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Synthesis of some Novel N-Substituted Aromatic Amines

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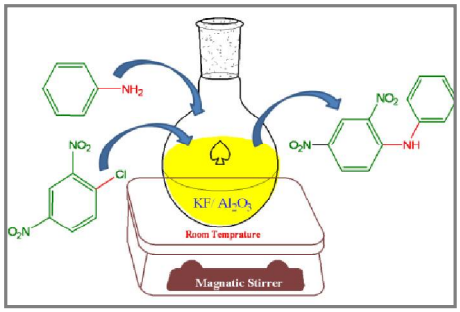
ABSTRACT

In this research work basic KF/Al_2O_3 catalyst being used in the N- arylation of various aromatic/aliphatic amines or N- heterocycles with aryl halides to produce desired coupled product in the presence of simple basic catalyst without using external ligands or additives or promoters. These heterocycles are an important class of compounds and are widely used as medicinal as analgesic drugs, antimalarial, antifungal and biological and N-heterocyclic catalyst chemistry. Some of the compounds have also been reported as antibacterial. N-Aryl heterocycles like imidazole, benzimidazole, benzotriazole and pyrazole are important core structure in many pharmaceutical drugs. Aromatic amines are organic nitrogen containing compounds that may be considered derivatives of ammonia with at least one of the hydrogen atoms replaced by an aryl group. The nitrogen must be react directly to the aromatic ring and so be able to interact with the aromatic p-electron system. Characterization done of synthesized products by analytical technique such as ^{1}H-NMR, ^{13}C-NMR and antimicrobial analysis. The resulting compounds possess symmetrical structures and have high yields.

Graphical Abstract



Keywords: 2,4-dinitrochlorobenzene, Heterocycles, Antimicrobial analysis, Basic aluminumoxide.

INTRODUCTION

Formation of C-N sigma bond plays important role in organic synthesis. The aniline moiety appears as subunits in a broad range of biologically dynamic and medicinally important molecules [**1**]. Thus, the synthesis of these compounds has been of longstanding interest. In recent years, several versatile

and widely employed copper-catalysed cross coupling methods of amines with aryl halides have been developed to construct aryl C-N bonds [2].

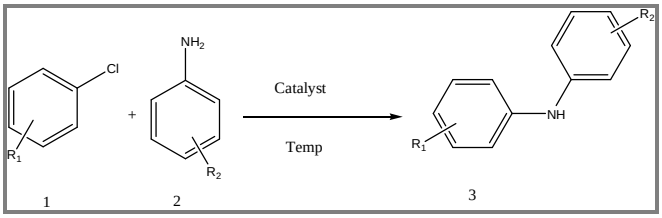
Diphenylamine is an organic compound with the formula $(C_6H_5)_2NH$. The compound is a derivative of aniline [3], with aryl halides. Diphenylamine is consisting of an amine bound (C-N) to two phenyl groups. The compound is a colorless solid, but commercial available samples are often yellow due to oxidized impurities [4]. Diphenylamine dissolves well in many common organic solvents, and is moderately soluble in water [5]. It is used mainly for its antioxidant properties. Diphenylamine is used as a pre- or post harvest blister inhibitor for apples applied as an indoor drench treatment. Its anti-scald activity is the result of its antioxidant properties, which protect the apple coat from the oxidation and products of alpha-farnesene during storage [6]. Alkylated diphenylamines function as antioxidants in lubricants, approved for use in machines, in which contact with food is not ruled out [7-10].

MATERIALS AND METHODS

Melting Point of compounds was taken by in open air capillary tube and uncorrected. ^{1}H-NMR spectra were recorded on Bruker Avance II 400 MHz NMR Spectrometer (SAIF, Punjab University, Chandigarh) using $CDCl_3$ as solvent. TLC; Thin-layer chromatography (TLC) was performed on precoated on merck silica gel 60 F254 plates. AR grade reagents and solvents were used without purification purchased from Loba Chem Pvt. Ltd.

