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Assessment of amination reactions via nucleophilic aromatic substitution using conventional and eco-friendly energies

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ABSTRACT

The efficiency of conventional heating energy source compared with Infrared (IR), Ultrasound (US), Microwave and the simultaneous combination US–IR eco-friendly approaches for preparation of new *N*-(5-*R*¹-amino-2-nitrophenyl)acetamides and 5-*R*¹-amino-2-nitroaniline by Nucleophilic Aromatic Substitution (S_NAr) via addition–elimination reactions on the halogens F, Cl, Br, I, employing amines as nucleophiles were explored. Moreover, phenyldiazenyl derivatives in good yields by an oxidative one-pot S_NAr -based amination reaction from an unusual oxidation of 2-phenylhydrazinyl derivatives in DMSO was prepared.

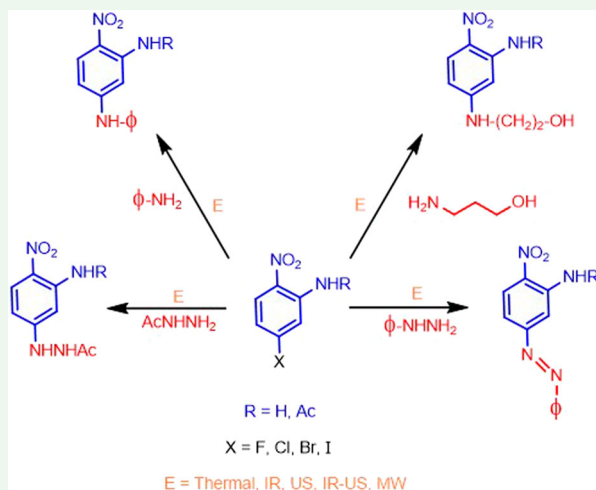
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S_NAr reactions; amino (acetamido)-halo-nitro aromatic compounds; assessment; thermal energy; alternative energy sources



Introduction


In general, S_NAr reactions are chemical transformations in which an anionic or neutral nucleophile displaces a potential leaving group attached to an aromatic ring. The presence of electron withdrawing groups in *ortho* and/or *para* positions with respect to the leaving group provides the main driving force to achieve S_NAr , which reduce the electronic density of the aromatic ring, favoring the nucleophilic reaction.

Nitro-halo aromatic derivatives are valuable building blocks to assemble simple and complex molecular

structures of pharmaceutical and industrial importance, such as Vancomycin (1). Due to their high capacity for reactivity under a wide range of conditions, S_NAr reactions have found important applications in the preparation of various kinds of biologically relevant intermediates, including azaheterocycle compounds such as benzimidazoles (2) I, 1-(phenyldi-2-yl) guanidine derivatives (3) II, and macrocyclic compounds (1) III (Figure 1).

The S_NAr -based reactions not only as a new avenue of inquiry to synthesize strategic functionalized building

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blocks and fine chemicals have been explored, but also as an important synthetic pathway to access elaborated natural products as well as their application in the combinatorial chemistry for the preparation of important heterocyclic compounds.

Among many reported S_NAr reactions are those made using 5-fluoro-2-nitroaniline (**4**) and 5-chloro-2-nitroaniline (**5**) as nucleophiles toward methanol (**5**) and phenol (**6**), sulfur, in the form of thiophenol (**7**) and butanethiol (**8**) and phenol, in sodium carbonate to form the thiophenoxide and phenoxide ions, are S_NAr reactions that use different primary amines, aliphatic and aromatic compounds, but they have been less widely reported (**9,10**).

Modifications of organic reactions not only aim to reduce reaction times or the number of synthetic steps in a process, but also to contribute to new trends in chemistry. Then, the implementation of greener technologies in some types of organic process may afford more reaction efficiency, high atom-economy and reaction yields, shorter reaction times and low-environmental charge, among other advantages. In consequence, there is a great tendency to reduce the high dependence on traditional chemical processes, while permitting the development of environmentally friendly chemical protocols that conserve both resources and energy and that best meet the principals of chemical sustainability and green chemistry. However, reinvestigation of novel greener protocols applicable to the preparative chemistry field is still a challenging problem. Processes including energy consumption, operating costs, improvement of overall yield of reaction, industrial, and environmental aspects remain to be fully explored.

In this paper, we present a S_NAr reaction under the protocol of Green Chemistry, using various energy sources such as thermal, Infrared (IR), Ultrasound (US), a simultaneous combination of IR-US, and Microwave (MW) for activating the reactions. We have implemented a series of reactions of S_NAr under an eco-friendly program toward the preparation of *N*-(5- R^1 amino-2-nitrophenyl)acetamides **3a-d**, Figure 2, and 5- R^1 amino-2-nitroanilines **5a-d** from appealing chemical precursors **1a-d** and **4a-d**, respectively. Conscious that many

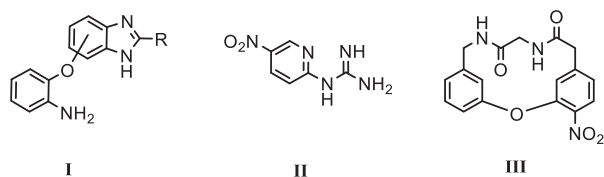


Figure 1. Selected compounds ensemble for a S_NAr reaction.

practical problems remain unsolved in this field, we undertook the use of environmentally friendly technologies such as IR, MW, US, and the simultaneous combination of US-IR to explore S_NAr -based amination reactions to prepare new nitro arylamines **5/7**, with the look toward the synthesis of appealing building blocks to synthesize many other molecules.

