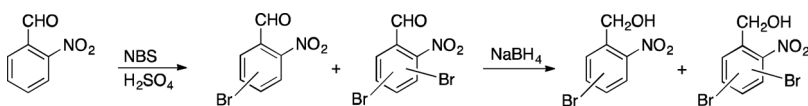


REEXAMINATION OF THE BROMINATION OF 2-NITROBENZALDEHYDE WITH NBS OR NaBr-NaIO₄ IN SULFURIC ACID

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GRAPHICAL ABSTRACT



Abstract Two literature procedures for selective bromination of 2-nitrobenzaldehyde using *N*-bromosuccinimide (NBS) or NaBr-NaIO₄ in sulfuric acid were examined. In contrast to the reports that 4-bromo-2-nitrobenzaldehyde is formed as a single product in good yield, reactions using NBS gave a number of isomeric mono- and dibrominated products identified by spectroscopical methods and by sodium borohydride reduction to the corresponding benzyl alcohol, and reactions using NaBr-NaIO₄ did not furnish any product.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications[®] for the following free supplemental resource(s): Full experimental and spectral details.]

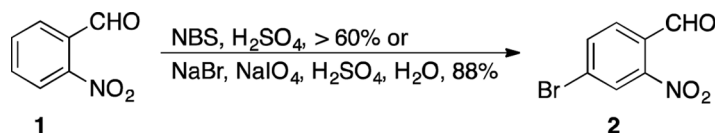
Keywords Bromination; *N*-bromosuccinimide; nitrobenzaldehyde

INTRODUCTION

A mild and attractive method for the bromination of deactivated aromatic compounds^[1] using *N*-bromosuccinimide (NBS) in sulfuric acid was reported by Rajesh et al. in 2007.^[2] Nine different substrates were examined and 60–92% yields of single products were reported. For eight of the starting materials, the directing effect of the functional groups present on the aromatic ring for aromatic electrophilic bromination coincided in the same position. Thus, the regioselectivity of the incoming electrophile was not an issue. The last substrate examined by the authors, 2-nitrobenzaldehyde (**1**), does not have this luxury, but nevertheless 4-bromo-2-nitrobenzaldehyde (**2**) was reported as the only product in more than 60% yield (Scheme 1). In addition to the reaction of **1** with NBS in sulfuric acid, a related regioselective bromination using sodium bromide–sodium periodate in sulfuric

Received June 5, 2013.

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Scheme 1. Previously reported brominations of 2-nitrobenzaldehyde.

acid–water to afford **2** in 88% isolated yield was reported by Kumar et al. in 2012 (Scheme 1).^[3] These two procedures were of interest to us because gram scale amounts of **2** were needed as a starting material for a total synthesis currently pursued in our laboratories.

The experimental procedures, as described in the literature, were repeated a number of times. However, in our hands, we were unable to duplicate the reported results in any of these experiments. Reaction with NBS gave a complex mixture of brominated products and attempted reaction using NaBr–NaIO₄ resulted only in quantitative recovery of starting material. Herein is reported the outcome of the experiments using NBS and a characterization of products from the complex reaction mixtures obtained. It should be noted that each of the products obtained are potentially useful building blocks in organic chemistry, although they are obtained in relatively poor yields.

RESULTS AND DISCUSSION

In an attempt to decipher the composition of the complex reaction mixtures obtained, 2-nitrobenzaldehyde (**1**) was reacted with NBS in sulfuric acid at the originally reported reaction temperature (25 °C) and at 60 °C. In addition, experiments employing different amounts of NBS were performed, and the results are summarized in Table 1. Complex mixtures containing the four possible monobrominated compounds (**2–5**) and three dibrominated products (**6–8**) were observed in the crude reaction mixtures of all reactions performed (Scheme 2).

