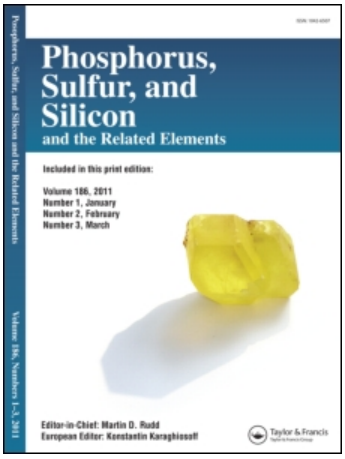

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Silica Sulfuric Acid/NaNO 2 as a Novel Heterogeneous System for the Chemoselective α-Nitrosation of β-Diketones Under Mild Conditions

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SILICA SULFURIC ACID/$NaNO_2$ AS A NOVEL HETEROGENEOUS SYSTEM FOR THE CHEMOSELECTIVE α-NITROSATION OF β-DIKETONES UNDER MILD CONDITIONS

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A combination of silica sulfuric acid and sodium nitrite in the presence of wet SiO_2 was used as an effective nitrosating agent for the nitrosation of β-diketones to their corresponding α-nitroso or α-oximinoketones under mild and heterogenous conditions in moderate to excellent yields.

Keywords: α-Oximination; β-diketones; nitrosation; silica sulfuric acid

Acids are catalysts which are used the most in industry for producing more than 1×10^8 Mt/year of products. Among the acid catalysts, the most commonly used are HF, H_2SO_4, $HClO_4$, and H_3PO_4 (in liquid form or supported on Kieselguhr). Solid acids have many advantages such as simplicity in handling, decreasing reactor and plant corrosion problems, and environmentally safe disposal.[1,2] Also, wastes and by-products can be minimized or avoided by developing cleaner synthesis routes.[3] On the other hand, any reduction in the amount of sulfuric acid needed and/or any simplification in handling procedures is required for risk reduction, economic advantage and environment protection. 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.[4]

Very recently, we among many others have demonstrated that heterogeneous reagent systems have many advantages such as simple

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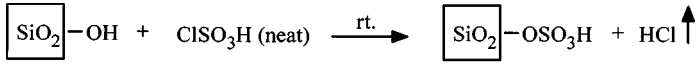
experimental procedures, mild reaction conditions and minimization of chemical wastes as compared to the liquid phase counterparts.[5–7] Therefore, we decided to apply a completely heterogeneous system and we have investigated a number of different reaction conditions based upon the in situ generation of HNO_2 by relatively strong inorganic acidic salts or inorganic acidic resins and sodium nitrite in the presence of wet SiO_2, used as an effective nitrosating agent for the nitrosation of β-diketones. In continuation of our studies on the application of inorganic acidic salts[5] and silica chloride[6] we found that silica gel reacts with chlorosulfonic acid to give a white powder namely silica sulfuric acid (**I**). It is interesting to note that the reaction is easy and clean without any work-up procedure because HCl gas is evolved from the reaction vessel immediately (Scheme 1).



I

SCHEME 1

We hoped that the silica sulfuric acid (**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-H (Nafion has the handicap of low surface area which renders it unrealistic for practical use)[2] for running reactions under heterogeneous conditions. On developing cleaner organic reactions and also applications of this new solid acid,[7] we were interested in using this inorganic acidic resin (**I**) for the in-situ generation of HNO_2 when used in conjunction with $NaNO_2$, wet SiO_2 and an organic solvent. Since the nitrosoketones 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 paper 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 report a simple, cheap, and chemoselective method for the effective nitrosation of β-diketones under mild and heterogeneous conditions.