Materials and methods

General

All commercial reagents and solvents were of reagent grade and used as received without further purification. Analytical thin-layer and preparative chromatography was performed on precoated Kieselgel 60F₂₅₄ plates and Gel silice MN-Kieselgel G/UV₂₅₄ respectively; spots were located using UV (254 nm). All melting points were measured with a Fisher-Johns SEV PF-300 apparatus and remain uncorrected. ¹H and ¹³C NMR spectra were obtained in either DMSO-*d*₆ or CDCl₃ using a 300 MHz spectrometer. Chemical shifts (δ) are expressed in ppm relative to the tetramethylsilane peak used as internal standard. The *J* values are in Hertz, and the splitting patterns are designated as follows: *s*, singlet; *d*, doublet; *t*, triplet; *m*, multiplet; and *bs*, broad singlet. IR spectra on a FT-IR Bruker spectrophotometer using Attenuated Total Reflection (ATR) method were recorded. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained using a JEOL AccuTOF JMS-T100LC spectrometer, by Direct Analysis in Real Time (DART) method.

Microwave-assisted reactions using a MW reactor ESEVE-MIC-1 with output power 762 W, irradiating at 60 Hz were performed. IR reactions were heating with wavelength of 1100 nm (9.09 cm⁻¹) using a home-

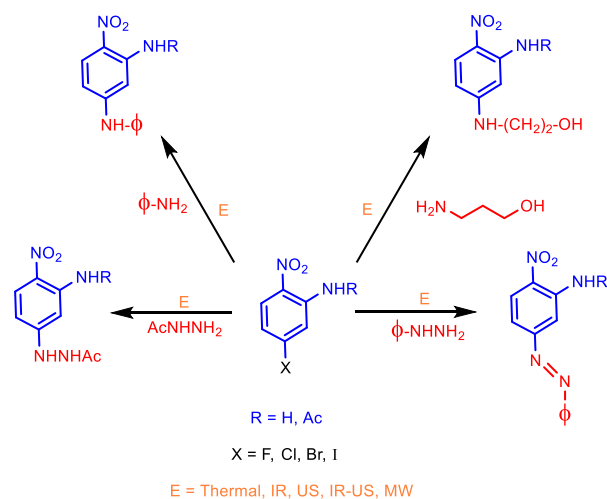


Figure 2. General reactions to obtain target molecules.

made device as reported previously (11). Ultrasound experiments were carry out in a Cole Parmer (500 W/115 V) equipment with an irradiation frequency of 20 KHz.

General procedure

Syntheses of 3a-d

Into a 25 mL flask equipped with a stirring bar was placed the corresponding aminoderivate **2a-d** (7 mmol), *N*-(5-haloderivate-2-nitrophenyl)acetamide **1a-d** (3.2 mmol) and dimethyl sulfoxide (10 mL), except for **5a** were dimethyl formamide was used as solvent. The mixture was submitted to react under the conditions indicated in Table 2. At the end of the required time, the mixture was poured onto crushed ice and the precipitated solid was filtered off and purified by preparative TLC (hexane/AcOEt, 7:3, v/v) to afford the pure products **3a-d**.

N-(5-(2-Acetylhydrazino)-2-nitrophenyl)acetamide

(3a). Yield 80%; mp 182°C; ¹H NMR (300 MHz; DMSO-*d*₆/TMS): δ 2.16 (s, 3H), 3.07 (s, 3H), 4.41 (t, *J* = 6.0 Hz, 1H); 6.56 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 8.02 (d, *J* = 9.6 Hz, 1H), 10.60 (s, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆/TMS): δ 22.7, 25.4, 102.4, 107.6, 126.6, 128.4, 136.8, 155.0, 169.5, 169.6; IR (ATR): 3470, 3358 (NH), 1699 (NHC=O), 1614 (CN), 1572, 1366 (NO₂), 962, 897, 802 (Ar_{1,2,4}-subst) cm⁻¹; MS (DART [+1]) *m/z* 253; HRMS (DART [+1]) Found: 306.95918, calcd for C₈H₈IN₂O₃: 306.95796.

