Monatshefte für Chemie (2002)
DOI 10.1007/s00706-002-0505-8

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Study of Ultrasound Promoted Aromatic Nucleophilic Substitution of Halobenzenes with Amines

Mária Mečiarová[1], **Štefan Toma**[1,*], **Jana Podlesná**[1], **Michal Kiripolský**[1], and **Ivana Císařová**[2]

[1] Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, SK-842 15 Bratislava, Slovak Republic
[2] Department of Inorganic Chemistry, Charles University, CZ-128 40 Praque 2, Czech Republic

Received May 6, 2002; accepted (revised) May 29, 2002
Published online September 19, 2002

Summary. The sonochemical nucleophilic aromatic substitution of substituted haloarenes with different amines were studied. The reaction course was found to be strongly depended on basicity, bulkiness, and boiling point of amines as well as on the electron-withdrawing property of the substituents.

Keywords. Nucleophilic aromatic substitution; Ultrasonic irradiation.

Introduction

Nucleophilic aromatic substitution of haloarenes with amines are generally difficult to achieve and are limited to fluorides having a strongly electron-withdrawing group, such as a nitro group at the *para* position. Thus, *Ibata et al*. [1] have described aromatic nucleophilic substitutions of nitrohalobenzenes with different amines. The yields range from moderate to excellent, but the reactions had to be carried out under high pressure (0.6–1.2 GPa) at 50–80°C, for 20–50 h, and five molar equivalents of amine were necessary. 4-Haloarylketones have underwent facile nucleophilic displacement in polar aprotic solvents (*DMSO*, *DMF*) with aliphatic and alicyclic amines using potassium carbonate as the base [2, 3]. Yields of the products have been 20–95% and the reactions were carried out at 95°C for 6 h [2]. *Bavetsian* and *Henderson* [4] have investigated the synthesis of *N*-substituted derivatives of *t*-butyl 4-aminobenzoate *via* a palladium catalyzed reaction. These reactions have been carried out in toluene at 100°C, with NaO^tBu as the base and $PdCl_2/P(o\text{-tolyl})_3$ as the catalyst. A non-conventional procedure for nucleophilic aromatic substitution with cyclic amines has been described recently

* Corresponding author. E-mail: toma@fns.uniba.sk

[5]. Different chloroaromatic compounds have underwent nuclephilic substitutions with secondary aliphatic cyclic amines without solvent under microwave irradiation. Reaction times have been 1–2 min with yields higher than 90%. *Prim* and *Kirsch* [6] have reported a convenient preparation of 5-*N,N*-disubstituted-aminothiophene-2-carboxaldehydes by S_NAr reactions in water from the corresponding bromo derivatives. Yields of 80–90% have been achieved with reaction times of 12–24 h and 3 equivalents of amine.

The main aim of this work was to study the ultrasound effect on nucleophilic substitutions of different haloarenes with amines. The second aim was to examine the structure effects of haloarenes as well as amines on their reactivity and therefore to study all these reactions under the same conditions.

Results and Discussion

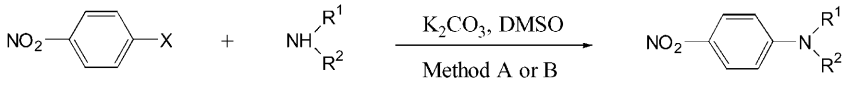
Acoustic energy is a mechanical vibration with frequencies many orders of magnitude below those of molecular vibrations. It is clear therefore, that ultrasonic irradiation cannot be directly absorbed by molecules. The indirect mechanism of activation of sonochemical transformation is known as acoustic cavitation [7]. During the compression phase, the cavities can collapse violently in a very short time (10^{-6} sec). Under these adiabatic conditions, their contents reach high temperatures (5000 K) and pressures (hundreds of MPa) [8]. Similar effects of high pressures and ultrasonic irradiation on chemical reactions are well known from literature [9–12]. Our results with 4-nitrohalobenzenes (Table 1) are in accordance with the theory of the effects of ultrasonic cavitation as well as with the experimental results described before. As follows from Table 1, application of ultrasonic irradiation allows to perform the reactions under normal pressure, for a shorter time, and the results are similar to those obtained under extreme conditions. We assume that ultrasonic acceleration in these reactions is caused by very powerful micro-streaming, which accompanies implosions of micro-bubbles and provides effective mass transfer. Potassium carbonate particles are disrupted and its active surface is therefore considerably enlarged which means that the catalytic activity of potassium carbonate is also enhanced [13]. Application of ultrasonic irradiation has also another positive effect. It enables to improve the atom economy of S_NAr reactions. All reactions described in this work were performed with an equimolar amount of amine. Unlike the methods described in Refs. [1, 2, 14], no molar excess of amine was necessary.

