

Use of Sodium Bromate for Aromatic Bromination: Research and Development

Amiram Groweiss

TAMI (IMI) Institute for Research and Development, P.O.Box 10140, Haifa-Bay 26111, Israel

Abstract:

Sodium bromate is a powerful brominating agent for aromatic compounds that contain deactivating substituents. A bromination process, in which sodium bromate was utilized, was optimized on laboratory scale. Addition of a strong acid into a stirred aqueous solution, or slurry, of the substrate and bromate salt at 40–100°C, leads to the decomposition of the bromate ions and production of the active brominating species. Substrates such as nitrobenzene, benzoic acid, and benzaldehyde were brominated in high yields (85–98%) and specificity. The reaction is especially useful for the bromination of disubstituted benzenes, such as 4-nitrofluorobenzene or 4-fluorobenzoic acid. Several substrates, such as dinitrobenzenes or nitrobenzoic acids, did not undergo bromination at all. The main parameters of the reaction and some of its synthetic potential are discussed.

The functionalization of aromatic compounds through brominated intermediates is a very useful synthetic method. Many reagents are used for the bromination step, including, besides Br₂ itself (with or without a catalyst), such compounds as NBS, 1,3-dibromodimethylhydantoin (DBDMH), benzyltrimethylammonium tribromide, etc. Most of these agents are used for the bromination of aromatic substrates that contain ring-activating groups, for example, toluene, aniline, and phenol. Very few reagents can be used to brominate compounds with strong electron-withdrawing groups, such as nitrobenzene, benzoic acid, or benzenesulfonic acid. The lack of an efficient and economical method for such bromination is probably one of the reasons meta-substituted compounds are less common in many applications than their ortho- or para-substituted isomers. This study deals with meta bromination and recommends the utilization of NaBrO₃ for the bromination of aromatic substrates that contain one or two such deactivating groups.

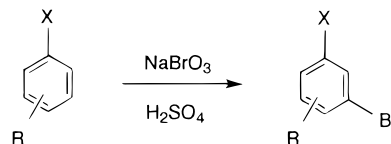
Severe regulations on the use of sodium and potassium bromate were imposed, in the past few years, by health and environmental protection authorities. Some of their regular uses (like KBrO₃ as a flour improver in baking processes) were banned.¹ In this atmosphere of diminishing markets and declining demands, other uses are being sought. One such potential utilization is in bromination and oxidation reactions. Price-wise, however, none of the brominating reagents, including bromates, can compete with Br₂, and usually the price of KBrO₃ is twice as much as that of bromine. Therefore, the use of bromate salts in processes may be economically justified only when they provide substantial advantages in the yield and reaction conditions over the use of Br₂. The best example is the bromination of nitrobenzene

(vide infra) where neither mild reagents (like DBDMH or NBS) nor Br₂ gives satisfactory results.

Initial work on bromination with KBrO₃ was carried out by Harrison and co-workers,² who prepared bromonitrobenzene and also bromobenzoic and phthalic acids. In another study Banerjee described the bromination of several other substrates by the same method.^{3–6} Thus far, the use of NaBrO₃ for such aromatic bromination has never been reported.⁷ Despite all of the similarities between the alkali metals, there are several differences in action between Na⁺ and K⁺ ions, and in many processes the use of the more delicate KOH and K₂CO₃ is preferred over the often sluggish NaOH and Na₂CO₃. In bromination, however, our study has proven that sodium and potassium bromate act very similarly, thus giving a commercial advantage to the less expensive sodium salt.

Results and Discussion

As shown in eq 1, sodium bromate was used to prepare



brominated aromatic substrates with one- and two-electron withdrawing groups (X = NO₂, COOH, COOMe, CHO, F, CF₃, etc.) (R = H, F, Cl, etc.) in the meta position, in high yields and good regioselectivities. The reactions were carried out by mixing the substrate, a mineral acid (usually concentrated H₂SO₄) and NaBrO₃. Since NaBrO₃ and H₂SO₄ are not compatible, the brominations were performed by gradually adding one of the two reagents into the reaction mixture (a semi-batch process). In this instance there were three possible modes of reaction:

- Addition of concentrated H₂SO₄ into a stirred slurry of substrate and bromate in water.
- Addition of solid NaBrO₃, in small portions, into a solution of the substrate in aqueous H₂SO₄.

