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Research Article

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Synthesis of N-arylamines in dry media and their antibacterial activity

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ABSTRACT

A number of N-arylamines have been synthesized by carrying out N-arylation of primary/secondary amines with activated aryl halides in presence of KF/Al_2O_3 (basic) dry media at room temperature. All the new compounds have been characterized by their spectral and micro analytical data. Compounds were examined for their antibacterial activity against Escherichia coli, Salmonella typhi, Bacillus substilis, and Staphylococcus aureus. Some of the synthesized compounds showed significant anti-bacterial activity.

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

INTRODUCTION

N-arylamines are an important class of compounds and are widely used as anticancer[1], antileishmanial[2], antidiabetic[3] and analgesic drugs[4]. Some of the compounds have also been reported as antibacterial[5].Transition metal mediated C-N bond formations areimportant fundamental transformations and are commonly used for N-arylation reactions. Mostly C-N bond formed by copper mediated[6-10] (Ullmann reaction) and palladium catalyzed[11-13] (Buchwald-Hartwig reaction) has received much attention. Recently, Bolm et al. reported the iron-catalyzed N-arylation of N-nucleophiles[14,15].Also Buchwald and co-workers used various copper-chelating ligands such as 1,10-phenoanthroline[16] and vicinal diamines[17] for N-arylation. Excess of bases (K_2CO_3, K_3PO_4, KOH) in polar solvents(DMF, DMSO)[18-20] have also been used for N-arylation and required longer time and gave moderate to good yields.

There is a need therefore to develop a transition metal free method, as they are expensive and cannot be removed completely from reaction mixture. Also ligand and solvent free method becomes a good alternative to avoid the inconvenience which arises during workup. The use of solid supported reagents[21] in organic synthesis has received considerable attention due to their eco-friendly nature, reaction rate enhancement, selectivity and avoidance of cumbersome aqueous workup.

In view of these facts we have developed a simple and time effective method for the synthesis of N-arylamines in presence of KF/Al_2O_3 dry media at room temperature. We report herein a rapid and efficient method for the synthesis of N-arylamines by the arylation of primary/secondary amines with activated aryl halides on the surface of KF/Al_2O_3 dry media at room temperature in solvent free condition. Benefit has been achieved by taking advantage of the strongly basic nature of KF/Al_2O_3, which replaces many organic bases in number of reactions[22-24].

EXPERIMENTAL SECTION

The melting points were determined using capillary tube and are uncorrected. The FTIR spectra were recorded on Spectrum One Perkin Elmer (US). The ^{1}H-NMR spectra were recorded on a Bruker AVANCE (300 MHz) spectrometer (with TMS as internal references).^{13}C-NMR spectra were recorded on Bruker AVANCE (75MHZ) spectrometer. Mass spectra were recorded on API-3000MD-series (US). UV spectra were recorded on Shimaduz

2401 PC and Shimaduz 2450, Japan, Spectrophotometer. 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).The reagents were purified by distillation before use.

Anti-bacterial screening

The anti-bacterial activity of the synthesized compounds was tested against *Escherichia coli (*ATCC 25922), *Salmonella typhi* (ATCC 700931), *Staphylococcus aureus (*ATCC 38591), *Bacillus subtilis* (ATTC 6633) using nutrient agar medium (Hi-Media Laboratories, India).

Agar-well diffusion method: The medium was 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 (121ºC) for 15 minutes. Petriplates 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 antibacterial activity. Ciprofloxacin was used as standard.

RESULTS AND DISCUSSION

To assess the efficiency and scope of our method, different amines were N-arylated with different activated aryl halides. 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 dry media at room temperature **(Schemes-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. Good yields (60-90%) of the N-arylated compounds were produced. The results are summarized in Tables 1 and 2. After that we carried out the reaction of different primary/secondary amines (0.005M) with different hetero aryl halides (0.005M) under same condition **(Schemes- 3, 4, 5)**. The results are summarized in Tables 3-5.

General Procedure:

In RBF mix dry KF (0.3g) and Basic Al_2O_3 (0.5 g). Add primary/secondary amines (0.005M) into it, stir it well. Wait for 5 mins. Now add activated aryl halide (0.005M) at room temperature with continuous stirring. After completion of reaction (TLC) the solid was extracted with chloroform and filtered. The chloroform extract was distilled and residue purified by crystallization/column chromatography.

