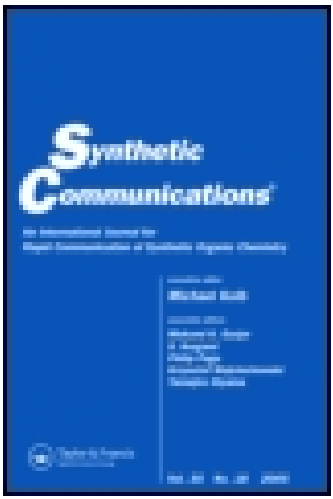

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Synthesis of Substituted Diphenylamines Under Phase Transfer Catalysis

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SYNTHESIS OF SUBSTITUTED DIPHENYLAMINES UNDER PHASE TRANSFER CATALYSIS

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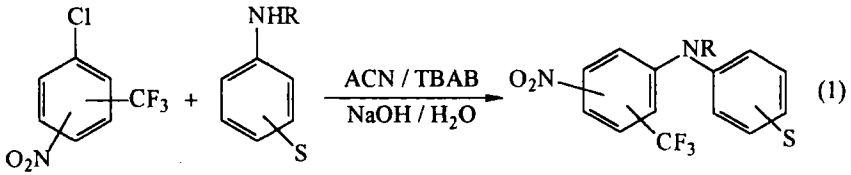
Abstract. A convenient procedure for the synthesis of N-[(trifluoromethyl) nitrophenyl] substituted anilines by means of a chloro-substitution reaction under conditions of phase-transfer catalysis (PTC) is reported. The ipso-substitution product is obtained with high yield. This method provides a general procedure for the synthesis of diphenylamines bearing electron-withdrawing groups in both aromatic rings.

Substituted diphenylamines are important in the synthesis of substances with biological activity[1] or potentially useful as non-linear optical materials[2]. The synthesis of diphenylamines bearing electron-withdrawing groups in just one of the aromatic rings can be easily accomplished by an S_NAr reaction between the aromatic substrate with an activated leaving group and the corresponding aniline in different solvents.[3,4] However, the nucleophilicity of the substituted anilines strongly decreases when the aromatic ring bears several electron-withdrawing groups and the conventional approach in such cases is not feasible. However, in the cases where the aniline NH-acidity is enhanced by the electron-withdrawing

substituents, an alternative way has been reported. This involves activation of the nucleophile either by potassium t-butoxide or by alkali metal carbonates in dipolar aprotic solvents.[4,5] The development of a negative charge on the nucleophile nitrogen atom was proposed as explanation for the observed activation.[5] Thus, fluorine displacement can be easily accomplished, when the starting anilines are treated with potassium t-butoxide in dimethylsulphoxide at room temperature. Yields of N-(nitrophenyl) nitroanilines from 63% to 74% were found.[5] The same reaction but using M_2CO_3 instead requires high temperatures and yields mostly triarylamines. Dealing with chloride as the leaving group, the reaction in the presence of potassium t-butoxide was inapplicable owing to concurrent hydrogen displacement. The yields were appreciable only with potassium or cesium carbonate at quite high temperature.[5]

Weak acid precursors (pKa < 38) can be effectively deprotonated and extracted to the organic phase when stirred with a concentrated aqueous sodium hydroxide solution under phase transfer catalysis conditions.[6] This fact suggested us that PTC could be a good approach when weakly basic anilines should be used as nucleophiles.

In this communication, we report the reactions between 2-chloro-5-nitro-1-(trifluoromethyl)benzene (2CNTFB) and the corresponding 4-nitro, 3-nitro and 4-cyanoaniline under PTC conditions in acetonitrile to afford, upon treatment with ammonium chloride, the corresponding N-[trifluoromethylnitrophenyl] substituted anilines (I). The same reaction was also carried out using 4-chloro-3-nitrotrifluoromethylbenzene (4CNTFB) with 4-nitroaniline (eqn. 1).



(1)

S = CN or NO_2
R = H, butyl, benzyl

(I)

R	Yield (%)
H	81-86
butyl, benzyl	0

In order to compare the effect of PTC with regular homogeneous phase conditions in the case of aliphatic amines, the same substrates were reacted with n-butylamine. 4CNTFB was also treated with benzylamine.

