

Tribromoisocyanuric Acid/ NaNO_2 : a New Reagent for Mononitration of Phenols under Mild and Heterogeneous Conditions

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ABSTRACT

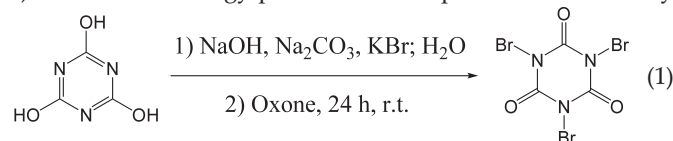
Nitrophenols can be obtained *via* direct nitration of phenols with tribromoisocyanuric acid, NaNO_2 and wet SiO_2 at room temperature in good to high yields.

KEYWORDS

Tribromoisocyanuric acid, nitrophenols, heterogeneous conditions, sodium nitrite, nitration of phenols.

1. Introduction

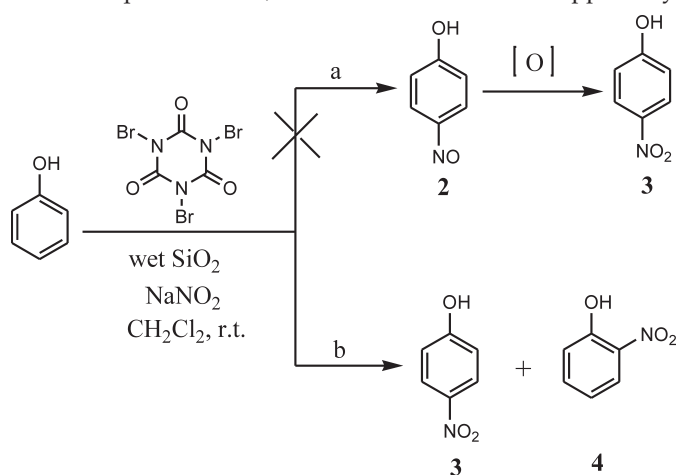
Nitration of aromatic compounds is an industrially prominent reaction,¹ as the nitrated products are important intermediates for fine chemicals and pharmaceuticals. Usually nitration reactions are not selective and are the cause of environmental concerns regarding the disposal of the large excess of mixed acids employed in these processes. Thus, implementation of these processes^{2,3} is generally rare. Besides mixed acids, several other nitrating agents, including concentrated nitric acid, acid anhydrides or triflates,⁴ peroxy nitrites,⁵ metal nitrates⁶ and nitrogen oxides⁷ have been utilized by many investigators. Catalytic nitration of aromatic hydrocarbons with concentrated nitric acid in the presence of solid acids⁸ and sodium nitrite with wet SiO_2 in the presence of solid acids⁹ has received attention with regard to regioselectivity. In some cases, the reaction has been performed in expensive media such as ionic liquids¹⁰ and microemulsions.¹¹ A sophisticated technique, microwave-assisted nitration of aromatic hydrocarbons with dilute nitric acid, has been also studied recently.¹² With regard 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%, making these existing processes uneconomical because of the above-mentioned side reactions in most of the cases.² Therefore, it is worthwhile to consider an alternative highly selective nitration process scheme by using a mild nitrating agent such as a combination of tribromoisocyanuric acid (TBCA) and sodium nitrite. Very recently, Mattos *et al.* have reported a new methodology for the preparation of TBCA by the reaction of an aqueous solution of oxone[®] with sodium cyanurate in the presence of KBr (Equation 1).¹³ This methodology proved to be simpler and considerably



