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Study of S_NAr Reactions of Halobenzenes with Imidazole under Ultrasonic and Microwave Irradiation

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Summary. Nucleophilic aromatic substitution reactions with imidazole of haloarenes having strongly electron-withdrawing groups were studied under ultrasonic and microwave irradiations. The course of the S_NAr reactions was found to be strongly dependent on the electron-withdrawing properties of the substituents as well as on the leaving ability of the halogen atom. Microwave irradiation allowed to shorten the reaction time and to increase the yields compared with ultrasonic irradiation.

Keywords. Nucleophilic aromatic substitutions; Halobenzenes; Imidazole; Microwave irradiation; Ultrasonic irradiation.

Introduction

Nucleophilic aromatic substitution of haloarenes with amines generally do not proceed smoothly under normal pressure and are limited to fluorides having a strongly electron-withdrawing group in the *para* position. The S_NAr reactions of the haloarenes having mild electron-withdrawing groups such as the formyl group need rather harsh conditions, like high pressure (up to 10^3 MPa) [1] or long reaction time and high temperature in dipolar aprotic solvents like *DMSO* or *DMF* [2, 3]. Several papers appeared describing the beneficial effect of ultrasonic irradiation [4–8] or microwave irradiation [9–13]. *Buchwald* [14] and *Hartwig* [15] described Pd catalyzed arylation of amines, which gives good results with aliphatic and especially alicyclic amines. The S_NAr reactions of haloarenes are much more difficult with azoles.

The aim of the present work was therefore to examine the effect of ultrasonic and microwave irradition on the course of different S_NAr reactions of halobenzenes with imidazole.

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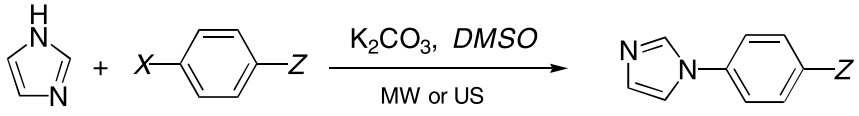
Results and Discussion

Cyclic secondary amines owing to its basicity, nucleophilicity, and bulkiness were the most reactive amines in the S_NAr reactions with 4-fluorobenzaldehyde, whereas imidazole and other aromatic amines were found to be less reactive or unreactive [5]. Thus, we decided to study the S_NAr reactions of haloarenes with imidazole under ultrasonic and microwave irradiation.

The most reactive haloarenes in the S_NAr reactions with imidazol (**1**) were 1-halo-4-nitrobenzenes **2a**–**2d**. 1-(4-Nitrophenyl)imidazole (**7**) was isolated after 15 min sonication in 31–53% yield, whereas 3 min of microwave irradiation gave **7** in 43–80% yield (Table 1). The positive effect of non-classic reaction conditions was demonstrated on the reactions of 1-iodo-4-nitrobenzene (**2d**) with **1**. Although **2d** was inactive in the S_NAr reaction with **1** under heating and stirring for 15 min at 150°C, 15 min of ultrasonic irradiation gave 31% of **7** and 3 min of microwave irradiation yielded 43% of **7** (Table 1).

4-Haloacetophenones **3a**–**3c** underwent the S_NAr reactions with imidazole giving 4-(imidazol-1-yl)acetophenone (**8**) in 10–65% yield (Table 1). The best yield of **8** (65%) gave 4-fluoroacetophenone after 3 min of microwave irradiation. 4-Chloro- or 4-bromoacetophenone (**3b**, **3c**) irradiated for 3 min gave 11 or 10% of **8**. Prolonging the reaction time to 7 min increased the yield of **8** to 37 or 36%. Further prolonging the time of irradiation did not increase the yields, but undesirable polymerisation reactions took place instead. Thus, unidentified black tarry materials were present in the reaction mixtures.