2, 3-Dihydro-N-(2, 4-dinitrophenyl)-1H-inden-5-amine (XIX):

Yield 80%, mp 140-142^{0}C, IR (KBr, cm^{-1}): 3340(N-H stretch.), 3105(C-H stretch.Ar-H), 2947(-CH_2-stretch.), 1338 (C-Nstretch.).^{1}H NMR (300MHz, $CDCl_3$) δ 9.94 (s,1H),9.18(d,1H,J=2.7Hz), 8.16(dd,1H,J=7.5Hz,J=2.7Hz), 7.34(d,1H,J=7.5Hz),7.14(d,1H,J=9.6Hz),7.06(s,1H),7.06(d,1H,J=9.6Hz),2.99(m,4H),2.21(m,2H).^{13}CNMR(75MHz, $CDCl_3$)δ147.66,146.71,144.25,137.06,134.60,130.79,129.77,125.74,124.06,123.55,121.73, 116.20, 32.92, 32.54, 25.61.MS m/z (%): 299 (M^+, 100), 253 (20), 207 (60), 133 (11). UV spectrum: λ_{max} 356.80, abs. 1.000. Molecular formula: $C_{15}H_{13}N_3O_4$. Elemental analysis: Calculated: C (60.20%), H (4.38%), N (14.04%), Found: C (60.31%), H (4.27%), N (13.91%).

N-(4-(trifluromethyl)-2, 6-dinitro phenyl)-2, 3-dihydro-1H-indene-5-amine (XXXIV):

Yield 85%, mp 133-135^{0}C, IR (KBr, cm^{-1}): 3340 (N-H stretch.), 3030 (C-H stretch. Ar-H), 2947 (-CH_2- stretch.), 1350 (C-N stretch.), 1400(C-F stretch.).^{1}H NMR (300MHz,$CDCl_3$)δ9.985 (s,1H),8.454 (s,2H),7.189 (d,1H, J=8.1 Hz), 6.905 (s,1H), 6.829 (d,1H,J=8.1Hz), 2.917 (m,4H), 2.151 (m,2H).^{13}CNMR (75MHz,$CDCl_3$)δ146.30, 143.36, 138.79, 137.80, 129.01, 128.97, 125.34, 118.61, 118.03, 116.84, 32.85, 32.41, 25.36. MS m/z (%): 367 (M^+, 100), 322 (50), 276 (38), 207 (12). UV spectrum: λ_{max} 255, abs. 1.140.Molecular formula: $C_{16}H_{12}F_3N_3O_4$. Elemental analysis: Calculated: C (52.32%), H (3.29%), N (11.44%), Found: C (52.21%), H (3.16%), N(11.32%).

N-cyclopentyl-4-(trifluromethyl)-2, 6-dinitrobenzene (XXXVI):

Yield 80%, mp 77^{0}C, IR (KBr, cm^{-1}): 3305 (N-H stretch.), 3074 (C-H stretch.Ar-H), 2973 (-CH_2- stretch.), 1360 (C-N stretch.), 1400 (C-F stretch.).^{1}H NMR (300MHz, $CDCl_3$)δ8.791 (s,1H), 8.385 (s,2H), 3.830 (m,1H), 2.009 (m,4H), 1.718 (m,4H).^{13}C NMR (300MHz, $CDCl_3$)δ140.52, 137.67, 129.06, 129.01, 124.23, 120.64, 57.67, 33.91, 23.68.MS m/z (%): 319 (M^+, 26), 301 (98), 238 (48), 192 (32), 146 (11).UV spectrum: λ_{max} 243, abs. 1.808. Molecular formula: $C_{12}H_{12}F_3N_3O_4$. Elemental analysis: Calculated: C (45.15%), H (3.79%),N (13.16%). Found: C (45.28%), H (3.90%), N (13.25%).