N-(2-Nitro-5-(phenylamino)phenyl)acetamide

(3b). Yield 78%; mp 128 °C; ¹H NMR (300 MHz; CDCl₃/TMS): δ 2.27 (s, 3H), 6.52 (s, 1H), 6.65 (dd, *J* = 9.3, 2.4 Hz, 1H), 7.06–7.36 (m, 3H), 7.27–7.53 (m, 2H), 8.15 (d, *J* = 9.6 Hz, 1H), 8.36 (d, *J* = 2.4 Hz, 1H), 10.93 (s, 1H); ¹³C NMR (75 MHz, CDCl₃/TMS): δ 25.8, 104.6, 108.4, 122.3, 125.1, 128.8, 129.7, 137.8, 138.8, 151.5, 169.5; IR (ATR): 3269 (NH), 1682 (HNC=O) 1620 (CN), 1544, 1298 (NO₂), 813, 752 (Ar_{1,2,4}-subst) cm⁻¹; MS (DART [+1]) *m/z* 272; HRMS (DART [+1]) Found: 272.10348, calcd for C₁₄H₁₄N₃O₃: 272.10352.

N-(5-(2-Hydroxyethylamino)-2-nitrophenyl)acetamide

(3c). Yield 93%; mp 180°C; ¹H NMR (300 MHz; CDCl₃/TMS): δ 2.27 (s, 3H), 3.42 (t, *J* = 5.4 Hz, 2H), 3.88 (t, *J* = 5.4 Hz, 2H), 5.01 (s, 1H), 6.30 (dd, *J* = 6.9, 2.7 Hz, 1H), 8.06 (d, *J* = 2.7 Hz, 1H), 8.13 (d, *J* = 9 Hz, 1H), 11.06 (s, 1H); ¹³C NMR (75 MHz, CDCl₃/TMS): δ 25.9, 45.2, 60.6, 107.8, 126.3, 126.9, 128.9, 138.1, 149.5, 169.6; IR (ATR): 3181, 3313 (NH), 1674 (NHC=O), 1621 (CN), 1593, 1317 (NO₂), 1059 (OH), 817, 852 (Ar_{1,2,4}-subst) cm⁻¹; MS (DART

[+1]) *m/z* 240; HRMS (DART [+1]) Found: 240.09853, calcd for C₁₀H₁₄N₃O₄: 240.09843.

N-(2-Nitro-5-(phenyldiazenyl)phenyl)acetamide

(3d). Yield 70%; mp 155°C; ¹H NMR (300 MHz; CDCl₃/TMS): δ 2.35 (s, 3H), 7.44–7.66 (m, 3H), 7.64 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.87–8.10 (m, 2H), 8.36 (d, *J* = 9.0 Hz, 1H), 9.30 (d, *J* = 2.1 Hz, 1H), 10.46 (s, 1H); ¹³C NMR (75 MHz, CDCl₃/TMS): δ 25.8, 104.6, 108.2, 122.3, 124.9, 128.8, 129.6, 137.7, 138.9, 151.7, 169.6; IR (ATR): 3472, 3358 (NH); 1691 (NHC=O); 1614 (CN); 1540, 1364, 1262 (NO₂); 1498, 1383 (N=N); 773, 755 (Ar_{ipso}), 848, 827, 807 (Ar_{1,2,4}-subst) cm⁻¹; MS (DART [+1]) *m/z* 285; HRMS (DART [+1]) Found: 285.09936, calcd for C₁₄H₁₃N₄O₃: 285.09876.

Syntheses of 4a-d

Method 1 (4a and 4c). A 50 mL round-bottomed flask fitted with a reflux condenser, was charged with a stirring bar, *N*-(5-halo-2-nitrophenyl)acetamide **1a** or **1c** (16.736 mmol), 2 ml of aqueous KOH (16.736 mmol) and 20 mL of dimethyl sulfoxide. The mixture was heated at 60°C for 20 min and poured onto crushed ice after cooling at room temperature. The precipitated solid was filtered off and purified by preparative TLC (hexane/AcOEt, 6:4, v/v) to afford either **4a** or **4c**.

Method 2 (4b/4d). Following the above approach, the corresponding *N*-(5-halo-2-nitrophenyl)acetamide **1b** or **1d** (16.736 mmol), 2 ml of aqueous solution of K₂CO₃ (16.736 mmol) and 20 mL of EtOH was submitted to react at 60°C for 50 min, and the crude product was processed according to *Method 1* to afford either **4b** or **4d**.

5-Fluoro-2-nitroaniline (4a). Yield 99%, mp 86-87°C; ¹H NMR (300 MHz; DMSO-*d*₆/TMS): δ 6.44–6.61 (m, 1H), 6.77 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.62 (s, 2H), 8.07 (dd, *J* = 6.0, 3.3 Hz, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆/TMS): δ 103.6 (²*J*_{CF} = 25.8 Hz), 104.6 (²*J*_{CF} = 25.1 Hz), 128.1, 129.4 (⁴*J*_{CF} = 12.4 Hz), 148.6 (³*J*_{CF} = 14.4 Hz), 166.5 (¹*J*_{CF} = 250.5 Hz); IR (ATR): 3489, 3467 (NH₂), 3363, 3344 (NH₂), 1636 (CN), 1594, 1331, (NO₂), 1244 (C-F), 837, 747 (Ar_{1,2,4}-subst) cm⁻¹; MS (DART[+1]) *m/z* 157; HRMS (DART [+1]) Found: 157.04104, calcd for C₆H₆FN₂O₂: 157.04133.

