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RESEARCH ARTICLE

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Synthesis of nitrophenyl and fluorophenyl azides and diazides by S_NAr under phase-transfer or microwave irradiation: Fast and mild methodologies to prepare photoaffinity labeling, crosslinking, and click chemistry reagents

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Abstract

Two fast and mild methodologies to prepare nitrophenyl and fluorophenyl azides are presented. These aryl azides are extensively used as crosslinking, photoaffinity labeling, and click chemistry reagents. Substituted aryl azides are prepared by performing a S_NAr substitution on halogenated benzenes with a phase-transfer catalyst (**PTC**) such as tetraethylammonium tetrafluoroborate (TEATFB), the reaction proceeds in several hours under rather mild temperatures (25°C to 70°C). Furthermore, aryl azides are also prepared within minutes under microwave irradiation at slightly higher temperatures (50°C to 70°C). These procedures could be applied in the preparation of other aryl azides. In the case of substituted pentafluoro benzene (**pF**), the type of products obtained in each reaction depends on the amount of sodium azide and the strength and position of electron-withdrawing substituents (COH, COR, COOR, CN, NO_2, or F). A discussion on the mechanisms and the products obtained in these S_NAr reactions is presented.

KEYWORDS

aryl azide, crosslinker, microwave, phase-transfer catalyst, photoaffinity labeling, S_NAr

1 | INTRODUCTION

Aryl azides are high-energy molecules with interesting photochemical and thermochemical properties.[1] Their complex chemistry has fascinated scientists for many years.[2] Spectroscopists have investigated the intermediates formed in the photochemistry of aryl azides by fast and high-resolution techniques. Theoretical chemists have studied the intrinsic interplay of intermediates formed under different reaction conditions.[3] Nitro- and fluoro-substituted aromatic azides have found applications in several areas of chemistry such as synthesis of heterocyclic compounds,[4] polymer chemistry as crosslinking agents,[5] and biochemistry as photoaffinity labeling reagents.[6] Due to their physicochemical properties, fluorophenyl azides have been applied in different areas of organic and material science.[7] They have been used in coupling polymers and other carbon materials to organic substrates and nanoparticles where a wide range of materials could be efficiently modified.

Aryl azides are usually prepared by treatment of diazonium salts with sodium azide.[8] Because this methodology has some limitations, several alternative procedures have been investigated. They are also prepared reacting Grignard reagents and aryl amide salts with *p*-toluenesulfonyl azide.[9] A potentially explosive reagent, triflyl azide has been used in the conversion of aromatic amines into the corresponding azides.[10] Upon refluxing with sodium azide, pentafluorobenzene containing an electron-withdrawing substituent (cyano, nitro, or carbonyl) undergoes selective aromatic *para*-substitution.[11] The preparation of several activated aryl and heteroaryl azides by nucleophilic aromatic substitution in an ionic liquid solution has also been reported.[12] All of these procedures require long reaction times, nonavailable reagents, and harsh conditions such as high temperatures, strong acids, or strong bases.

In search of milder conditions, an alternative preparation of *para*-substituted fluorophenyl azides by S_NAr under microwave irradiation **mw** was recently reported by us.[13] In the present investigation, this procedure is applied to the preparation of several nitro- and fluoro-substituted aryl azides. The application of microwave irradiation **mw** as a source of energy for reactions as become a convenient technique for organic chemistry. In general, the use of this type of energy results in enhanced conversion rates and cleaner reactions demonstrating the practical advantages of this methodology.[14]

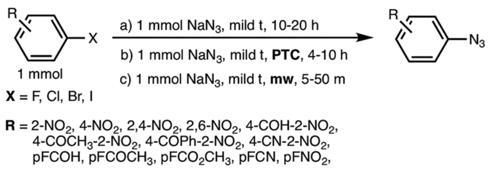
S_NAr reactions are heterogeneous processes involving the reaction of an aromatic substrate in an organic phase and an inorganic salt in an aqueous phase. In this particular case, an organic solution (halogenated benzene in acetone or DMF) is mixed with an inorganic solution (sodium azide in water). In order to make these reactions to proceed, high temperatures and long reaction times are usually required.[11] Therefore, these aromatic substitution reactions could be improved utilizing a phase-transfer catalyst (**PTC**) to favor transfer an inorganic salt into an aromatic mixture.[15] The use of a **PTC** catalyst (tetraethylammonium tetrafluoroborate [TEATFB]) in the S_NAr reaction of *ortho*-halogenated nitrobenzenes has been recently reported.[16]

In general, azido compounds have to be considered and handled as explosive materials. Organic and aryl azides have remarkable lower ignition temperatures in comparison with inorganic metal azides.[17] Because nitrophenyl and fluorophenyl azides easily decompose with heat, it is important to develop methods to prepare them using mild and homogeneous temperatures. In this paper, two different S_NAr methodologies, phase-transfer conditions and microwave irradiation, were investigated for the preparation of nitrophenyl and fluorophenyl azides and diazides.

