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Nitration of Phenol and Substituted Phenols with Dilute Nitric Acid Using Phase-Transfer Catalysts

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Abstract:

Highly selective nitration of phenol and substituted phenols to the corresponding nitro compounds is accomplished under mild conditions in a liquid−liquid two-phase system with dilute nitric acid (6 wt %) and in the presence of a phase-transfer catalyst. The consequence of various phase-transfer catalysts on the reaction rate is contemplated. Tetrabutylammonium bromide (TBAB) was found to be the most effective phase-transfer catalyst in terms of conversion and selectivity. The experimental results are accounted for by a binary role of the phase-transfer catalyst in this system. It is anticipated to extract nitric acid into the organic phase via the hydrogen-bonded complex and to supply HBr, formed in situ in the reaction scheme by anion exchange, which is believed to be the key for generation of the active nitration species, nitronium ion in the organic phase.

Introduction

Nitration of aromatic compounds is an industrially consequential reaction[1] as the nitrated products are important intermediates for fine chemicals and pharmaceuticals. Usually, nitration reactions are not selective and are the cause of environmental concerns regarding the disposal of the large excess of mixed acids employed in these processes. Thus, the utility of this processes[2,3] are generally low. Besides mixed acids, several other nitrating agents, including concentrated nitric acid, acid anhydrides or triflates,[4] peroxy nitrite,[5] metal nitrates,[6] and nitrogen oxides,[7] have been utilized by many investigators. Catalytic nitration of aromatic hydrocarbons with concentrated nitric acid in the presence of solid acids[8] has received attention with regards to the regioselectivity. In some cases, the reaction has been performed in expensive media such as ionic liquids[9] and microemulsions.[10] A sophisticated technique, microwave-assisted nitration of aromatic hydrocarbons with dilute nitric acid, has also been studied recently.[11] With regards to nitration of phenols, concentrated nitric acid or mixed acids are promising; their use is always associated with the formation of dinitro compounds, oxidized products, and unspecified resinous tarry materials resulting from the over-oxidation of the substrate. Noteworthy, the typical yield of direct nitration never exceeds 60%[2] because of the above-mentioned side reactions in most of the cases, making these existing processes uneconomical. Therefore, it is worthwhile to consider an alternative highly selective nitration process scheme by using a mild nitrating agent such as dilute nitric acid. Thus, in this work, we will report results of the selective nitration of phenols with 6 wt % nitric acid in the presence of a phase-transfer catalyst, namely, tetrabutylammonium bromide (TBAB).

Results and Discussion

Conversions for various phenolic compounds are shown in Table 1. In case of unsubstituted phenol the selectivity was less. This is due to the oxidation of phenol to 1,4-benzoquinone (10%). A 90% yield of mononitrophenol was concurrently obtained (ortho/para ratio was 6:4). In the absence of TBAB only traces of nitrophenol were detected under the above reaction conditions. Noteworthy, when para-substituted phenols were used, the nitration occurred at the

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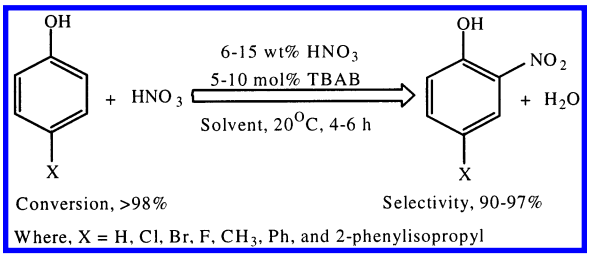
Table 1. **Nitration with various phenols**[a]

entry	reactant	TBAB, mol %	*t*, h	% yield of mononitrated derivative
1[b]	phenol	0	4	0.4
2[b]	phenol	5	4	90
3[b]	*4*-cresol	10	5	97
4[b]	*4*-chlorophenol	10	6	97
5[b]	*4*-flurophenol	10	6	97
6[c]	*4*-cumylphenol	10	3	97
7[c,d]	*4*-phenylphenol	10	5	96

[a] Reaction conditions: substrate, 10 mmol; catalyst, TBAB; nitric acid (70 wt %, 20 mmol); solvent, EDC, 20 mL; calculated amount of water was added to make particular concentration of nitric acid (wt/wt); temperature, 20 °C. [b] 6 wt % HNO_3 was used. [c] 15 wt % HNO_3 was used. [d] Reaction was carried out in 20 mL of ether. [e] GC yields.