RESULTS AND DISCUSSION

General procedure: In a beaker mixture of dry KF (0.3gm) and basic Al_2O_3 (0.5 gm) was mixed with primary or secondary amines (0.005 mol) and mixture was stirred well. After 5 min at room temperature, activated aryl halide (0.005 mol) was added with continuous stirring. After completion of reaction the solid was extracted with chloroform and filtered. The chloroform extract was distilled and residue purified by recrystallisation with suitable solvent. Completion of reaction was monitered by single spot T.L.C. [M.P. was recorded in range of ± 2°C.].



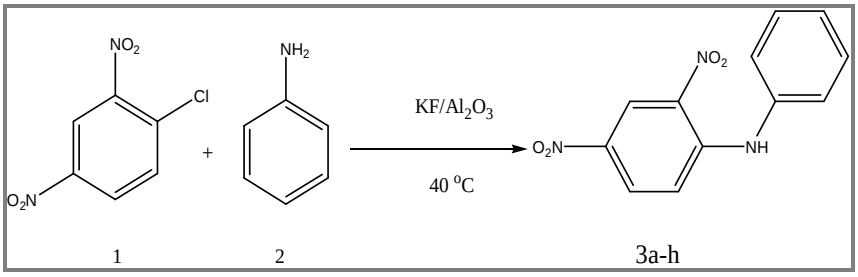
Scheme 1: General reaction for the formation of N-arylamines.

Table 1. Optimization of reaction parameters[a]

Entry	Catalyst	Isolation Solvent	Time (Min)	Temperature (^{o}C)	Yield[b] (%)
1	KF/Al_2O_3	Ethanol	6	05	-
2	KF/Al_2O_3	CH_2Cl_2	6	10	Trace
3	KF/Al_2O_3	$CHCl_3$	6	20	Trace
4	KF/Al_2O_3	Ethanol	5	10	10
5	KF/Al_2O_3	CH_2Cl_2	5	15	15
6	KF/Al_2O_3	$CHCl_3$	5	30	20
7	KF/Al_2O_3	$CHCl_3$	5	40	40
8	KF/Al_2O_3	Ethanol	8	70	70
9	**KF/Al_2O_3**	**$CHCl_3$**	**10**	**40**	**92**
10	KF/Al_2O_3	Ethanol	12	50	86

[a]Reaction conditions: 2,4 dinitrochlorobenzene (0.005 mol), aniline (0.005 mol), under 40 ^{o}C, [b]Isolated yield

It has studied the role of the solvent, temperature time and yield on the said reaction and got results as shown in above table 1. The Chloroform was used for isolation of product (Table 1, entries 3, 7, 9). Moreover, in this study 40°C gives good yield. The reaction time was optimized at 10 min. giving 92% yields (Table 1, entries 9). Further increase of temperature does not increase of yield of product (Table 1, entries 10).



Scheme 2: Formation of N-arylamines using KF/Al_2O_3 as catalyst.

Analytical and Spectral Data for the Synthesized Compounds

3-chloro-*N*-(2,4-dinitrophenyl)benzenamine (3a): M.P.; 44°C; ^{1}H NMR (400MHzCDCl$_3$) δ: 3.75(s,1H), 7.28(m, 4H), 7.84 (d,1H), 8.43(dd,1H), 8.77(d,1H).;^{13}C NMR (400MHz CDCl$_3$) δ: 121.15,121.48, 127.37, 133.28, 133.98, 146.30, 147.76.

2-methyl-*N*-(2,4-dinitrophenyl)benzenamine (3b): M.P.; 48°C;^{1}H NMR (400MHz CDCl$_3$) δ: 2.28(s,3H), 6.8-7.41 (m,4H), 7.82-8.76 (m, 3H), 9.1 (s,1H);^{13}C NMR (400MHz CDCl$_3$) δ: 17.83, 115.92, 121.15, 124.15, 126.82, 127.66, 128.46, 130.06, 131.86, 133.98, 134.95, 147.54.

3-nitro-*N*-(2,4-dinitrophenyl)benzenamine(3c): M.P.; 42°C;^{1}H NMR (400MHz CDCl$_3$) δ: 3.75 (s,1H), 6.94-7.56(m,4H), 7.83(d,1H), 8.41(dd,1H), 8.7(d,1H);^{13}C NMR (400MHz CDCl$_3$) δ: 108.96, 113.6, 120.67, 121.14, 121.99, 127.98, 129.93, 133.29, 133.98, 146.27, 147.51, 149.17.