2 | RESULTS AND DISCUSSION

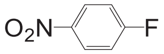
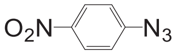
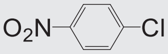
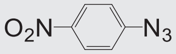
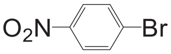
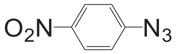
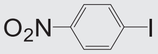
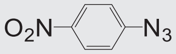
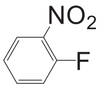
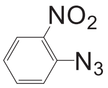
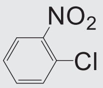
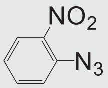
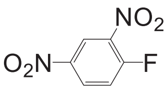
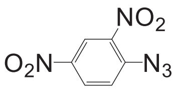
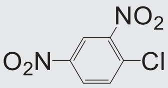
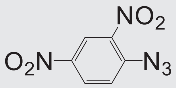
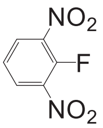
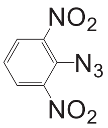
First, the S_NAr reaction was performed under conventional heating and *para*-fluoro nitrobenzene was reacted with sodium azide by refluxing in several solvent mixtures such as acetone/water, $CHCl_3$/water, and DMF/water. Because the reaction proceeded only with a DMF/water mixture, it must require a rather polar solvent.[11] Thus, several *para*-halogen nitrobenzene derivatives (Scheme 1) were reacted with sodium azide in DMF/water for several hours (10 to 20) at mild temperatures (55°C or 70°C). Because sodium azide is not soluble in DMF, an aqueous solution of sodium azide (1 mmol/2 ml H_2O) was combined with an organic solution of the halogenated benzene (1 mmol/6 ml DMF). The flask containing the reaction mixture was stirred and kept in a hot water bath. In each case, the temperature reported was found to be the minimum temperature to perform the substitution (Table 1). Each mixture was analyzed by TLC, and when the reaction was completed, a volume (20 ml) of cold water was added to induce the precipitation of the aryl azide. The product was separated by filtration, purified, and characterized. In the case where the leaving halogen has a small size and strong electron-withdrawing properties like a fluoro atom, the reaction proceeds at lower temperature (55°C) and within 10 h. Having a larger size and weaker electron-withdrawing leaving substituent like Iodo increases the reaction temperature (70°C) and the reaction time considerably, from 10 to 20 h.

Nucleophilic aromatic substitution reactions (S_NAr) have been investigated for many years. Classical S_NAr reactions of aryl halides were demonstrated to take place when a strong electron-withdrawing group like a nitro is located *ortho* or *para* to the leaving halogen atom.[18] Up to 2013, the generally accepted mechanism involved an addition–elimination process with an intermediate Meisenheimer complex (Scheme 2). This intermediate was easily formed under S_NAr conditions because it is stabilized by the presence of a nitro group. Further evidence of this mechanism is the fact that a fluorine is a faster leaving group.[18] Therefore, milder conditions were usually required with fluoro-substituted



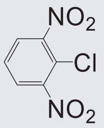
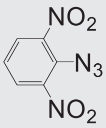
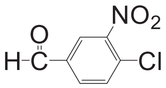
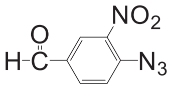
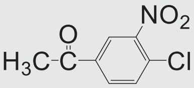
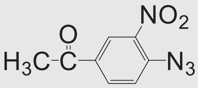
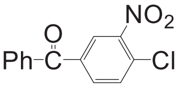
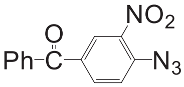
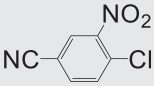
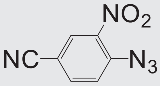
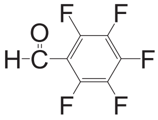
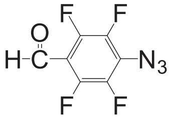
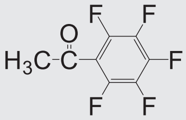
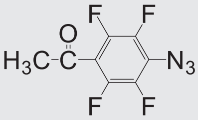
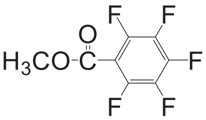
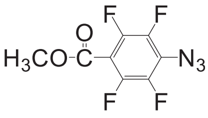
SCHEME 1 Synthesis of aryl azides by S_NAr under different experimental condition

TABLE 1 Yields of nitrophenyl and fluorophenyl azides under different experimental conditions

		Mild *t*, no PTC[a]			**Mild *t*, with PTC**[b]			**mw**[c]		
Reagent	**Aryl azide**	***t* (°C)**	**Time (h)**	**Yield (%)**	***t* (°C)**	**Time (h)**	**Yield (%)**	***t* (°C)**	**Time (min)**	**Yield (%)**
		55	10	85	55	4	91	70	10	85
		60	12	70	60	6	75	70	30	75
		70	16	60	70	8	65	70	50	70
		70	20	60	70	10	65	70	20	70
		55	10	80	55	4	90	70	25	70
		60	12	80	60	6	85	70	40	70
		50	10	80	50	4	85	50	5	85
		50	12	80	50	6	81	50	5	82
		50	12	70	50	6	75	50	5	83