These S_NAr reactions proceed through the *Meisenheimer* type intermediate and the difference in reactivity of amines is attributed both to their basicity and bulkiness [1]. Cyclic secondary amine (piperidine, **2a**) was found to be the most reactive among the amines used in this work (Scheme 1, Table 1). On the contrary, the low reactivity of secondary acyclic amines was due to their bulkiness as well as to their low boiling point. Diethylamine (**2d**) gave at 15 min of sonochemical reaction 9% of **3d**. Prolonging the reaction time to 30 min did not increase the yield (Table 1, Entries 14, 15). This is probably due to its low boiling point (55°C) because amine could evaporate from the reaction mixture at a temperature at about 140–150°. Boiling points of diisobutylamine (**2e**) (137–139°C) as well as dibenzylamine (**2f**) (300°C) are higher, but their bulkiness lowered the reactivity. Bulkiness as well as

Table 1. Results of S_NAr reactions of 4-halonitrobenzenes **1** with amines **2**

	1	HNR^1R^2	X	Time min	Method	Product	Yield %
1	**1a**	piperidine (**2a**)	F	15	A	**3a**	82
2	**1a**	**2a**	F	15	B	**3a**	80
3	**1b**	**2a**	Cl	15	A	**3a**	56
4	**1b**	**2a**	Cl	15	B	**3a**	50 (100[a])
5	**1c**	**2a**	Br	15	A	**3a**	74
6	**1d**	**2a**	I	15	A	**3a**	50
7	**1d**	**2a**	I	15	B	**3a**	16 (100[a])
8	**1a**	imidazole (**2b**)	F	15	A	**3b**	53
9	**1b**	**2b**	Cl	15	A	**3b**	32
10	**1c**	**2b**	Br	15	A	**3b**	42
11	**1d**	**2b**	I	15	A	**3b**	31
12	**1d**	**2b**	I	30	B	**3b**	0
13	**1a**	dipentylamine (**2c**)	F	30	A	**3c**	62 (56[b])
14	**1a**	diethylamine (**2d**)	F	15	A	**3d**	9
15	**1a**	**2d**	F	30	A	**3d**	10
16	**1b**	**2d**	Cl	15	A	**3d**	0 (39[a])
17	**1c**	**2d**	Br	15	A	**3d**	0
18	**1d**	**2d**	I	15	A	**3d**	0
19	**1a**	diisobutylamine (**2e**)	F	30	A	**3e**	0
20	**1a**	dibenzylamine (**2f**)	F	30	A	**3f**	0

[a] Reactions were carried out under high pressure (0.6–1.2 GPa), with 5 equivalents of amine, reaction time 20–50 h, reaction temperature 50°C [1]; [b] reaction was carried out without solvent, with two equivalents of amine, gently boiling for 1–3 days [14]



1	X	**2**	R^1	R^2	**3**	R^1	R^2
1a	F	**2a**	$-(CH_2)_5-$		**3a**	$-(CH_2)_5-$	
1b	Cl	**2b**	$-CH=N-CH=CH-$		**3b**	$-CH=N-CH=CH-$	
1c	Br	**2c**	$-(CH_2)_4CH_3$	$-(CH_2)_4CH_3$	**3c**	$-(CH_2)_4CH_3$	$-(CH_2)_4CH_3$
1d	I	**2d**	$-CH_2CH_3$	$-CH_2CH_3$	**3d**	$-CH_2CH_3$	$-CH_2CH_3$
		2e	$-CH_2-CH(CH_3)_2$	$-CH_2-CH(CH_3)_2$	**3e**	$-CH_2-CH(CH_3)_2$	$-CH_2-CH(CH_3)_2$
		2f	$-CH_2Ph$	$-CH_2Ph$	**3f**	$-CH_2Ph$	$-CH_2Ph$