Scheme-1

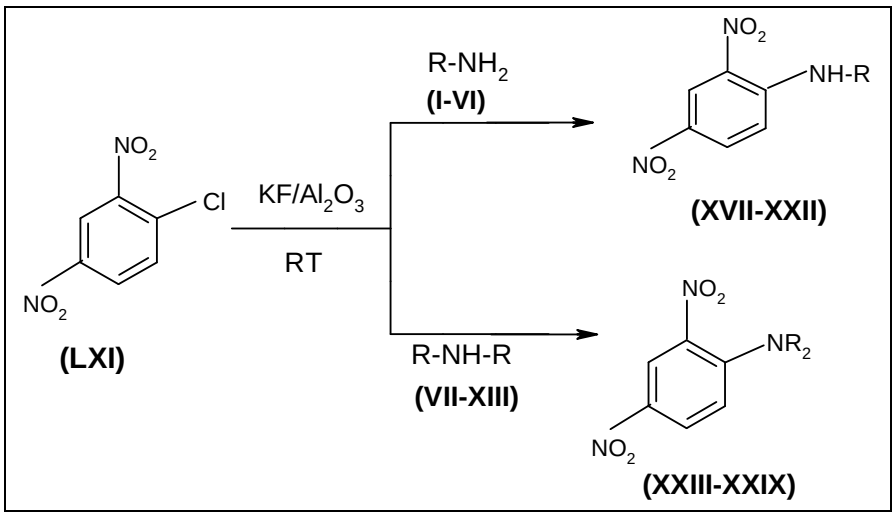
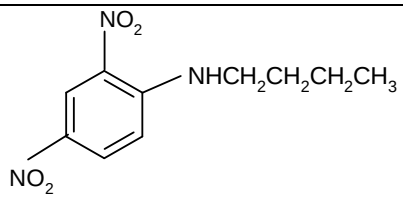
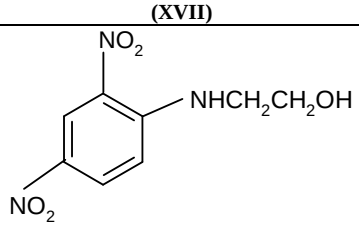
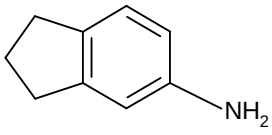
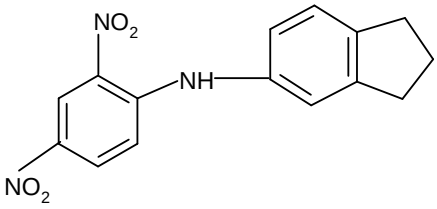
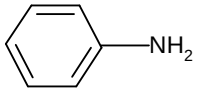
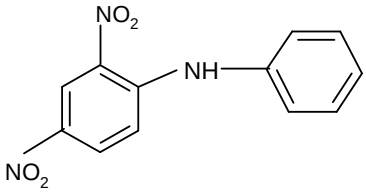
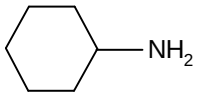
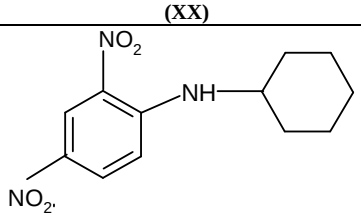
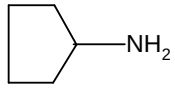
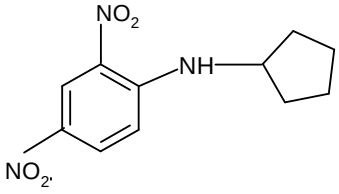
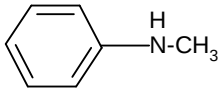
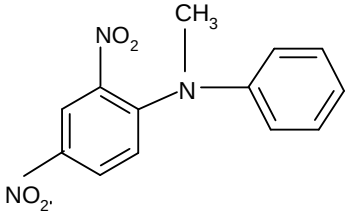
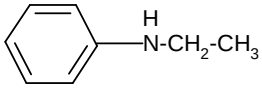
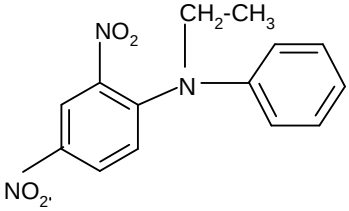
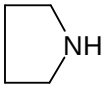
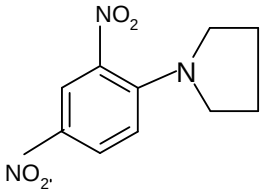
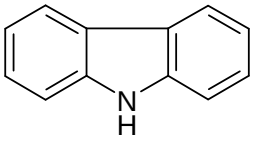
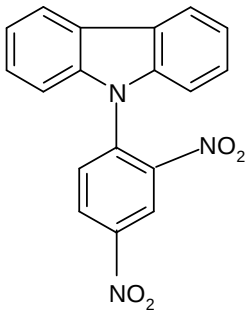
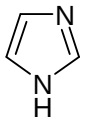
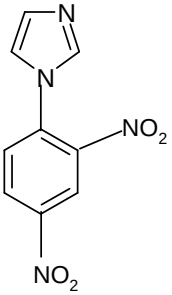
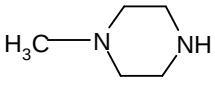
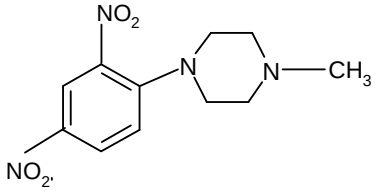
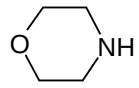
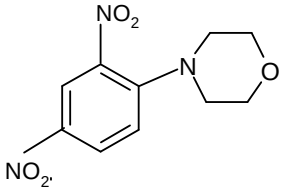


Table 1: N-arylation of amines(I-XIII) with 2,4-dinitrochlorobenzenene[25](LXI) in presence of KF/Al_2O_3 dry media at room temperature.