These experiments demonstrate that PTC is a worthy approach to the synthesis of diphenylamines bearing electron-withdrawing groups in both aromatic rings. Good yields (81-86%) under relatively mild conditions could be obtained when dealing with chlorine as leaving group. Moreover, aqueous sodium hydroxide is employed instead of potassium t-butoxide and expensive anhydrous dipolar solvents are no longer required. The pure product can be isolated from the reaction mixture by means of flash chromatography.

As can be appreciated from the data reported in the Table, PTC conditions allow the synthesis of N-(trifluoromethylnitrophenyl) substituted anilines from N-unsubstituted anilines. It should be pointed out that in acetonitrile without base addition there was no substitution reaction between the CNTFB and the corresponding substituted anilines when heated at 50 ^{o}C for at least six hours.

On the other hand when primary amines are involved, the PTC conditions offer no advantage over the homogeneous media. This is probable due to the low

Table. PTC vs. Homogeneous medium. Reactions between CTFNB isomers and different amines.

Entry	Substrate	Amine	Homogeneous medium	PTC
			k_{obs}/ s^{-1}	k_{obs}/ s^{-1}
1	4CNTFB	n-butylamine [a]	1.94×10^{-5}	5.8×10^{-5}
2	4CNTFB	benzylamine [b]	9.86×10^{-6}	2.8×10^{-5}
3	4CNTFB	4-nitroaniline [c]	no reaction	7.0×10^{-4}
4	2CNTFB	n-butylamine [d]	0.88×10^{-6}	3.2×10^{-4}
5	2CNTFB	4-nitroaniline [c]	no reaction	3.6×10^{-4}
6	2CNTFB	3-nitroaniline [c]	no reaction	6.8×10^{-4}
7	2CNTFB	4-cyanoaniline [c]	no reaction	1.2×10^{-3}
8	2CNTFB or 4CNTFB	N-butyl-2-nitro-4-trifluoromethyl aniline [c]	no reaction	no reaction
9	2CNTFB	N-benzyl-2,4-dinitroaniline [c]	no reaction	no reaction

[a] [n-butylamine] = 1.04 M, benzene, 31.0 °C - From Ref. 7; PTC: Same as in homogeneous medium plus [TBAB] = 4.5×10^{-3} M and [NaOH] = 50% w/w. [b] [benzylamine]= 1.11 M, toluene, 40.0°C; PTC: Same as in homogeneous medium plus [TBAB] = 9.0×10^{-3} M and [NaOH] = 52.9 % w/w;. [c] Organic solvent: acetonitrile, see experimental section; [d] [n-butylamine] = 1.04 M, benzene, 40.0 °C; PTC: Same as in homogeneous medium plus [TBAB] = 2.0×10^{-3} M and [NaOH] = 50% w/w.

acidity of the N-H bond that precludes the generation of sufficient concentration of nitranions in the organic phase.

Nevertheless, the influence of a nitro group ortho to the leaving group should also be stressed. In the case of 4CNTFB with n-butylamine (entry 1) an intramolecular hydrogen bond could stabilize the zwitterionic transition state increasing the reactivity in homogeneous phase. This kind of "built-in" solvation was already proposed for the reaction of 2,4-dinitrochlorobenzene and n-butylamine.[8] With 2CNTFB, substrate which does not have a nitro group ortho to the leaving group (entry 4), the reactivity under PTC conditions is over 360 times higher than in homogeneus medium.

Bulky N-substituted anilines such as N-n-butyl and N-benzyl substituted anilines (entries 8 and 9) neither react in homogeneous nor under PTC conditions.

PTC allows the use of the more readily available chloro aromatic substrates at somewhat mild experimental conditions instead of the more expensive fluoro derivatives. Moreover, the relatively easy work up of the reaction mixture as well as the observed yields makes the PTC procedure particularly attractive in the synthesis of this kind of diphenylamines.

Experimental Section

General. The melting point was determined with a Büchi apparatus. UV-visible spectra were recorded on a Hewlett-Packard HP 8452 spectrophotometer. The HPLC measurements were performed on a Varian 5000 liquid chromatograph; equipped with a UV-visible variable λ detector (Varian 2550) operating at 250 nm

for all assays. The solvent system used was 5% iso-propanol in n-hexane. The column used was a Varian MicroPak SI-5 (150 mm x 4 mm I.D.). NMR spectra were acquired at a 200 MHz Brucker spectrometer. IR spectra were recorded with a Nicolet Impact 400 FT-IR. Mass spectra were taken by laser desorption time of flight mass spectrometry with a Varian Matt 311 apparatus, operating in EI mode 70 eV and with a Vestec Laser Tec Research Instrument. Matrix used: α-CN-4-OH-cinnamic acid.