Scheme 1. Method A: sonochemical reaction; method B: thermal heating with stirring

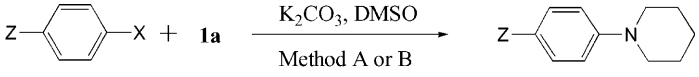
basicity of dipentylamine (**2c**) are similar to those of diethylamine (**2d**), but its boiling point is 202–203°C. Thus **2c** does not evaporize from the reaction mixture. The yield of **3c** was 62% (Table 1, Entry 13). We attained in 30 min better results than *Mansour et al*. by his solvent free procedure [14] (56%) after 2–3 days. Later on, we have studied the effect of an electron-withdrawing group on the course of S_NAr reactions under our conditions.

Table 2. Results of S_NAr reactions of haloarenes **4** with **2a**

Entry	**4**	Z	X	Time (min)	Method	Product	Yield %
1	**4a**	H	F	30	A	**5a**	0
2	**4b**	$COCH_3$	F	15	A	**5b**	25 (80[a])
3	**4b**	$COCH_3$	F	30	A	**5b**	59
4	**4b**	$COCH_3$	Cl	15	A	**5b**	0
5	**4b**	$COCH_3$	Br	15	A	**5b**	0
6	**4c**	CHO	F	15	A	**5c**	85
7	**4c**	CHO	F	15	B	**5c**	48 (70[a])
8	**4c**	CHO	Cl	15	A	**5c**	0
9	**4c**	CHO	Br	15	A	**5c**	0
10	**4c**	CHO	I	15	A	**5c**	0
11	**4d**	CN	F	15	A	**5d**	55 (77[a])
12	**4d**	CN	Cl	15	A	**5d**	0
13	**4d**	CN	Br	15	A	**5d**	0

[a] Reaction was carried out in *DMSO*, at 95°C, for 6 h [2]

From the results given in Tables 1 and 2 it follows that the fluoro compounds underwent S_NAr reactions with amines much easier than their chloro and bromo analogues. These experimental results are in accordance with the theory of the leaving group effect, as the approximate order is F > Cl, Br, I [15]. The S_NAr mechanism is an addition-elimination mechanism involving the formation of a carbanion with delocalized electrons. The carbanion is stabilized by electron-withdrawing groups in the positions *ortho* and *para* to the halogen atom. The stabilizing effect of an electron-withdrawing group on S_NAr reactions decreases in the order $NO_2 > COR > COH > CN$ [15]. This explains the observed lower reactivity of 4-haloacetophenones **4b**–**4d**, 4-halobenzaldehydes **4e**–**4h**, and 4-halobenzonitriles **4i**–**4k** in comparison to the reactivity of 4-halonitrobenzenes **1a**–**1d** (Scheme 2, Tables 1 and 2).



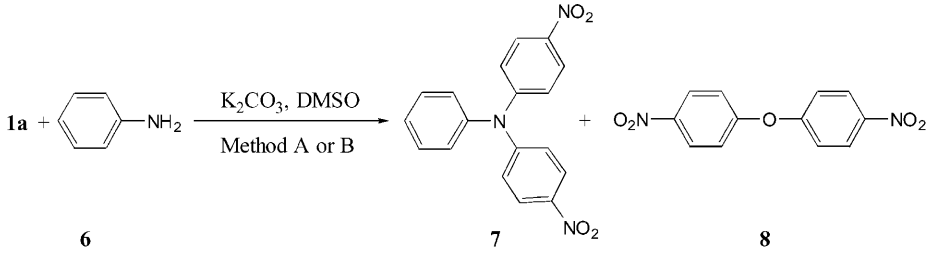
4	Z	X
4a	H	F
4b	$COCH_3$	F
4c	$COCH_3$	Cl
4d	$COCH_3$	Br
4e	CHO	F
4f	CHO	Cl
4g	CHO	Br
4h	CHO	I
4i	CN	F
4j	CN	Cl
4k	CN	Br

