

Use of Polymeric Nitrosation Reagents for the N-Nitrosation of Secondary Amines Under Mild and Heterogeneous Conditions

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ABSTRACT: A combination of crosslinked poly(4-vinylpyridinium)chloride [P₄-H]Cl (**I**) and sodium nitrite or quaternized crosslinked poly(*N*-methyl-4-vinylpyridinium)-nitrite [P₄-Me]NO₂ (**II**) was used as effective nitrosating agents for the N-nitrosation of secondary amines under mild and heterogeneous conditions in moderate to excellent yields.

The spent polymeric reagents can usually be removed quantitatively and regenerated. © 2007 Wiley Periodicals, Inc. *J Appl Polym Sci* 104: 1064–1067, 2007

Key words: N-nitrosation; secondary amines; heterogeneous condition; N-nitrosoamines

INTRODUCTION

Nitrosation chemistry has been a fruitful area for mechanistic organic and biological chemists,^{1–3} and effort has also been made to combine both the synthetic and mechanistic aspects of nitrosation or transnitrosation.⁴ N-nitrosation of amines is an important reaction in organic synthesis. N-nitrosoamines have drawn considerable interest in recent years mainly due to their strong mutagenic and carcinogenic properties,⁵ it has also been found that these compounds have vasorelaxant activity have been used as pesticides.⁶ These compounds are also useful synthetic intermediates for the preparation of various N,N-bonded functionalities. Furthermore, owing to their easy lithiation, followed by reaction with electrophiles and subsequent denitrosation, they can be used for the electrophilic substitution of the secondary amines at the α -carbon in a regio- and stereoselective manner.⁷ A hindered rotation about the N–N bond, being a consequence of a partial double-bond character between two adjacent nitrogens, results in many intriguing stereochemical features in this class of compounds.^{8,9} The most general reagent for synthesis of nitroso amines is nitrous acid generated from sodium nitrite and mineral acid, in water or in mixed alcohol–water solvents.^{10,11} Other nitrosating agents such as Fremy's salt,¹² *N*-haloamides and sodium nitrite under phase-transfer conditions,¹³ oxyhyponitrite,¹⁴ dinitrogen tetroxide,¹⁵ oxalic acid dihydrate,¹⁶ or trichloroiso-

cyanuric acid¹⁷ and sodium nitrite have also been used.

Although polymer-supported reagents especially anion exchange resins have been widely applied in organic synthesis,^{18–29} there is not any report in the literature for the synthesis of N-nitroso compounds based on polymeric acid or polymer-supported reagents.

Recently, we reported synthesis of nitroalkanes from alkyl halides under mild and nonaqueous conditions by using crosslinked poly(*N*-methyl-4-vinylpyridinium)nitrite [P₄-Me]NO₂ (**II**) reagent. This heterogeneous system has many advantages such as simple experimental procedures, mild reaction conditions, and minimization of chemical wastes.²⁰ Therefore, we decided to apply a completely heterogeneous system, and we have investigated a number of different reaction conditions based upon the generation of HNO₂ by relatively strong organic acidic resins and polymer-supported nitrite or sodium nitrite for the nitrosation of secondary amines.

On the other hand, any reduction in the amount of strong inorganic acids needed and any simplification in handling procedures are required for risk reduction, economic advantage, and environment protection.²¹ In addition, there is current research and general interest in heterogeneous systems because of the importance such systems have in industry and in developing technologies.²²

We hoped that the [P₄-H]Cl (**I**) would be a superior proton source to all of the reported acidic solid supports or acidic resins such as polystyrene sulfonic acid and Nafion-H²³ for running reactions on the heterogeneous conditions. Therefore, we were interested in using this acidic resin (**I**) as a new solid acid for the generation of HNO₂ (as a nitrosating agent) when

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used in conjunction with sodium nitrite (procedure a, in Scheme 1) or $[P_4\text{-Me}]NO_2$ (II) (procedure b, in Scheme 1) in an organic solvent (such as ethanol). Since the *N*-nitrosoamines are highly toxic and carcinogenic chemicals, its production with any dispersion is very interesting for organic and biological chemists. Although a key feature of the present article is its clean work-up with easy removal of nitroso adducts due to the heterogeneous nature of the reaction, all due precaution should be taken. We wish to report a simple, cheap, and chemoselective method for the effective nitrosation of secondary amines under mild and heterogeneous conditions

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Quaternized crosslinked $[P_4\text{-Me}]NO_2$ (II) was synthesized according to our procedure.²⁰ The reactions were monitored by TLC, and on completion of the reaction, the pure products were obtained by simple filtration and washing with alcohol. Products were characterized by comparison of their IR and NMR spectra and physical data with those of authentic samples. All yields refer to the isolated products.

