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***P*-TSA/NaNO₂/NaN₃ a mild and efficient system for easy and fast conversion of arylamines to azides at room temperature**

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Abstract

This article describes easy, fast and efficient method for the diazotization and azidation of different aromatic amines over *p*-TSOH hydrate, sodium nitrite and sodium azide under mild condition at room temperature. Various aryl amines possessing electron-withdrawing groups or electron-donating groups were converted into the corresponding aryl azides in 75-99% yields. The use of mild reaction conditions, avoiding the use of harmful acids and toxic solvents and short reaction time are advantages of this methodology. The selected catalyst is found to be highly efficient.

Keywords: *p*-Toluenesulfonic acid, Aryl azides, Diazotization, Sodium azide, Green chemistry.

1. Introduction

Aromatic azides are useful intermediate with various applications in organic and bioorganic chemistry [1]. Two important applications of these compounds are 1,3-dipolar cycloaddition to produce five membered heterocycles [2,3] and their use as photo affinity labeling agents for proteins[4,5]. Thus the synthesis of aryl azides is one of prime importance. A number of methods have been developed to synthesis aryl azides, for example: reaction of *p*-tosyl azide with aryl Grignard or lithium reagent derived from the corresponding aryl halides [6,7], reaction of arylamine with TfN₃, CuSO₄ and triethylamin [8], direct coupling of arylhalides [9] or arylboronic acids [10] with NaN₃ catalyzed by copper salts, and combination of aryl amines with *t*-BuONO followed by addition of NaN₃ or TMSN₃ [11]. Furthermore, [ArN₂][BF₄] salts immobilized in [bmim][PF₆] ionic liquid have been shown to react with TMSN₃ to yield the desired azides [12]. Although there are specific merits to each of these methods, different kind's drawbacks include long reaction times, highly expensive reagents and use of toxic solvents

commonly required. Hence, there is still considerable high interest in developing simple methods for synthesis of arylazides that requires a low manufacturing cost while minimizing environmental pollution are preferable. Recently, Zarei and co-workers reported the use of grinding of ArNH₂/SSA/NaNO₂ in a mortar and then addition of solution of NaN₃ for the synthesis of aromatic azides [13]. To broaden the scope of arenediazonium salt applications, recently, the synthesis of new and highly stable arenediazonium tosylate salts with various applications are reported [14-17]. It is well known that arenediazonium tosylate salts are highly stable and non-explosive because of, the close and multiple contacts between the N atom in the diazonium cation and the O atoms of the tosylate anion [16].

2. Experimental

Chemical were purchased from the Fluka, Merck and Aldrich chemical companies. Melting point was determined on Electrothermal 9100 without further corrections. TLC on commercial aluminum-backed plates of silica gel 60 F254 was used to monitor the

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progress of reactions. Infrared spectra were recorded on a Shimadzu 8400s spectrometer with KBr plates. NMR spectra were taken in CDCl_3 on a Bruker Avance 3-400 MHz instrument at 20-25 °C. Elemental analyses were performed by Perkin-Elmer CHN analyzer, 2400 series II.

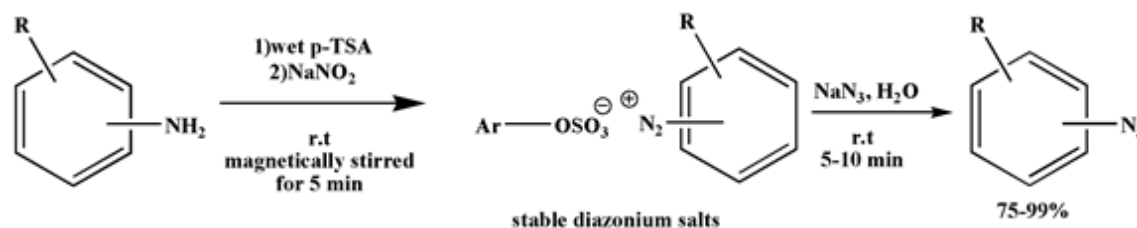
2.1. Experimental detail for Synthesis of 4-azido benzoic acid:

4-aminobenzoic acid (2 mmol, 0.274 g) and *p*-TSA (6 mmol, 1.146 g) were charged into a 25 mL round-bottom flask, then 0.2 mL of water was added and the mixture magnetically stirred to afford a homogeneous mixture, consequently NaNO_2 (4 mmol, 0.138g) was added. The reaction mixture stirred for 5 minutes. In this period of time the starting amine disappear. The solution of NaN_3 (5 mmol, 0.326g) in H_2O (6 ml) was added gradually to the diazonium salt and stirring was continued for 5 minutes. The mixture volume increased due to the evolution of nitrogen gas. The reaction completion was indicated by a negative test with β -naphthol. The mixture was diluted with EtOAc (30 mL) and after vigorous stirring, was treated with 5% NaOH solution (15 mL) (If a substrate has a carboxyl group the reaction mixture should be acidified to pH=1), then dried over anhyd. Na_2SO_4 . The solvent