Amine	Product	M.P ^{0}C	Reaction time (mins)	Yield %
CH_3-$(CH_2)_3$-NH_2 **(I)**	 **(XVII)**	90-91 [26]	10	85
HO-CH_2-CH_2-NH_2 **(II)**	 **(XVIII)**	89-90 [27]	6	86
 **(III)**	 **(XIX)**	140-142	20	80
 **(IV)**	 **(XX)**	156-157 [28]	10	90
 **(V)**	 **(XXI)**	151-153 [26]	15	76

 **(VI)**	 **(XXII)**	72-75 [29]	15	81
 **(VII)**	 **(XXIII)**	164 [28]	6	75
 **(VIII)**	 **(XXIV)**	95-96 [28]	8	76
 **(IX)**	 **(XXV)**	65-67 [30]	10	80
 **(X)**	 **(XXVI)**	188-190 [31]	40	77
 **(XI)**	 **(XXVII)**	144 [32]	40	68
 **(XII)**	 **(XXVIII)**	55-57 [33]	5	87

 (XIII)	 (XXIX)	117-118 [26]	5	89

Scheme-2

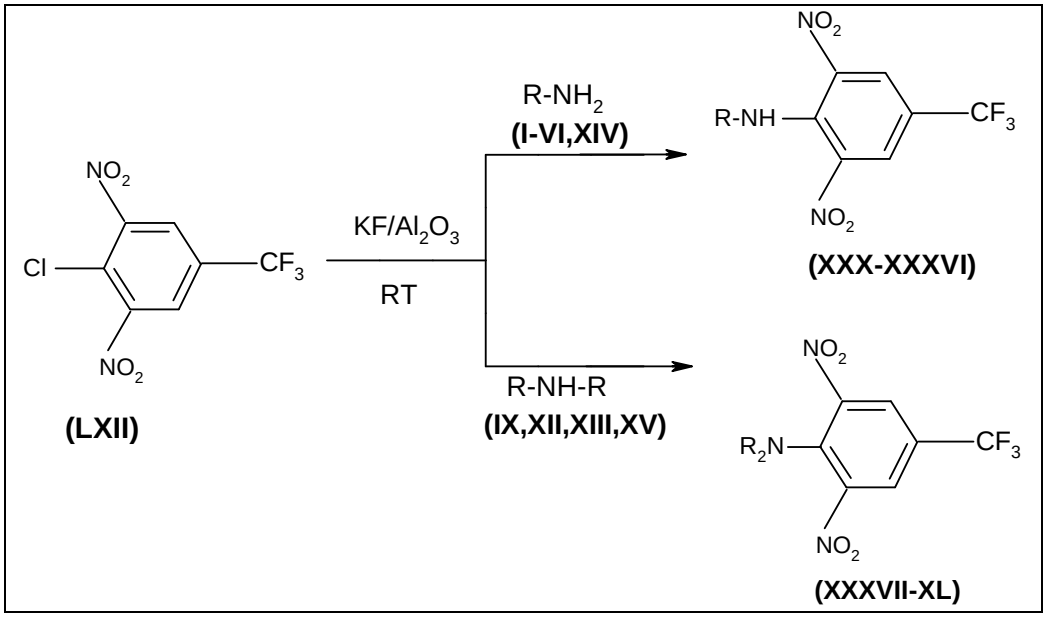
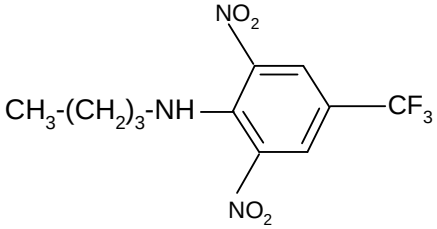
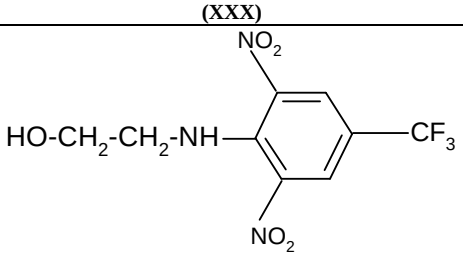
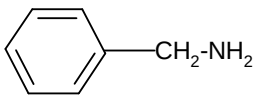
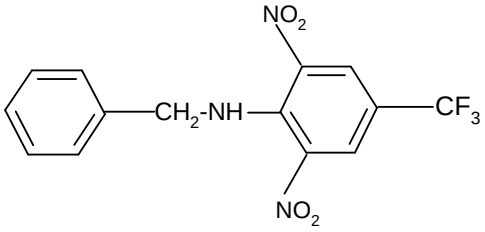
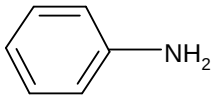
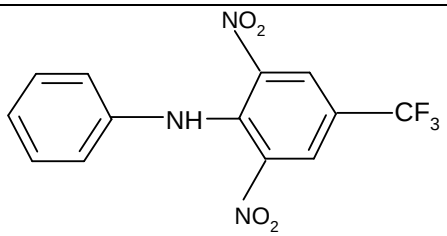
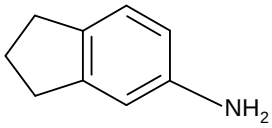
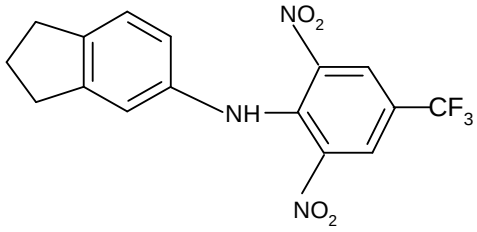
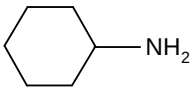
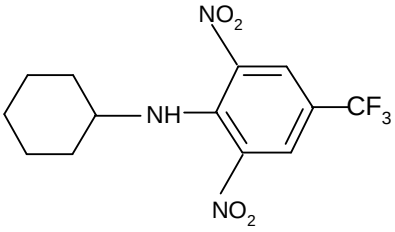
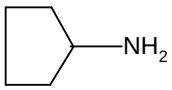
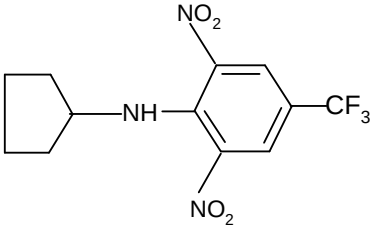
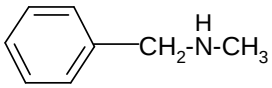
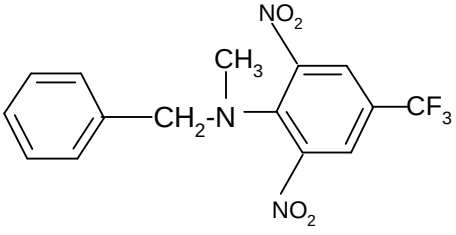
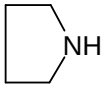
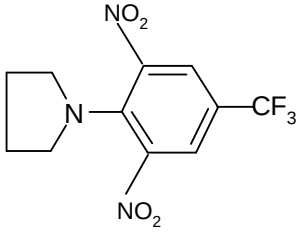
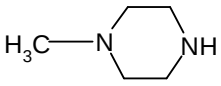
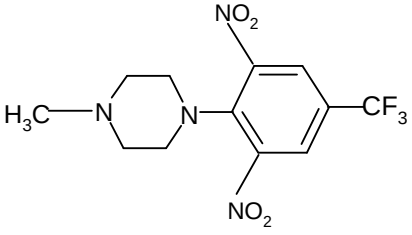
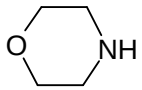
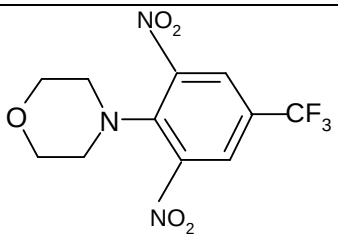