- Harrison, J. J.; Pellegrini, J. P.; Selwitz, C. M. *J. Org. Chem.* **1981**, *46*, 2169–2171.
- Banerjee, A.; Banerjee, S.; Samaddar, H. *J. Ind. Chem. Soc.* **1979**, *56*, 985–987.
- Banerjee, A.; Banerjee, S.; Samaddar, H. *J. Ind. Chem. Soc.* **1979**, *56*, 988–990.
- Banerjee, A.; Banerjee, G. C.; Dutt, S.; Banerjee, S.; Samaddar, H. *J. Ind. Chem. Soc.* **1980**, *57*, 640–642.
- Banerjee, A.; Banerjee, G. C.; Adak, M. M.; Banerjee, S.; Samaddar, H. *J. Ind. Chem. Soc.* **1981**, *58*, 985–988.
- Two recent reports on bromination by NaBrO₃: (a) bromination of *N,N*-disubstituted benzamides: Dong, C.-H.; Julia, M.; Tang, J. *Eur. J. Org. Chem.* **1998**, 1689–1696. (b) Benzylic bromination of alkylbenzenes: Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6023–6026.

(1) *Chem. Ind. (London)* **1989**, 22, 734.

(c) As in method b, but the added reagent was in solution. The latter mode was less successful because the low solubility of NaBrO₃ in water (365 g/L at 20 °C) led to dilution of the acid and hence reduced the yield of the obtained brominated products.

To optimize the yields, the main parameters of the reaction have been studied and determined as herein discussed.

Bromate to Substrate Molar Ratio. For many substrates it was found that even when excess of NaBrO₃ was used, the conversion still did not reach 100%, and addition of more bromate resulted only in higher quantities of dibrominated derivatives. Therefore, in most cases an optimal ratio of 0.95–0.97 was taken. This yielded maximum conversion (usually >90%) and a limited amount (usually <4%) of dibromo compounds. Only for disubstituted substrates were there cases where an excess of bromate was essential (e.g., 4-fluoronitrobenzene).

Regioselectivity and Specificity. The regioselectivity is herein defined as the quantity of the desired product (a meta isomer) divided by the total amount of brominated products. Our observations have revealed that the selectivity for monobromination is between 85% and >99%, and is definitely comparable to the action of Br₂. Two extreme cases were nitrobenzene, with a selectivity of >96% and benzoic acid, which yielded more dibromo isomers, and the regioselectivity was only 80–85%, depending on the temperature employed. The latter molecule indeed gave inferior selectivity compared with the traditional bromination with Br₂ and a Lewis acid catalyst. In a few cases of 1,4-disubstituted substrates, where the combined orientation effect of both substituents point to the same carbon, for example, 4-fluoronitrobenzene, the specificity was literally 100%.

Temperature. As expected, the temperature played a major role in the reaction, affecting both the conversion and the selectivity. Benzoic acid, again, served as an indicative example: up to 50 °C, the conversions were very low but changed from 8% at 35 °C to ~96% at 90–100 °C.

The strongly exothermic reaction made it very difficult to control the temperature inside the reactor, which fluctuated when the reagents (either NaBrO₃ or H₂SO₄) were added. Therefore, in this investigation, three temperature ranges were defined: 40–50, 60–65, and 85–100 °C, and for each substrate, one of these ranges was selected. This approach was well-illustrated in the bromination of 4-fluoronitrobenzene when the product to starting material ratio was improved from 47:53 at 35 °C to 81:19 at 65 °C and remained almost the same (80:19) when the temperature was elevated to 85 °C. Not just the conversion, but also the regioselectivity was dependent on the temperature, as the amounts of the accompanying ortho and para isomers and especially dibrominated products increased at higher temperatures (above 80 °C).

Stirring. This reaction is a two-phase system, and efficient stirring (725 rpm or higher) was essential for mixing the hydrophobic aromatic compounds with the aqueous inorganic medium and for preventing local high concentrations of the active bromo species.

Table 1: Comparison of methods for the bromination of nitrobenzene

	sodium bromate	bromine
temperature	45 °C	140 °C
reaction time	2 h	8 h
catalyst	none	Fe (10% w/w)
“Br” amount	stoichiometric	60% excess
yield	85–88%	60–75%
regioselectivity	96–99%	94%

The Acid. A strong acid was needed to convert NaBrO₃ to the “bromonium” active species. The first choice is H₂SO₄ which is involved only in the desired reaction, while other strong acids (HCl, HBr, HNO₃) undergo oxidation–reduction reactions with bromate salts. H₃PO₄ was useful only in a very few cases (e.g., benzaldehyde). The preferred concentration of H₂SO₄ was 30–65% (w/w), depending on the substrate, and inter-related with the reaction temperature.

The advantages of NaBrO₃ over Br₂ in the bromination of nitrobenzene are shown in Table 1.⁸ The table clearly demonstrates that with NaBrO₃ milder conditions were required and a higher yield and improved regioselectivity were obtained. Even the price advantage of Br₂ over NaBrO₃ was diminished by the need for a large excess of bromine. Another advantage was the easy purification of the product by either extraction or crystallization from the aqueous medium.