Starting materials. 2-Chloro-5-nitro-1-(trifluoromethyl)benzene (2CNTFB), 4-chloro-3-nitro-1-(trifluoromethyl)benzene (4CNTFB), 4-nitroaniline and 3-nitroaniline from Aldrich, 4-cyanoaniline and tetrabutylammonium bromide (TBAB) from Fluka were used without further purification. N-butyl-2-nitro-4-trifluoromethyl aniline and N-benzyl-2,4-dinitroaniline were prepared by a method described previously.[7] n-Butylamine and benzylamine from Aldrich were purified as previously reported.[7] Acetonitrile, toluene and dichloromethane from Sintorgan (HPLC quality) were used as received.

Procedures. The kinetic experiments were carried out as previously described.[9] The reaction mixtures were neutralized with ammonium chloride solution. The kinetic of the reactions were followed either measuring by HPLC the disappearance of the substrate or analyzing by UV-visible spectroscopy the increase in the absorbance of the products. The data treatment was accomplished as already reported.[9]

General Procedure for the synthesis of the products. 2CNTFB or 4CNTFB (2.27 mmol), substituted aniline (5.11 mmol) and TBAB (0.32 mmol) in 5 mL of

acetonitrile were placed in a 3-necked flask equipped with an efficient mechanic stirrer and a thermometer. After a short period of stirring, 4 mL of a 52.9% NaOH aqueous solution was added. The mixture was kept at 40±0.5 °C for six hours. The crude mixture was first neutralized with ammonium chloride solution, washed with water and extracted with dichloromethane. The organic phase was dried with $MgSO_4$ and the solvent removed. Flash chromatography (silica gel, Merck, 60 mesh, eluent: from petroleum ether to 1:1 petroleum ether - dichloromethane) provided the pure product as determined by HPLC. The characterization and yields of the compounds obtained are reported below.

N-[4-(Trifluoromethyl)-2-nitrophenyl]-4-nitroaniline: **M.p.**: 150-151 °C. **UV-visible**: λ_{max} = 338 nm (log ε = 4.10) and 402 nm (log ε = 4.11) in dichloromethane. **FT-IR** (KBr) $\nu_{max}(cm^{-1})$: 3328.7 (st. NH); 3104.9 (st. C_{Ar}-H); 1538.6 (st. as. NO_2); 1328.0 (st. sy. NO_2). **^{1}HNMR** (200.13MHz, DMSO-d_6, TMS): δ [ppm] = 7.47 (dd, 2H, J=8.7Hz; J=2.0Hz); 7.68 (d, 1H, J=9.0Hz); 8.23 (dd, 2H, J=8.7Hz; J=2.0Hz); 7.94 (dd, 1H, J=9.0Hz; J=2.6Hz); 8.41(d, 1H, J=2.6Hz); 9.87 (s, 1H, -NH). **^{13}CNMR** (50.32 MHz, DMSO-d_6, TMS): δ [ppm] = 120.0, 120.4, 120.5, 121.2, 123.7 (-CF_3), 125.2, 131.3, 136.7, 140.5, 142.1, 146.4. **MS**: m/z 297,0 (M-30), 327,0 (M^+). **Yield:** 84%.

N-[2-(Trifluoromethyl)-4-nitrophenyl]-4-nitroaniline: **M.p.**: 132-133 °C. **UV-visible**: at λ_{max} = 378 nm (log ε = 4.43) in dichloromethane. **FT-IR** (KBr) $\nu_{max}(cm^{-1})$: 3387.9 (st. NH); 3091.8 (st. C_{Ar}-H); 1512.2 (st. as. NO_2); 1315,0 (st. sy. NO_2). **^{1}HNMR** (200.13MHz, DMSO-d_6, TMS): δ [ppm] = 7.35 (dd, 2H,

J=9.2Hz; J=2.2Hz); 7.68 (d, 1H, J=9.0Hz); 8.20 (dd, 2H, J=9.2Hz; J=2.2Hz); 8.42 (dd, 1H, J=9.0Hz; J=2.7Hz); 8.46(d, 1H, J=2.7Hz); 9.14 (s, 1H, -NH). **^{13}CNMR** (50.32 MHz, DMSO-d_6, TMS): δ [ppm] = 118.7, 119.4, 120.1, 120.6, 122.9, 123.4 (-CF_3), 125.5, 128.8, 141.4, 145.5, 148.5. **MS**: m/z 297,0 (M-30), 327,0 (M^+). **Yield:** 86%.

