

Tungstate Sulfuric Acid (TSA) / NaNO₂ as a Novel Heterogeneous System for the *N*-Nitrosation of Secondary Amines under Mild Conditions

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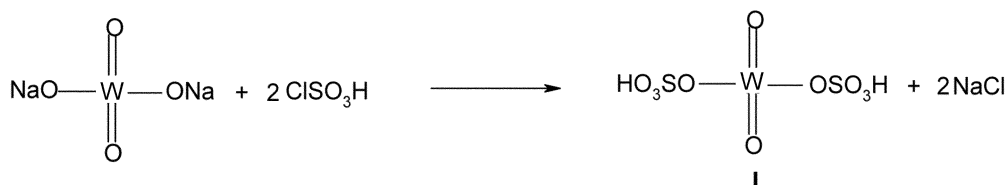
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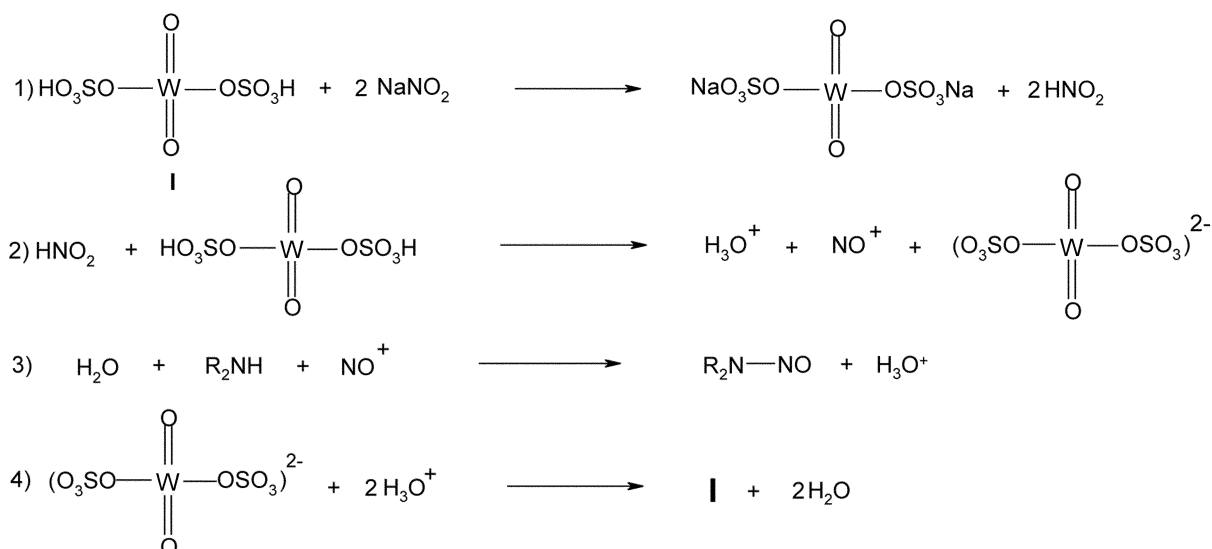
Nitrosation chemistry has been introduced as an active area for organic and biological chemists.¹ Their strong mutagenic and carcinogenic properties of *N*-nitrosamines have caused considerable attraction in this view. Also they have been used as pesticides, lubricant and antioxidants.² *N*-Nitrosamines have key role in preparation of various *N,N*-bonded functionalities and their easy lithiation followed by denitrosative electrophilic reaction which can be applied for the electrophilic substitution of secondary amines at the *α*-position.³ *In situ* generated HNO₂ from sodium nitrite and inorganic acids in water or water/alcohol mixture solvent, is the most general reagent for nitrosation. Some other nitrosating agents, such as fermy's salt,⁴ *N*-haloamides/NaNO₂ under phase-transfer conditions,⁵ nitrogen tetroxide,⁶ oxyhyponitrite⁷ and oxalic acid⁸ have been reported.