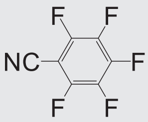
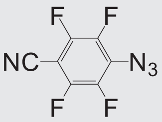
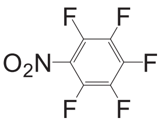
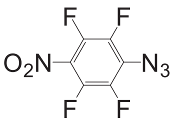
(Continues)

TABLE 1 (Continued)

		Mild *t*, no PTC[a]			Mild *t*, with PTC[b]			mw[c]		
Reagent	**Aryl azide**	***t* (°C)**	**Time (h)**	**Yield (%)**	***t* (°C)**	**Time (h)**	**Yield (%)**	***t* (°C)**	**Time (min)**	**Yield (%)**
		50	12	70	70	6	75	70	5	76
		50	12	80	50	6	92	70	5	87
		50	12	81	50	6	90	70	5	80
		50	12	75	50	6	91	70	5	80
		50	12	80	50	6	76	70	5	85
		40	10	80	40	4	90	70	15	85 (Leyva et al.[13])
		40	10	80	40	4	85	70	15	85 (Leyva et al.[13])
		40	10	80	40	4	85	70	15	70 (Leyva et al.[13])

(Continues)

TABLE 1 (Continued)

		Mild *t*, no PTC[a]			Mild *t*, with PTC[b]			mw[c]		
Reagent	**Aryl azide**	***t*** **(°C)**	**Time (h)**	**Yield (%)**	***t*** **(°C)**	**Time (h)**	**Yield (%)**	***t*** **(°C)**	**Time (min)**	**Yield (%)**
		25	12	85	25	4	95	70	15	90 (Leyva et al.[13])
		25	12	85	25	4	95	70	15	90 (Leyva et al.[13])

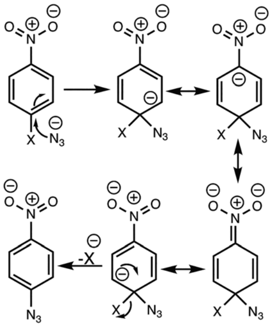
[a] A mixture of halogenated benzene (1 mmol) in DMF or acetone (6 ml) and sodium azide (1 mmol) in water (2 ml) was reacted at mild temperature.

[b] A mixture of halogenated benzene (1 mmol) in DMF or acetone (6 ml) and sodium azide (1 mmol) and TEATB (0.1 mmol) in water (2 ml) was reacted at mild temperature.

[c] A mixture of halogenated benzene (1 mmol) in DMF or acetone (6 ml) and sodium azide (1 mmol) in water (2 ml) was irradiated in a microwave reactor (Discover CEM, 50 W) at mild temperature.

nitrobenzenes. The leaving group ability for S_NAr reactions is different from the one observed in nucleophilic substitution at a saturated carbon. In aryl halides, fluoro is a better leaving group than any of the other halogens. The main reason for the order I > Br > Cl > F in regular S_N2 reactions is the strength of carbon–halogen bond (increasing from I to F). This physicochemical property is not important in a reaction involving a S_NAr mechanism, because bond breaking is not part of the rate-determining step (Scheme 2). Furthermore, the highly electronegative fluoro atom favors the addition step making the reacting carbon highly positive.[19]

In recent years, several studies have demonstrated that many S_NAr reactions could actually proceed through a concerted mechanism.[20] In these latter examples, substitution reactions could occur even without the presence of a highly activating substituent like a nitro group. Therefore, further investigations are required to expand the scope of reactions involving a S_NAr mechanism opening the possibility to prepare novel aromatic compounds.



SCHEME 2 Addition–elimination mechanism for a classical S_NAr reaction for *para*-halogenated nitrobenzene with sodium azide

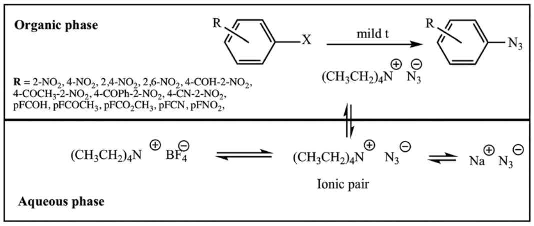
Under similar experimental conditions, *ortho*-nitrophenyl azide (Table 1) was obtained in good yields (80%) when the leaving group was a chloro or fluoro atom. This procedure was also applied in the preparation of other nitrophenyl derivatives; several substituted 2-nitrophenyl, 2,4-dinitrophenyl, and 2,6-dinitrophenyl azides were also prepared. Experimentally, lower temperatures were required to initiate the reaction when two electron-withdrawing substituents are present in *ortho*- and/or *para*-position due to enhanced inductive effects. However, the presence of two nitro substituents *ortho* to the leaving halogen required longer reaction times and lower yields of azides (70%) were obtained. All of this is due to enhanced steric effects in the first step of the S_NAr mechanism.