was evaporated in vacuum and the 4-azidobenzoic acid obtained as an uncontaminated product. M. P. 180°C; ^1H NMR (CDCl_3 , 400 MHz) δ 8.14 (d, $J=8.4$ Hz, 1H, Ar-H-1); 7.14 (d, $J=8.4$ Hz, 1H, Ar-H-2); ^{13}C NMR (CDCl_3 , 100 MHz) δ 167.92 (CO), 149.27 (C-4), 132.24 (C-1), 131.17 (C-2), 129.02 (C-3); IR (KBr, cm^{-1}): 2400-3400 as a broad band (OH), 2106 (N_3), 1681 (CO); Anal. Calcd. for $\text{C}_7\text{H}_5\text{N}_3\text{O}_2$: C, 51.53; H, 3.06; N, 25.76%, Found: C, 51.59; H, 3.10, N, 25.69%. The other products were purified by flash chromatography (n-hexane-EtOAc, 95:5). The most of the products must be kept away from direct sunlight. All the products are known and characterized by IR and ^1H NMR, and were identified by comparison of the spectral data with those reported in literature.

3. Results and discussion

In our pursuit of improved synthetic method for the preparation of organic compounds [18], we decided to look at the use of arenediazonium tosylate salts for the synthesis of aryl azides. To the best of our knowledge, the similar syntheses of arylazide derivatives using arenediazonium tosylate salts had not yet been reported prior to this study (Scheme 1).



Scheme 1. The synthesis of arylazides under mild condition

In a model reaction, 4-aminobenzoic acid was homogenized by mixing by solid *p*-TSOH hydrate and 0.2 mL of water into a round-bottom flask and magnetically stirred. Then NaNO_2 was added, the diazotization, proceed in few minutes. Followed by, the solution of NaN_3 in H_2O was added to the diazonium salt and thoroughly mixed at room temperature. The reaction proceeds smoothly and rapidly to afford 4-azidobenzoic acid in 99% yield. The amount of water present in the first step of reaction was very important for successful diazotization. In the absence of water, diazotization did not occur at all. Whereas, in aqueous solution side reactions occurred. Based on the above results, this process was then extended to other structurally varied amines to investigate its scope and limitations. The results are presented in Table 1.

In contrast to the related SSA procedure [13], arylamines including electron-withdrawing groups (e.g. entry 1), electron rich groups (e.g. entry 4) as well as ortho-substituted anilines (e.g. entry 2) were found to react well to give the corresponding

arylazides in high yields and no undesirable side reactions, although, the yields and the time of the reaction were dependent on the substituent (Table 1). Interestingly, amino benzoic acid derivatives afforded the corresponding azides in excellent yield and did not require further purification. It should be noted that the arenediazonium tosylate salts were stable to be kept at room temperature and could be stored for 4 days in a desiccators without any lose of activity. All the aryl diazonium obtained employing in this methodology were safe and non-explosive. The reason for their increased stability of these salts relative to $\text{ArN}_2^+\text{Cl}^-$ is that, decomposition of a diazonium salt is dependent on the donor properties of the conjugated anion.¹⁹ The sulfate anions are less nucleophile than free chloride anions therefore of increasing stabilization in diazonium salt.

The feasibility of large-scale synthesis was demonstrated by the diazotization and azidation of some aryl amines in the reaction condition (Table 2).

Table 1. Azidation of Aromatic Amines with wet *p*-TSA/NaNO₂/NaN₃ (solution in H₂O) at room temperature

Entry	ArNH ₂ ^a	Product ^b	Yield(%) ^c	IR(KBr,cm ⁻¹)	Ref.
1	4-NO ₂ C ₆ H ₄ NH ₂	4-NO ₂ C ₆ H ₄ N ₃	91	2129	[22]
2	2-NO ₂ C ₆ H ₄ NH ₂	2-NO ₂ C ₆ H ₄ N ₃	89	2150	[22]
3	4-MeC ₆ H ₄ NH ₂	4-MeC ₆ H ₄ N ₃	86	2130; 2106	[21]
4	4-MeOC ₆ H ₄ NH ₂	4-MeOC ₆ H ₄ N ₃	90	2260; 2106	[21]
5	2-MeOC ₆ H ₄ NH ₂	2-MeOC ₆ H ₄ N ₃	89	2016	[20]
6	4-BrC ₆ H ₄ NH ₂	4-BrC ₆ H ₄ N ₃	95	2249, 2291	[21]
7	4-ClC ₆ H ₄ NH ₂	4-ClC ₆ H ₄ N ₃	87	2133; 2096	[12]
8	3,4-Cl ₂ C ₆ H ₃ NH ₂	3,4-Cl ₂ C ₆ H ₃ N ₃	83	2113	-
9	2,4-Cl ₂ C ₆ H ₃ NH ₂	2,4-Cl ₂ C ₆ H ₃ N ₃	75	2113	[20]
10	4-NH ₂ C ₆ H ₄ COOH	4-N ₃ C ₆ H ₄ COOH	99	2106	-
11	3-NH ₂ C ₆ H ₄ COOH	3-N ₃ C ₆ H ₄ COOH	99	2129	[21]
12	2-NH ₂ C ₆ H ₄ COOH	2-N ₃ C ₆ H ₄ COOH	95	2106	[21]
13	2-I C ₆ H ₄ NH ₂	2-I C ₆ H ₄ N ₃	91	2125, 2088	[22]
14	C ₆ H ₅ NH ₂	C ₆ H ₅ N ₃	82	2101	[12]

