_{14}H_{11}N_3O_6$: C, 53.00; H, 3.49; N, 13.24. Found: C, 52.85; H, 3.48; N, 13.23.

N-(2,4-dinitrophenyl)quinolin-3-amine (17)

Yield 80%.mp 172^{0}C, IR (KBr, cm-1): 3293 (N-H stretching), 3088 (C-H stretching, Ar-H), 1354 (C-N stretching).^{1}H NMR (300MHz, $CDCl_3$) δ10.05 (s, -NH), 9.20 (d, 1H, J=2.7Hz), 8.90 (d, 1H, J=2.4Hz), 8.25 (dd, 1H, J=6.9Hz, J=2.7Hz), 8.21 (m, 1H), 7.88 (d, 1H, J=2.4Hz), 7.84 (m, 1H), 7.69 (m, 2H), 7.21 (d, 1H, J=6.9 Hz).^{13}C NMR (75MHz, $CDCl_3$)δ 147.7, 145.0, 144.2, 137.6, 135.5, 133.2, 129.8, 129.7, 129.5, 129.0, 128.0, 127.4, 124.0, 113.2. MS m/z (%): 309.96 (M+, 100). Anal. Calcd. For $C_{15}H_{10}N_4O_4$: C, 58.07; H, 3.25; N, 18.06. Found: C, 58.05; H, 3.24; N, 18.00.

N-(2,6-dinitro-4-(trifluoromethyl)phenyl)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine (22)

Yield 80%.mp 140^{0}C, IR (KBr, cm-1): 3295 (N-H stretching), 3081 (C-H stretching, Ar-H),1302 (C-N stretching), 1405 (C-F stretching).^{1}H NMR (300MHz, $CDCl_3$) δ 9.88 (s, -NH), 8.44 (s, 2H), 6.82 (d, 1H, J=8.1Hz), 6.60 (d, 1H, J=2.7Hz), 6.55 (dd, 1H, J=8.1Hz, J=2.7Hz), 4.26 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$)δ 154.5, 144.2, 138.7, 137.9, 131.5, 129.0, 128.9, 123.4, 118.6, 118.1, 114.2, 64.2. MS m/z (%): 384.90(M+, 100). Anal. Calcd. For $C_{15}H_{10}N_3O_6F_3$: C, 46.76; H, 2.62; N, 10.91. Found: C, 46.74; H, 2.60; N, 10.89.

N-(2,6-dinitro-4-(trifluoromethyl)phenyl)quinolin-3-amine (23)

Yield 81%.mp 150^{0}C, IR (KBr, cm-1): 3250 (N-H stretching), 3070 (C-H stretching, Ar-H),1319 (C-N stretching), 1401 (C-F stretching).^{1}H NMR (300MHz, $CDCl_3$) δ10.05 (s, -NH), 8.77 (d, 1H, J=2.4Hz), 8.52 (s, 2H), 8.13 (d, 1H, J=2.4Hz), 7.74 (m, 2H), 7.60 (m, 2H).^{13}C NMR (75MHz, $CDCl_3$)δ 155.0, 145.0, 144.2, 139.3, 135.5, 129.7, 129.5, 129.0, 129.0, 128.0, 127.4, 127.2, 125.6, 124.5. MS m/z (%): 377.86 (M+, 66). Anal. Calcd. For $C_{16}H_9N_4O_4F_3$: C, 50.80; H, 2.40; N, 14.81. Found: C, 50.78; H, 2.27; N, 14.80.

