Tributylstannyl Azide as Efficient Reagent in the Synthesis of Aryl Azides from Aryl Amines

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Abstract

An efficient and straightforward method for one-pot synthesis of aryl azides from the corresponding amines, employing tributylstannyl azide as transfer reagent of N_3 group is described. In this procedure diazotization of aryl amines occurs under mild conditions using *tert*-butyl nitrite (*t*-BuONO) and *p*-toluenesulfonic acid (TsOH). A variety of substituted aryl amines, with both electron-withdrawing and electron-donating groups were transformed into aryl azides in good to excellent yields. An important advantage of the present method is that, despite their high toxicity, tin byproducts can be reconverted into the starting tributylstannyl azide by treatment with sodium azide (NaN_3) and reused after chromatographic separation of the aryl azide.

Keywords: aryl azides, aryl amines, tributylstannyl azide.

Introduction

Over the years, aryl azides have achieved increased importance as valuable synthetic intermediates due to their potential applications in chemistry, biology and materials science. Because of their relatively high stability, these compounds have found industrial use as cross-linkers in photoresistors, for conducting polymers, and for light-induced activation of polymer surfaces.[1] More interestingly, aryl azides are well known for their ability as photoaffinity labeling agents for proteins. This function relies on the fact that, upon irradiation an aryl azide expels molecular nitrogen to produce an electron-deficient nitrene species that is capable of inserting into a C–H bond thereby forming a covalent bond between a labelling agent and a protein.[2] In addition, aryl azides are useful synthones in order to obtain various

heterocyclic compounds and transition metal complexes,[3] having applications in pharmaceutical, agricultural and materials chemistry.[4]

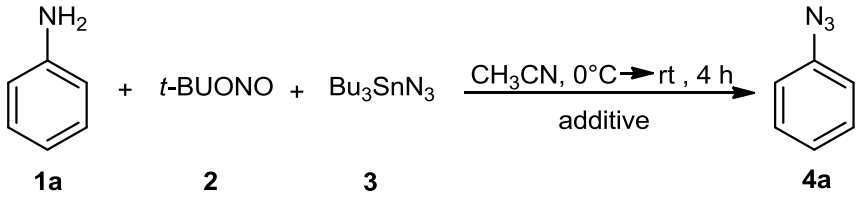
In particular, in recent years, these compounds have been popularized in the field of "click chemistry"[5] due to their participation in Cu-(I)-catalyzed Huisgen 1,3-dipolar cycloaddition to terminal alkynes (CuAAC),[6] for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles. Because of their wide applications in chemical, material and biological sciences,[7] these heterocyclic derivates have increasingly received significant attention. Therefore, given the importance of aryl azides, the development of new methodologies for their synthesis is an area of permanent interest.

Throughout the years, several procedures have been developed for the synthesis of these compounds. Typically, they are prepared from aromatic amines with nitrous acid followed by addition of NaN_3 at low temperature.[3a,8] Recently, Das *et al*. reported the use of *t*-BuONO in combination with NaN_3 in the synthesis of these compounds.[9] Aryl azides have also been synthesized using a combination of aryl amine, TfN_3, $CuSO_4$, and triethylamine;[10] employing stable aryl diazonium silica sulfates[11] or arenediazonium tosylates[12] with NaN_3 in water, and by reaction of $[ArN_2][BF_4]$ salts immobilized in $[BMIM][PF_6]$ ionic liquid with trimethylsilyl azide ($TMSN_3$).[13] Furthermore, aryl azides have also been prepared from aromatic amines with *t*-BuONO, followed by addition of ($TMSN_3$) in acetonitrile under mild conditions.[14] Among the several existing methods, we focused our attention on the latter. Although this procedure is highly efficient with excellent yields, the use of $TMSN_3$ has some downsides; this compound is volatile and hydrolytically unstable resulting in the release of toxic and explosive hydrazoic acid.[14] Furthermore, it has a high cost and a tedious synthetic method.[15] On the other hand, trialkylstannyl azides, which can also act as transfer reagent of N_3 group, are more stable, more resistant to hydrolysis and are easily obtained by the reaction of the corresponding trialkyltin chloride with sodium azide.[16] These properties, together with the importance of aryl azides, encouraged us to initiate a study in order to determine the ability of the tributylstannyl azide as transfer reagent of N_3 group in this transformation.

Results and discussion

Initially, we decided to apply the conditions developed by Moses and coworkers[14] as starting point for our investigation (Table 1, entry 1) and we chose aniline (**1a**) as a model substrate to optimize the reaction conditions.

Table 1 Optimization of the reaction conditions for diazotization-azidation of aniline.