Table 2: N-arylation of amines(I-VI,IX,XII-XV) with 2-chloro-1, 3-dinitro-5-(trifluoromethyl) benzene[34] (LXII) in presence of KF/Al_2O_3 dry media at room temperature.

Amine	Product	M.P ^0C	Reaction time (mins)	Yield %
CH_3-$(CH_2)_3$-NH_2 (I)	 (XXX)	37-39 [35]	15	65
HO-CH_2-CH_2-NH_2 (II)	 (XXXI)	81-83 [36]	15	68
 (XIV)	 (XXXII)	45-47 [37]	10	66

 **(IV)**	 **(XXXIII)**	119-121 [38]	5	61
 **(III)**	 **(XXXIV)**	133-135	20	85
 **(V)**	 **(XXXV)**	83-84 [2]	15	78
 **(VI)**	 **(XXXVI)**	77	20	80
 **(XV)**	 **(XXXVII)**	80 [39]	32	77
 **(IX)**	 **(XXXVIII)**	90-93 [40]	20	61
 **(XII)**	 **(XXXIX)**	65-67 [40]	20	60

 (XIII)	 (XL)	141-142 [2]	20	72

Scheme-3

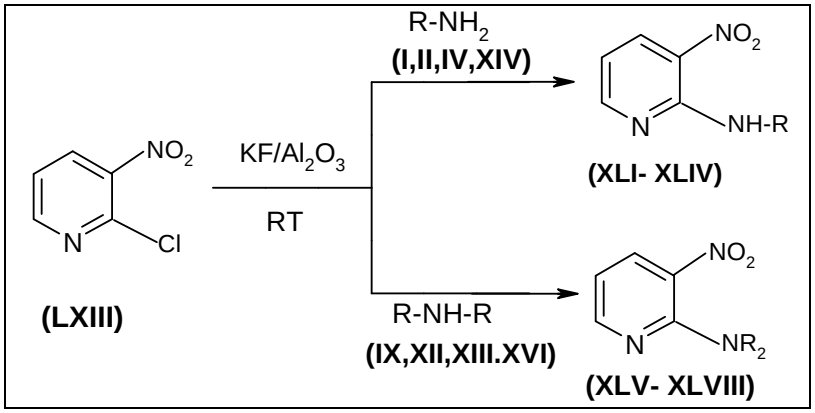
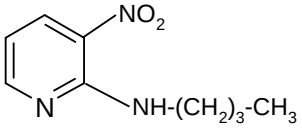
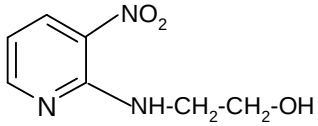
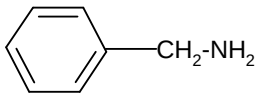
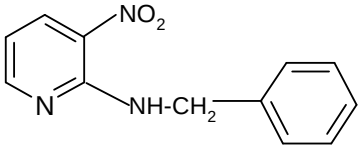
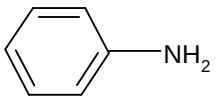
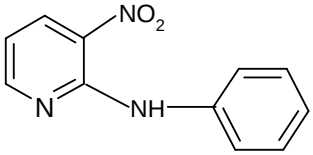
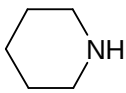
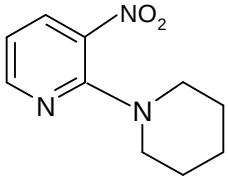
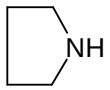
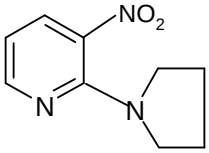
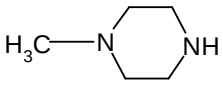
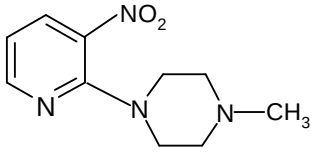
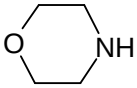
