

A Mild and Clean Synthesis of Alkyl Azides from Alkyl Halides Mediated by Poly(4-vinylpyridine)-Supported Sodium Azide Under Nonaqueous Conditions

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ABSTRACT: Alkyl halides were efficiently converted to their corresponding alkyl azides under mild nonaqueous conditions with a polymer-supported azide as a new polymeric reagent at room temperature at high yields and purities. All of the byproducts were removed by filtration, and pure products were obtained by the evaporation of the solvent. The spent polymeric reagent could

usually be removed quantitatively and regenerated. The regenerated polymeric reagent could be reused several times. © 2011 Wiley Periodicals, Inc. *J Appl Polym Sci* 121: 1916–1920, 2011

Key words: crosslinking; functionalization of polymers; heterogeneous polymers; ion exchangers; modification

INTRODUCTION

Organoazides are one of the most important synthetic intermediates for the preparation of nitrogen-containing organic compounds, for example, amines via reduction,¹ imines via rearrangement,² and triazoles and other nitrogen-containing heterocyclic via cycloaddition reactions.³ The azido functionality not only reacts with nucleophiles and electrophiles but also serves as a nitrene precursor in thermolysis or photolysis. Although organic azides are generally safe compounds, those of low molecular weight can be unstable and, therefore, difficult to handle.⁴ This is especially true for small molecules with several azide functionalities, which would be of great interest for the generation of polyvalent structures. Thus, a methodology that prevents the isolation of organic azides is desired.

There are many methods available for the synthesis of azo compounds.^{5–20} Nucleophilic substitution by azide ions is a well-established synthetic pathway to alkyl azides. Some of the problems associated with this preparative method, such as the low solubility of inorganic azides in organic solvents, have been solved by the use of more soluble tetraalkylammonium^{10,11} or guanidinium azides,¹² by phase-transfer conditions,¹³ through the use of polymeric reagent,¹⁴ and by Lewis acid catalysis,¹⁵ with the lat-

ter being mainly used with tertiary or activated alkyl halides or alcohols. Because azides are thermally and photochemically labile and are often explosive, it is preferable to avoid heating during the reaction and purification.

Although polymer-supported reagents, especially anion-exchange resins, have been widely applied in organic synthesis,^{21–36} there is only one report in the literature for the synthesis of organic azides based on polymer-supported azides.¹⁴ Hassner and Stern, in 1986,¹⁴ reported the use of a polymeric quaternary ammonium azide for synthesis of alkyl azides from alkyl halides or esters.

When polymeric quaternary ammonium azides are used, the reaction time is very long (many hours or many days), and some products remain adsorbed on the polymer.

Here, we report an improved, efficient, and easy method for preparing alkyl azides from alkyl halides with a polymer-supported sodium azide under mild and nonaqueous conditions at high yields.

EXPERIMENTAL

General

Poly(4-vinylpyridine) crosslinked with 2% divinyl benzene was purchased from Fluka, (Buchs, Switzerland) and other chemicals were either prepared in our laboratories or were purchased from Fluka or Merck (Darmstadt, Germany). Crosslinked poly(*N*-methyl-4-vinylpyridinium) iodide was synthesized according to our procedure.^{29–33} The progress of the reaction was followed by gas liquid chromatography

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TABLE I
Conversion of Alkyl Halides to Corresponding Alkyl Azides with
Poly(4-vinylpyridine)-Supported Sodium Azide in CH₂Cl₂
at Room Temperature

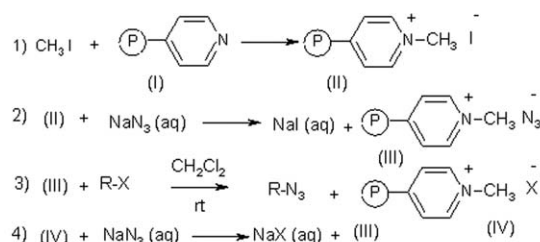
Entry	Substrate	Product ^a	Time (min)	Yield (%) ^b
1	CH ₃ (CH ₂) ₇ -Br	CH ₃ (CH ₂) ₇ -N ₃	300	87
2	PhCH(Br)Ph	PhCH(N ₃)Ph	80	90
3	CH ₃ (CH ₂) ₃ -Br	CH ₃ (CH ₂) ₃ -N ₃	320	40
4	PhCH ₂ CH ₂ Br	PhCH ₂ CH ₂ -N ₃	330	85
5	(CH ₃) ₃ C-Cl	(CH ₃) ₃ C-N ₃	330	Trace
6			150	78
7			300	50
8			250	55
9			100	82
10			120	80
11			90	89
12			150	82
13			120	81
14			50	88
15			80	85
16			110	86
17			100	90
18			300	25