Recently, several heterogeneous reagent systems using Nafion-H[®],⁹ silica sulfuric acid and trichloroisocyanuric acid¹⁰ in combination with NaNO₂ have also been used.

Today, heterogenation of chemical systems is an active field in industrial and laboratorial chemistry because of simplification in handling procedures, reduction of corrosion, green chemistry point of view, avoidance of by-products, easy and clean reaction and simple work-up. With regard to wide application of acids as reagent or catalyst in organic chemistry, (for producing more than 1 × 10⁸ mt/year of products) introduction of a new inorganic solid acid can be useful in this direction. Recently silica sulfuric acid¹¹ and Nafion-H[®]¹² have been used for a wide variety of reactions such as production of disulfides from thiols, oxidation of 1,4-dihydropyridines,¹³ *N*-nitrosation of secondary amines,¹⁴



Scheme 1. Preparation of TSA (I).



Scheme 2. Proposed mechanism for *N*-nitrosation.













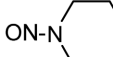
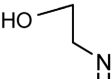
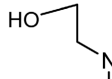
deprotection of acetals,¹⁵ oxidation of alcohols¹⁶ and alkylation with olefins, alkyl halides, alkyl esters, isomerization, transalkylation, acylation, nitration, ether and ester synthesis, acetal formation and chemical rearrangement.¹⁷ In continuation of above and our studies¹⁸ on the application of inorganic solid acid, we found that anhydrous sodium tungstate reacts with chlorosulfonic acid (1 : 2 mole ratio) to give tungstate sulfuric acid **I** (TSA). The reaction is performed easy, clean and without any work-up (Scheme 1).

After preparing TSA (**I**), we were interested to examine it as proton source in combination with various oxidants in organic solvents. For this investigation, we chose wet **I**

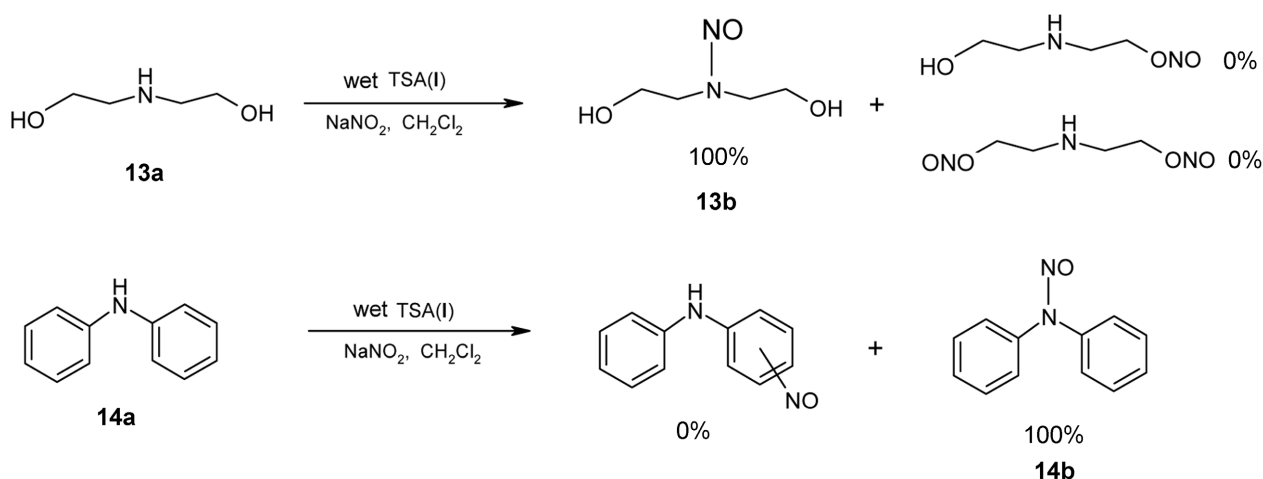
(10%w/w)/NaNO₂ for *N*-nitrosation of secondary amines (**1-14a**) to related *N*-nitrosamines (**1-14b**).