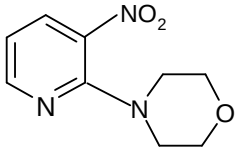


Table 3: N-arylation of amines (I,II,IV,IX,XII-XIV,XVI) with 2-chloro-3-nitropyridine[41] (LXIII) in presence of KF/Al_2O_3 dry media at room temperature.

Amine	Product	M.P ^{0}C	Reaction time (mins)	Yield %
CH_3-$(CH_2)_3$-NH_2 **(I)**	 **(XLI)**	93-95 [42]	10	73
HO-CH_2-CH_2-NH_2 **(II)**	 **(XLII)**	131-132 [43]	10	70
 **(XIV)**	 **(XLIII)**	78 [44]	20	68
 **(IV)**	 **(XLIV)**	74-75 [45]	10	73
 **(XVI)**	 **(XLV)**	50-51 [46]	15	71

 (IX)	 (XLVI)	41-42 [47]	5	74
 (XII)	 (XLVII)	133-135 [48]	15	69
 (XIII)	 (XLVIII)	85-86 [49]	20	72

Scheme-4

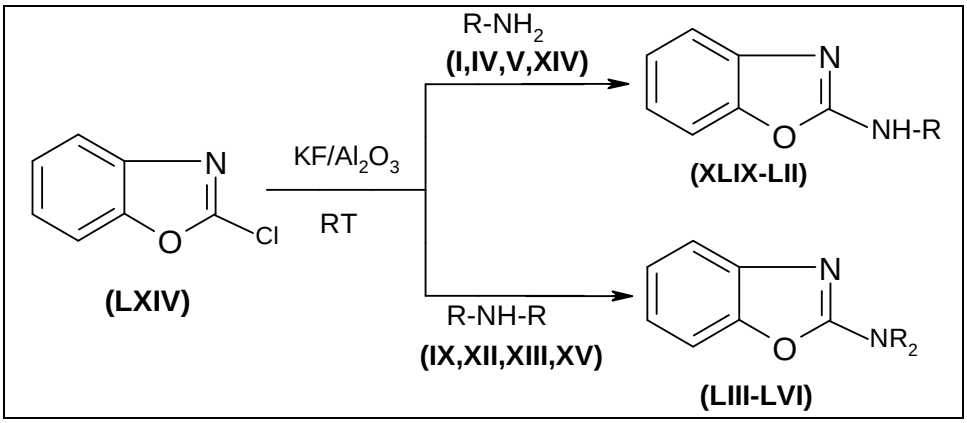
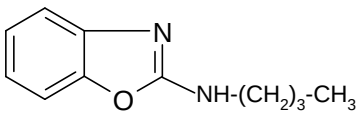
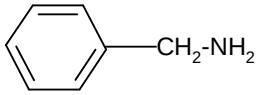
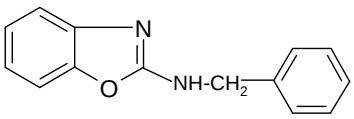
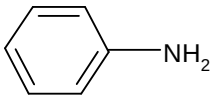
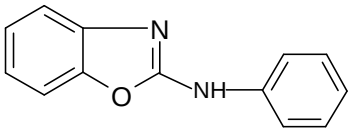
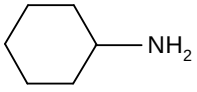
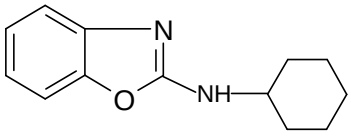
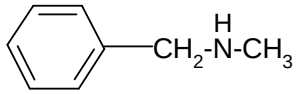
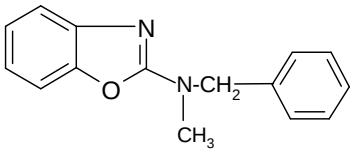
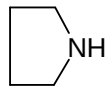
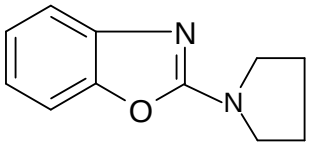
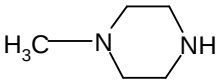
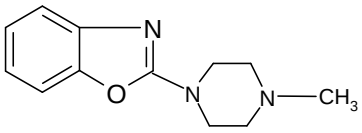
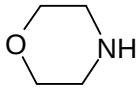
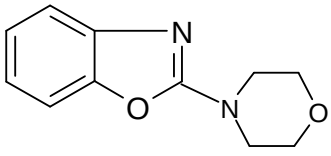