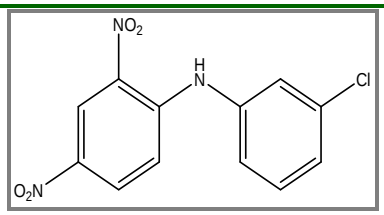
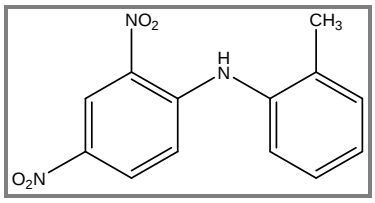
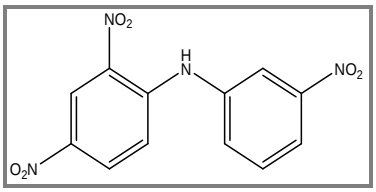
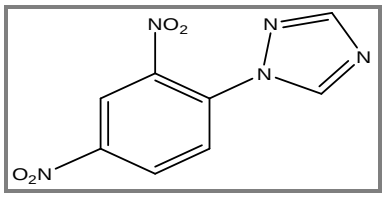
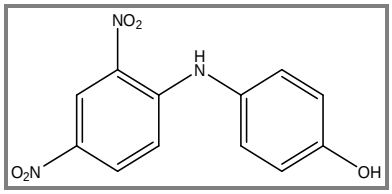
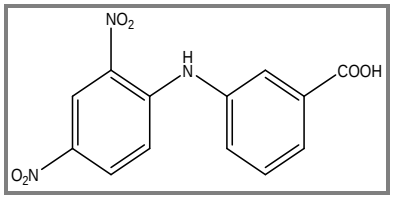
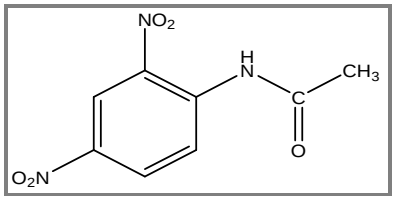
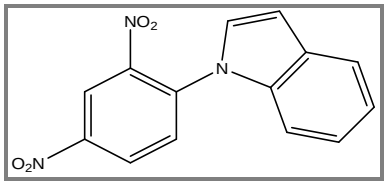
1-(2,4-dinitrophenyl)-1*H*-1,2,4-triazole(3d): M.P.; 48°C;^{1}H NMR (400MHz CDCl$_3$) δ: 7.27 (d,1H), 7.83(d,1H), 8.42(dd,1H), 8.7(d,2H);^{13}C NMR (400MHz CDCl$_3$) δ: 121.15, 127.35, 133.98, 146.29, 147.77.

1-(2,4-dinitrophenyl)-1*H*-indole (3h): M.P.; 80°C; ^{1}H NMR (CDCl$_3$) δ: 7.04-7.57(m,6H), 8.03 (d,1H), 8.17-8.14(dd,1H), 8.60(d,1H);^{13}C NMR (CDCl$_3$) δ: 102.50, 111.10, 119.82, 121.01, 121.98,124.32,127.23,127.78,133.08,133.83,135.69,146.07,147.51.

Antimicrobial study: Antimicrobial activities of any therapeutic agent are understood by its extent of development inhibition of microorganisms as well as bacterial assets [**11**]. The antibacterial study of a synthesized compounds convey as its inhibition outcome in the course of the growth of the bacterium in nutrient agar medium. The antimicrobial activities expressed as zone diameter in millimetres in disk diffusion method, which is measured by a scale mm. Test solutions were prepared by Agar-100 mg, sample compound- 1gm, distilled water-10 mL Thus, the final concentration of test obtained was 10 mg mL^{-1}[**12**].

The compounds 3b, 3c and 3d have shown good antimicrobial activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus niger* and *Candida albicans*. The compound 3a show antifungal activity only against *Candida albicans* as well as *Asperagillus niger* while compound 3h fail to show activity against *Escherichia Coli* and *Bacillus subtills* (Table 3 and Figure 1).