The α-oximinoketones have been known to be an important intermediate for the synthesis of aminoacids,[8] nitrosopyrazoles,[9] 2-vinylimidazole,[10] and so on. Although nitrous acid or one of its esters,[11] alkyl thionitrite or thionitrate,[12] nitrosyl halides,[13] sodium nitrite and oxalic acid[14] are used for the synthesis of α-oximinoketones but the yields, selectivity for mono oximination and chemoselectivity on the methylene carbon where there are two possible sites of nitrosation are low.[12] This situation contrasts markedly with N-nitrosation and

also to a lesser extent with O and S-nitrosation. It is clear that, on the basis of the above facts there is a need for more regioselective control of nitrosation of carbonyl compounds. Therefore, we decided to choose a new system for this purpose. Our goal, in undertaking this line of work, was threefold: (a) to overcome the limitations and drawbacks of the reported methods such as tedious work-up, low yields, and selectivity; (b) to replace labor-extensive trial and error improvement with rational design; and (c) moreover, constraining a reaction to the surface of solid habitually allows to use milder conditions and increases its reactivity. However, we report an one-pot heterogeneous procedure for chemoselective mono oximination of β-diketones by silica sulfuric acid (**I**) and sodium nitrite.

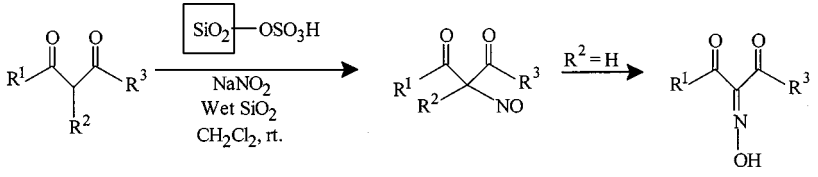
Different kinds of β-diketones (**1**) were subjected to the nitrosation reaction in the presence of silica sulfuric acid (**I**), $NaNO_2$ (**II**), and wet SiO_2 (50% *w/w*) in dichloromethane (Scheme 2). The nitrosation reactions proceeded under mild and completely heterogeneous conditions at room temperature in moderate to excellent yields (Table I). When reaction occurs at the methylene group, the nitroso compound formed initially rapidly rearranges to form the oxime. This method is very mild because a retro-Claisen C—C bond cleavage or hydrolysis of the β-keto esters were not observed.[15]

The present nitrosation reaction can be readily carried out only by placing silica sulfuric acid (**I**), $NaNO_2$ (**II**), β-diketones (**1**), wet SiO_2 (50% *w/w*), and CH_2Cl_2 as the inert usable solvent in a reaction vessel and efficiently stirring the resultant heterogeneous mixture

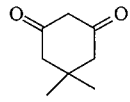
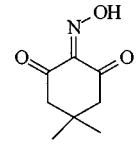
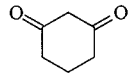
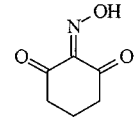
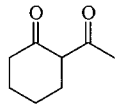
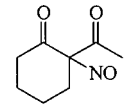
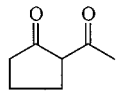
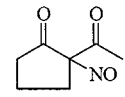
TABLE I Nitrosation of β-Diketones (**1**) to Their Corresponding α-Nitrosoketones (**2**) or α-Oximinoketones (**3**) with a Combination of Silica Sulfuric Acid (**I**), $NaNO_2$ (**II**) and Wet SiO_2 (50% *w/w*) in Dichloromethane at Room Temperature

Entry	Substrate	Product	Reagent/Substrate[a]		Time (min)	Yields[b] %
			I (g)	**II** (mmol)		
1	**1a**	**3a**	0.4	4	75	61
2	**1b**	**3b**	0.8	8	90	92
3	**1c**	**3c**	0.8	8	155	99
4	**1d**	**3d**	1.2	12	120	83
5	**1e**	**3e**	1.2	12	120	60
6	**1f**	**3f**	0.4	4	45	60
7	**1g**	**3g**	0.4	4	85	70
8	**1h**	**2h**	0.4	4	60	80
9	**1i**	**2i**	0.4	4	75	80

[a]Wet SiO_2/substrate (0.2 g/1 mmol).
[b]Isolated yields.