less expensive than the preparation proposed by Gottardi *et al.*¹⁴

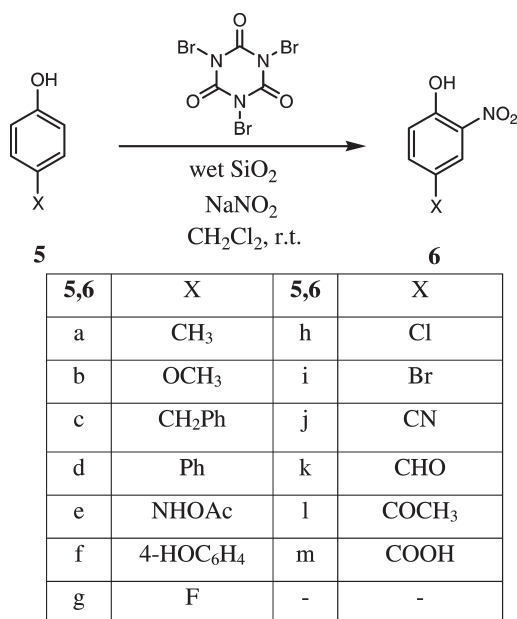
There are a few reports on the application of TBCA in organic transformations, and recently, Mattos and co-workers have reported the use of TBCA for the deprotection of silyl ethers,^{15a} and regioselective bromination of activated aromatic rings,^{15b} and bromination of alkenes.¹³ Here, we wish to report an alternative procedure for the selective nitration of phenols with TBCA/ NaNO_2 in the presence of wet SiO_2 (Schemes 1 and 2).

During the course of our studies on the utilization of NO^+ in functional transformations,¹⁶ we thought that phenol (**1**) could be selectively converted into the 4-nitroso derivative (**2**) by tribromoisocyanuric acid (**I**), NaNO_2 (**II**), and wet SiO_2 (50% m/m) in CH_2Cl_2 *via in situ* generation of HNO_2 . In addition, phenol nitrosation is rapid and yields almost entirely the *para* isomer, which can be readily converted to 4-nitrophenol (the desired product which is a precursor of acetaminophene) *via* a mild oxidation with HNO_3 ,¹⁷ $\text{H}_2\text{O}_2/\text{Na}_2\text{WO}_4$,¹⁸ etc. (Scheme 1, path a). Therefore, we decided to produce 4-nitrophenol *via* a nitrosation-oxidation strategy^{17,18} in a one-pot reaction under mild and heterogeneous conditions. We chose tribromoisocyanuric acid (**I**), NaNO_2 (**II**) and a wet SiO_2 system for the nitrosation of phenol (Scheme 1, path a). In contrast to the reported procedures in aqueous media,^{16–18} we have observed that apparently



Scheme 1

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Scheme 2

direct formation of 2-nitrophenol (4) and 4-nitrophenol (3) occurred (Scheme 1, path b, and Table 1).

Different kinds of 4-substituted phenols (5) were also subjected to nitration in the presence of tribromoisocyanuric acid (I), NaNO₂ (II), and wet SiO₂ (50% m/m) in CH₂Cl₂ (Scheme 2).

The nitration reactions were performed under mild and completely heterogeneous conditions at room temperature with moderate to good yields (Schemes 1 and 2, Table 1). The present nitration reactions can be readily carried out by placing the nitrating agents, phenols (1 or 5) and the solvent used in a reaction vessel and efficiently stirring the resultant heterogeneous mixture at room temperature. Highly pure mono-nitrophenols can be obtained by simple filtration and then evaporation of the

solvent. In fact, a combination of sodium nitrite and tribromoisocyanuric acid (I) can act as a solid nitrating agent which can be readily weighed, handled and used for different purposes in the presence of moist SiO₂.¹⁶

A competitive reaction was performed between phenol (1) and anisole. It was observed that exclusive phenol nitration proceeded, anisole remaining intact in the reaction mixture after 24 h. Selective mononitration of 4,4'-dihydroxydiphenyl (5f) was also achieved by controlling the stoichiometry of the reagents (Table 1, entry 7). Phenol nitration did not occur in the absence of TBCA (Table 1, entry 17). Also bromination and oxidation of phenols did not occur under the described reaction conditions, presumably due to *in situ* generation of HOBr and HNO₂ respectively (see Scheme 3). Meanwhile, the effects of substituents (HO-Ar-X) were negligible.