Table 4: N-arylation of amines(I,IV,V,IX,XII-XV) with 2-chlorobenzoxazole[50] (LXIV) in presence of KF/Al_2O_3 dry media at room temperature.

Amine	Product	M.P ^0C	Reaction time (mins)	Yield %
CH_3-$(CH_2)_3$-NH_2 (I)	 (XLIX)	158-160 [51]	10	76
 (XIV)	 (L)	111-113 [52]	10	84
 (IV)	 (LI)	162-164 [53]	25	71
 (V)	 (LII)	108-110 [54]	10	86

 (XV)	 (LIII)	50-53 [55]	25	62
 (IX)	 (LIV)	136-139 [51]	10	75
 (XII)	 (LV)	36-39 [55]	30	63
 (XIII)	 (LVI)	84 [55]	20	72

Scheme-5

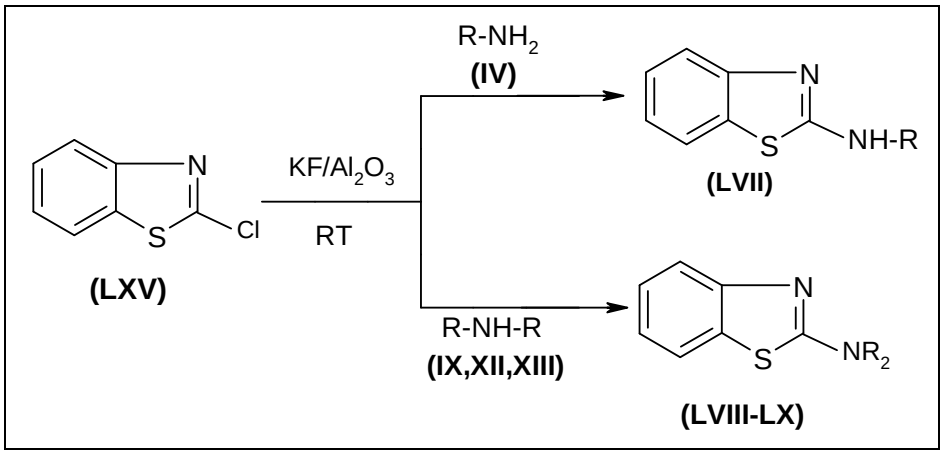
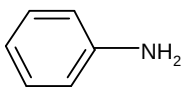
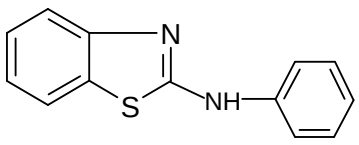
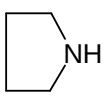
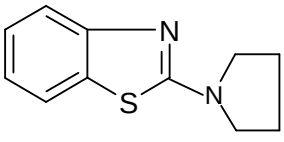


Table 5: N-arylation of amines(IV,IX,XII,XIII) with 2-chlorobenzothiazole[56](LXV) in presences of KF/Al_2O_3 dry media at room temperature.