Table 2. Substrate study for N- arylamine derivatives[a]

Compounds	Name of Products	Time Min	Temperature (^oC)	Yield [c] (%)	M.P.
3a		65	40^{o}C	88	44°C
3b		20	40^{o}C	90	48°C
3c		25	40^{o}C	86	42°C
3d		145	40^{o}C	82	48°C
3e		190	40^{o}C	88	46°C
3f		150	40^{o}C	80	44°C
3g		180	40^{o}C	81	48°C
3h		50	40^{o}C	71	80°C

[a]Reaction conditions: 2,4 dinitrochlorobenzene (0.05mol), Pri/Sec amines (0.05 mol), under 40^{o}C. [b]Isolated yield

Table 3. Antimicrobial activity of compounds 3a-d,h

Compound	*E. Coli*	*P. aeruginosa*	*S. aureus*	*B. subtills*	*C. albicans*	*A. niger*
3a	-	-	-	-	>18	>18
3b	11.68	13.21	20.97	17.23	>18	>18
3c	14.23	19.96	24.07	19.75	>18	>18
3d	12.81	17.00	26.90	22.75	>18	>18
3h	-	8.38	13.87	-	>18	>18
Chloromphenicol	24.90	12.16	28.45	28.32	NA	NA
Amphotericin-B	NA	NA	NA	NA	12.46	16.50

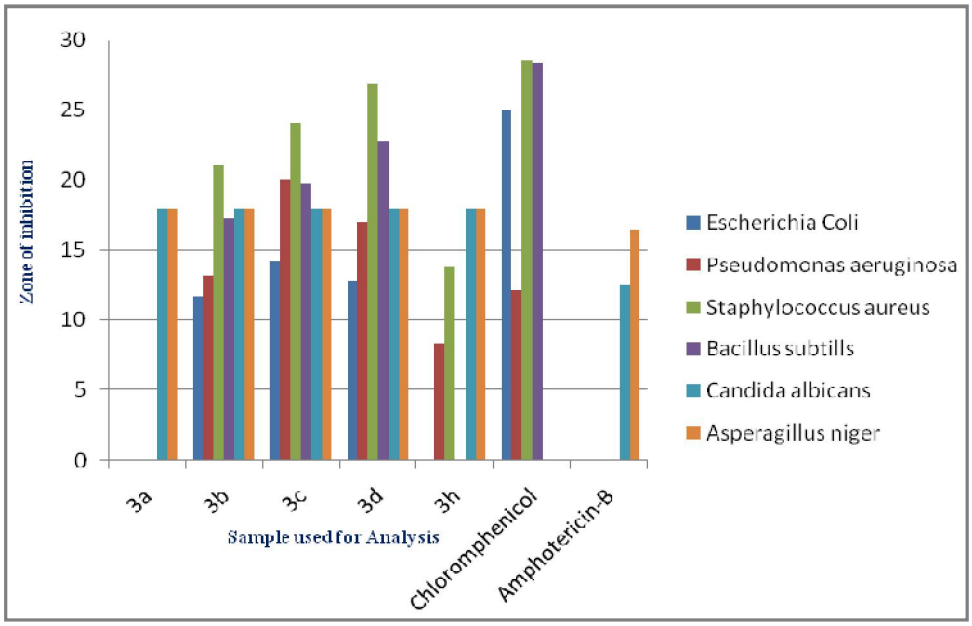


Figure 1. Comparative graph of antimicrobial activity of Compounds 3a-d,h

APPLICATION

Synthesized heterocycles has wide application and importance as medicinal API. They possess analgesic drugs, antimalarial, antifungal activity and biologically active. Some compounds showing antibacterial properties, N-aryl heterocycles having imidazole, benzimidazole, pyrazole and benzotriazole in their structures shows useful core structure in many pharmaceutical drugs.

CONCLUSION

In conclusion we have used an efficient KF/Al_2O_3 catalyzed, solvent free method for the synthesis of various derivatives of N- arylamine. The procedure has mild reaction conditions, operational simplicity, and application of nontoxic and organic solvent soluble compounds. High yield and fast development of the products are the excellent advantages of this method. All compounds were tested for microbial activities.

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