4-Fluorobenzaldehyde (**4a**) gave 4-(imidazol-1-yl)benzaldehyde (**9**) in 75% yield after 15 min ultrasonic irradiation. A very similar yield of **9** (74%) was



		Z	*X*
1	**2a**	NO_2	F
	2b	NO_2	Cl
	2c	NO_2	Br
	2d	NO_2	I
	3a	$COCH_3$	F
	3b	$COCH_3$	Cl
	3c	$COCH_3$	Br
	4a	CHO	F
	4b	CHO	Cl
	4c	CHO	Br
	4d	CHO	I
	5a	CN	F
	5b	CN	Cl
	5c	CN	Br
	6	H	F

	Z
7	NO_2
8	$COCH_3$
9	CHO
10	CN
11	H

Scheme 1

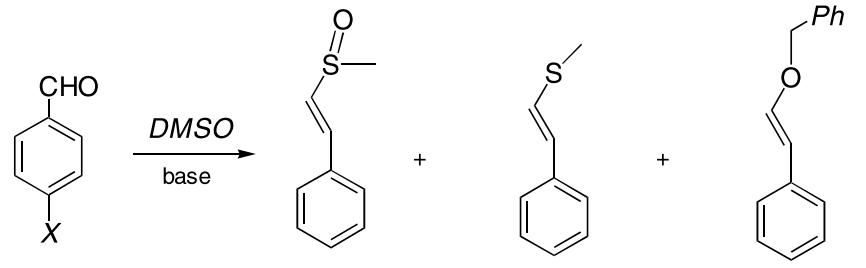
Table 1. Results of the S_NAr reactions of haloarenes with imidazole

XC_6H_4Z	Z	X	Conditions	Product	Yield/%
2a	NO_2	F	US, 15 min, 140°C	**7**	53
2a	NO_2	F	MW, 3 min, 240 W, $t_{fin} = 165$°C	**7**	80
2b	NO_2	Cl	US, 15 min, 140°C	**7**	37
2b	NO_2	Cl	MW, 3 min, 240 W, $t_{fin} = 172$°C	**7**	72
2c	NO_2	Br	US, 15 min, 140°C	**7**	42
2d	NO_2	I	US, 15 min, 140°C	**7**	31
2d	NO_2	I	MW, 3 min, 240 W, $t_{fin} = 173$°C	**7**	43
2d	NO_2	I	Δ, 15 min, 150°C	**7**	0
3a	$COCH_3$	F	MW, 3 min, 240 W, $t_{fin} = 150$°C	**8**	65
3a	$COCH_3$	Cl	MW, 3 min, 240 W, $t_{fin} = 153$°C	**8**	11
3b	$COCH_3$	Cl	MW, 7 min, 240 W, $t_{fin} = 180$°C	**8**	37
3c	$COCH_3$	Br	MW, 3 min, 240 W, $t_{fin} = 146$°C	**8**	10
3c	$COCH_3$	Br	MW, 5 min, 240 W, $t_{fin} = 154$°C	**8**	22
3c	$COCH_3$	Br	MW, 7 min, 240 W, $t_{fin} = 157$°C	**8**	36
4a	CHO	F	US, 15 min, 140°C	**9**	75
4a	CHO	F	MW, 3 min, 240 W, $t_{fin} = 140$°C	**9**	74
4b	CHO	Cl	US, 15 min, 140°C	**9**	0
4b	CHO	Cl	MW, 5 min, 240 W, $t_{fin} = 164$°C	**9**	19
4c	CHO	Br	US, 15 min, 140°C	**9**	0
4c	CHO	Br	MW, 5 min, 240 W, $t_{fin} = 162$°C	**9**	19
4d	CHO	I	US, 15 min, 140°C	**9**	0
5a	CN	F	MW, 3 min, 240 W, $t_{fin} = 181$°C	**10**	77
5b	CN	Cl	MW, 5 min, 240 W, $t_{fin} = 186$°C	**10**	38
5c	CN	Br	MW, 5 min, 240 W, $t_{fin} = 134$°C	**10**	57
6	H	F	US, 30 min, 140°C	**11**	0
6	H	F	MW, 5 min, 240 W, $t_{fin} = 134$°C	**11**	0

achieved after 3 min of microwave irradiation. Although 4-chloro-, 4-bromo-, and 4-iodobenzaldehydes (**4b**–**4d**) were inactive in the sonochemical S_NAr reactions with **1**, 4-chloro- and 4-bromobenzaldehydes (**4b**, **4c**) gave 19% of **9** after 5 min of microwave irradiation (Table 1). 4-Chloro- and 4-bromobenzaldehydes (**4b**, **4c**), which were less reactive in the S_NAr reactions, gave **12a**, **12b**, **13a**, **13b**, **14a**, and **14b** (Scheme 2) as the products of competitive reactions with the solvent. The yields of **12a**, **12b**, **13a**, **13b**, **14a**, and **14b** were according to ^{1}H NMR and GC-MS analyses less than 5%. The results of the reactions of aromatic aldehydes with *DMSO* in the presence of a base are in accord with the facts described in literature [16].

