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Solvent free reaction of 1-chloro-2-nitrobenzene with anilines

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ABSTRACT

An efficient solvent free reaction of 1-chloro-2-nitrobenzene with anilines to give N-substituted nitro anilines by nucleophilic aromatic substitution in good to excellent yields has been described. The effect of different salts on the reaction has also been studied.

Keywords: Substituted nitro-anilines, salts, solvent free synthesis, nucleophilic aromatic substitution

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INTRODUCTION

The N-substituted nitro-anilines or their reduced product, N-substituted aminoanilines are important intermediates that have been frequently required for the synthesis of widely used biologically active molecules [1-5] like, isoalloxazines, benzimidazoles, benzotrizoles & other biologically active benzo-fused hetrocycles [6-12]. These group of compounds find their applications in pharmaceuticals [12], agrochemicals [14], and natural as well synthetic products [15]. The halogen atom in aryl halides is relatively inert and requires activation from electron withdrawing groups attached at 2- and/or 4-position while undergoing nucleophilic aromatic substitution [16,17]. The traditional method involves long reaction time, high temperature, use of high boiling solvents like DMF, DMSO, ionic liquids etc, expensive bases or combination of above factors [18-21]. Solvent free organic synthesis is a versatile technique in promoting variety of chemical reactions and a good approach towards green chemistry [22,23]. Herein, we report a mild and efficient procedure for the synthesis of N-substituted nitro anilines under solvent free condition.

MATERIALS AND METHODS

Melting points were determined on a Thomas Hoover Capillary melting point apparatus and are uncorrected. The purity of the compounds was determined on silica-coated Al plates (Merck). Infrared spectra were recorded on Perkin Elmer 1710 spectrophotometer and ν_{max} are expressed in cm^{-1}. ^1H NMR spectra were recorded on Bruker Avance 300 spectrophotometer (300 MHz) and the chemical shifts were expressed in ppm.

General Procedure for preparation of 2-Nitro-N-Substituted anilines (3):
A mixture of 1-chloro-2-nitrobenzene (**1**) (10 mmol), aniline (**2**) (10 mmol) and salt (16.32 mmol) was taken in a round bottom flask (100 ml) and heated at ~ 50^oC for the time specified in the table 1. The reaction mixture was cooled to room temperature and partitioned between acidic water-chloroform (1:1 v/v). The chloroform layer was dried (anhydrous Na_2SO_4) and the solvent was evaporated by distillation. The residue was adsorbed on silica gel (60-120 mesh) to make slurry and subjected to column chromatography, eluting with petroleum ether (60-80^oC). The unreacted 1-chloro-2-nitrobenzene was eluted first, followed by the highly orange to red colored product **3**.

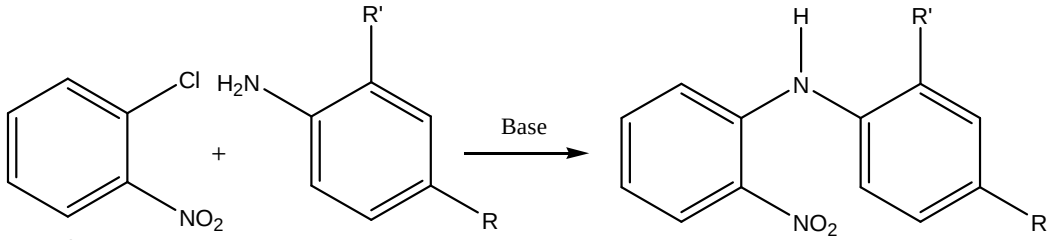
2-Nitro-N-phenylaniline (3a)
Mp.: 76 °C (lit mp. [18] 76 °C); IR (KBr): 3356, 2365, 1615, 1593, 1570, 1501, 1409, 1346, 1258, 1143, 1258, 1143, 1073, 1029 and 741 cm^{-1}; ^1H NMR ($CDCl_3$): 6.80-6.74 (m, 3H, H-3', H-4' & H-5'), 7.29-7.21 (m, 2H, H-4 and H-5), 7.44-7.33 (m, 3H, H-2', H-6' and H-6) and 8.20 (dd, 1H, H-3, *J* = 8.1 Hz & 2.2 Hz).

2-Nitro-N-(4'-methylphenyl)aniline (3b)
Mp.: 69 °C (lit mp. [18] 69-70 °C); IR (KBr): 3322, 2932, 2810, 2361, 1608, 1564, 1514, 1442, 1345, 1289, 1213, 1160, 1045, 954, 851, 773 and 651 cm^{-1}; ^1H NMR ($CDCl_3$): 1.98 (s, 3H, CH_3), 6.49 (d, 1H, H-6, *J* = 8.1 Hz), 6.71 (t, 1H, H-5), 7.28-7.46 (m, 4H, H-2', H-3', H-5' & H-6'), 7.57 (t, 1H, H-4) and 8.12 (d, 1H, H-3, *J* = 8.2 Hz).

2-Nitro-N-(2'-methylphenyl)aniline (3c)
Mp.: 76 °C (lit mp. [18] 76 °C); IR (KBr): 3321, 2932, 2810, 2361, 1608, 1564, 1514, 1442, 1345, 1289, 1213, 1160, 1045, 954, 851, 773 and 651 cm^{-1}; ^1H NMR ($CDCl_3$): 1.95 (s, 3H, CH_3), 6.36 (dd, 1H, H-6, *J* = 8.0 & 2.2 Hz), 6.69 (t, 1H, H-5), 7.21-7.26 (m, 2H, H-3'& H-4'), 7.29-7.31 (m, 2H, H-6' & H-5'), 7.38 (t, 1H, H-4) and 8.20 (dd, 1H, H-3, *J* = 8.0 & 2.2 Hz).