5-Chloro-2-nitroaniline (4b). Yield 99%; m.p. 126-129°C; ¹H NMR (300 MHz; CDCl₃/TMS): δ 6.12 (s, 2H), 6.67 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 8.06 (d, *J* = 9.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃/TMS): δ 117.6, 117.8, 127.7, 139.6, 142.0, 145.1; IR (ATR): 3493, 3381 (NH₂), 1633 (CN), 1558, 1493 (NO₂), 1245 (C-Cl), 849, 797, 748 (Ar_{1,2,4}-subst) cm⁻¹; MS (DART[+1]) *m/z* 173;

HRMS (DART [+1]) Found: 173.01120, calcd for $C_6H_6ClN_2O_2$: 173.01178.

5-Bromo-2-nitroaniline (4c). Yield 88%; mp 151-153°C; 1H NMR (300 MHz; DMSO- d_6 /TMS): δ 6.97 (d, $J=9.0$ Hz, 1H), 7.48 (dd, $J=9.3, 2.4$ Hz, 1H), 7.56 (s, 2H), 8.03 (d, $J=2.1$ Hz, 1H); ^{13}C NMR (75 MHz, DMSO- d_6 /TMS): δ 105.5, 121.8, 127.4, 131.0, 138.5, 145.5; IR (ATR): 3470, 3347 (NH $_2$), 1557 (CN), 1495, 1243 (NO $_2$), 1751 (C-Br), 813, 713 (Ar $_{1,2,4}$ -subst) cm^{-1} ; MS (DART[+1]) m/z 216; HRMS (DART [+1]) Found: 216.96168, calcd for $C_6H_6BrN_2O_2$: 216.96127.

5-Iodo-2-nitroaniline (4d). Yield 85%; mp 174°C; 1H NMR (300 MHz; DMSO- d_6 /TMS): δ 6.59 (dd, $J=2.4$ Hz, $J=9.6$ Hz, 1H); 7.06 (d, $J=2.1$ Hz, 1H); 7.52 (s, 2H, NH $_2$); 7.95 (d, $J=9.3$ Hz, 1H); ^{13}C NMR (75 MHz, DMSO- d_6 /TMS): 115.5, 117.6, 127.5, 129.3, 140.2, 146.7; IR (ATR): 3287, 3252 (NH $_2$), 1579 (CN), 1482, 1253 (NO $_2$), 1899 (C-I), 843, 827, 734 (Ar $_{1,2,4}$ -subst) cm^{-1} ; MS (DART[+1]) m/z 264; HRMS (DART [+1]) Found: 264.94637, calcd for $C_6H_6IN_2O_2$: 264.94739.

Syntheses of 5a-d

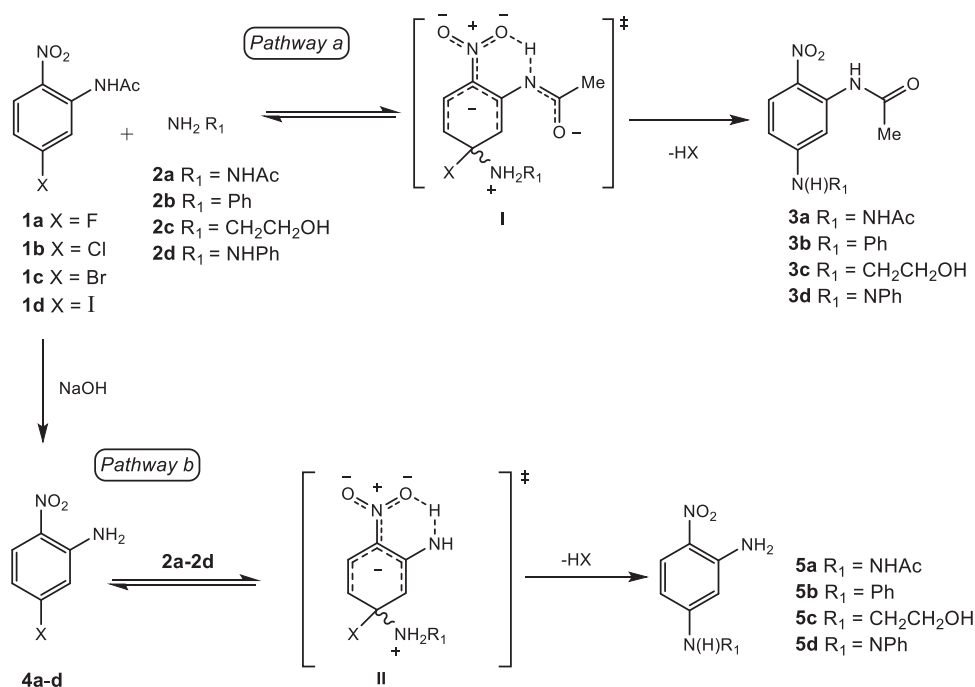
A mixture of the corresponding compound **2a-d** (7 mmol) and 5-haloderivative-2-nitroaniline **4a-d** (3.2 mmol) in dimethyl sulfoxide (10 mL) (except for **4a** were dimethyl formamide as solvent) was submitted to react under the conditions shown in Table 3. After the required time, the mixture of reaction was poured onto

crushed ice and the precipitated solid was filtered off and purified by preparative TLC (hexane/AcOEt, 6:4, v/v) to afford **5a-d**.