Reactions of 4-halobenzonitriles **5a**–**5c** with **1** under microwave irradiation gave 4-(imidazol-1-yl)benzonitrile (**10**) in 38–77% yield after 3–5 min (Table 1). Fluorobenzene (**6**) was inert in the S_NAr reactions with **1** under both, ultrasonic and microwave irradiations. Only starting materials were detected in the reaction mixtures (Table 1).

To conclude we have proved that both, ultrasonic and microwave irradiation accelerate the S_NAr reactions of imidazole with haloarenes, but microwave irradiation is more effective because even less reactive haloarenes like



4	*X*	**12**	*X*	**13**	*X*	**14**	*X*
4b	Cl	**12a**	Cl	**13a**	Cl	**14a**	Cl
4c	Br	**12b**	Br	**13b**	Br	**14b**	Br

Scheme 2

4-chloroacetophenone (**3b**) or 4-chlorobenzonitrile (**5b**) gave reasonable yields of the target products.

Experimental

Starting materials were commercially available or were prepared according to literature procedures and purified (crystallized or distilled) before reactions. All products were analyzed by ^{1}H NMR spectroscopy and GC-MS. The ^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer in $CDCl_3$ with *TMS* as internal standard. GC spectra were recorded on a GC Trace 2000 Series instrument, mass spectra were recorded on a Voyager spectrometer. All sonochemical experiments were carried out in a glass reactor fitted with an ultrasonic horn Ultragen (20 kHz, 300 W) under pulsed conditions (pulse length: 4 s, 50% duty) for 15 or 30 min under air atmosphere. All microwave experiments were carried out in the Synthewave 402, Prolabo reactor (600 W); the power settings, final temperatures, and reaction times are given in Table 1.

Compounds **7** [7], **8** [8], **9** [9], **10** [13], **12a** [16], **12b** [16], **13a** [16], **13b** [16], **14a** [16], and **14b** [16] were found to be identical (^{1}H NMR data) with the data described in literature.

Microwave S_NAr Reactions (MW)

Potassium carbonate (0.76 g, 5.5 mmol) was added to a solution of 0.374 g of **1** (5.5 mmol) and 5.5 mmol of haloarene in 7.5 cm^3 of *DMSO*. The reaction mixture was irradiated for 3–7 min under conditions given in Table 1. The reaction mixture was cooled to 30°C and then poured into 200 cm^3 of distilled H_2O. The precipitated products were usually analytically pure; they were collected by filtration under reduced pressure. When the product was an oil or not pure enough, the emulsion formed was extracted three times with 50 cm^3 of diethyl ether. The ether solution was washed with H_2O and dried (Na_2SO_4). Ether was evaporated *in vacuo* and the product was purified by column chromatography on silica using isohexane/ethyl acetate (9/1–6/1) as the eluent.

Sonochemical S_NAr Reactions (US)

Potassium carbonate (1.38 g, 11 mmol) was added to a solution of 0.68 g of **1** (10 mmol) and 10 mmol of haloarene in 20 cm^3 of *DMSO*. The reaction mixture was sonicated for 15 or 30 min. The tempera-

ture of the reaction mixture attained 140°C at the end of sonication. The reaction mixture was then worked up as described above.

Classic S_NAr Reactions (Δ)

Potassium carbonate (1.38 g, 11 mmol) was added to a solution of 0.68 g of **1** (10 mmol) and 10 mmol of haloarene in 20 cm^3 of *DMSO*. The reaction mixture was heated at 150°C for the time period given in Table 1. The reaction mixture was then worked up as described above.

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