

1-1-2010

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AKHLAGHINIA, BATOOL and POURALI, ALI REZA (2010) "Bromodimethylsulfonium bromide/tetrabutylammonium nitrite: an efficient catalyst mixture for the nitration of phenols," *Turkish Journal of Chemistry*. Vol. 34: No. 5, Article 6. <https://doi.org/10.3906/kim-0909-246>
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Bromodimethylsulfonium bromide/tetrabutylammonium nitrite: an efficient catalyst mixture for the nitration of phenols

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Received 19.09.2009

Nitrophenols were obtained via direct nitration of phenols with tetrabutylammonium nitrite in the presence of bromodimethylsulfonium bromide at room temperature in high yields under aprotic conditions.

Key Words: Bromodimethylsulfonium bromide, nitration, nitrophenol, tetrabutylammonium nitrite

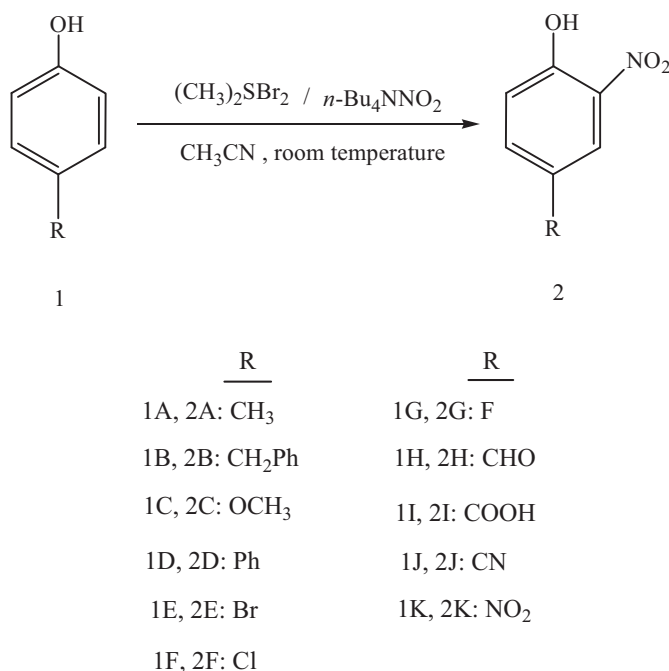
Introduction

The nitration of aromatic compounds is an important industrial process and nitro aromatic compounds so produced are widely utilized for the synthesis of dyes, pharmaceuticals, perfumes, and plastics.¹ Therefore, the nitration of aromatic rings has received considerable attention of late, due to unsolved problems pertaining to regioselectivity, polynitration, and competitive oxidation of substrates.^{2,3} Nitration of the phenol as a special case has been studied by various nitrating agents under different conditions.^{1–26} Among the methods that have been reported in the literature for the regioselective nitration of phenols, 3 procedures yield excellent results. Two of them used microemulsion and a surface mediated system.²¹ In the third one, an enzymatic method was reported for the nitration of phenols.²² Zolfigol and co-workers have reported the use of some hydrated metal nitrates and their dinitrogen tetroxide complex analogues, as well as ionic metal nitrates or nitrites in the presence of inorganic acidic salts, for the nitration of phenols under various conditions.²³ They have also reported the application of trichloroisocyanuric acid/ NaNO_2 /wet SiO_2 for mononitration of phenols.²⁶

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To overcome the limitations and drawbacks of the classic methods such as strongly acidic media,^{15b} tedious work-up,^{16,17} oxidation and polynitration, and safety problems (storage, handling, using, and also presence of toxic transition metal cations such as Cr^{+3} , Hg^{+2} , and Cu^{+2} within molecular structure of the reagents),^{24,25} and to develop a high-yielding one-pot synthesis of nitrophenols, in this research a novel combination of bromodimethylsulfonium bromide (BDMS) and tetrabutylammonium nitrite is introduced.

In recent years, the use of BDMS has gained more attention in synthetic organic chemistry.²⁷ This reagent is a readily accessible, conveniently stored, less hazardous, easy to handle crystalline solid. So far, BDMS has been utilized for the transformation of alcohols to the corresponding bromides,^{28a} oxidation of thiols to disulfides,^{28b} deprotection of dithioacetals,^{28c} preparation of α -bromoenones from the corresponding enones,^{28d} electrophilic aromatic bromination,^{28e} regioselective α -bromination of β -keto esters and 1,3-diketones,^{28b} and thiocyanation of aromatic compounds.^{28f} Herein, we report a novel, mild, and efficient approach for the nitration of aromatic compounds using BDMS in the presence of tetrabutylammonium nitrite (Scheme 1).