^a In the all substrates the time of reactions were between 10-15 minutes. ^bThe products were characterized from their spectral data especially IR, ¹H NMR or mp by comparison with reported samples. ^c The yields refer to isolated products.

Table 2. Azidation of Aromatic Amines with wet *p*-TSA/NaNO₂/NaN₃ (solution in H₂O) in large scale.

Entry	ArNH ₂	Product	Yield(%) ^a
1	4-NO ₂ C ₆ H ₄ NH ₂	4-NO ₂ C ₆ H ₄ N ₃	81
3	4-MeC ₆ H ₄ NH ₂	4-MeC ₆ H ₄ N ₃	72
4	4-MeOC ₆ H ₄ NH ₂	4-MeOC ₆ H ₄ N ₃	70
6	4-BrC ₆ H ₄ NH ₂	4-BrC ₆ H ₄ N ₃	75
7	4-ClC ₆ H ₄ NH ₂	4-ClC ₆ H ₄ N ₃	59
10	4-NH ₂ C ₆ H ₄ COOH	4-N ₃ C ₆ H ₄ COOH	86

^a The isolated product for 20 mmol aryl amine.

As is evident from Table 2, this new methodology successfully applied on a larger scale. For example up to 20 mmol 4-nitro aniline could produce 1-azido-4-nitro benzene with yield up to 80%.

Table 3 is compared the efficiency of our method for synthesis of aromatic azides with some other published works. Each of these methods have their own advantages, but some of them often suffer from some troubles inclusive of use of organic solvent, necessity of control of temperature (entries 1 and 3), long reaction time (entries 1 and 2) and employ of expensive catalyst

or reagent (entry 3), so the present method could be economical than the other methods.

In summary, we have established a practical and simple protocol for the preparation of arylazides. The procedure offers several advantages including high reaction yields, broad application scope, short reaction times and simple experimental process. On the other hand *p*-TSA was identified as the efficient, safe and easily available catalyst. Therefore, the present method is expected to serve as an alternative process for the preparation of arylazide derivatives.

Table 3. Comparison of results using p-TSA/NaNO₂/KI with results obtained by other works for conversion of 4-methoxy aniline to azide

Entry	Reagents	Conditions	Time (min)	Yield (%)	Ref.
1	ArN ₂ ⁺ BF ₄ ⁻ /TMSN ₃	Under N ₂	Over night	98	[12]
2	t-BuONO/TMSN ₃	CH ₃ CN/RT	90	71	[11]
3	TfN ₃ aq. CuSO ₄ /Et ₃ N	CH ₂ Cl ₂ /MeOH, 0°C	40	90	[8]
4	wet SSA/NaNO ₂ /NaN ₃ (aq.)	Solvent free/RT	10	78	[13]
5	p-TsOH/ NaNO ₂ /NaN ₃ (aq.)	Solvent free/RT	10	90	This work

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تبدیل سریع و آسان آریل آمین‌ها به آریل آزیدها با استفاده از سیستم پارا-تولوئن سولفونیک اسید/ سدیم نیتريت / سدیم آزید

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چکیده:

در این مقاله روشی برای آزید دار شدن آمین‌ها از طریق نمک پایدار دی آزونیم توسط سیستم پارا-تولوئن سولفونیک اسید آب دار، سدیم نیتريت و سدیم آزید تحت شرایط معتدل در دمای اتاق ارائه شده است. آریل آمین‌های مختلف دارای گروه‌های الکترون کشنده یا الکترون دهنده با راندمان ۷۵-۹۹٪ به آریل آزیدها تبدیل شده اند. شرایط معتدل، پرهیز از استفاده از اسیدهای مضر و حلالهای سمی و زمان کوتاه انجام واکنش از مزیت‌های روش به کار رفته است. کاتالیست اسیدی انتخاب شده بسیار کارا عمل کرده است.

کلمات کلیدی: پاراتولوئن سولفونیک اسید، آریل آزیدها، دیازوئه کردن، سدیم آزید، شیمی سبز.