5	Z
5a	H
5b	$COCH_3$
5c	CHO
5d	CN

Scheme 2. Method A: sonochemical reaction; method B: thermal heating with stirring

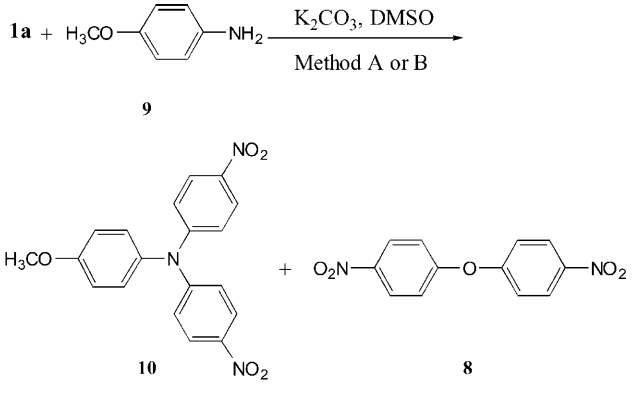
We have to stress that our experiments were not optimized. The yields of the products can be increased by reaction time prolongation, as was documented in the reaction with 4-fluoroacetophenone (**4b**) (Table 2, Entries 2, 3).

The low basicity of aniline (**6**) is probably responsible for its poor reactivity in S_NAr reactions. *Ibata et al*. [1] achieved very low yield of 4-nitrodiphenylamine (7%) under high pressure (0.9 GPa) at 50°C for 50 h with 5 equivalents of aniline. Sonochemical reaction of **6** with **1a** gave 9% of bis-(4-nitrophenyl)-phenylamine (**7**) and 9% of bis-(4-nitrophenyl)-ether (**8**). Starting material was only detected in the reaction mixture at the silent reaction (Scheme 3). To increase the reactivity of aromatic amines in S_NAr rections on **1a**, we performed reactions with anilines having strong electron-donating groups in the *para* position. Sonochemical S_NAr reaction on **1a** with 4-methoxyaniline (**9**) gave 46% of 4-methoxyphenylbis-(4-nitrophenyl)-amine (**10**) and 10% of bis-(4-nitrophenyl)-ether (**8**) isolated by column chromatography. Classical reaction gave at the same time (30 min) 11% of **10** and just traces of **8** were detected in the reaction mixture by NMR spectroscopy (Scheme 4). Similarly, we isolated by column chromatography 54% of (4-*N*,*N*-diethylaminophenyl)-bis-(4-nitrophenyl)amine (**12**) after the sonochemical S_NAr reaction on **1a** with 4-(*N*,*N*-diethylamino)-aniline (**11**) and 10% of **8**. Silent reaction gave at the same time (30 min) just 12% of **12** and just traces of **8** were detected in the reaction mixture by NMR spectroscopy (Scheme 5).



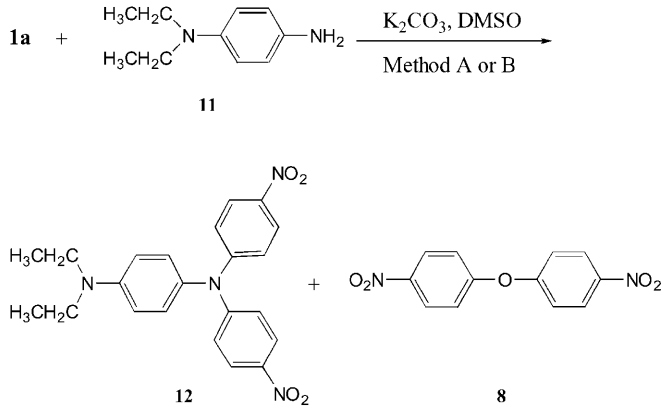
6 7 8

Scheme 3. Method A: sonochemical reaction, 30 min, 9% of **7**, 9% of **8**; method B: thermal heating with stirring, 30 min, 0% of **7**, 0% of 8



9 10 8

Scheme 4. Method A: sonochemical reaction, 30 min, 46% of **10**, 10% of **8**; method B: thermal heating with stirring, 30 min, 11% of **10**, traces of **8**



Scheme 5. Method A: sonochemical reaction, 30 min, 54% of **12**, 10% of **8**; method B: thermal heating with stirring, 30 min, 12% of **12**, traces of **8**

Experimental

Reagents and solvents were standard grade commercial products and were used without further purification. The ^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. GC spectra were recorded on a GC TRACE 2000 Series instrument, MS spectra were recorded on a VOYAGER spectrometer. Melting points were determined on a *Kofler*-hot stage and are uncorrected. All sonochemical experiments were carried out in a glass reactor fitted to an ultrasonic horn Ultragen (Nitra, Slovakia) (20 kHz, 300 W) for 15 min under an air atmosphere.