1 2 3

1	Structure of substrates	2 or 3	Structure of products
a	$CH_3COCH_2COCH_3$	3a	$CH_3COC(NOH)COCH_3$
b	$PhCOCH_2COCH_3$	3b	$PhCOC(NOH)COCH_3$
c	$PhCOCH_2COPh$	3c	$PhCOC(NOH)COPh$
d	$PhCOCH_2COOEt$	3d	$PhCOC(NOH)COOEt$
e	CH_3COCH_2COOEt	3e	$CH_3COC(NOH)COOEt$
f		3f	
g		3g	
h		2h	
i		2i	

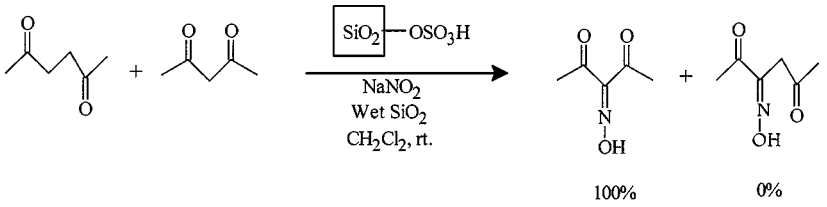
SCHEME 2

at room temperature for 45–155 min. The α-nitrosoketones (**2**) or α-oximinoketones (**3**) can be obtained by simple filtration and evaporation of the solvent. The results and reaction conditions are given in Table I.

Although the nitrosation (some of the nitroso products were converted to the corresponding α-oximinoketones immediately, entries

1–7) reaction also occurs in the absence of wet SiO_2, the reaction times are very long and the reactions only go to completion after several days. Therefore, we think that the wet SiO_2 acts as a reaction medium providing a heterogeneous effective surface area for in situ generation of HNO_2 in low concentrations. It also makes work-up easy.

In order to show the chemoselectivity of this method a competitive reaction was performed between acetylacetone and 2,5-hexadione. It was observed that exclusively acetylacetone nitrosation was performed. 2,5-Hexadione remained intact in the reaction mixture after 2 h (Scheme 3).



SCHEME 3

Similarly, this new system in situ generates HNO_2 and NO^+, respectively, and acts as N_2O_4 because a number of reactions are known in which nitrogen tetroxide ($N_2O_4 \Leftrightarrow NO^+NO_3^-$) acts as a nitrosating agent. Therefore, on the basis of our observations, the previously reported results about the applications of N_2O_4,[16] we think that in situ generation of NO^+ is an effective factor for the nitrosation reactions.[17–19]

In conclusion, the low cost and the availability of the reagents, easy and clean work-up, and high yields make this an attractive method for organic synthesis. This simple procedure is highly selective and contamination by products is avoided. In contrast to the reported procedures in aqueous media[20] isolation of products containing multifunctional polar groups i.e., 2 and 3 are very simple and practical. We are expecting the number of reactions carried out on silica sulfuric acid to enormously increase in the future and to substitute other less environment-friendly acids such as H_2SO_4. We also believed that the present methodology is an important addition to existing methodologies.

EXPERIMENTAL

General: Chemicals were purchased from the Fluka, Merck, and Aldrich chemical companies. Proton and carbon nuclear magnetic

resonance spectra were recorded on a JEOL NMR-Spectrometer FX 90Q. IR spectra were recorded on a Shimadzu 435 IR spectrophotometer. Thin layer chromatography (TLC) on commercial aluminium-backed plates of silica gel 60 F_{254} was used to monitor the progress of the reactions. The nitrosation products were characterized by comparison of their spectral (IR, ^{1}H-NMR), TLC and physical data with authentic samples which were obtained by $H_2SO_4/NaNO_2$/dioxan-water.[20]

General Procedure for α-Nitrosation of β-Diketones

A suspension of sodium nitrite, solid acid (the molar ratio of silica sulfuric acid (**I**) and sodium nitrite (**II**) to the substrate **1** were given in the Table I), β-diketones **1** (10 mmol) and wet SiO_2 (50 *w/w*, 2 g) in dichloromethane (50 ml) was stirred vigorously magnetically at room temperature. The progress of the reaction was followed by TLC. Reactions were completed after 45–155 min (Table I). After the reaction was completed, dry silica gel (5 g) was added to the reaction mixture, the solid materials were removed by filtration and washing with dichloromethane (50 ml). The solvent was evaporated and the α-nitrosoketones (**2**) or α-oximinoketones (**3**) was obtained (Table I). If further purification is needed, flash chromatography on silica gel was used [eluent: acetone/petroleum ether (1:5)] to give highly pure **2** or **3**.

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