^a The products were characterized by the comparison of their IR and ¹H-NMR spectra and physical data with those of known samples.

^b Yields refer to the isolated pure products.

or thin-layer chromatography (TLC) with silica gel PolyGram SIL G/UV 254 plates Fluka (Buchs, Switzerland). All products were characterized by the comparison of their IR and ¹H-NMR spectra and physical data with those of known samples, and all

yields refer to the isolated pure products. Fourier transform infrared (FTIR) (Germany) and ¹H-NMR spectra were obtained on a Bruker Equinox (model 55) spectrometer and a JNM-EX 90 MHz spectrophotometer, respectively (JEOL).



(I)=Poly(4-vinylpyridine) cross-linked with 2 % DVB, R= alkyl or benzyl, X=I or Cl

Scheme 1 Mechanism of the reaction and regeneration of polymeric reagent.

Preparation of the crosslinked poly(4-vinylpyridine)-supported sodium azide

Crosslinked poly(4-vinylpyridinium) iodide (2.3 g) was added to an excess aqueous solution of sodium azide in a round-bottom flask (100 mL), and the mixture was stirred for 24 h at room temperature. The mixture was filtered and washed with distilled water (5–10 mL). It was then dried *in vacuo* at 40°C to produce 1.068 g of polymeric reagent. The activity of the polymeric reagent was determined by potentiometric titration with a 0.1M solution of silver nitrate. The activity of the polymeric reagent was obtained as 3.4 mmol of azide ion/g of polymer.

General procedure for the conversion of alkyl halides to the corresponding alkyl azides with the crosslinked poly(4-vinylpyridine)-supported sodium azide

To a mixture of alkyl halide (1 mmol) and dry dichloromethane (10 mL) in a round-bottom flask (50 mL), 1.7 mmol (0.5 g) of crosslinked poly(4-vinylpyridinium)-supported sodium azide was added, and the mixture was stirred at room temperature for 50–330 min. Reaction monitoring was accomplished by gas liquid chromatography or TLC. The products were obtained at 26–89% yields. The polymeric reagent

was regenerated by treatment with an aqueous solution of sodium azide.

Preparation of 4-bromobenzyl azide with the crosslinked poly(4-vinylpyridine)-supported sodium azide: A typical procedure

To a suspension of crosslinked poly(4-vinylpyridine)-supported sodium azide (3.4 mmol, 1.0 g) in CH_2Cl_2 (10 mL) was added 4-bromobenzyl bromide (1.7 mmol, 0.42 g). The mixture was stirred for 90 min at room temperature. Reaction monitoring was accomplished by TLC with dichloromethane/*n*-hexane (10/90) as an eluent. On completion of the reaction, the mixture was filtered and washed with dichloromethane (5 mL) and ether (5 mL). The combined filtrate was evaporated to obtain 4-bromobenzyl azide at an 89% yield (0.322 g).

FTIR (ν_{max} , neat, cm^{-1}): 2100 (N_3 , azide); 1488, 1592 ($\text{C}=\text{C}$); 1285 ($\text{C}-\text{N}$); 1430 (CH_2); 830 (*p*-substituted). $^1\text{H-NMR}$ (90 MHz, CDCl_3 , δ): 4.1 (2H, s, CH_2), 7.2 (2H, d, aromatic), 7.6 (2H, d, aromatic).