Scheme 1

Experimental

The products were purified by column chromatography and the purity determinations of the products were accomplished by GLC on a Shimadzu model GC-10A instrument or by TLC on silica-gel polygram STL G/UV 254 plates. FT-IR spectra were recorded on a Shimadzu-IR 470 spectrometer. NMR spectra were recorded on a Bruker AC 300 MHz instrument. Elemental analyses were performed using a Thermofinnigan Flash EA 1112 Series instrument.

All products were identified by their comparison with authentic samples. Bromodimethylsulfonium bromide was prepared and purified by the method described in the literature.^{28f}

General Procedure for Nitration of Substituted Phenols with Bromodimethylsulfonium Bromide/*n*-Bu₄NNO₂

To a yellow suspension of bromodimethylsulfonium bromide (0.332 g, 1.5 mmol) and tetrabutylammonium nitrite (0.864 g, 3 mmol) in anhydrous CH₃CN (10 mL) was added the substrate (1 mmol) in one portion. The reaction mixture was stirred at r.t. until complete consumption of the starting material as observed by TLC. After completion of the reaction, it was quenched with saturated solution of NaHCO₃ (10 mL) and the solid residue was removed by filtration and the residue was washed with EtOAc. The organic layer was separated, washed with H₂O (10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give the crude nitro product. Pure product was obtained after column chromatography using *n*-hexane/ethylacetate (3/2 v/v) as eluent.

Results and discussion

To begin our study, the effect of various reaction conditions on the nitration of *p*-cresol was examined. The reaction was carried out with different molar ratios of *p*-cresol, bromodimethylsulfonium bromide and tetrabutylammonium nitrite. The optimized stoichiometric molar ratios of *p*-cresol/BDMS/*n*-Bu₄NNO₂ were found to be 1/1.5/3 and the best results (1 h, 100% conversion) were obtained when the reaction was performed in CH₃CN at room temperature (Table, entry A).

Different kinds of 4-substituted phenols were also subjected to nitration in the presence of BDMS /*n*-Bu₄NNO₂ in acetonitrile (Scheme 1). The nitration reactions were performed under mild and non-acidic conditions at room temperature with excellent conversion and high isolated yields (Table). The present nitration reactions can be readily carried out by placing the nitrating agents, phenols, and the solvent in a reaction vessel and efficiently stirring the resultant mixture at room temperature. Highly pure mono nitrophenols can be obtained.

All the substrates, even those with electron-withdrawing substituents, exhibit high reactivity toward nitration and the corresponding mononitrated phenols were produced in good to excellent yields.

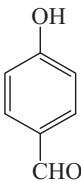
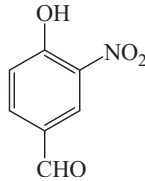
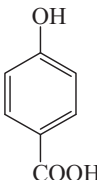
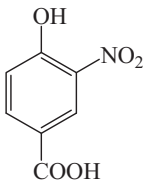
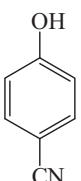
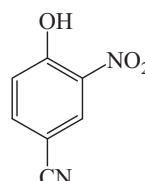
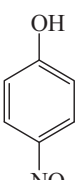
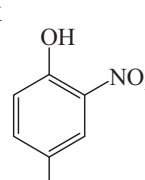
These results indicate that bromodimethylsulfonium bromide is a more superior reagent for electrophilic aromatic nitration than the previous reported methods. Its high reactivity makes it the reagent of choice for the nitration of a variety of arenes.

In fact, the mixture of bromodimethylsulfonium bromide and tetrabutylammonium nitrite could promote the electrophilic reaction via oxidation of nitrite ion (Scheme 2). The mechanism in Scheme 2 suggests that an initial interaction within bromodimethylsulfonium bromide and tetrabutylammonium nitrite causes the oxidation of nitrite ion, which generates **1**. Then, upon electrophilic attack of **3** as a source of NO₂⁺, nitrated phenols are produced followed by elimination of HBr molecule and (CH₃)₂S. Nevertheless, at this time there is no experimental evidence for this feature of **3**, and the actual role of this reagent should be further studied in detail.