Entry	**1a [M]**	**2** (equiv)	**3** (equiv)	Additive (equiv)	Yield (%)[a]
1	0.625	1.5	1.2	none	trace[c]
2	0.312	1.5	1.2	$BF_3{\cdot}OEt_2$ (1.2)	68
3	0.312	1.5	1.8	$BF_3{\cdot}OEt_2$ (1.2)	75
4	0.143	1.5	1.2	TsOH (1.2)	85
5	0.143	1.5	1.8	TsOH (1.2)	96
6	0.143	2	1.2	TsOH (1.2)	88

[a] Determined by GC for 0.5 mmol scale reaction using *o*-$Cl_2C_6H_4$ as internal standard. [c] 19 h, **1a** was recovered.

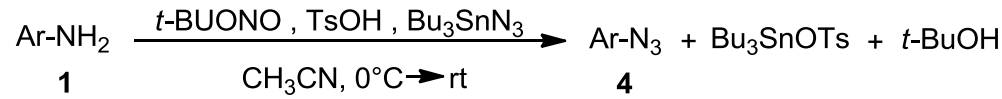
To our disappointment, after 19 h at room temperature, most of the starting material remained unchanged and we could only observe trace of azidobenzene (**4a**). Taking into account that the presence of an acidic additive facilitate the diazotization process,[17] we observed that the reaction was significantly improved by adding 1.2 equiv of $BF_3{\cdot}OEt_2$ (entry 2). Next, we tried to improve the yield of **4a** by increasing the amount of tributylstannyl azide to 1.8 equiv. Under these conditions, the desired product was obtained in higher yield (entry 3).

When the reaction was carried out under the initial conditions, in the presence of *p*-toluenesulfonic acid (TsOH) an increment of the aryl azide yield was achieved (compare entries 2 and 4). Furthermore, we observed that the use of 1.8 equiv. of **3** and TsOH as additive were the optimal conditions, providing the desired product in 96% yield (entry 5).

Next, given the high toxicity of tributylstannyl azide, we tried to avoid the use of large excess of this compound increasing the amount of *t*-BuONO to 2 equiv. Unfortunately, under these conditions, **4a** was obtained in a lower yield (compare entries 5 and 6).

With the optimized reaction conditions in hand, we explored the reaction scope by testing other aryl amines with different substituents. The results are summarized in Table 2.

Table 2 One pot synthesis of aryl azides from aryl amines and tributylstannyl azide[a]



Entry		$ArNH_2$	[M]		ArN_3	Time (h)	Yield (%)[b]
1	**1b**	4-$MeOC_6H_4NH_2$	0.114	**4b**	4-$MeOC_6H_4N_3$	2	98 (92)[c]
2	**1c**	4-$NO_2C_6H_4NH_2$	0.357	**4c**	4-$NO_2C_6H_4N_3$	4	75
4	**1d**	4-$ClC_6H_4NH_2$	0.357	**4d**	4-$ClC_6H_4NH_2$	4	96

[a]Reaction conditions: $ArNH_2$ (0.5 mmol), TsOH (1.2 equiv), *t*-BuONO (1.5 equiv), Bu_3SnN_3 (1.8 equiv). [b]Determined by GC using *o*-$Cl_2C_6H_4$ as internal standard. [c]Isolated yield after column chromatography from 1.5 mmol scale reaction

First, when we carried out the reaction with *p*-anisidine (**1b**), after 2 h of stirring at room temperature, the desired product (**4b**) was obtained in excellent yield (Table 2, entry 1). Taking into account that the optimal reaction conditions required the use of a large excess of the stannylazide and, given the high toxicity of tin compounds, we decided to investigate if tin byproducts generated in this reaction could be reconverted into the starting tributylstannyl azide. In order to accomplish this transformation, after total disappearance of **1b** (as indicated by TLC analysis),

1.2 equivalents of sodium azide were added to the mixture and stirring was continued overnight at room temperature (eq 1).

$$Bu_3SnOTs + NaN_3 \longrightarrow Bu_3SnN_3 + NaOTs_{(s)} \quad \text{(eq 1)}$$

After usual work-up, the ^{119}Sn-NMR spectrum of the crude mixture showed only one signal at δ=111.09 ppm, which agreed with commercial tributylstannyl azide ^{119}Sn-NMR spectrum. This confirmed that tin byproducts were completely converted to the starting stannyl azide. Once regenerated, tributylstannyl azide was reused after chromatographic separation of the aryl azide (see Experimental Section).

From Table 2, it is clearly seen that both electron-donating and electron-withdrawing groups on the aromatic ring were suitable for this conversion, giving the corresponding aryl azides in good to excellent yields in 2 – 4 hours.

Conclusions

In summary, we have developed a simple, efficient and straightforward method for one-pot diazotization-azidation of aryl amines to produce aryl azides, using tributylstannyl azide as an effective azidating reagent.