All the above S_NAr substitution reactions were also investigated under phase-transfer conditions. To do this, all the reactions were performed at the same experimental conditions (Table 1) in the presence of a **PTC**, TEATFB salt (0.1 mmol). In each case, the crude mixture was analyzed by thin-layer chromatography, and it was observed that the reaction was cleaner and proceeded very fast. When the reaction was completed, a volume

(20 ml) of cold water was added to induce the precipitation of the aryl azide. The crystalline product was separated by filtration, recrystallized in ethanol, and characterized.

It is well known that all quaternary ammonium salts, like TEATFB, act as **PTCs**.[15] This particular S_NAr reaction is an example of a biphasic phase-transfer process where the catalyst accelerates the reaction by solubilizing the azide ion (N_3^-) into the organic phase (Scheme 3). Under phase-transfer conditions, this azide ion is in close contact with the halogenated benzene and the reaction takes place faster. The fact that all reactions proceed faster clearly indicates a catalytic effect (Table 1).

In the case of substituted pentafluoro benzene (**pF**) derivatives, the S_NAr reaction was also investigated under conventional heating and each derivative was reacted with sodium azide by refluxing in several solvent mixtures such as acetone/water, $CHCl_3$/water, and DMF/water. Due to polarity of the pentafluoro derivatives, the reaction only proceeded with a mixture of acetone/water.[11] Because sodium azide is not soluble in acetone, these substitution reactions were performed with some modifications (Table 1). An organic solution of a **pF** (1 mmol) in acetone (6 ml) was combined with an inorganic solution of sodium azide (1 mmol) in water (2 ml). The reaction mixture was stirred for several hours (10 to 12) and kept in a hot water bath at 25°C or 40°C. Experimentally, it was found that this was the minimum temperature to perform the reaction for these highly activated derivatives. Having a very strong electron-withdrawing group like a CN or nitro in the *para*-position of the carbon containing the leaving fluoro atom, makes the reaction to proceed at room temperature (25°C) with rather high yields (85%). The reaction was monitored by TLC and when it was completed, a volume (20 ml) of cold water was added. The reaction mixture was extracted with ether and the organic extract was dried, filtered, and concentrated. Each aryl azide was purified by column chromatography. Performing the same substitution reactions on **pF** derivatives under phase-transfer conditions, shorter reactions times (4 h) were required and cleaner products were obtained (Table 1).



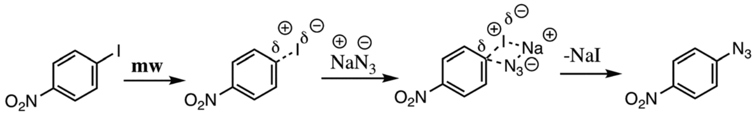
SCHEME 3 S_NAr reaction of halogenated benzene with sodium azide under phase-transfer conditions

There are many reports about the use of **mw** irradiation in the synthesis of a variety of organic compounds.[14,21–26] They provide information about basic theory and equipment to perform reactions with **mw**. Heating with this type of energy depends on the property of several materials to absorb this energy and convert it into heat. Two basic mechanisms operate: dipolar polarization and ionic induction. Upon **mw** irradiation, dipoles and ions in a reaction mixture align with the applied electric field. Because this field oscillates, dipole and ion fields attempt to realign themselves and, consequently, energy is converted into heat upon molecular friction and dielectric energy lost. In a **mw** process, the amount of heat is directly proportional to the capacity of a given field to align itself with the frequency of the applied field. The frequency in all commercial instruments is just sufficient to allow for molecular dipoles and ions to align with the applied field. Under these experimental conditions, rapid and homogeneous heating of reaction mixtures is achieved. In the bulk of a given reaction mixture under **mw** heating, an inverted gradient is achieved in comparison with conventional heating. Several studies have demonstrated the higher energy efficiency obtained upon **mw** heating.[27–29]

Because the preparation of some *para*-substituted fluorophenyl azides using **mw** irradiation has been reported,[13] this procedure was also applied in the preparation of several nitrophenyl azides (Table 1). To start these experiments, a solution of a *para*-halogenated nitrobenzene (1 mmol) in DMF (6 ml) and a solution of sodium azide (1 mmol) in water (2 ml) were placed in a flask. The resulting mixture was placed in a **mw** reactor and irradiated for several minutes (10 to 50). In all the experiments, TLC analysis of reaction mixtures indicated the reactions proceeded very fast and clean. After cooling, the mixture was poured into a volume (20 ml) of cold water. It was extracted with ether and the organic extract was dried, filtered, and concentrated. Each aryl azide was purified by column chromatography.