Table. Nitration of substituted phenols using bromodimethylsulfonium bromide/*n*-Bu₄NNO₂ in CH₃CN at room temperature.

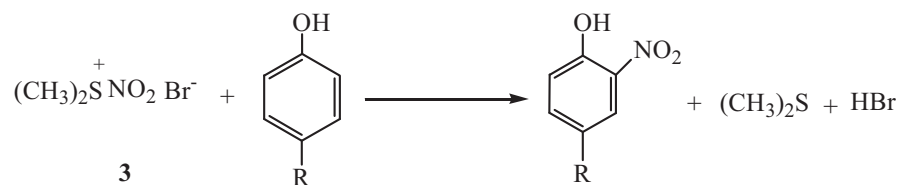
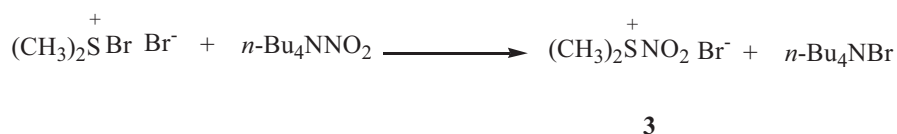
Entry	Substrate 1	Product ^a 2	Time(h)	Conversion % ^b (substrate consumption)	Isolated Yield %
A	1A 	2A 	1	100	96
B	1B 	2B 	70(min)	100	98
C	1C 	2C 	75(min)	100	95
D	1D 	2D 	1.5	100	96
E	1E 	2E 	75(min)	100	98
F	1F 	2F 	90(min)	100	88
G	1G 	2G 	1.5	100	90

Table. Continued.

Entry	Substrate 1	Product ^a 2	Time(h)	Conversion % ^b (substrate consumption)	Isolated Yield %
	1H	2H			
H			2	100	95
	1I	2I			
I			2	100	93
	1J	2J			
J			2.5	100	96
	1K	2K			
K			24	100	97

^a The products was identified by the comparison of its physical constants and IR and NMR spectral data with those of an authentic sample. **2A**: Mp 28-30 °C, Lit^{17,29}: 31 °C, **2B**: Mp 60-64 °C, Lit^{23d}: 61-66 °C, **2C**: Mp 53-55 °C, Lit^{23d}: 54-56 °C, **2D**: Mp 63-65 °C, Lit³⁰: 66 °C. **2E** Mp 81-83 °C, Lit^{17,29}: 84 °C, **2F**: ¹H-NMR (CDCl₃): δ 7.13 (d, 1 H, J= 9.27 Hz), 7.53 (dd, 1 H, J=9.1, 2.4 Hz) 8.09 (d, 1 H, J=2.4 Hz), 10.46 (1 H) Mp 88-90 °C, Lit^{17,29}: 91 °C, **2G**: Mp 71-74 °C, Lit^{15c}: 73-74 °C, **2H**: ¹H-NMR (CDCl₃): δ 7.29 (d, 1 H, J=9 Hz), 8.4 (dd, 1H, J= 8.58, 2.07 Hz), 8.62 (d, 1 H, J= 2 Hz), 9.92 (1H), 10.9 (1 H, CHO). Mp 138-142 °C, Lit^{15c}: 140-142 °C, **2I**: Mp 179-182 °C, Lit^{23d}: 180-184 °C, **2J**: Mp 141-143 °C, Lit^{15c,29}: 145 °C, **2K**: ¹H-NMR (CDCl₃): δ 7.32 (d, 1 H, J= 9.0 Hz), 8.44 (dd, 1H, J= 9.27, 2.76 Hz), 9.4 (d, 1 H, J=2.76 Hz), 10.99 (1 H). Elemental analysis data: C%: 38.49 (calc. 39.13), H%: 2.14 (calc.: 2.17), N%: 16.05 (calc.: 15.22).

^b GC yield using internal standard (Decalin).



Scheme 2

To conclude, in this research, we have developed a novel method for aromatic nitration of phenols using a combination of bromodimethylsulfonium bromide and tetrabutylammonium nitrite under aprotic conditions. The method is a regioselective, efficient, and mild mononitration of phenols with good to excellent yields and short reaction times.

Acknowledgements

We gratefully acknowledge the partial support of this study by Ferdowsi University of Mashhad Research Council (Grant no. P/27).

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