Sonochemical reaction

Potassium carbonate (2.9 g, 20 mmol) was added to the solution of the appropriate amine (20 mmol) and 20 mmol 4-haloarene in 20 cm^3 *DMSO*. The reaction mixture was sonicated for 15 (30) min. The temperature of the reaction mixture attained 150 °C at the end of sonication. Then the reaction mixture was cooled down to 60 °C and poured into 400 cm^3 distilled H_2O. In most cases analytically pure products were collected by filtration with suction. In the case when the product was an oil or not pure (*TLC*), the emulsion was extracted three times into 75 cm^3 diethyl ether. Then the ether solution was washed with H_2O and dried (anhydrous Na_2SO_4) and the ether was removed on a rotary vacuum evaporator. The crude products (**3a** and **3b**) were purified by crystallization from isohexane or by chromatography (**3c**, **3d**, **5b**, **5c**, **5d**, **7**, **8**, **10**, and **12**) on silica using isohexane/ethyl acetate (9/1) as the eluent. The results are given in the Tables 1 and 2.

Classical reaction

Potassium carbonate (2.9 g, 20 mmol) was added to the solution of the appropriate amine (20 mmol) and 20 mmol 4-haloarene in 20 cm^3 *DMSO*. The reaction mixture was vigorously stirred for 15 min. Then the reaction mixture was worked-up as described above.

Products **3a** [3, 16], **3b** [17, 18], **3c** [14], **3d** [19], **5b** [2, 20], **5c** [3, 21], **5d** [2, 20], **8** [23, 24], and **10** [25] were found to be identical (melting points and NMR data) with the data described in literature.

Bis(4-nitrophenyl)phenylamine (**7**)

Yellow solid; m.p. 194–196°C (Ref. [22] 194.5–195.8°C); ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.14–7.20 (m, $6H_{arom}$), 7.32 (t, $J = 9.0$, $1H_{arom}$), 7.44 (t, $J = 9.0$, $2H_{arom}$), 8.15 (d, $J = 9.0$, $4H_{arom}$) ppm; GC-MS: $m/z = 335$ (100, M^+), 305 (38), 259 (30), 243 (82), 166 (22), 139 (20), 77 (27).

(4-N,N-Diethylaminophenyl)-bis-(4-nitrophenyl)-amine (**12**)

Red solid; m.p. 158–161°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.21 (t, $J = 7.2$, $2CH_3$), 3.39 (q, $J = 7.2$, $2CH_2$), 6.67 (d, $J = 9.0$, $2H_{arom}$), 6.97 (d, $J = 9.0$, $2H_{arom}$), 7.15 (d, $J = 9.0$, $2H_{arom}$), 8.11 (d, $J = 9.0$, $2H_{arom}$) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 12.55, 44.46, 112.65; 121.36, 125.41, 128.88, 131.88, 142.07, 147.02, 152.19; GC-MS: $m/z = 406$ (100, M^+), 391 (100), 362 (28), 345 (22), 270 (23), 241 (43).

Acknowledgements

The authors thank Dr. *E. Solčániová* and her staff from the Institute of Chemistry of Comenius University for ^{1}H NMR and ^{13}C NMR analyses, and Dr. *R. Kubinec* and his staff from the Institute of Chemistry of Comenius University for GC-MS analyses. Our thanks are due to Dr. *D. Végh* from the Faculty of Chemistry and Technology of STU, Bratislava for 4-fluoronitrobenzene. This work was supported by the VEGA – Grant Agency, Grant No. 1/7348/20 and the auspicies COST – Chemistry Project No. D-10/0008/98.

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