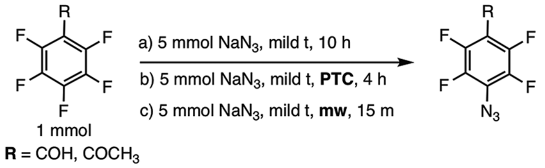
Contrasting results were observed in the preparation of *para*-nitrophenyl azide under **mw** irradiation (Table 1). In agreement with the classical S_NAr mechanism, reaction time increased when the reaction was performed with a nitrobenzene containing a halogen with increasing atom size and decreasing electronegativity ($F > Cl > Br$).[19] However, the reaction of a nitrobenzene containing a larger Iodo atom was faster than the reaction of the same aromatic compound containing another smaller halogen ($I > Cl > Br$). Under **mw** irradiation, the large Iodo atom is strongly polarized and the C–I bond becomes weak. This polarization effect could easily

SCHEME 4 Concerted mechanism for a S_NAr reaction for *p*-Iodo nitrobenzene with sodium azide under **mw** irradiation



induce a change on the mechanism involving a concerted process for the Iodo derivative (Scheme 4). This type of mechanism has been demonstrated to occur in some S_NAr reactions by means of computational studies.[20]

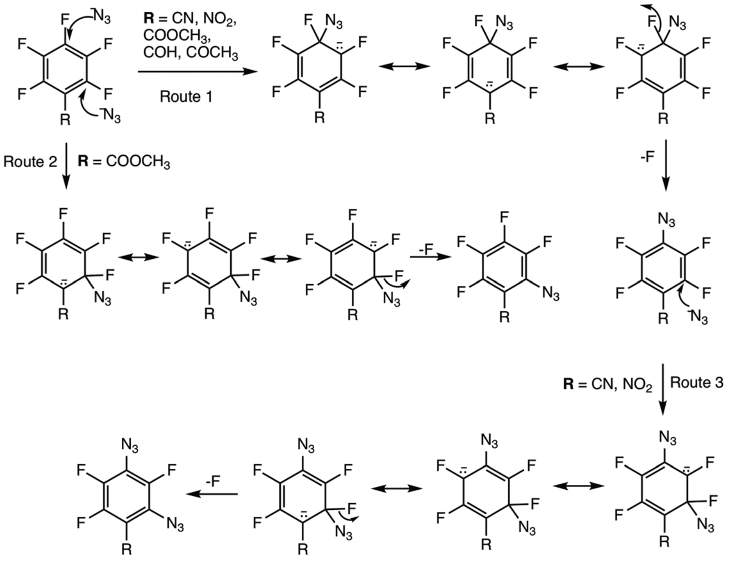
The preparation of other nitro-substituted aryl azides under **mw** irradiation was also investigated (Table 1). Halogenated benzenes containing two electron-withdrawing groups reacted very fast (5 min). Under these mild conditions, also the **pF** compounds reacted rather fast (15 min). Because all these **pF** compounds are highly activated for S_NAr substitution,[13] the effect of the amount of sodium azide in the products obtained was also investigated. Instead of using an equivalent molar ratio (1 mmol of azide/1 mmol of **pF**), an excess of sodium azide was added.



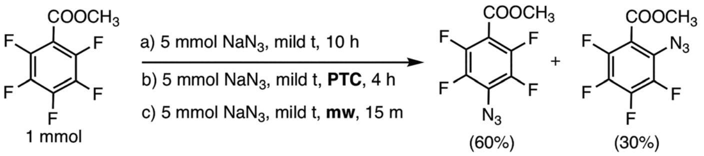
SCHEME 5 Product obtained in the reaction of **pF** compounds (**R** = COH, $COCH_3$) with an excess of sodium azide under different experimental conditions

Under different experimental conditions, reacting a **pF** containing a weakly activating substituent (COH or $COCH_3$), with an excess of sodium azide (5 mmol of azide/1 mmol **pF**), results in the exclusive formation of *para*-substituted perfluoro aryl azide (Scheme 5). Therefore, this particular **pF** reacts only by one pathway because only the *para*-position is sufficiently activated for the reaction to take place (Route 1, Scheme 6).

The reaction of a **pF** (1 mmol) containing a medium electron-withdrawing substituent (COOR) with an excess of sodium azide (5 mmol) results in the formation of a mixture of products (Scheme 7). For this particular reagent, two energy pathways are close in energy and compete (Routes 1 and 2, Scheme 6). Reacting an amount (1 mmol) of a **pF** (derivative containing a strong electron-withdrawing group [nitro or cyano]) with an excess of sodium azide (5 mmol) gave two products



SCHEME 6 Products obtained in the reaction of **pF** compounds with an excess of sodium azide under a classical S_NAr mechanism



SCHEME 7 Products obtained in the reaction of **pF** compound (**R** = $COOCH_3$) with an excess of sodium azide under different experimental conditions

(Scheme 8) essentially monoazide and diazide under different experimental conditions. Once the first substitution takes place, a *para*-substituted (CN or NO_2) phenyl azide contains two *ortho*-positions strongly activated for a second substitution to take place (Route 3, Scheme 6).

