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Facile, Regioselective and Green Synthesis of Ortho-nitrophenoles Using $NaNO_2$, $KHSO_4$

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Certain phenols and naphtols were nitrated regioselectively with $NaNO_2$ in the presence of $KHSO_4$ at 50 °C in high yields.

Keywords: Nitration; Phenols; Sodium nitrites; $KHSO_4$.

INTRODUCTION

Nitration of phenols using the traditional procedure of nitric acid in sulfuric acid, generally gives complex mixtures containing o and p-nitro phenols, dinitrated phenols, along with inextractable tars of phenolic oxidation products.[1] The distribution of the isomer ratio in electrophilic substitution of phenols continues to challenge organic chemists. Consequently, alternative nitration procedures have been sought to fulfill, clean and regioselect nitration of phenols. In 1995 Lazslo et al. demonstrated that phenol can be nitrated with a reagent called clay-cop (cupric nitrate supported onto montmorillonite) in 92% yield with an o/p ratio of 13.3.[2] Nitration of phenols as a special case has been studied using various reagents in different conditions.[3] In this communication, we wish to reveal our results for the selective, facile and green nitration of phenols by a mixture of $NaNO_2$, $KHSO_4$.

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,[4-6] strongly acidic media,[7] oxidation ability of the reagent and safety problems (storage, handling);[8,9] b) to reach a high yielding one-pot synthesis of mono nitro phenol using a combination of reagent and c) to consider the rules of green chemistry to implement nitration in eco-friendly conditions.

RESULTS AND DISCUSSION

Green chemistry is one of the main concerns and topics in our laboratory.[10] Nitrites are widely recognized as safe environmental compounds. Nitrites are a relevant source of $OH^{\cdot}$ in the atmosphere, both in the gas phase via photolysis of gaseous HNO_2 and atmospheric hydrometeors by photolysis of NO_2^-.[11] Recently, in an unrelated study, phenols have been nitrated with a combination of silica sulfuric acid, $NaNO_2$ and wet SiO_2.[12] In this paper, it has been reported that without wet SiO_2, the reaction times are very long, taking several days to complete. In this paper a mechanism for using nitration, sodium nitrite has proposed.[12] However in the mechanism, the role of wet SiO_2 has been overlooked. As far as green chemistry is concerned, sulfuric acid in any form is notorious, and its safe disposal is one of the problems and concerns of chemical industries and therefore its replacement with safer reagents is desirable. As mentioned before, $NaNO_2$ as an eco-friendly reagent has been used along with silica sulfuric acid and wet SiO_2 for nitration of phenols.[12] We have recently used $KHSO_4$ as a safe and green reagent in the synthesis of 1,1-diacetales[13a] and facile synthesis of quinoxallines.[13b] Armed with these experiences, it occurred to us that the replacement of silica-sulfuric acid and wet SiO_2 with $KHSO_4$ as a safe counterpart of H_2SO_4 might result in a more efficient, selective and high yielding nitration with a more reasonable mechanism for generation of NO_2^+. Thus we have treated a variety of phenols and substituted phenols having at least one unsubstituted ortho position with $NaNO_2$/$KHSO_4$ as shown in Scheme II and Table 1, and obtained o-nitro phenols in all cases.

The plausible mechanism is given in Scheme I. The reaction of sodium nitrate and $KHSO_4$ gives HNO_2. It is

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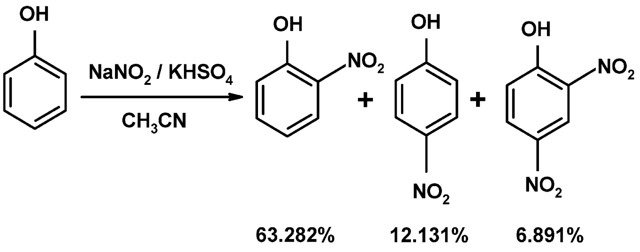
Scheme I

$$NaNO_2 + KHSO_4 \longrightarrow HNO_2 + Na^+ + KSO_4^-$$

$$3\ HNO_2 \longrightarrow HNO_3 + 2\ NO + H_2O$$

$$HNO_3 + KHSO_4 \longrightarrow NO_2^+ + H_2O + KSO_4^-$$

Scheme II

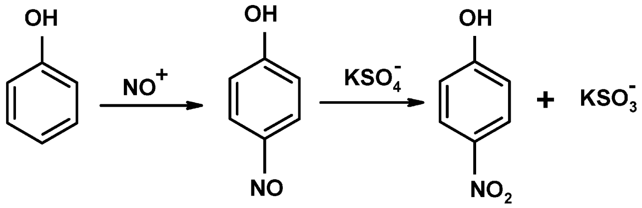


well known that nitrous acid decomposes to nitric acid, particularly when warmed.[14] HNO_3 and $KHSO_4$ provide nitronium ions for the nitration.