Cautions

All *N*-nitrosoamines $[R_1R_2N\text{-N=O}]$ should be regarded as potentially powerful carcinogens, since

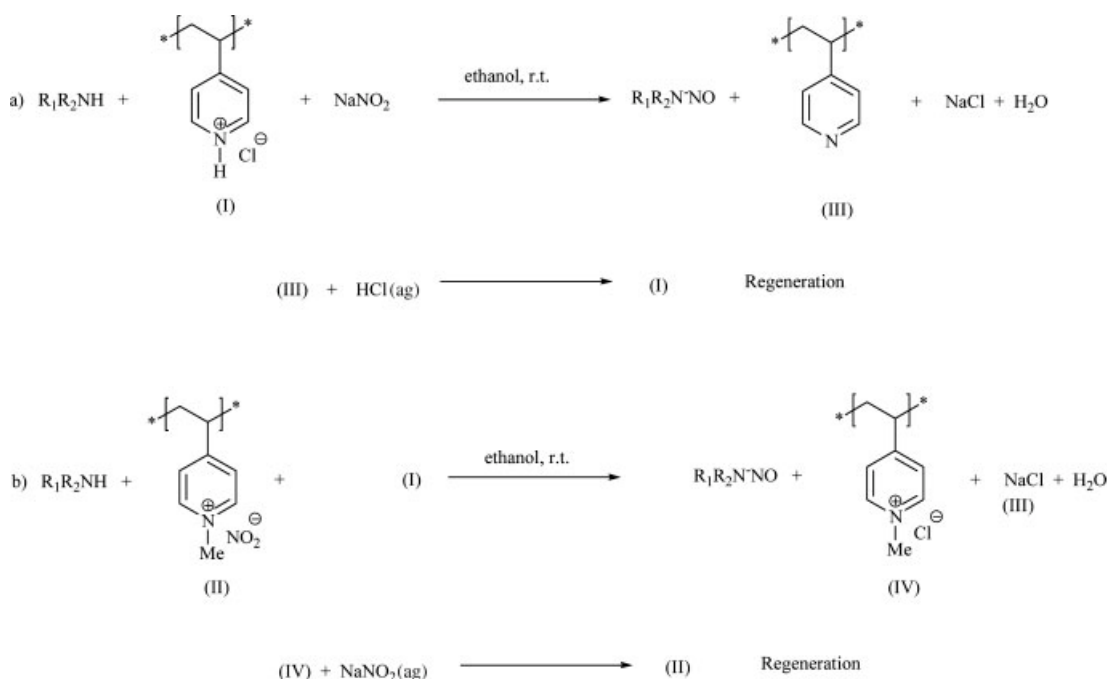
most compounds of these types have been shown to possess high carcinogenic activity in experimental animals.¹⁹

General procedure for *N*-nitrosation of secondary amines

To a suspension of polymeric reagent (I) (1 g, 5 mmol) and sodium nitrite (0.21 g, 3 mmol) or polymeric reagent (II) (1.36 g, 3 mmol) in ethanol (10 mL) was added secondary amine (1 mmol), and it was stirred magnetically either at room temperature or at 50°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the suspension was filtered and washed with ethanol (2×5 mL). Solvent was evaporated and the *N*-nitroso compounds were obtained in high yields (Table I). If further purification was needed, flash chromatography on silica gel [eluent: acetone–petroleum ether (10 : 90)] provides highly pure products.

Preparation of $[P_4\text{-H}]Cl$ (I)

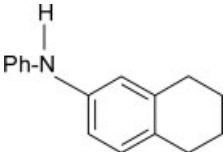
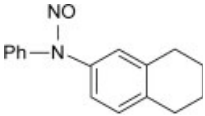
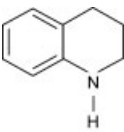
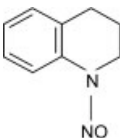
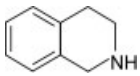
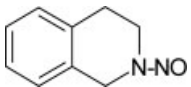
To a concentrated hydrochloric acid (10 mL) was added crosslinked poly(4-vinylpyridine) (1 g), and it was stirred for 24 h. The mixture was filtered, washed with distilled water until the filtrate gave a negative test for HCl. Then it was dried in vacuum at 50°C for 5 h to give 1.2 g of $[P_4\text{-H}]Cl$ (I). The capacity was determined to be 5 mmol per gram of polymer.



R_1 and R_2 = Alkyl, aryl

Scheme 1

TABLE I
Conversion of Secondary Amines to Their Corresponding *N*-nitrosoamines

Entry	Substrate	Product ^a	(I) ^b		(II) ^c	
			Time (min)	Yield ^d (%)	Time (min)	Yield ^d (%)
1	Ph ₂ NH	Ph ₂ N—NO	50 (5)	95 (95) ^e	55 (6)	90 (93) ^e
2	PhNHC ₂ H ₅	PhN(NO)C ₂ H ₅	10 (3)	93 (95)	12 (4)	91 (93)
3	PhNHCH ₂ CH ₂ OH	PhN(NO)CH ₂ CH ₂ OH	10 (3)	90 (92)	11 (4)	88 (90)
4	(PhCH ₂) ₂ NH	(PhCH ₂) ₂ N—NO	10 (2)	95 (96)	11 (3)	93 (94)
5	PhCH ₂ NHC ₂ H ₅	PhCH ₂ N(NO)C ₂ H ₅	10 (2)	95 (93)	11 (3)	90 (93)
6	PhNHCH ₂ Ph	Ph-N(NO)CH ₂ Ph	5 (2)	95 (96)	7 (3)	92 (94)
7			40 (7)	89 (90)	45 (9)	88 (90)
8			11 (1)	95 (95)	15 (4)	87 (92)
9			10 (2)	93 (95)	13 (3)	90 (92)
10	(C ₆ H ₁₃) ₂ NH	(C ₆ H ₁₃) ₂ N—NO	30 (1)	100 (100) ^f	30 (1)	100 (100) ^f