On the other hand, the water molecules of wet SiO₂ are necessary for the nitration of phenols (Table 1, entries 12 and 18). In order to further clarify the role of wet SiO₂, the nitration reaction was carried out in the presence of water in a two-phase system (CH₂Cl₂-H₂O). It led to similar yields but the process of separation is more tedious. Therefore, it appears that the presence of wet SiO₂ acts as a heterogeneous effective surface area for *in situ* generation of HNO₂, ensuring an easy work-up.

It appears that this new system generated HNO₂ and NO⁺ *in situ*. Therefore, the nitrous acid-catalysed mechanism may be proposed (Scheme 3).⁹

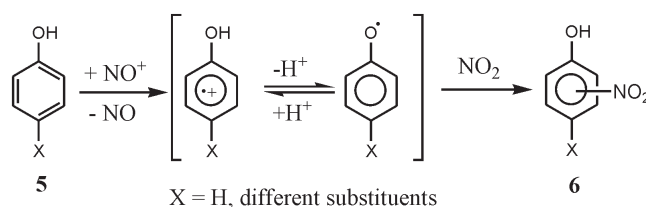
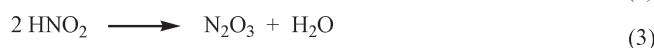
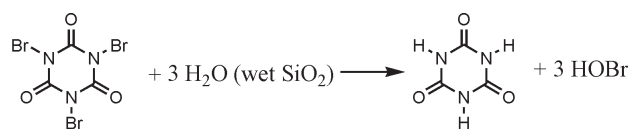
The results which were obtained by the described system compared well with our previous reports on nitration of phenols with sodium nitrite and wet SiO₂ in the presence of trichloroisocyanuric acid (TBCA), 1,3-dichloro-5,5-dimethylhydantoin, and 1,3-dibromo-5,5-dimethylhydantoin (Table 2). As shown in Table 2, the reaction times are slightly longer, but in most cases the yields are higher.

In conclusion, safe, eco-friendly, inexpensive and readily available reagents, easy and clean work-up and good yields make this method attractive for organic chemists.

Table 1 Mononitration of phenols to their corresponding nitro derivatives with a combination of tribromoisocyanuric acid (TBCA) (I), NaNO₂ (II) and wet SiO₂ (50% m/m) in dichloromethane at room temperature.

Entry	Substrate	Product	Amount/mmol ^a		Reaction time/min	Yield b/%	M.p./°C	
			Substrate I	Reagent II			Found	Reported
1	1	3 4	2	2	60	30 40	111–113 44–46	115 44
2	5a	6a	1	1	60	91	29–31	31
3	5b	6b	1	1	60	92	57–58	54–56
4	5c	6c	1	1	70	90	63–65	61–66
5	5d	6d	1	1	60	80	61–63	66
6	5e	6e	1	1	80	85	78–180	180
7	5f	6f	1	1	65	75	183–186	183–184
8	5g	6g	1	1	60	90	73	73–74
9	5h	6h	1	1	60	95	89	91
10	5i	6i	1	1	60	92	87	84
11	5i	6i	1	1	75	83 ^c	87	84
12	5i	6i	1	1	80	85 ^d	87	84
13	5j	6j	1	1	75	90	140–142	145
14	5k	6k	1	1	60	91	143–145	140–142
15	5l	6l	1	1	60	89	122–124	123
16	5m	6m	1	1	60	76	180–182	180–184
17	1	3,4	–	2	10 (h)	No reaction ^e		
18	1	3,4	2	2	10 (h)	No reaction ^f		

^a Wet SiO₂: substrate (1 and 5) (0.5 g, 1 mmol). ^b Isolated yield. ^c Reaction was performed in two-phase system (CH₂Cl₂-H₂O). ^d Reaction was performed by addition of two drops of water (instead of wet SiO₂) to the reaction mixture. ^e Reaction did not occur in the absence of tribromoisocyanuric acid (I). ^f Reaction did not occur in the absence of wet SiO₂.