Scheme III

$$NaNO_2 + KHSO_4 \longrightarrow HNO_2 + Na^+ + KSO_4^-$$

$$HNO_2 + 2\ KHSO_4 \longrightarrow NO^+ + H_3O^+ + 2KSO_4^-$$



The percentages of products were obtained by GC/MS analysis. The alternative mechanism, involving the generation of nitrosonium ion NO^+ and nitrosation followed by oxidation to obtain the nitro compound, can be ruled out with this fact that via this mechanism the major product[15] should be p-nitro phenol which is contrary to our results.

Among the solvents used such as CH_2Cl_2 and CH_3CN, the latter gave the best yields of the o-nitro phenols at 50 °C. The absence of dinitro-phenols as well as hydroxylation and coupling products was ascertained by GC/MS

Table 1. Selective and eco-friendly nitration of phenols and naphtol

Entry	Substrate	Products	Time (h)	Yields
1	phenol	O-nitro phenol		63
		p-nitro phenol	7	12
		dinitro phenol		6
2	4-nitro phenol	2,4-dinitro phenol	5	92
3	4-bromo phenol	2-nitro4-bromo phenol	5	92
4	4-methoxy phenol	2-nitro4-methoxy phenol	4	94
5	2-naphtol	1-nitro2-naphtol	5	94

Table 2. Nitration of phenol with different methods

Entry	Reagent	o-nitro phenol (%)	p-nitro phenol (%)
1	$NaNO_2/KHSO_4$	62	12
2	$Fe(NO_3)_3.\ 9H_2O$[16]	50	50
3	$Mn(NO_3)_3.\ 2H_2O$[16]	60	40
4	$Cu(NO_3)_2.\ 3H_2O$[16]	40	60
5	HNO_3/Microemulsion[4]	50	50
6	$ZrO(NO_3)_2.\ XH_2O$[3a]	40	60
7	$NaNO_3/Mg(HSO_4)_2$[17]	36	26
8	$NaNO_2$/Silica sulfuric acid[18]	30	20
9	HNO_3/Sulfated titania[19]	68.6	2.3

analyses of the crude reaction mixtures. The scope of this nitration was widened by nitration of naphtols to give mono-nitrated compounds in high yields (Table 1).

The superior regioselectivity of our method is clear and can be justified by comparison of percentages of ortho isomers with previously reported protocols (Table 2).

In conclusion, a regioselective ortho nitration of various phenols and naphtols using green, available, inexpensive and easy to handle $NaNO_2/KHSO_4$ reagent has been reported. We believe this protocol is an important tool in organic chemistry.

EXPERIMENTAL

Chemicals were purchased from the Fluka, Merck and Aldrich chemical companies. Melting points were measured with a Bamstead Electrothermal 9200 apparatus and are uncorrected. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. Yields refer to isolated pure products. Products were identified by GC/MS and the data were compared to those of the authentic samples purchased from commercial sources.

Nitration of phenols with $NaNO_2/KHSO_4$. Typical procedure

4-Bromo phenol (0.14 g, 1 mmol), $NaNO_2$ (0.1 g, 1.5 mmol) and $KHSO_4$ (0.27 g, 2 mmol) in acetonitril was stirred at 50 °C. After the completion of reaction, the reaction mixture was filtered (the progress of the reaction was monitored by TLC). The residue was washed with acetonitril (2 × 5 mL). Anhydrous Na_2SO_4 (5 g) was added to the filtrate. The mixture was filtered. The solvent was removed by distillation using a water bath (35-40 °C). The obtained crude was pure enough (checked by tlc). For further purification, this crude was passed through a small pad of silica gel using ethyl acetate/pet ether 1:3 to obtain the pure product. Yield 0.2 g, (92%), mp 92 °C.

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