^a The structures were confirmed by comparison of the boiling point, melting point, IR, and NMR spectra with those of authentic specimen.

^b Molar ratio of [P₄-H]Cl (I) : NaNO₂:amine is equal to 5 : 3 : 1 and the reactions take place in ethanol at room temperature.

^c Molar ratio of [P₄-H]Cl (I) : [P₄-Me]NO₂ (II) : amine is equal to 5 : 3 : 1 and the reactions take place in ethanol at room temperature.

^d Isolated yields.

^e Values in the parentheses correspond to the reactions that take place at 50°C.

^f Conversion percent.

N-nitrosation of diphenylamine with NaNO₂ and [P₄-H]Cl (I): A typical procedure

The suspension of polymeric reagent (I) (1 g, 5 mmol), in ethanol (10 mL), diphenyl amine (169 mg, 1 mmol), and NaNO₂ (0.21 g, 3 mmol) was added and stirred at room temperature for 50 min or at 50°C for 5 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the suspension was filtered and washed with ethanol (2 × 5 mL). Ethanol was removed by simple distillation. The crystalline yellow solid of *N*-nitrosodiphenylamine (188 mg) was achieved [95% yield; mp: 63–66°C (lit^{10,11} mp: 67°C); FTIR (KBr) ν (cm⁻¹): 3050(C—H, aromatic), 1450, 1600(C=C, aromatic), 1490–1500, (N=O, stretch), 1050 (N—N, stretch)].

Regeneration of the polymer-supported nitrite

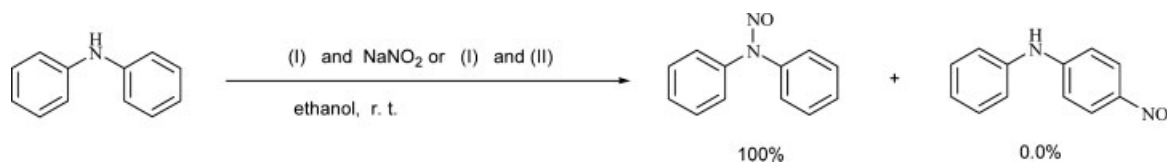
To a solution of aqueous sodium nitrite, 1 g of cream-colored of the used polymeric reagent was added and stirred for 24 h. The mixture was then filtered and

washed several times with distilled water and dried under vacuum. The activity of the polymer was determined by our procedure (3.7–4.8 mmol per gram of polymer).²⁰

RESULTS AND DISCUSSION

[P₄-H]Cl (I) and [P₄-Me]NO₂ (II) are easily prepared and used as an efficient procedure for the chemoselective *N*-nitrosation of secondary amines under mild and heterogeneous conditions. Different types of secondary amines were subjected to the nitrosation reaction in the presence of [P₄-H]Cl (I) and NaNO₂ or [P₄-Me]NO₂ (II) in ethanol (Scheme 1).

The nitrosation reactions were performed under mild and completely heterogeneous conditions at room temperature or at 50°C (with increase in the temperature, the reaction time decreases) and take place with excellent to moderate yields (Table I). The nitrosoamines can be obtained simply by filtration



Scheme 2

and evaporation of the solvent. The results and reaction conditions are given in the Table I.

To demonstrate the chemoselectivity of this method, a competitive reaction was performed between diphenylamine and anisole. It was observed that amine nitrosation occurred exclusively, whereas anisole remained intact in the reaction mixture after 1 h. The nitrosation reaction of diphenylamine further showed the chemoselectivity of the method, as the *N*-nitrosodiphenylamine is the only product. The nitrosation of a mixture of *N*-arylamine and *N,N*-diarylamines shows further the chemoselectivity of the method as the *N*-nitrosoarylamine was the only product. Thus, this system behaves differently to some other reported methods^{10,11,17} in that nitrosonium ion (NO^+) attacks the nitrogen sites of the secondary amines even where an aromatic moiety is connected directly to the nitrogen atom (Scheme 2).

CONCLUSIONS

Polymer-supported nitrite is an efficient and chemoselective nitrosating agent for *N*-nitrosation of secondary amines under mild and heterogeneous conditions at room temperature. This simple procedure is highly selective, and contamination by *C*-nitrosation side-products is avoided. In conclusion, easy and clean work-up, chemoselectivity, and high isolated yields make this method attractive for large-scale operation.

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