Based on the products obtained in these S_NAr reactions, three different free energy diagrams are proposed (Figure 1). Under mild experimental conditions, for the **pF** compound containing a COH or COR only one energy route is available (Figure 1A). For the **pF** containing COOR, two compounds are obtained; therefore, two pathways close in energy compete (Figure 1B). In the case of a **pF** with NO_2 or CN, once the low energy *para*-substituted azide is formed (Figure 1C), it reacts to give the diazide. It has been reported in the literature that reactions proceeding by a classical S_NAr mechanism are accelerated by electron-withdrawing groups specially when these groups are located in *para*-position. The activating ability has been measured in terms of the substituent (NO_2 > CN > COOR > COH > COR).[30]

Contrasting results were obtained with 2,3,4-trifluoro-1-nitrobenzene. In this particular case, a complex mixture, containing the starting material, an azide and diazide (Scheme 9), was obtained even when the reaction was performed with an equivalent amount of sodium azide (1 mmol of azide/1 mmol of 2,3,4-trifluoro-1-nitrobenzene). Thus, to investigate which product was favored, the reaction was performed with a large excess (5 mmol) of sodium azide. In this latter experiment, the diazide was obtained in greater yields (Scheme 9).

SCHEME 8 Products obtained in the reaction of **pF** compounds (**R** = CN, NO_2) with an excess of sodium azide under different experimental conditions

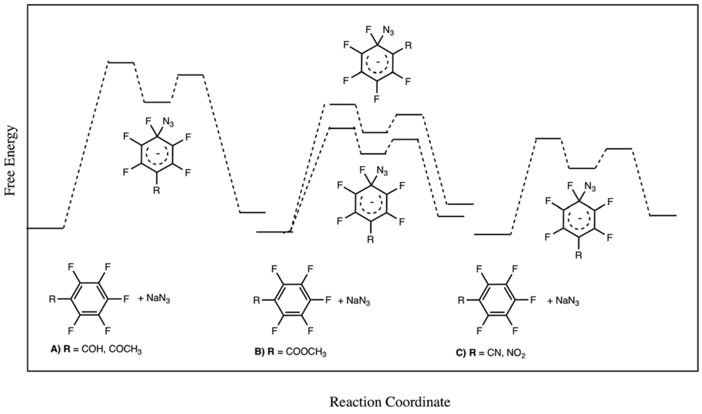
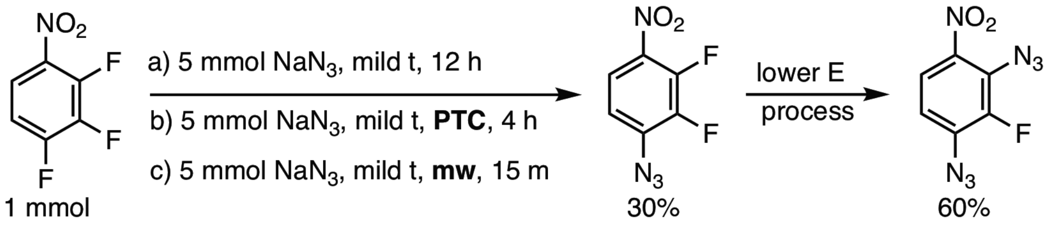
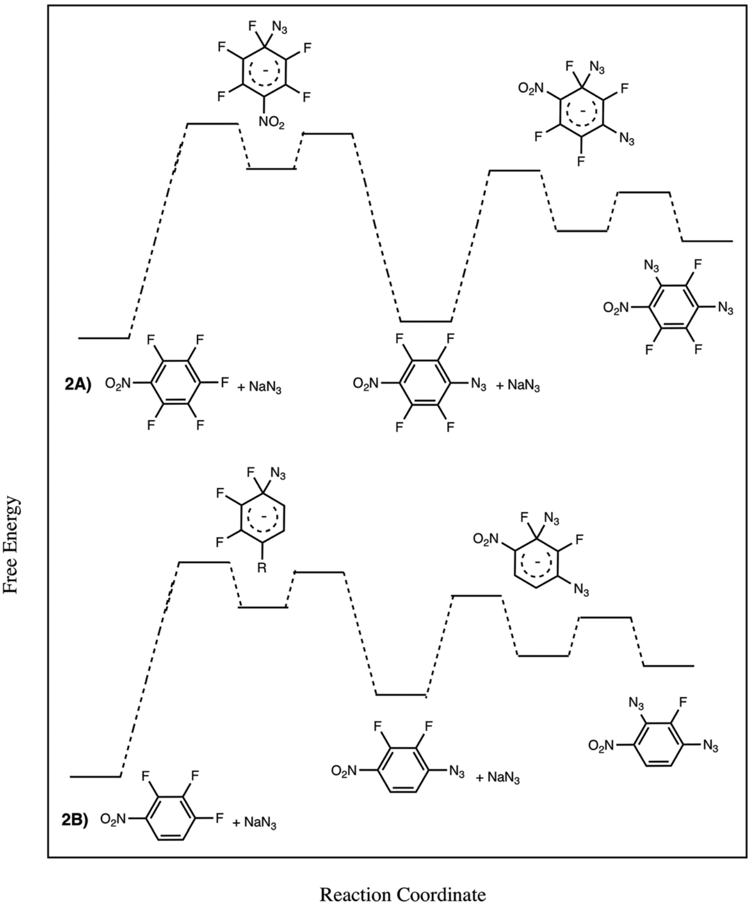