Scheme 1. **Nitration of phenol and substituted phenols**



ortho position to the OH functionality. However, in most of the above-mentioned cases, complete conversion of the starting phenols was achieved under the reaction conditions.

Incidentally, TBAB (5 mol %) was found to be the most active catalyst (Scheme 1). Tetrahexylammonium bromide exhibited similar catalytic activity. Surprisingly, when bromide salts of quaternary ammonium were replaced with 5 mol % of any one of fluoride, chloride (TBAC) or nitrate salts, almost no nitration of phenol was observed after 4 h under similar reaction conditions. Using 5 mol % tetrabutylammonium iodide (TBAI) as the catalyst, a 5% conversion to nitrophenol along with a 4% conversion to iodophenol was detected after 4 h of reaction time under identical conditions. A complete conversion of phenol to nitrophenol occurred when the reaction was performed either with a higher loading (10 to 15 mol %) of TBAC or in the presence of 5 mol % HBr as a promoter together with 5 mol % TBAC. Also, aliquat-336 (5 mol %) failed to activate the nitration reaction.

The reaction was studied at different temperatures. The time required to convert 100% phenol was 4 h at 20 °C, 1.5 h at 28 °C, whereas 100% conversion took 45 min at 40 °C. Taking into account the exothermicity of this reaction, we tried to measure the rise in temperature (ΔT) after 3 min of the batch-mode addition of HNO_3 to the reaction mixture under vigorous stirring. The rise in temperature was measured by a tiny finely tuned thermocouple. The increase in temperature was 2 °C at 20 °C, 3 °C at 28 °C, and about 7 °C when the reaction was performed at 40 °C. Thus, for safe practice it is very important to perform the reaction at low temperature and also in a reactor connected externally to a cooling system.

In a special set of trial runs, to obtain better understanding of the catalytic extraction of HNO_3 from the aqueous phase into the ethylenedichloride (EDC) phase, 6 wt % nitric acid was combined with 10 mol % of TBAB in a biphasic aqueous−EDC system (identical to that in the reaction). Only 10% of the initially introduced amount of acid could be extracted. The explicit experimental assays on acidity and of bromide anion concentration in the aqueous phase confirmed for us the complete mass balance of the system. Hence, we concluded that two parallel processes are simultaneously taking place in this reaction scheme: (a) bromide/nitrate anion exchange as depicted in eq 1 and (b) extraction of both HBr and HNO_3 into the organic phase (eqs 2 and eq 3), presumably via hydrogen bonding with the phase-transfer catalyst. In fact, a set of in situ Raman spectroscopy experiments on a mixture of any one of TBAB, TBAC, or TBAI, and HNO_3 exclusively supports the reaction in eq 1. In fact, several researchers in the past[12] have documented similar extractions (eqs 2 and 3) of various acids into the organic phase by phase-transfer agents.

$$\mathrm{QBr\ (org) + HNO_3\ (aq) \rightarrow QNO_3\ (org) + HBr\ (aq)} \quad (1)$$

$$\mathrm{QBr\ (org) + HNO_3\ (aq) \rightarrow QBr\ (HONO_2)\ (org)} \quad (2)$$

$$\mathrm{QBr\ (org) + HBr\ (aq) \rightarrow QBr\ (HBr)\ (org)} \quad (3)$$

Obviously, nitronium ion, which is believed to form in situ in the organic phase by the reaction between the extracted species, in turn reacts with phenol, possibly via the classical nitration mechanism pathway[13] to yield the desired nitrophenol.