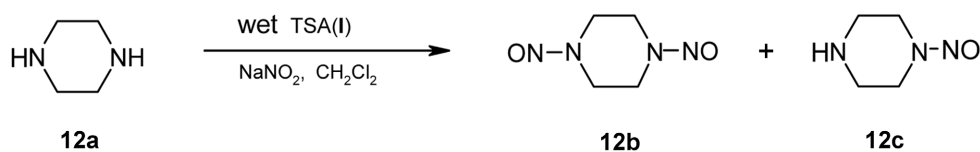
Among many others in this work we wish to report a simple and convenient method for the *N*-nitrosation of secondary amines under mild and heterogeneous conditions. Variety of secondary amines (**1-14a**) were subjected to the nitrosation reaction in the presence of wet **I** (10%w/w)/NaNO₂ in dichloromethane. The nitrosation reactions were done under mild and heterogeneous conditions at room temperature and led to excellent yields (Table 1). Based on other reports in literature^{9,14} we proposed reaction proceeds via formation of NO⁺ by reaction of wet TSA (**I**) and NaNO₂

Table 1. Nitrosation of Secondary Amines **1-14a** (2 mmol) to their Corresponding Nitrosamines **1-14b** with a Combination of 1 mmol wet TSA (**I**) and 2 mmol NaNO₂ in Dichloromethane at Room Temperature^a

| $\text{R}^1\text{R}^2\text{NH} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{Wet TSA(I), RT}]{\text{TSA(I), NaNO}_2} \text{R}^1\text{R}^2\text{N-NO}$ | | | | |
|--|--|---|-------------|------------------------|
| Entry | Substrate a | Product ^b b | Time (min.) | Yield ^c (%) |
| 1 | Me ₂ NH | Me ₂ N-NO | 5 | 98 |
| 2 | Et ₂ NH | Et ₂ N-NO | 5 | 98 |
| 3 | (<i>i</i> -Pr) ₂ NH | (<i>i</i> -Pr) ₂ N-NO | 5 | 98 |
| 4 | (<i>c</i> -C ₆ H ₁₁)CH ₃ NH | (<i>c</i> -C ₆ H ₁₁)CH ₃ N-NO | 5 | 97 |
| 5 | (<i>c</i> -C ₆ H ₁₁) ₂ NH | (<i>c</i> -C ₆ H ₁₁) ₂ N-NO | 5 | 97 |
| 6 |  |  | 5 | 98 |
| 7 |  |  | 5 | 98 |
| 8 |  |  | 5 | 97 |
| 9 |  |  | 5 | 96 |
| 10 |  |  | 8 | 97 |
| 11 | PhNH-CH ₃ |  | 7 | 96 |
| 12 |  |  | 10 | 90 |
| 13 |  |  | 12 | 95 |
| 14 | Ph ₂ NH | Ph ₂ N-NO | 10 | 98 |

^aFor entry 12, amine (**12a**) 2 mmol, 2 mmol TSA (**I**), 4 mmol NaNO₂ were used. ^bAll of the isolated products are known and their spectra and physical data have been reported in the literature.^{1,9,14} ^cIsolated yields.





Scheme 4

(Scheme 2).

All nitrosation reactions were performed in short time (about 5-12 min.) without formation of any by product. The *N*-nitrosamines (**1-14b**) were obtained by simple filtration and evaporation of solvent. As shown in Scheme 2, TSA (**I**) play a catalytic role. To test it, recovered TSA (**I**) from the nitrosation reaction of **14a** was used again in other reaction with NaNO_2 and related nitrosamine **14b** was obtained in 96%. This incident supported our suggestion about catalytic role of TSA (**I**).

The amines of entry **12**, **13** and **14** have two positions for nitrosation. The amine of entry **13** can be undergone *O*-nitrosation or *N*-nitrosation but the result showed only *N*-nitrosation was occurred (Scheme 3). In the case of the amine of entry **14** could undergo nitrosation on aromatic ring although we did not observe (Scheme 3). These results highlighted the chemoselectivity of our method in *N*-nitrosation of secondary amines (**1-14a**).