3-Amino-4-nitrophenylhydrazine (5a). Yield 48%; mp 177-178°C; 1H NMR (300 MHz; DMSO- d_6 /TMS): δ 3.07 (s, 3H), 5.96 (s, 1H), 6.21 (d, $J=9.6$ Hz, 1H), 7.26 (s, 2H), 7.63 (s, 1H), 7.81 (d, $J=9.6$ Hz, 1H); ^{13}C NMR (75 MHz, DMSO- d_6 /TMS): δ 25.4, 95.2, 104.6, 122.6, 127.7, 148.7, 155.0, 169.5; IR (ATR): 3472, 3358 (NH); 1691 (C=O); 1614 (CN); 1540, 1364, 1262 (NO $_2$); 1498, 1383, 1465, 1437, 1420 (N=N); 848, 827, 807 (sust 1,2,4); MS (DART[+1]) m/z 211; HRMS (DART [+1]) Found: 211.05260, calcd for $C_8H_{11}N_4O_3$: 211.05339.

2-Nitro-5-anilinoaniline (5b). Yield 72%; mp 143°C; 1H NMR (300 MHz; CDCl $_3$ /TMS): δ 6.14 (s, 3H), 6.18 (d, $J=2.4$ Hz, 1H), 6.23 (dd, $J=9.6, 2.4$ Hz, 1H), 7.03-7.30 (m, 3H), 7.25-7.50 (m, 2H), 8.02 (d, $J=9.3$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl $_3$ /TMS): δ 98.2, 107.0, 122.4, 124.6, 128.6, 129.6, 136.3, 139.4, 147.3, 150.8; IR (ATR): 3451, 3325 (NH), 1626 (CN), 1579, 1545 (as), 1226 (NO $_2$), 850, 821, 809 (Ar $_{1,2,4}$ -subst) cm^{-1} ; MS (DART[+1]) m/z 230; HRMS (DART [+1]) Found: 230.09333, calcd for $C_{12}H_{12}N_3O_2$: 230.09295.

5-(2-Hydroxyethylamino)-2-nitroaniline (5c). Yield 62%, mp 177 °C; 1H NMR (300 MHz; DMSO- d_6 /TMS): δ 3.15 (td, $J=6.0, 5.1$ Hz, 2H), 3.58 (td, $J=6.0, 5.4$ Hz, 2H), 4.83 (t, $J=5.4$ Hz, 1H), 5.87 (d, $J=2.4$ Hz, 1H), 6.08 (dd, $J=7.2,$



Scheme 1. Synthetic Pathway to synthesize **3a-d** and **5a-d**.

Table 1. Screening the S_NAr reaction conditions for the preparation of **3b** and **3c**.

Entry*	Solvent	Base	3b	3c
			Yield (%)	
1	EtOH	–	38	53
2	–	N(Et) ₃	40	53
3	DMF	K ₂ CO ₃	78	79
4	N(Me) ₃	Pyridine	47	58
5	DMSO	Aniline	88	88
6	THF	NaOH	60	17
7	MeOH	NaHCO ₃	39	48
8	<i>i</i> -PrOH	N(Et) ₃	42	40

2.4 Hz, 1H), 6.96 (t, *J* = 5.4 Hz, 1H), 7.35 (s, 2H), 7.74 (d, *J* = 9.3 Hz, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆/TMS): δ 45.6, 59.6, 93.3, 106.9, 122.3, 127.7, 149.7, 154.9; IR (ATR): 3467, 3351 (NH₂), 3324 (NH), 3275; 1051 (OH), 1632 (CN), 1632, 1287 (NO₂), 848, 827, 807 (Ar_{1,2,4}-subst) cm⁻¹; MS (DART[+1]) *m/z* 198; HRMS (DART [+1]) Found: 198.08810, calcd for C₈H₁₂N₃O₃: 198.08787.