FIGURE 1 Proposed free energy diagrams for the S_NAr reactions of sodium azide with different **pF** compounds. (A) **R** = COH, $COCH_3$; (B) **R** = $COOCH_3$; and (C) **R** = CN, NO



SCHEME 9 Products obtained in the reaction of 2,3,4-trifluoro-1-nitrobenzene with an excess of sodium azide under different experimental conditions

FIGURE 2 Proposed free energy diagrams for the S_NAr reactions of sodium azide (A) with symmetric pentafluoro nitrobenzene and (B) with asymmetric 2,3,4-trifluoro-1-nitrobenzene



Based on the products obtained in the reaction of each nitro- and fluoro-substituted benzene, two different free energy diagrams are proposed (Figure 2). In *para*-nitro-tetrafluorophenyl azide, there are two positions (*ortho* to nitro) equally activated for a second substitution to take place (Figure 2A). In the case of 2,3,4-trifluoro-1-nitrobenzene, once the asymmetric mono azide is obtained, it contains one exclusive position (*ortho* to nitro) that is strongly activated towards a second substitution and the formation of the diazide becomes a rather lower energy process (Figure 2B). In polymer modifications and material science diazide compounds are particularly important for crosslinking experiments.[3]

3 | CONCLUSION

In conclusion, we developed two mild and fast methodologies to prepare nitrophenyl and fluorophenyl azides; these compounds are extensively used as a crosslinking, photoaffinity labeling, and click chemistry reagents. Performing a S_NAr substitution on halogenated benzenes with a **PTC** such as TEATFB, the reaction proceeds within hours under rather mild temperatures (25°C to 70°C). Performing the same S_NAr substitution under **mw** irradiation, the reaction proceeds within minutes at slightly higher temperatures (50°C to 70°C).

In substituted **pF**s, the type of products obtained depends on the amount of sodium azide and the strength and position of electron-withdrawing substituents (COH, COR, COOR, CN, NO_2 and F). Performing the reaction with an equivalent amount of sodium azide (1 mmol of azide/1 mmol of **pF**) results in the exclusive formation of *para*-substituted tetrafluoro benzene. Having an excess of sodium azide (5 mmol of azide/1 mmol of **pF**) results in the formation of different products. A **pF** containing a weak electron-withdrawing group (COH and COR) gives only the *para*-substituted tetrafluorophenyl azide. A **pF** with a medium strength group (COOR) gives two monosubstituted (*ortho* and *para*) phenyl azides. Having a strong electron-withdrawing substituent (CN or NO_2) in symmetric R-pentafluorobenzene results in the formation of two products, the *para*-azide (60%) and the disubstituted (*ortho*- and *para*-) azide (30%). In contrast, having a nitro substituent in asymmetric 2,3,4-trifluoro-1-nitrobenzene results in the formation of a small amount (30%) of monoazide (4-azido-2,3-difluoro-nitrobenzene) and a greater amount (60%) of diazide (2,4-diazido-3-nitrobenzene).

Under **mw** irradiation, the S_NAr substitution in *para*-nitro halogenated benzene (F, Cl, and Br) must follow a classical addition–elimination mechanism because its rate decreases ($F > Cl > Br$) when atom size increase and electronegativity decrease. However, this same reaction takes place rather fast for a larger and less electronegative Iodo atom ($I > Cl > Br$). In this latter case, it must follow a concerted mechanism for a highly polarizable atom. Because S_NAr methodologies could undergo either a concerted or a classical addition–elimination mechanism they could be applied in the preparation of other derivatives, studies are in progress to investigate the synthesis of different substituted aromatic compounds using the methodologies described in here.