Dinitrosation of **12a** occurred easily using the appropriate molar ratio of the reagents, but mononitrosation only of this amine **12a** could not be achieved. Without any separation by chromatography method, several attempts at producing pure mononitrosamine **12c** as the single product, unfortunately failed (Scheme 4).

In another study, we designed two parallel reactions with dry and wet TSA (**I**). The observations suggest that the water is essential to generate HNO_2 (Scheme 2).

In conclusion, we think TSA (**I**) is a fine solid acid in the reaction in which proton is needed as catalyst or reagent due to efficiency, easy production, insolubility to all organic solvents, simple for handling, convenient work-up of products, cheap and available, clean reactions, short times and high yields of reactions. In this paper we tried to report a convenient, efficient and practical method for *N*-nitrosation versus *C*-nitrosation or *O*-nitrosation. Structural investigation of TSA (**I**) and similar solid acids and other applications of them in various organic reactions are current researches in our laboratory.

Experimental Section

General. Amines (**1-14a**) and other chemicals were purchased from Merck, Fluka, and Aldrich chemical companies. The reactions were monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data with authentic samples that prepared according to previous method.^{4,9-17} IR spectra were recorded on FT-IR Jasco- 680 and the $^1\text{H-NMR}$ spectra were obtained on a Bruker-instrument 300 MHz model.

Preparation of Tungstate Sulfuric Acid (I). To a 0.2 mol chlorosulfonic acid (23.304 g, 13.31 mL) in 250 mL round bottom flask equipped with ice-bath, 0.1 mol (29.38 g) anhydrous sodium tungstate was added gradually. After the completion of addition the mixture was shaken for 1 h. A yellowish-white solid (TSA) of 40 g was obtained.

General Procedure for *N*-Nitrosation of Secondary Amines (I). To a solution of 2 mmol secondary amine (**1-14a**) in 8 mL dichloromethane, 1 mmol wet TSA (**I**) (10% w/w) and 2 mmol NaNO_2 were added. The heterogeneous reaction mixture was stirred at room temperature. The reaction completed as monitored by TLC (*n*-hexane : ethylacetate 8 : 2). The reaction mixture was filtered and washed with 4 mL dichloromethane. Then anhydrous Na_2SO_4 was added to the filtrate and was filtered after 10 min. Dichloromethane removed by water bath (40-50 °C) and simple distillation and *N*-nitrosamines (**1-14b**) were obtained (Table 1). For further purification flash chromatography on silica gel (*n*-hexane : ethyl acetate 8 : 2) was used.

***N*-Nitrosation of Diphenyl Amine (14a) with Wet TSA (I) and NaNO_2 ; Typical Procedure.** To a solution of 2 mmol (0.338 g) amine (**14a**) in 8 mL dichloromethane, 1 mmol (0.579 g) wet (10%w/w) TSA (**I**) and 2 mmol (0.138 g) NaNO_2 were added. The heterogeneous reaction mixture was stirred at room temperature. The reaction completed as monitored by TLC (*n*-hexane : ethylacetate 8 : 2) after 10 min. The reaction mixture was filtered and washed with 4 mL dichloromethane. Then anhydrous Na_2SO_4 was added to the filtrate and was filtered after 10 min. Dichloromethane removed by water bath (40-50 °C) and simple distillation and *N*-nitrosamine (**14b**) was obtained 0.389 g (98%) as crystalline yellow solid, mp 64-66 °C [Lit.¹⁴ mp 63-66 °C]. IR (KBr), ν cm^{-1} : 3050-3100 (C-H, arom. Stretch.), 1500 and 1600 (C=C, arom.), 1450 (N=O, stretch. and CH_2 , bend.), 1300 (C-N), 1050 (N-N, stretch.). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 7-7.3 (m, aromatic).

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