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An Efficient and Chemoselective Method for Oximination of β-Diketones Under Mild and Heterogeneous Conditions

Mohammad Ali Zolfigol

Department of Chemistry, College of Science, University of Bu-Ali Sina, Postal code 65174, P.O. Box No. 4135, Hamadan, I.R. Iran; Fax: (+98) 811 8272404; e-Mail: Zolfi@basu.ac.ir

Abstract: A combination of oxalic acid dihydrate 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-oximinoketones in moderate to excellent yields under mild and heterogenous conditions.
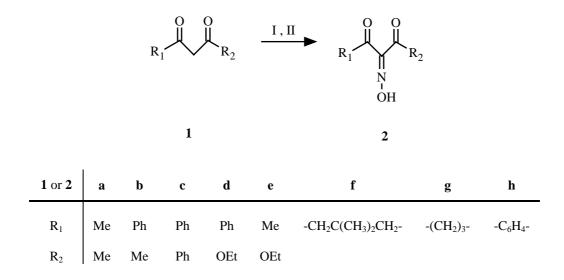
Introduction

The α-oximinoketones are known to be important intermediates for the synthesis of aminoacids [1], nitrosopyrazoles [2], 2-vinylimidazoles [3] and so on. Although nitrous acid or one of its esters [4], alkyl thionitrite or thionitrate [5], nitrosyl halides [6] and sodium nitrite in acetic acid [7] are all used for the synthesis of α-oximinoketones, the yields, selectivity for mono oximination and chemoselectivity on the methylene carbon where there are two possible sites of nitrosation are low [5]. 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 three-fold: 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 improvements with a rational design, (c) moreover, constraining a reaction to the surface of solid habitually allows to use milder conditions and increases its reactivity [7]. We now wish to report a one-pot heterogeneous procedure for

chemoselective mono oximination of β-diketones by oxalic acid dihydrate ($C_2H_2O_4 \cdot 2H_2O$, $_pk_a \sim 2$) and sodium nitrite.

Results and Discussion

Different kinds of β-diketones (**1**) were subjected to the nitrosation reaction in the presence of $NaNO_2$ (**I**), wet SiO_2 (50% *w/w*) and $C_2H_2O_4 \cdot 2H_2O$ (**II**) in dichloromethane (Scheme 1). The nitrosation reactions were performed under mild and completely heterogeneous conditions at room temperature and gave moderate to excellent yields (Table). When reaction occurs at the methylene group, the nitroso compound formed initially rapidly rearranges to form the oxime. This method is very mild because retro-Claisen C-C bond cleavege or hydrolysis of β-keto esters were not observed [8].

1 or **2**	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R_1	Me	Ph	Ph	Ph	Me	-CH_2C(CH_3)_2CH_2-	-(CH_2)_3-	-C_6H_4-
R_2	Me	Me	Ph	OEt	OEt			

Scheme 1

The reported nitrosation reaction can be readily carried simply by placing $NaNO_2$ (**I**), $C_2H_2O_4 \cdot 2H_2O$ (**II**), β-diketones (**1**), wet SiO_2 (50% *w/w*) and CH_2Cl_2 as the inert solvent in a reaction vessel and efficiently stirring the resultant heterogeneous mixture at room temperature for 0.25-3 hours. The initial nitroso products were converted to the corresponding α-oximinoketones (**2**) immediately and the products can be isolated by simple filtration and evaporation of the solvent. The results and reaction conditions are given in Table 1.
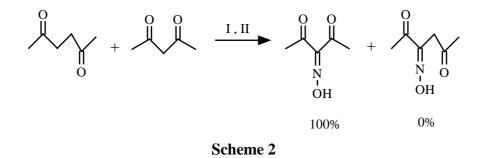
Although the nitrosation reaction also occurs in the absence of wet SiO_2, the reaction times are very long and the reactions only go to completion after several days. Therefore, we think that the wet SiO_2 acts as a reaction medium providing a heterogeneous effective surface area for *in situ* generation of HNO_2 in low concentrations. It also makes work-up easy.

Table 1. Nitrosation of β-Diketones to
the Corresponding α-Oximinoketones (2)

Entry	1	2	(mmol)[a]			Time	Yields[b]
			Substrate	NaNO$_2$	C$_2$H$_2$O$_4$·2H$_2$O	(h)	%
1	**a**	**a**	1	2	2	1	88
2	**b**	**b**	1	6	6	1	86
3	**c**	**c**	1	7	7	1.5	75
4	**d**	**d**	1	12	12	3	81
5	**e**	**e**	1	12	12	2.5	84
6	**f**	**f**	1	2	2	1	88
7	**g**	**g**	1	2	2	0.25	90
8	**h**	**h**	1	2	2	2	50

[a] Wet SiO$_2$/substrate (0.2 g/1mmol) . [b] Isolated Yields.

In order to show the chemoselectivity of this method a competitive reaction was performed between acetylacetone and 2,5-hexadione. It was observed that exclusive nitrosation of acetylacetone occurred, whereas the 2,5-hexadione remained intact in the reaction mixture, even after 5 hours (Scheme 2).

Scheme 2

Similarly, this new system generates HNO$_2$ and NO$^+$ respectively, in-situ, and thus acts as a N$_2$O$_4$ equivalent because a number of reactions are known in which nitrogen tetroxide (N$_2$O$_4 \Leftrightarrow$ NO$^+$NO$_3^-$) acts as a nitrosating agent. Therefore, on the basis of our observations, the previously reported results about the applications of N$_2$O$_4$ [9], we show that *in situ* generation of NO$^+$ is an effective factor for the nitrosation reactions [7].

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. We believed that the present methodology is an important addition to existing methodologies.

Acknowledgments

Experimental

General

Chemicals were purchased from the Fluka, Merck and Aldrich chemical companies. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL FX 90Q NMR spectrometer. 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, ^{13}C-NMR), TLC and physical data with authentic samples obtained by the H_2SO_4/$NaNO_2$/dioxane-water method [10].

WARNING: The nitroso diketones reported in this paper are highly toxic and although a key feature of the procedure is its clean workup with easy removal of nitroso adducts due to the heterogeneous nature of the reaction, all due precautions should be taken.

General Procedure for Oximination of β-Diketones

A suspension of sodium nitrite, solid acid (the molar ratios of oxalic acid dihydrate and sodium nitrite to the substrate **1** were given in the Table), β-diketones **1** (10 mmol) and wet SiO_2 (*50 w/w*, 2 g) in dichloromethane (40 mL) was stirred vigorously magnetically at room temperature. The progress of the reaction was followed by TLC. Reactions went to completion after 0.25-3 hours (Table). After the reaction was complete, dry silica gel (5 g) was added to the reaction mixture, the solid materials were removed by filtration and washed with dichloromethane (40 mL). The solvent was evaporated from the combined filtrate and washings and the α-oximinoketones **2** were obtained (Table). If further purification is needed, flash chromatography on silica gel [eluent: acetone / petroleum ether (1:5)] give highly pure **2**.

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Sample availability: Not available.