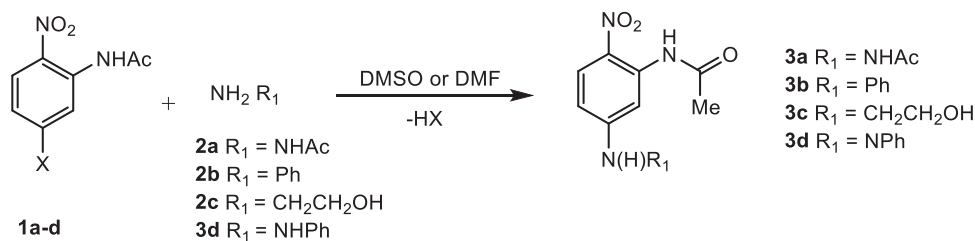
2-Nitro-5-(phenyldiazonyl)aniline (5d). Yield 69%; mp 77°C; ¹H NMR (300 MHz; CDCl₃/TMS): δ 6.23 (s, 2H), 7.10–7.30 (m, 2H), 7.33 (d, *J* = 2.1, 1H), 7.42–7.60 (m, 2H), 7.82–8.00 (m, 2H), 8.26 (d, *J* = 9 Hz, 1H); RMN ¹³C NMR

(75 MHz, DMSO-*d*₆/TMS): δ 110.5, 114.1, 123.5, 124.6, 127.8, 129.5, 132.4, 145.3, 151.7, 156.8; IR (ATR): 3475, 3364 (NH₂); 1542, 1378, 1249 (NO₂), 1499, 1461, 1426 (N=N), 875, 838, 808 (Ar_{1,2,4}-subst) cm⁻¹, 769 (Ar_{ipso}); MS (DART[+1]) *m/z* 243; HRMS (DART [+1]) Found: 243.08915, calcd for C₁₂H₁₁N₄O₂: 243.08820.

Results and discussion

The general overview behind our synthetic design in **Scheme 1** is depicted, starting with compounds **1a-d**, previously prepared in our laboratory by a nitration reaction and subsequent acetylation reaction of the corresponding 3-haloaniline.

To investigate the generality of the S_NAr-based amination, we examined the model reactions of the conversion of *N*-(5-fluoro-2-nitrophenyl)acetamide **1a** into *N*-(2-nitro-5-(phenylamino)phenyl)acetamide **3b** as well as *N*-(5-(2-hydroxyethylamino)-2-nitrophenyl)acetamide **3c**, focusing on the effects of leaving groups, the base as catalyst and solvent used (**Table 1**). When **1a** with 1.1 equiv. of base at 150°C in the appropriate solvent reacts with either base **2b** or **2c** under conventional

Table 2. Preparation of **3a-d** from **1a-d** by thermal and alternative energies.

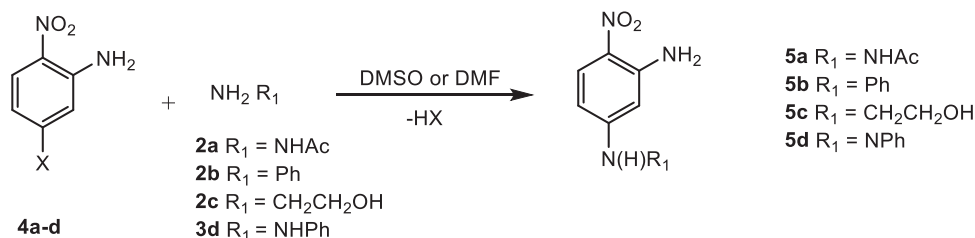
Entry	1a-d (X)	NHR ¹	Thermal	IR	US ^b	IR-US ^c	MW ^d	Product
			(150°C)	(90°C)	(100°C) Time (h)/yield (%)	(100°C)	(100°C)	
1		2a ^a	1.17/32	2.17/50	1.00/52	2.00/69	0.42/55	3a
2		2b	0.70/78	1.25/56	1.34/50	7.00/53	1.00/60	3b
3	F	2c	0.70/85	0.75/93	0.75/70	0.30/63	0.59/78	3c
4		2d	0.70/70	2.00/42	1.00/30	3.00/56	0.50/48	3d
5		2a ^a	7.00/47	5.00/80	1.50/68	4.50/77	1.00/48	3a
6		2b	10.0/27	8.00/27	1.00/15	8.00/18	2.00/20	3b
7	Cl	2c	1.75/70	3.50/57	1.50/74	2.00/70	0.92/64	3c
8		2d	6.00/40	3.50/19	2.50/24	4.00/52	1.00/48	3d
9		2a ^a	4.50/30	4.50/30	4.00/24	6.50/20	1.50/39	3a
10		2b	19.0/12	6.00/20	15.34/5	9.00/14	5.00/21	3b
11	Br	2c	5.12/38	5.00/49	10.0/20	7.00/19	2.00/42	3c
12		2d	4.00/12	7.00/24	9.00/18	8.00/6	2.00/32	3d
13		2a ^a	6.00/16	7.00/24	5.00/13	6.50/13	4.00/26	3a
14		2b	13.5/10	10.5/12	14.0/9	10.0/NR	8.00/9	3b
15	I	2c	8.00/22	7.00/34	6.50/14	8.00/20	3.50/26	3c
16		2d	5.00/18	8.00/14	8.00/9	10.0/NR	6.00/20	3d

^aDMF was used as solvent.