4 | EXPERIMENTAL

4.1 | General procedures

Caution! Organic azides should be considered explosive. Because they are thermally, photochemically, and frictionally sensitive, their manipulation should take place behind a blast shield and under diminished light.[13]

All the starting halogenated benzenes, solvents, and other reagents were obtained from commercial suppliers. The **PTC** used was TEATFB ($(C_2H_5)_4N^+(BF_4)^-$). Melting points were measured with a Fisher Johns apparatus. UV-VIS spectra were obtained on a Shimadzu UV-2401 PC spectrophotometer. IR spectra were recorded on a Nicolet 15-10 Thermo Scientific FTIR spectrophotometer. ^1H NMR spectra were obtained on a Mercury 400-MHz spectrometer. HRMS analysis was performed on a Finnigan MAT 8400 mass spectrometer. Reactions under microwave irradiation were performed in a CEM microwave reactor, Discover System DU8756. All the azides reported in this article have been prepared by other methodologies, and they were characterized by UV-VIS, IR, NMR spectroscopy, and mass spectrometry to confirm their structure.[2,3,8–13,16,31,32] All aryl azides give two strong bands in IR (around 2100 cm^{-1}) due to symmetric and asymmetric stretching of azide group (N_3). The purity of aryl azides was verified by melting point and/or ^1H NMR spectroscopy.

4.2 | Preparation of nitrophenyl azides by S_NAr reaction under conventional heating

An organic solution of halogenated nitrobenzene (1 mmol) in DMF (6 ml) and an inorganic solution of sodium azide (1 mmol) in water (2 ml) were placed in a flask. The resulting reaction mixture was stirred and heated with a hot water bath at mild temperature (50°C to 70°C) for several hours (10–20). In each case, the minimal temperature to induce reaction was determined experimentally. After cooling, a volume (20 ml) of cold water was added and the mixture was placed in an ice-water bath for 30 min to induce precipitation. The solid aryl azide was separated by filtration and purified by column chromatography on a silica column using a mixture hexane/ethyl acetate (70/30) as the eluent solvent.

4.3 | Preparation of nitrophenyl azides by S_NAr reaction under phase-transfer conditions

An organic solution of halogenated nitrobenzene (1 mmol) in DMF (6 ml) and an inorganic solution of containing sodium azide (1 mmol) and **PTC** (TEATFB, 0.1 mmol) in water (2 ml) were placed in a flask. The reaction mixture was heated in a hot water bath at mild temperature (50°C to 70°C) for several hours (4–10). After this time, the reaction mixture was placed in a water bath for cooling. Then, it was added 20 ml of cold water, and it was placed in an ice-water bath for 30 min to induce precipitation. A crystalline solid precipitated and was separated by filtration and recrystallized in ethanol.

4.4 | Preparation of nitrophenyl azides by S_NAr reaction under microwave heating

An organic solution of halogenated nitrobenzene (1 mmol) in DMF (6 ml) and an inorganic solution of sodium azide (1 mmol) in water (2 ml) were placed in a flask. The resulting reaction mixture was irradiated in a microwave reactor (at 50 W) and mild temperature (50°C to 70°C) for several minutes (5–50). After this time, it was added 20 ml of cold water and was placed in an ice-water bath for 30 min to induce precipitation. The solid crystalline aryl azide was separated by filtration and recrystallized in ethanol.

4.5 | Preparation of fluorophenyl azides by S_NAr reaction under conventional heating

An organic solution of a **pF** compound (1 mmol) in acetone (6 ml) and an inorganic solution of sodium azide (1 or 5 mmol) in water (2 ml) were placed in a flask equipped with a reflux condenser. The mixture was stirred at mild temperature (25°C or 40°C) for several hours (10–12). After cooling, the reaction mixture was poured into 20 ml of cold water and the aryl azide was extracted with ether. The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated. Each azide was purified by column chromatography on a silica column using a mixture hexane/ethyl acetate (70/30) as the eluent solvent.

4.6 | Preparation of fluorophenyl azides by S_NAr reaction under phase-transfer conditions

An organic solution of a **pF** compound (1 mmol) in acetone (6 ml) and an inorganic solution of sodium azide (1 or 5 mmol) and **PTC** (TEATFB, 0.1 mmol) in water (2 ml) were placed in a flask equipped with a reflux condenser. The mixture was stirred at mild temperature (25°C or 40°C) for 4 h. After cooling, the reaction mixture was poured into 20 ml of cold water and the aryl azide was extracted with ether. The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated. Each azide was purified by column chromatography on a silica column using a mixture hexane/ethyl acetate (70/30) as the eluent solvent.

4.7 | Preparation of fluorophenyl azides by S_NAr reaction under microwave heating

An organic solution of a **pF** compound (1 mmol) in acetone (6 ml) and an inorganic solution of sodium azide (1 or 5 mmol) in water (2 ml) were placed in a flask equipped with a reflux condenser. The resulting reaction mixture was irradiated in a microwave reactor (at 50 W) and mild temperature (70°C) for several minutes (15). After cooling, the reaction mixture was poured into 20 ml of cold water and the aryl azide was extracted with ether. The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated. Each azide was purified by column chromatography on a silica column using a mixture hexane/ethyl acetate (70/30) as the eluent solvent.

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