Amine	Product	M.P ^{0}C	Reaction time (mins)	Yield %
 (IV)	 (LVII)	156 [53]	40	87
 (IX)	 (LVIII)	96 [57]	45	69

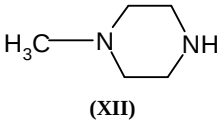
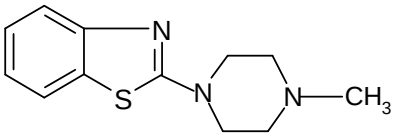
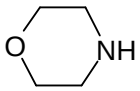
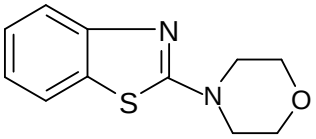
 **(XII)**	 **(LIX)**	89-91 [57]	40	62
 **(XIII)**	 **(LX)**	112 [57]	40	75

Table 6: Antibacterial activity of synthesized compounds.

Compounds	*E. coli*			*S. aureus*			*S. typhi*			*B. subtilis*		
	250	500	1000	250	1000	4000	250	1000	3000	250	1000	4000
XVII	-	-	+	+	++	+++	-	-	-	-	+	++
XVIII	-	+	++	-	+	++	-	-	-	-	-	++
XIX	-	-	-	-	-	-	-	-	-	-	-	+
XX	-	-	-	-	-	-	-	-	-	-	-	-
XXI	-	-	-	-	-	-	-	-	-	-	-	-
XXII	-	-	-	-	-	-	-	-	-	-	-	-
XXIII	-	-	-	-	-	-	-	-	-	-	-	-
XXIV	-	-	-	-	-	-	-	-	-	-	-	-
XXV	+	+	++	+	+++	+++	-	+	++	-	-	+
XXVI	+	++	+++	-	-	-	-	+	++	-	-	+
XXVII	-	-	-	+	++	+++	-	++	+++	-	+	++
XXVIII	-	-	-	-	-	-	-	-	-	-	+	+++
XXIX	-	-	-	-	-	+++	-	+	++	++	+++	+++
XXX	-	-	-	-	-	-	-	-	-	-	-	-
XXXI	-	-	-	-	-	-	-	-	-	-	-	-
XXXII	-	-	-	-	-	-	-	-	-	+	++	+++
XXXIII	++	+++	+++	-	-	-	-	+++	+++	-	-	-
XXXIV	-	-	-	-	-	-	-	-	-	-	-	-
XXXV	-	-	-	-	-	-	-	-	-	-	-	-
XXXVI	-	-	++	-	-	-	-	-	-	+	++	+++
XXXVII	-	-	-	-	-	-	-	-	-	-	-	-
XXXVIII	-	-	-	-	-	-	-	-	-	-	-	-
XXXIX	-	-	-	-	-	-	-	-	-	-	-	-
XL	-	-	-	-	-	-	-	-	-	-	+	+++
XLI	-	-	-	-	-	-	-	-	-	-	-	-
XLII	-	-	-	-	-	-	-	-	-	-	-	-
XLIII	-	+	++	-	-	-	-	-	-	-	++	+++
XLIV	-	-	-	-	-	-	-	-	-	-	-	-
XLV	-	-	-	-	-	-	-	-	-	-	-	-
XLVI	-	-	-	-	-	-	-	-	-	-	-	-
XLVII	-	-	-	-	-	-	-	-	-	-	-	-
XLVIII	-	-	-	-	-	-	-	-	-	-	-	-
XLIX	-	-	-	-	-	-	-	-	-	-	-	-
L	-	-	-	-	-	-	-	-	-	-	-	-
LI	-	-	-	-	-	-	-	-	-	-	+	++
LII	-	-	++	-	-	-	-	++	+++	-	-	+
LIII	-	-	-	-	-	-	-	-	-	-	-	+
LIV	-	-	-	-	-	-	-	-	-	-	-	++
LV	-	-	-	-	-	-	-	-	-	-	-	-
LVI	-	-	-	-	-	-	-	-	-	-	-	-
LVII	-	-	-	-	-	-	-	-	-	-	-	-
LVIII	-	-	-	-	-	-	-	-	-	-	-	-
LIX	-	-	-	-	-	-	-	-	-	-	-	-
LX	-	-	-	-	-	-	-	-	-	-	-	-
DMSO	-	-	-	-	-	-	-	-	-	-	-	-
Ciprofloxacin	++	+++	+++	++	+++	+++	++	+++	+++	++	+++	+++

(-) No antibacterial activity, (+) Mild activity, (++) Moderate activity, (+++) Marked activity. All the concentrations are in ppm.

CONCLUSION

We have described an efficient and novel method for the synthesis of N-arylamines by N-arylationof primary/secondary amines with activated aryl halides in presence of KF/Al_2O_3 (basic) dry media at room temperature. The method is eco-friendly, inexpensive, easy to handle, good yielding and KF/Al_2O_3 can be reused. The antibacterial activity of the synthesized compounds was examined and many of the compounds were found to exhibit marked to moderate activity.

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