The results obtained to date indicate that this procedure allows synthesizing aryl azides with both electron-withdrawing and electron-donating groups, in good to excellent yields, from aryl amines. An important advantage of this protocol over conventional methods is that the azide source can be easily regenerated and reused after chromatographic separation of the aryl azide product. Further expansion of the substrate scope is currently ongoing in our laboratory and the results will be reported in due course.

Experimental Section

General experimental methods

Aryl amines, *tert*-butyl nitrite and *p*-toluenesulfonic acid were commercially available and used without further purification. Only aniline was distilled under nitrogen before use. Tributylstannyl azide was obtained by the reaction of tributyltin

chloride with sodium azide, according to the literature procedures, and used without further purification.[16] Acetonitrile was distilled from calcium hydride and dried over molecular sieves prior to use. Reactions were monitored by thin-layer chromatography carried out on silica gel plates (60F-254) and visualized under UV light or using 5% phosphomolybdic acid in ethanol. Flash chromatography was performed over silicagel (0.040-0.063 mm). For infrared analysis a FT-IR spectrophotometer was used and wavenumbers are given in cm^{-1}. The NMR spectra were recorded on a 300 MHz spectrometer (300.1 MHz for ^{1}H, 75.5 MHz for ^{13}C and 111.92 MHz for ^{119}Sn). Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane, with residual non deuterated solvent resonance as internal reference ($CDCl_3$: δ 7.27 for ^{1}H and δ 77.0 for ^{13}C) and coupling constants (J) are in Hz. Identity and purity of the products (crude or purified) were established using a GC/MS instrument (HP5-MS capillary column, 30 m × 0.25 mm × 0.25 μm) equipped with 5972 mass selective detector operating at 70 eV (EI). Program: 50°C for 2 min with increase 10°C/min to 280°C; Inj. Temp: 200ºC.[a] For gas-liquid chromatography (GC) an instrument equipped with a flame-ionization detector and a HP5 capillary column (30 m × 0.25 mm × 0.25 μm) was used; Program: 50°C for 2 min with increase 10°C/min to 280°C; Inj. Temp: 200ºC.

Representative procedure for the conversion of aryl amines into azides: Synthesis of 1-azido-4-methoxybenzene (4b)[14]

A 10 mL round-bottomed flask was charged with *p*-anisidine (**1b**, 0.185 g, 1.5 mmol), $TsOH \cdot H_2O$ (0.342 g, 1.8 mmol) and CH_3CN (13 mL) and cooled to 0°C in an ice bath. To the stirred mixture, *t*-BuONO (0.232 g, 268 µL, 2.25 mmol) and then Bu_3SnN_3 (0.902 g, 744 µL, 2.7 mmol) were added dropwise. After addition of 30 µL of 1,2-dichlorobenzene (internal standard), the resulting solution was stirred at room temperature until total disappearance of **1b** (monitoring by TLC). To this solution, 1.8 mmol (0.117 g) of NaN_3 was added and kept under stirring overnight at room temperature. At this point, the white solid NaOTs formed in the mixture

[a] If the injector temperature is above 200°C, azobenzene derivatives are observed arising from the decomposition of the aryl azide.

was collected by vacuum filtration and washed with Et_2O (2 × 5 mL). Another portion of Et_2O (10 mL) was added to the remaining solution and then washed with water (4 × 25 mL) to remove most of the CH_3CN. The organic phase was dried with anhydrous $MgSO_4$, filtered, analyzed by GC, and then concentrated under vacuum. Purification by flash chromatography gave 0.205 g (92 %) of **4b** as yellow oil (petroleum ether 30-65 °C) and 0.811 g (90%) of Bu_3SnN_3 (petroleum ether/AcOEt, 4:6).

1-azido-4-methoxybenzene (**4b**): **IR** (film) 2097, 1501, 1284, 1241 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.70 (s, 3H), 6.81 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) 55.6, 115.2, 120.0, 132.4, 157.0.; **MS** *m/z* (% rel. intensity, ion) 149 (20, $M^{+\cdot}$), 121 [100, ($M^{+\cdot}$- N_2)], 107 (42, *p*-An^+), 78 (54), 52 (38).

1-azido-4-nitrobenzene (**4c**): **MS** *m/z* (% rel. intensity, ion) 164 (20, $M^{+\cdot}$), 136 [56, ($M^{+\cdot}$- N_2)], 90 (71), 63 (100).

1-azido-4-chlorobenzene (**4d**): **MS** *m/z* (% rel. intensity, ion) 153 (22, $M^{+\cdot}$), 125 [100, ($M^{+\cdot}$ - N_2)], 90 (69), 63 (48).

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