Scheme 3

2. Experimental

2.1. General

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies, Tehran. The nitration products were characterized by comparison of their spectral (IR and $^1\text{H NMR}$), TLC and physical data with authentic samples.^{6–9,19}

2.2. Mononitration of Phenol (1) with Tribromoisoctanuric Acid (I), NaNO_2 (II) and Wet SiO_2 : a Typical Procedure.

A suspension of compound **1** (0.188 g, 2 mmol), **I** (1.464 g, 4 mmol), **II** (0.276 g, 4 mmol) and wet SiO_2 (50% m/m, 0.5 g) in CH_2Cl_2 (10 mL) was stirred at room temperature. The reaction was complete after 1 h and the mixture filtered and the residue washed with CH_2Cl_2 (2×10 mL). Anhydrous Na_2SO_4 (3 g) was added to the filtrate. After 15 min the resulting mixture was also filtered. Dichloromethane was distilled off using a water bath (35–40 °C).²⁰ The residue was a mixture of 2- and 4-nitrophenol. 4-Nitrophenol (**3**) is insoluble in *n*-pentane, 0.08 g, 30%, m.p.

110–113 °C [Lit.¹⁹ m.p. 114 °C]. The *n*-pentane fraction was evaporated on a water bath (35–40 °C),²⁰ to give 2-nitrophenol (**4**), 0.115 g, 40%, m.p. 44–45 °C [Lit.¹⁹ m.p. 44 °C]. The ratio of *o/p* is about 1.32:1.0 (Table 1, Scheme 1).

2.3. Mononitration of 4-Chlorophenol (5h) with Tribromoisoctanuric Acid (I), NaNO_2 (II) and Wet SiO_2 : a Typical Procedure

A suspension of compound **5h** (0.257 g, 2 mmol), **I** (0.732 g, 2 mmol), **II** (0.138 g, 2 mmol) and wet SiO_2 (50% m/m, 0.5 g) in CH_2Cl_2 (10 mL) was stirred at room temperature. The reaction was complete after 1 h and the mixture filtered and the residue washed with CH_2Cl_2 (2×10 mL). Anhydrous Na_2SO_4 (3 g) was added to the filtrate. After 15 min the resulting mixture was also filtered. Dichloromethane was distilled off on a water bath (35–40 °C). The yield was 0.296 g (92%) of crystalline pale yellow solid (**6h**), m.p. 88–90 °C [Lit.^{19c} m.p. 91 °C]. $^1\text{H NMR}$ (FT-90 MHz, CDCl_3 , TMS): δ 7.12 (dd, 1 H), 7.42 (dd, 1 H), 8.02 (s, 1 H), 10.31 (b, 1 H) ppm. The $^1\text{H NMR}$ spectrum was identical with the reference one.^{19c}

Table 2 Comparison of tribromoisoctanuric acid (TBCA) (**A**), trichloroisoctanuric acid (TCCA) (**B**),^{9d} 1,3-dibromo-5,5-dimethylhydantoin (**C**)^{9a} and 1,3-dichloro-5,5-dimethylhydantoin (**D**)^{9a} in the nitration reaction of phenols with NaNO_2 (**II**) and wet SiO_2 (50% m/m) in dichloromethane at room temperature.

Entry	Substrate	Product	Amount/mmol		Reaction time/min				Yield %/°			
			Substrate	Reagent	A	B	C	D	A	B	C	D
1	5a	6a	1	1	60	30	45	45	91	74	89	60
2	5b	6b	1	1	60	15	45	45	92	80	85	75
3	5d	6d	1	1	60	20	45	45	80	74	88	60
4	5e	6e	1	1	80	30	60	60	85	70	– ^b	– ^b
5	5h	6h	1	1	60	15	30	45	95	99	90	75
6	5i	6i	1	1	80	30	45	45	85	91	91	75

^a Isolated yield. ^b No reaction.

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- 20 Dichloromethane is the best solvent for the nitration of phenols due to its low boiling point. We know that 4-nitrophenols are very volatile and should be distilled with high boiling point solvents otherwise the yield of reaction will be decreased (due to intramolecular hydrogen bonding).