Table 6: Antifungal activity of synthesized compounds (6-39)

	C. albicans		S. cerevisie	
Compounds	**100**	**250**	**100**	**250**
6	+	++	-	-
7	-	-	-	-
8	-	-	-	-
9	+	++	-	+
10	-	-	-	-
11	-	-	+	++
12	+	++	-	+
13	-	-	-	-
14	+	++	+	++
15	-	+	-	-
16	-	-	-	-
17	+	++	++	+++
18	-	+	-	-
19	-	-	-	-
20	-	-	-	-
21	-	-	-	-
22	-	-	-	-
23	++	+++	+	++
24	-	-	-	-
25	-	-	-	-
26	-	-	-	-
27	-	-	-	-
28	-	+	-	-
29	+	++	-	-
30	-	-	-	+
31	-	-	-	-
32	+	++	-	+
33	+	++	+	++
34	-	-	-	-
35	-	-	-	-
36	-	+	-	-
37	-	-	-	+
38	-	-	-	-
39	-	+	-	-
DMSO	-	-	-	-
Amphoterin	+++	++++	+++	++++

(-) No antifungal activity, (+) Less than 15mm, (++) 15-20mm, (+++) 20-25mm, (++++) 25-30mm. All the concentration are in ppm.

N-cyclopropyl-3-nitropyridin-2-amine (**30**)

Yield 82%.mp 55^{0}C, IR (KBr, cm-1): 3380 (N-H stretching), 3048 (C-H stretching, Ar-H),1352 (C-N stretching).^{1}H NMR (300MHz, $CDCl_3$) δ 8.65 (dd, 1H, J=6Hz, J=1.5Hz), 8.30 (s, -NH), 8.26 (dd, 1H, J=6Hz, J=1.5Hz), 7.50 (q, 1H), 1.35 (m, 1H), 0.80 (m, 4H).^{13}C NMR (75MHz, $CDCl_3$)δ 152.3, 152.0, 134.1, 129.7, 111.2, 25.1, 7.8. MS m/z (%): 179.93 (M+, 100). Anal. Calcd. For $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.48; H, 5.03; N, 23.40.

N-cyclohexyl-3-nitropyridin-2-amine (**31**)

Yield 81%.mp 40^{0}C, IR (KBr, cm-1): 3382 (N-H stretching), 3043 (C-H stretching, Ar-H), 1317 (C-N stretching).^{1}H NMR (300MHz, $CDCl_3$) δ 8.64 (dd, 1H, J=6Hz, J= 1.5Hz), 8.25 (dd, 1H, J=6Hz, J=1.5Hz), 8.25 (s, -NH), 7.49 (q, 1H), 4.28 (m, 1H), 2.07 (m, 4H), 1.82 (m, 4H), 1.68 (m, 2H).^{13}C NMR (75MHz, $CDCl_3$)δ 155.7, 152.0, 135.2, 127.6, 111.2, 49.4, 32.9, 25.6, 24.7. MS m/z (%): 221.01(M+, 80). Anal. Calcd. For $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.58, H, 6.80; N, 18.95.

N-(3-nitropyridin-2-yl)quinolin-3-amine (**32**)

Yield 82%.mp 165^{0}C, IR (KBr, cm-1): 3317 (N-H stretching), 3047 (C-H stretching, Ar-H), 1327 (C-N stretching).^{1}H NMR (300MHz, $CDCl_3$) δ 8.63 (dd, 1H, J=6Hz, J=1.8Hz), 8.55 (d, 1H, J=1.8Hz), 8.53 (dd, 1H, J=6Hz, J=1.8Hz), 8.25 (m, 1H), 8.20 (m, 1H), 8.07 (s, -NH), 7.82 (d, 1H, J=1.8Hz), 7.53 (m, 2H), 6.94 (q, 1H).^{13}C NMR (75MHz, $CDCl_3$)δ 155.0, 150.9, 146.5, 145.2, 135.5, 134.1, 129.7, 129.1, 128.3, 128.2, 127.2, 125.6, 114.9. MS m/z (%): 265.06(M+, 100). Anal. Calcd. For $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 62.97; H, 3.65; N, 21.02.

CONCLUSION

We have described an efficient method for the synthesis of N-arylamines by reacting primary/secondary amines with activated aryl halides in presence of solid supported reagent, KF/Al_2O_3 at room temperature. The method is eco-friendly, good yielding and inexpensive. The benefits of this method are the easy handling and reusability of KF/Al_2O_3. The antifungal activity of the synthesized compounds was examined and many of the compounds were found to exhibit good antifungal activity.

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