RESULTS AND DISCUSSION

During our investigation of multiple-phase techniques in organic synthesis, we observed that crosslinked poly(4-vinylpyridine)-supported sodium azide can be easily prepared and used as a mild and efficient polymeric reagent for the conversion of alkyl halides to the corresponding alkyl azides. The crosslinked poly(4-vinylpyridine)-supported sodium azide (III) was prepared by an exchange reaction between crosslinked poly(*N*-methyl-4-vinylpyridinium) iodide with a slight excess of sodium azide in water. These heterogeneous-reagent-converted alkyl halides to alkyl azides in dry dichloromethane proved to be the solvent of choice among other organic solvents. This method represents an extremely convenient procedure for obtaining a wide variety of alkyl azides at high yields and sufficient purity. The

TABLE II
Some Characteristic Data of the FTIR and $^1\text{H-NMR}$ Spectra of Selected Alkyl Azide Products

Entry	Product	ν_{max} (cm^{-1})	δ (ppm)
1	$\text{CH}_3(\text{CH}_2)_7-\text{N}_3$	2095 (N_3), 1263 ($\text{C}-\text{N}$)	0.9 (3H, t, CH_3), 1.3–1.7 [10H, m, (CH_2) ₅], 3.2 (2H, t, CH_2-N_3)
2	$\text{C}_6\text{H}_5\text{CH}_2-\text{N}_3$	2099 (N_3), 1254 ($\text{C}-\text{N}$)	4.3 (2H, s, CH_2N_3), 7.1 (5H, aromatic)
3	$2-\text{ClC}_6\text{H}_4\text{CH}_2-\text{N}_3$	2101 (N_3), 1261 ($\text{C}-\text{N}$)	4.5 (2H, s, CH_2N_3), 7.5 (4H, aromatic)
4	$\text{PhCH}_2\text{CH}_2-\text{N}_3$	2096 (N_3), 1261 ($\text{C}-\text{N}$)	2.7 (2H, t, CH_2Ph), 3.5 (2H, t, CH_2N_3), 7.2 (5H, aromatic)
5	1-Azidonaphthalene	2098 (N_3), 1240 ($\text{C}-\text{N}$)	—
6	$3-\text{ClC}_6\text{H}_4\text{CH}_2-\text{N}_3$	2101 (N_3), 1259 ($\text{C}-\text{N}$)	4.4 (2H, s, CH_2N_3), 7–8 (4H, aromatic)
7	$4-\text{NO}_2\text{C}_6\text{H}_4\text{CH}_2-\text{N}_3$	2094 (N_3), 1250 ($\text{C}-\text{N}$), 1329 and 1516 (NO_2)	4.5 (2H, s, CH_2N_3), 7.5 (2H, d), 8.4 (2H, d)
8	$4-\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2-\text{N}_3$	2098 (N_3), 1251 ($\text{C}-\text{N}$)	2.4 (3H, s, CH_3), 4.3 (2H, s, CH_2N_3), 7.2 (4H, aromatic)
9	$4-\text{BrC}_6\text{H}_4\text{CH}_2-\text{N}_3$	2100 (N_3), 1285 ($\text{C}-\text{N}$)	4.3 (2H, s, CH_2N_3), 7.2 (2H, d), 7.6 (2H, d)
10	$2-\text{BrC}_6\text{H}_4\text{CH}_2-\text{N}_3$	2099 (N_3), 1255 ($\text{C}-\text{N}$)	4.4 (2H, s, CH_2N_3), 7.4 (4H, aromatic)

TABLE III
Conversion of Alkyl Halides to Corresponding Alkyl Azides in Various Reported Methods