^bKeystrokes were carry out by cycling sequences composed of 2 minutes of activation and 5 minutes of cooling.

^cKeystrokes were carry out by cycling sequences composed of 1 minute of activation and 5 minutes of cooling.

^dMicrowave protocol include keystrokes of 20 minutes, following of 10 minutes of cooling. NR (No Reaction).

Table 3. Preparation of **5a-d**.

Entry	4a-d (X)	NHR ¹	Thermal	IR	US ^b	IR-US ^c	MW ^d	Product
			(150°C)	(90°C)	(100°C)	(100°C)	(100°C)	
Time (h)/yield (%)								
17		2a ^a	1.50/40	3.34/38	1.59/40	3.00/38	0.44/48	5a
18		2b	4.50/72	2.50/12	1.84/42	10.0/42	0.75/51	5b
19	F	2c	1.00/69	0.34/70	1.50/65	0.50/53	0.42/69	5c
20		2d	2.00/69	1.50/36	2.00/14	6.00/54	0.40/45	5d
21		2a ^a	7.00/58	6.50/73	3.34/64	7.00/55	1.42/59	5a
22		2b	16.0/NR	10.0/20	4.00/19	10.0/12	2.50/15	5b
23	Cl	2c	4.67/62	4.50/47	3.00/54	3.00/63	0.75/69	5c
24		2d	7.00/20	5.00/17	3.67/10	10.0/37	2.00/48	5d
25		2a ^a	8.00/20	7.00/27	6.00/19	8.00/20	2.00/27	5a
26		2b	24.0/9	11.9/17	14.0/NR	14.0/NR	8.00/16	5b
27	Br	2c	7.50/16	8.00/39	7.00/12	9.00/9	3.50/36	5c
28		2d	6.00/9	9.00/18	6.50/9	9.00/NR	3.00/17	5d
29		2a ^a	10.0/12	10.0/32	8.00/16	8.00/9	6.00/23	5a
30		2b	28.0/NR	16.0/NR	18.0/NR	15.0/NR	12.0/NR	5b
31	I	2c	9.00/15	8.00/30	9.50/10	11.0/8	5.00/17	5c
32		2d	8.00/13	9.50/9	9.00/NR	12.0/NR	6.00/NR	5d

^aDMF was used as solvent.

^bKeystrokes were carry out by cycling sequences composed of 2 minutes of activation and 5 minutes of cooling.

^cKeystrokes were carry out by cycling sequences composed of 1 minute of activation and 5 minutes of cooling.

^d(762 W), Microwave protocol include keystrokes of 20 minutes, following of 10 minutes of cooling. NR (No Reaction).

heating source, the generation of the desired products ranged from moderate to good overall yield (17–88%) within 40 min determined by TLC and confirmed by NMR spectroscopy after their isolation and purification.

Among the various bases that we examined, excess of aniline in DMSO (entry 5) provided the desired product with the best yield (88%). Conversely, stronger organic bases, such as trimethylamine and pyridine, decreased by almost 50% the overall yield of the target product, regardless of the nature of the solvent used even under solventless condition (entries 2, 4 and 8). Such results were comparable to the yield obtained with uncatalyzed reaction and NaHCO_3 in a protic solvent and (entries 1 and 7). In contrast, improved results with K_2CO_3 and NaOH in DMSO and THF, respectively (entries 3 and 6) were obtained; further, **3c** was formed in similar yield, but when NaOH in THF was used, the overall yield decreased substantially (17%, entry 6).

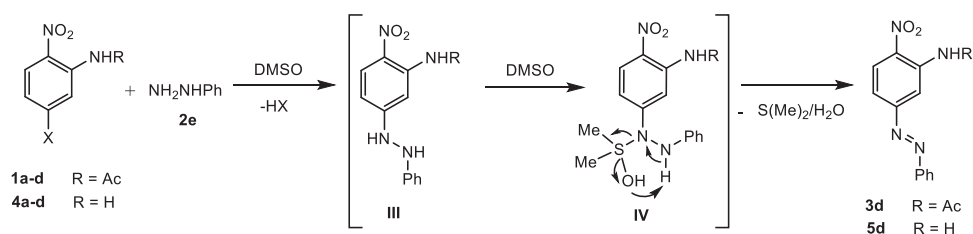
In the same way, when the binucleophile 2-aminoethanol **2c** was reacted with **1a** in the presence of a strong non-nucleophilic base (entry 2), *N*-(5-(2-hydroxyethylamino)-2-nitrophenyl)acetamide **3c** was isolated as the unique product in good yield without the

formation of *N*-(5-(2-aminoethoxy)-2-nitrophenyl)acetamide. This outcome suggested that the reactivity by orbital control instead of charge control, apart from the easy of stabilization (**12**) of δ^{L} -complex **I** might be ruled.

Thus, ready formation of intramolecular N-H \cdots O-N hydrogen bonds between the amide moiety and the adjacent nitro group to form the stable δ^{L} -complex **I** at the transition state would contribute significantly to the success of the reaction. So, the combination of a weak base, aprotic solvents (mainly DMSO), and good nucleophiles was proposed as the standard screening condition to be implemented in the preparation of (5- R^1 amino-2-nitrophenyl)acetamides.