It was pointed out² that a gas evolved in the bromination of nitrobenzene and contained not only O₂, but also some CO₂. Since the only source of carbon is the starting material, it was assumed that CO₂ was produced by the oxidation of a small amount of substrate. Our study has shown that this oxidation is not general and was detected in only a few substrates.

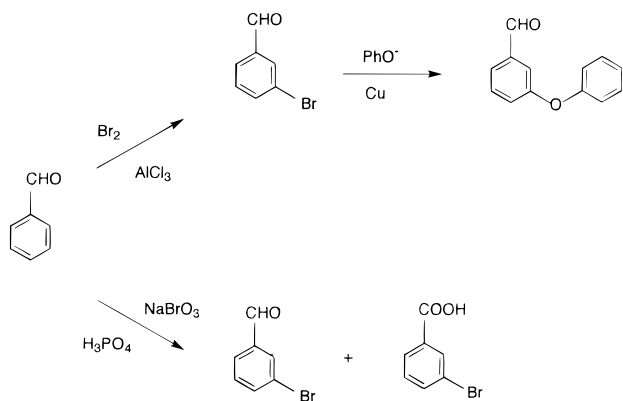
The reaction was also utilized for the preparation of 3-bromo-4-fluoronitrobenzene, a potential intermediate for ciprofloxacin (Cipro, Ciloxan) and other fluoroquinolone antibiotic drugs. The bromination step was carried out at 65 °C with 1.2 equiv of NaBrO₃. The yields varied between 85–98%, and the regioselectivity was 100%.

There were several nitro-containing substrates, such as 1,3-dinitrobenzene or *m*-nitrobenzoic acid, for which bromination did not occur. In these cases an excess of bromine was liberated, which could be observed visually and indicated that no reaction had taken place, even before it was proven by analysis.

The bromination of benzoic acid was performed at 85–100 °C with an H₂SO₄ concentration of 30–65% and afforded a yield of 92%, but with a regioselectivity of only 85%. A much higher selectivity was obtained when methylbenzoate was brominated. This reaction was carried out at 35–40 °C, and 99% conversion was reached after 4 h. The isolated yield was 91%, and two dibromo derivatives were also formed, comprising 5% of the product mixture. At 40

(8) The procedure for the latter reaction was taken from: Johnson, J. R.; Gauerke, C. G. *Organic Syntheses*, 2nd ed.; Wiley: New York, 1944; Collect. Vol. I, pp 123–124.

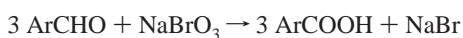
Scheme 1: Bromination of benzaldehyde



°C no hydrolysis of the ester was observed, despite the strongly acidic conditions. Only when the temperature was elevated to 60 °C was the rate of hydrolysis increased and the reaction mixture then contained brominated products of both methyl-benzoate and of benzoic acid.

The bromination of 4-fluorobenzoic acid was the first step used for the preparation of 3-phenoxy-4-fluorobenzoic acid, an intermediate for the synthesis of fluoro-pyrethroids. In this bromination, the combined orientation by both substituents toward C-3 results in a >97% regioselectivity. The effective temperature range is wide (50–80 °C), and the average yield, 90%. In contrast, bromination of other bifunctional carboxylic derivatives with stronger deactivating groups, for example, phthalic or 4-nitrobenzoic acid, was found to give low yields, usually between 5 and 40%.

The most surprising result in this study was obtained when the bromination of benzaldehyde was attempted. 3-Bromobenzaldehyde is an intermediate for the preparation of the synthetic pyrethroids, deltamethrin and cypermethrin, and converted to 3-phenoxy-benzaldehyde by the Ullmann reaction (Scheme 1). Usually 3-bromobenzaldehyde is prepared by bromination with Br₂ and a large excess of AlCl₃, and it was surprising that a reaction of an aldehyde with a strong oxidizing agent could lead to anything other than benzoic acid. Indeed, Banerjee showed that when benzaldehyde was reacted with KBrO₃ in H₂SO₄ (4 N), a mixture of benzoic and 3-bromobenzoic acids were obtained.⁴ We have found, however, that upon careful selection of the reaction conditions it was possible to prepare a mixture of 3-bromobenzaldehyde and 3-bromobenzoic acid in a ratio of 7:2. The bromination and oxidation are competitive; to increase the fraction that undergoes bromination one must work at 90–100 °C and in concentrated acid (90% H₃PO₄). Milder temperatures or more diluted acids led eventually to oxidation. The reason for the temperature differences is explained by the fact that while oxidation occurred at the whole range of temperatures, bromination took place only above 60–70 °C. Therefore attempts to “protect” the aldehyde by employment of a lower temperature resulted in the increased production of benzoic acid instead. Another disadvantage arises from the stoichiometry of the reaction; only 1/3 equiv of bromate is sufficient to oxidize all of the aldehyde:



The oxidation is visually observed by the liberation of bromine by the following reaction:



To improve the extent of bromination and minimize oxidation, the addition of solid bromate into the reactor was commenced only at 80 °C. Even then, before the first crystals of NaBrO₃ were added, there was already 5% of benzoic acid in the reaction mixture (probably due to air oxidation). When optimized, the benzaldehyde conversion was >95%, giving a mixture of 70:20 bromobenzaldehyde/bromobenzoic acid. The other reaction products were benzoic acid and two isomers of dibromobenzaldehyde.

Conclusions

The use of NaBrO₃ for bromination was investigated, and the following advantages over other methods were found:

- (1) Bromates are efficient brominating agents for aromatic substrates with one and two deactivating groups.
- (2) Unlike other efficient agents, for example, dibromoisocyanuric acid,⁹ this reagent is commercially available.
- (3) Unlike bromine, bromates are easy-to-handle solids.
- (4) There is no evolution of HBr in the reactions.
- (5) The reactions are performed in aqueous solution, without the use of expensive or hazardous solvents.
- (6) The reaction medium (excess of acid) is mostly recyclable in the process.

There are a few disadvantages that should be mentioned if large-scale implementation of the reaction is desired:

- (1) Sodium bromate is more expensive than bromine.
- (2) *Hazard*: bromates are strong oxidizing agents and oxygen is liberated during the reactions.
- (3) The effluents of the bromination are NaHSO₄ and the excess sulfuric acid, which need to be treated.

Experimental Section

General Procedures. The yields, conversions, and selectivities were determined by GC, HPLC, and NMR quantitative and qualitative methods, and the products were identified by comparison with authentic standards. GC were measured with HP-5890 equipped with HP-3992-A integrator, on capillary phenyl-silicone (5 or 12 m) columns. GC/MS were obtained with HP-5890 GC, equipped with HP-5970 mass selective detector, on a capillary column. HPLC were measured with a Varian model Vista 5500 liquid chromatograph on a fully end-capped Regis Val-U-Pak 25 cm × 4.6 μm ODS column with a UV detector operating at 230 nm. ¹H NMR spectra were taken on a Bruker WP-200-SY in CDCl₃ or *d*₆-DMSO solutions and TMS as internal standard for calibration. Amounts of inorganic bromides, acid concentration, water content and other wet analyses were determined in conventional titrimetric methods.

Bromination of Benzoic Acid by Addition of H₂SO₄ (Method a). A 1 L, four-necked flask, equipped with a mechanical stirrer, a reflux condenser, a digital thermometer, and a dropping funnel, was charged with 61.0 g of benzoic

(9) Gottardi, W. *Monatsh. Chem.* **1968**, *99*, 815–822.

acid (0.5 mol), 71.7 g of finely ground NaBrO_3 (0.475 mol), 300 mL of water, and 1 g of K_2SO_4 . The reactor was warmed to 85–90 °C, and then 122 mL of concentrated H_2SO_4 was added dropwise over 1 h. The stirring and temperature were maintained for another 30 min. The mixture was allowed to cool to room temperature, water was added, and the product was filtered under reduced pressure, washed with cold water, and dried in a vacuum oven at 60 °C; 92.3 g (yield = 93.7%) of a light-yellow material was obtained.

Bromination of Nitrobenzene by Addition of Solid NaBrO_3 (Method b). A 2 L four-necked flask, equipped with a mechanical stirrer, a reflux condenser, a digital thermometer, and a funnel, was charged with 123.1 g of nitrobenzene (1.0 mol), 500 mL of concentrated H_2SO_4 , 500 mL of water, and 1.5 g of K_2SO_4 . The reactor was warmed to 40–45 °C, and then 143.3 g of NaBrO_3 (0.95 mol) was added in portions of 4–5 g over 1 h. During the bromate addition, the

temperature was kept at 40–50 °C with an ice bath. When the addition was completed, stirring was maintained for another 1 h, the mixture was then cooled, and the crystalline product was filtered, washed with cold water, and dried in a vacuum oven at 55 °C; 186.2 g of a light yellow material was obtained, which still contained 9% humidity. The product (net weight: 169.4 g, yield = 85.6%) contained 96.1% 3-nitrobromobenzene.

Acknowledgment

The excellent technical assistance of Orly Cohen and Muhammad Jamal is gratefully acknowledged. The author expresses special thanks to Dr. A. Kampf (Bromine Compounds Ltd.) for a generous gift of sodium bromate.

Received for review April 30, 1999.

OP9901947