Entry	Substrate	Product	Time	Yield (%) ^a	Reference
1	PhCH ₂ CH ₂ -Br	PhCH ₂ CH ₂ -N ₃	12 h	97	16
2	PhCH ₂ CH ₂ -Br	PhCH ₂ CH ₂ -N ₃	5.5 h	85	Entry 4 in Table I
3	PhCH ₂ -Cl	PhCH ₂ -N ₃	2 h	80	Entry 10 in Table I
4	PhCH ₂ -Cl	PhCH ₂ -N ₃	2 h	91	14
5	PhCH ₂ -Br	PhCH ₂ -N ₃	1 h	100 ^b	14
6	PhCH ₂ -Br	PhCH ₂ -N ₃	6 h	84	17
7	PhCH ₂ -Br	PhCH ₂ -N ₃	6 h	84	20
8	PhCH ₂ -Br	PhCH ₂ -N ₃	100 min	82	Entry 9 in Table I
9	4-BrC ₆ H ₄ CH ₂ -Br	4-BrC ₆ H ₄ CH ₂ -N ₃	2 h	100 ^b	14
10	4-BrC ₆ H ₄ CH ₂ -Br	4-BrC ₆ H ₄ CH ₂ -N ₃	1.5 h	89	Entry 11 in Table I
11	4-CH ₃ C ₆ H ₄ CH ₂ -Cl	4-CH ₃ C ₆ H ₄ CH ₂ -N ₃	24 h	97	16
12	4-CH ₃ C ₆ H ₄ CH ₂ -Cl	4-CH ₃ C ₆ H ₄ CH ₂ -N ₃	2.5 h	82	Entry 12 in Table I
13	4-CH ₃ C ₆ H ₄ CH ₂ -Cl	4-CH ₃ C ₆ H ₄ CH ₂ -N ₃	6 h	83	18
14	4-NO ₂ C ₆ H ₄ CH ₂ -Br	p-NO ₂ C ₆ H ₄ CH ₂ -N ₃	5 h	91	19
15	4-NO ₂ C ₆ H ₄ CH ₂ -Br	4-NO ₂ C ₆ H ₄ CH ₂ -N ₃	50 min	88	Entry 14 in Table I
16	4-NO ₂ C ₆ H ₄ CH ₂ -Br	4-NO ₂ C ₆ H ₄ CH ₂ -N ₃	5 h	91	20

^a Isolated pure products.

^b Conversion percent (some product remains adsorbed on the polymer).

reactions were performed under mild and completely heterogeneous conditions at room temperature, and the alkyl azides were obtained simply by filtration and evaporation of the solvent. The results and reaction conditions are summarized in Table I.

In these conversions, the best molar ratio of reagent to substrate was 1.7.

Moreover, the order of reactivity of the alkyl halides was RI > RBr > RCl (where the larger R group in alkyl halide decreased its activity). It was observed that the activity of alkyl halides was Benzyl > 1° > 2° > 3°, which was in agreement with a nucleophilic substitution process.

The reaction was believed to follow the typical pathway shown in Scheme 1 [eqs. (1)–(3)]. The spent polymeric reagent was easily regenerated by treatment with a sodium azide solution [eq. (4) in Scheme 1].

The pure alkyl azides were analyzed by FTIR and ¹H-NMR spectroscopy (Table II). Although the chemical shift of CH₂-X in alkyl or benzyl halides were nearly identical to the chemical shift of CH₂-N₃ in alkyl or benzyl azides, the appearances of a strong peak at 2095–2105 cm⁻¹ (N₃) and a peak at 1230–1340 cm⁻¹ (C-N) in their FTIR spectra and a signal at 3.2–3.5 ppm (CH₂-N₃ in alkyl azides) or at 4.3–4.5 ppm (CH₂-N₃ in benzyl azides) indicated the formation of the corresponding alkyl or benzyl azides.

In Table III, other reported methods for the preparation of alkyl azides from alkyl halides are compared. As demonstrated, a reaction time was developed that was shorter than that in previously reported methods. This was probably due to the local concentration of azide ion species inside the pores.

In summary, we demonstrated that crosslinked poly(4-vinylpyridine)-supported sodium azide acted as an efficient polymeric reagent for the suspended solution-phase synthesis of alkyl azides from alkyl halides. Alkyl azides were obtained at good yields and high purity by simple filtration and evaporation of the solvent. The exploitation of this reagent for improving the performance of other nucleophilic displacement is under investigation.

CONCLUSIONS

In this article, we presented crosslinked poly(4-vinylpyridine)-supported sodium azide as a useful and convenient alternative to the existing method for the synthesis of alkyl azides from alkyl halides. With this reagent, the workup of the reaction mixture was easy, the reaction took place at room temperature, and the reaction time was shorter than that in previously reported methods. Further application of this system in organic synthesis is currently under investigation.

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