To explore the scope and limitations of these transformations using IR, MW, US, and simultaneous combination US–IR as alternative heating methods, a series of (5- R^1 amino-2-nitrophenyl)acetamides **3a–3d** were prepared (Table 2) by $\text{S}_{\text{N}}\text{Ar}$ reaction of *N*-(5-halo-2-nitrophenyl)acetamides **1a–d** with **2a–d** as shown in Scheme 1 (Pathway a).

Among the explored methods, MW heating at 100°C in DMSO afforded the desired products with the best



Scheme 2. Proposed mechanism to the preparation of phenyldiazenyl derivatives **3d** and **5d**.

time of reaction and good overall yields (entries 1, 5, 9 and 13, using DMF as solvent). These outcomes were reasonably comparable with the yields obtained with the remaining methods. For example, in the preparation of compound **3a** by MW (entry 1), similar results were obtained with IR (50%) or US (52%) methods, although longer reaction times were needed. By the same reason, the US–IR combination gave improved yield (69%) while the thermal approach afforded the lowest yield (32%). Importantly, the overall yields strongly depended upon the nucleofugacity capacity of the halogen atoms present in the starting material as well as the nature of nucleophile used in the reaction, **3c** vs **3b** (entries 3 and 6).

Therefore, the general order of reactivity deduced from all examined reactions, regardless of the approach used, appeared as $F > Cl > Br > I$. Further, the S_NAr reactions proceeded better with an alkylamine, which contrasted with an arylamine (e.g. **3c** vs **3b**, entries 7 and 6), and even acyl or arylhydrazines (for example **3c** vs **3a/3d**, entries 15 and 16/13), in spite of the α -effect contribution present in the latter. Therefore, the relative nucleophilicity seemed to decrease in the following order: $NH_2CH_2CH_2OH > NH_2NHAc > NH_2NHAr > NH_2Ar$. Accordingly, the worst yields and the longer time of reaction were observed under thermal (entry 10) and US (entry 14) conditions. The simultaneous combination of IR–US failed to give **3b** and **3d**, in spite of prolonged time of reaction (entries 14 and 16). Similar results were generated for the reactions of **4a-d** with **2a-d** to obtain **5a-d** (Scheme 1, Pathway b, Table 3), but in general with either lower reaction yields or no reaction of substrates (entries 26, 28, 30 and 32). We proposed that this behavior can be explained by the formation and stabilization of the δ^L -complex at TSI vs TSII (Scheme 1, Pathways a and b, respectively), because a weaker intramolecular $H^{\delta^L} \cdots O-N$ hydrogen bonding is formed in TS II, as well as the involvement of the amino group in π -electron delocalization on the aromatic ring, which would lead to the destabilization of TS II.

Interestingly, we observed that when either **1a-d** or **4a-d** reacted with phenylhydrazine **2d**, the unexpected

N-[2-nitro-5-(phenyldiazenyl)phenyl]acetamide **3d** (Table 2, entries 4, 8, 12 and 16) and 2-nitro-5-(phenyldiazenyl)aniline **5d** (Table 3, entries 20, 24, 28 and 32) were isolated as the main products in moderate yields through an oxidative S_NAr -based amination reaction. This reaction by an unusual oxidation of the 2-phenylhydrazinyl derivative **III** through its reaction with DMSO can be explained, which allegedly led to the formation of the species **IV**, which finally decomposed into the phenyldiazenyl derivative **3d/5d**, dimethyl sulfide and water (Scheme 2).

Notably, **3d** was obtained in high yield (70%, Table 2 entry 4) when **1a** was used as the feedstock and the reaction was activated by thermal energy. However, the MW approach afforded better results with **1b-d**, while the IR–US method gave the poorer result when **1c-d** were used as starting materials in spite of prolonged time of reaction (Table 2 entries 12 and 16). A similar result was found with **5d**, however, no desired product was obtained when **1d** was reacted under US, US–IR, and MW conditions. Product **3d** was supported by the diagnostic hydrogens of the 2-nitrophenylacetamide moiety at δ 7.64 (H-4) and 9.30 (H-6) in 1H NMR and 151.7 (C-5) in ^{13}C NMR as well as their HRMS and IR data which showed the characteristic diazenyl fingerprint at 1383 cm^{-1} .

Conclusion

Nucleophilic Aromatic Substitution reactions with several amines on 5-halo-2-nitroaniline(acetanilide) using infrared, ultrasound, simultaneous IR–US irradiation and microwave alternative energy sources and conventional thermal energy were successfully realized. In general, according with the results obtained microwave energy represents the best option to achieve target molecules starting from either amine or acetanilide derivatives, where the azo-oxidation product is obtained when phenylhydrazine as nucleophilic agent is used.

Disclosure statement

No potential conflict of interest was reported by the authors.

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