N-[2-(Trifluoromethyl)-4-nitrophenyl]-3-nitroaniline: **M.p.**: 193-194 °C. **UV-visible**: λ_{max} = 352 nm (log ε = 4.37) in dichloromethane. **FT-IR** (KBr) ν_{max} (cm^{-1}): 3406.3 (st. NH); 3097.5 (st. C_{Ar}-H); 1508.5 (st. as. NO_2); 1317.3 (st. sy. NO_2). **^{1}HNMR** (200.13MHz, DMSO-d_6, TMS): δ [ppm] = 7.37 (d, 1H, J=9.3Hz); 7.68 (d, 1H, J=8.0Hz); 7.75 (dd, 1H, J=8.0Hz; J=2.0Hz); 8.00 (dd, 1H, J=8.0Hz; J=2.0Hz); 8.13(d, 1H, J=2.0Hz); 8.28 (dd, 1H, J=9.2Hz, J=2.7Hz); 8.40 (d, 1H, J=2.7Hz); 8.87 (s, 1H, -NH). **^{13}CNMR** (50.32 MHz, DMSO-d_6, TMS): δ [ppm] = 117.2, 117.9, 118.7, 120.3, 123.4 (-CF_3), 123.6, 128.7, 128.9, 130.7, 139.0, 141.6, 147.2, 148.6. **MS**: m/z 297,1 (M-30), 327,1 (M^+). **Yield:** 81%.

N-[2-(Trifluoromethyl)-4-nitrophenyl]-4-cyanoaniline: **M.p.**: 153-154 °C. **UV-visible**: λ_{max} = 360 nm (log ε = 4.42) in dichloromethane. **FT-IR** (KBr) ν_{max}(cm^{-1}): 3367.5(st. NH); 3091.8 (st. C_{Ar}-H); 1511.9 (st. as. NO_2); 1314.8 (st. sy. NO_2), 2227.3 (st. CN). **^{1}HNMR** (200.13MHz, DMSO-d_6, TMS): δ [ppm] = 7.38 (dd, 2H, J=8.7Hz; J=2.0Hz); 7.53 (d, 1H, J=9.0Hz); 7.78 (dd, 2H, J=8.7Hz; J=2.0Hz); 8.34 (dd, 1H, J=9.0Hz; J=2.7Hz); 8.43(d, 1H, J=2.7Hz); 8.86 (s, 1H, -NH). **^{13}CNMR** (50.32 MHz, DMSO-d_6, TMS): δ [ppm] = 104.6, 118.9, 120.1, 120.6, 120.8, 123.4 (-CF_3), 123.5, 125.5, 128.8, 133.6, 140.3, 145.6. **MS**: m/z 277,1 (M-30), 307,1 (M^+). **Yield:** 83%.

N-butyl-2-trifluoromethyl-4-nitroaniline[7]: **UV-visible:** λ_{max} = 358 nm (log ε = 4.26) in dichloromethane. Orange oil. **FT-IR** (KBr) $\nu_{max}(cm^{-1})$: 3466.9 (st. NH); 3104.9 (st. C_{Ar}-H); 1512.2 (st. as. NO_2); 1328,0 (st. sy. NO_2). **^{1}HNMR** (200.13MHz, DMSO-d_6, TMS): δ [ppm] = 0.89 (t, 3H, J=7.2Hz); 1.31 (m, 2H); 1.52 (m, 2H); 3.33 (m, 2H); 6.95 (d, 1H, J=9.2Hz), 7.03 (dd, 1H, J=9.2Hz; J=2.6Hz); 8.19 (s, 1H, -NH); 8.23 (d, 1H, J=2.6Hz). **^{13}CNMR** (50.32 MHz, DMSO-d_6, TMS): δ [ppm] = 13.4, 19.2, 29.7, 42.2, 111.4, 120.7, 123.3 (-CF_3), 126.1, 127.0, 134.4, 149.8. **Yield:** 95%.

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