2-Nitro-N-(4'-chlorophenyl)aniline (3d)
Mp.: 146 °C (lit mp. [18] 145-146 °C); IR (KBr): 3314, 2930, 2860, 1570, 1532, 1440, 1355, 1258, 1147, 1042, 971, 854, 832, 650 and 451 cm^{-1}; ^1H NMR ($CDCl_3$): 6.85-7.25 (m, 2H, H-4 & H-6), 7.45-7.60 (m, 4H, H-2', H-3', H-5' & H-6'), 7.85 (d, 1H, H-5, *J* = 8.0 Hz) and 8.10 (d, 1H, H-3, *J* = 8.0 Hz).

2-Nitro-N-(2'-chlorophenyl)aniline (3e)
Mp.: 115 °C (lit mp. [18] 116-117 °C); IR (KBr): 3284, 2924, 2855, 1587, 1530, 1461, 1357, 1258, 1147, 1058, 953, 854, 775, 733, 649, 474 and 457 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): 6.81-7.10 (m, 2H, H-4 & H-6), 7.29-7.38 (m, 4H, H-3', H-4', H-5' & H-6'), 7.80 (d, 1H, H-5, *J* = 8.0 Hz) and 8.20 (d, 1H, H-3, *J* = 8.0 Hz).



2a: R = H, R' = H
2b: R = CH_3, R' = H
2c: R = H, R' = CH_3
2d: R = Cl, R' = H
2e: R = H, R' = Cl

Scheme 1: Synthesis of 2-nitro-N-arylanilines

Table 1: Synthesis of N-Substituted 2-Aminoanilines (3)

S. No.	Salts	Compounds prepared		Isolated Yield (%)	
		R	R'	5 hr	24 hr
1	Sodium carbonate	H	H	88	88
2	Sodium carbonate	CH_3	H	90	90
3	Sodium carbonate	H	CH_3	79	80
4	Sodium carbonate	Cl	H	75	75
5	Sodium carbonate	H	Cl	70	70
6	Potassium acetate	H	H	55	58
7	Potassium acetate	CH_3	H	59	63
8	Potassium acetate	H	CH_3	55	60
9	Potassium acetate	Cl	H	42	49
10	Potassium acetate	H	Cl	41	45
11	Copper acetate monohydrate	H	H	48	48
12	Copper acetate monohydrate	CH_3	H	31	33
13	Copper acetate monohydrate	H	CH_3	28	30
14	Copper acetate monohydrate	Cl	H	40	41
15	Copper acetate monohydrate	H	Cl	28	28
16	Lead acetate	H	H	43	45
17	Lead acetate	CH_3	H	30	33
18	Lead acetate	H	CH_3	23	25
19	Lead acetate	Cl	H	28	31
20	Lead acetate	H	Cl	23	28

RESULTS AND DISCUSSION

The solvent free reaction of 1-chloro-2-nitrobenzene (**1**) with aniline (**2a**) in the presence of sodium carbonate for 5 hours at ~ 50^{o}C gave 2-Nitro-N-phenylaniline (**3a**) in 88% yield (Scheme 1, Table 1, entry 1). No further increase in product formation achieved even after heating the reaction mixture for 24 hours (Table 1). Similarly, **1** was reacted with other anilines (**2b-e**) to give appreciable yield of **3b-e** (Table 1, entry 2-5). The reaction was extended to 24 hours duration to check the optimization of the reaction. It was observed that the extension of reaction time at same temperature (~ 50^{o}C) have very little effect on the isolated yield (Table 1).

To explore the scope of this reaction, substituent having electron withdrawing (R = R' = Cl) and releasing (R = R' = CH_3) have been prepared. In all the cases, the nucleophilic substitution reaction was successful in good to excellent yield with sodium carbonate. The electron withdrawing nature of the chloro group is responsible for the lower yield of products in case of **3d** and **3e**. The products were easily separated by simple extraction with chloroform-water mixture. All the products were purified by column chromatography over silica gel and characterized by melting point, mixed melting point, IR and ^{1}H NMR spectroscopic data (materials and methods).

To check the effect of salt on product formation, four different types of salts were used for the reaction. The maximum yield was obtained with sodium carbonate. We tried this reaction with simple zinc dust also, but failed to get any desired product. The basic purpose of using these salts is to scavenge the released hydrochloric acid (HCl) as their chloride salts so that the reaction can proceed in forward direction. If the hydrochloric acid is not removed, this reacts with the reactant aniline to for anilinium salt which reduces the nucleophilicity of aniline. This does not allow the reaction to proceed further.

CONCLUSION

In conclusion, we have developed a rapid, efficient and solvent free procedure for the synthesis of 2-nitro-N-arylanilines by aromatic nucleophilic substitution of 1-chloro-2-nitrobenzene with various anilines in the presence of sodium carbonate. The formation of product in the presence of other salts like potassium acetate, lead acetate and copper acetate has also been studied. Good to excellent yields were obtained in very short reaction time with sodium carbonate.

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