Consequently, in this work, it is proposed that the phase-transfer catalyst has two functions: (i) to act as the source of the strong acid (HBr) which is required for the in situ generation of the active nitronium cation and (ii) to extract two essential acids, viz., nitric acid and hydrobromic acid, into the EDC phase where the nitration of the substrate seems to take place. Apparently, the other quaternary ammonium salts such as fluoride and nitrate failed to activate the nitration process candidly because the acid generated from them was not sufficiently strong[14] in comparison to that from HBr, actualized when TBAB was used as the phase-transfer agent. Why higher loading (10−15 mol %) of TBAC is needed for the nitration reaction is not understood; however, the plausible explanation could be due to its low liphophilicity and extraction capability in comparison to those of TBAB.[15]

Performing the reaction in the presence of 5 mol % TBAI, we detected 4% (0.4 mmol) iodinated product and 5% nitrated product on the basis of the starting phenol after 4 h of reaction time. This clearly suggests that 0.4 mmol out of total 0.5 mmol TBAI which is initially added to the reaction

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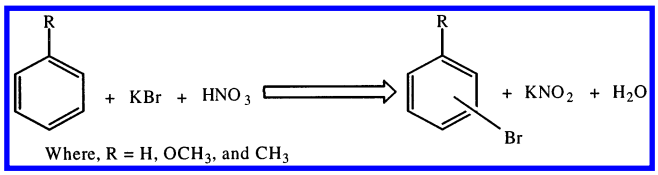
Scheme 2. **Oxidative bromination with dilute nitric acid**



mixture is consumed by the iodination reaction. Thus, the remaining 0.1 mmol (1 mol %) TBAI is not sufficient to activate the nitration reaction. It is to be noted that under similar conditions no halogenated product was observed with 5 mol % TBAC. However, when using TBAB as the catalyst only a trace amount of bromo compounds were detected together with the desired nitro products. The halogenated products are most likely formed by the oxidative halogenation[16] of the starting phenols in the presence of TBAX (X = I, Br) and HNO_3. However, it was observed that in the presence of TBAB the rate of oxidative bromination of phenols was slower than that of nitration under identical reaction conditions. Certainly, the chemoselectivity of the oxidative bromination reaction increased when a less nucleophilic aromatic substrate such as anisole was used. In our laboratory, studies have been initiated to modulate a simple oxidative bromination process scheme by using bromide salts as a bromine source and dilute nitric acid as a mild oxidizing agent. (Scheme 2).

Conclusions

Finally, we found a simple method for using dilute nitric acid as the nitrating agent in conjunction with a catalytic amount of tetrabutylammonium bromide. Accordingly, this could be a potentially environmentally friendly alternative for the present nitration processes.

Experimental Section

Nitration of Phenols: As, for Example, Nitration of 4-Chlorophenol. In a typical reaction 4-chlorophenol (10 mmol), TBAB, 10 mol % of substrate, nitric acid (70 wt %, 20 mmol), water to make up the nitric acid concentration to 6 wt %, and ethylenedichloride (20 mL), were mixed together in a 50-mL glass reactor and stirred at 20 °C for 4−6 h. Reaction progress was monitored by GC. Products were identified by GC−MS, and the data were compared to those of the authentic samples purchased from commercial sources. After the completion of reaction, the organic layer was separated from the aqueous layer. It was then washed with 3 × 25 mL water, separated, and finally dried over magnesium sulfate. The anhydrous ethylenedichloride layer thus obtained was distilled to remove solvent. The residue was then crystallized in ethanol to obtain 1.41 g (81 mol %) of 4-chloro-2-nitrophenol. The observed mp was 86.5 °C which was in good agreement with the literature[17] (mp 85−87 °C).

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