Table 1. Molar ratios^a and isolated yields^b of brominated products

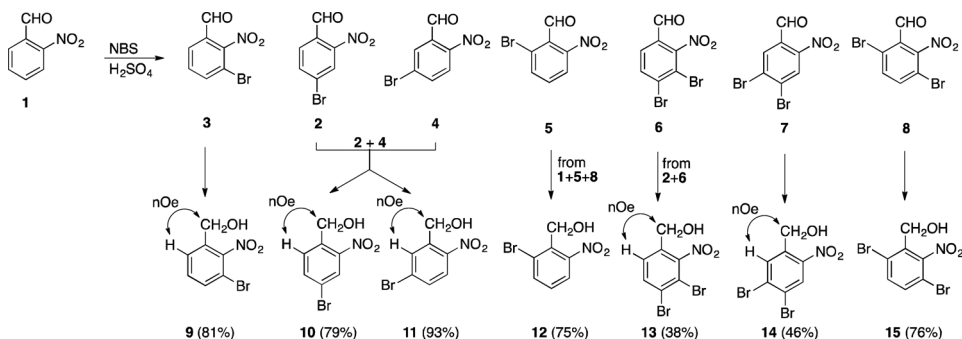
Equivalent(s) NBS ^c									Total isolated yield (%)
	1	2	3	4	5	6	7	8	
0.75	45.1 (<i>41</i>)	17.8 (<i>19</i>)	2.9 (<i>4</i>)	10.6 (<i>12</i>)	19.3 (<i>24</i>)	1.6	1.2 (<i>1</i>)	1.6 (<i>2</i>)	62
1.25	18.4 (<i>17</i>)	24.9 (<i>21</i>)	4.0 (<i>4</i>)	14.4 (<i>9</i>)	24.9 (<i>20</i>)	5.0 (<i>5</i>)	3.5 (<i>1</i>)	5.0 (<i>3</i>)	63
1.25 ^d	17.6 (<i>4</i>)	25.9 (<i>10</i>)	3.2 (<i>3</i>)	12.1 (<i>3</i>)	20.9 (<i>8</i>)	5.2 (<i>9</i>)	10.3 (<i>2</i>)	4.8 (<i>1</i>)	32
2.5	2.6 (<i>3</i>)	27.0 (<i>20</i>)	3.1 (<i>8</i>)	12.0 (<i>8</i>)	17.1 (<i>14</i>)	14.0 (<i>12</i>)	9.7 (<i>9</i>)	13.8 (<i>13</i>)	84
5.0	0	13.5 (<i>4</i>)	0.6	3.4	1.1	28.7 (<i>24</i>)	26.7 (<i>19</i>)	26.1 (<i>17</i>)	64

^aThe first number represents the molar ratios of products from ¹H NMR spectra of crude reaction mixtures.

^bThe number in parenthesis represents isolated yields of products after chromatography. Yields in parentheses and italics were calculated from ¹H NMR spectra of mixtures.

^cThe brominations were performed at ambient temperature.

^dBromination at 60 °C.



Scheme 2. NBS bromination followed by NaBH₄ reduction of 2-nitrobenzaldehyde.

Starting material (1) was detected in all reactions except for the reaction using 5 equivalents of NBS. Chromatographic purification on silica gel was only partially successful in separating the isomers. Pure 3 was isolated using <5 equivalents of NBS, pure 7 could be isolated at any NBS amount, and pure 6 and 8 were isolated at 5 equivalents of NBS. Compounds 2, 4, and 5 were always isolated as inseparable mixtures containing two or three components. The identities of compounds 2–5 and 8 were verified by comparison with literature NMR, infrared (IR), and melting-point data. Compound 6 has not been previously reported and for the dibrominated product 7, only a melting point was found in the literature. ¹H NMR, ¹³C NMR, and IR spectra and HRMS (for 6) were obtained, all in agreement with the structure of 6 and 7.

To further corroborate the identity of each isomeric compound, all pure compounds and some of the mixtures were reduced using sodium borohydride to give the corresponding benzylalcohols, and the results are summarized in Scheme 2. Reduction of 3 gave the known benzylalcohol 9 in 81% isolated yield. The aromatic ¹H NMR splitting pattern, consisting of two doublets and a triplet, and a nuclear Overhauser effect (nOe) between the methylene and one of the aromatic doublets confirmed the structure of 9 and thus of isomer 3. This transformation also verified the structure of 5, the other monobrominated product with the same aromatic doublet–doublet–triplet ¹H NMR splitting pattern. We were unable to separate 1, 5, and 8; however reducing the mixture with sodium borohydride gave pure 12, the reduction product of 5.

Compounds 2 and 4 could not be separated but upon treatment with sodium borohydride gave a separable mixture of the known benzyl alcohols 10 and 11. The benzyl alcohols also provided the opportunity to corroborate the structure of 2 and 4 by nOe experiments.

As expected, no nOe was observed between the methylene protons of 15 derived from 8 and either of the two aromatic protons. Compound 7 was the only isomer exhibiting two singlets in the ¹H NMR spectrum. Reductions to give 13 and 14 corroborated the structures of 6 and 7, because the expected nOes were observed between the benzylic CH₂ and one of the aromatic protons.

Monobrominated products dominated at lower amounts of NBS and, not surprisingly, dibrominated products were the major products using a large excess of

NBS. A much lower total yield of bromination products was obtained at 60 °C using 2.5 equivalents of NBS (compared to entries 2 and 3). Because only a small amount of dibrominated products were formed using 0.75 equivalents of NBS, the ratio of 2–4 is a rough measure of the reactivity of the different positions in 1 toward electrophilic aromatic bromination. The reactivity was normalized to compound 3, the minor monobrominated product, and was calculated to be 6.1:1:3.7:6.7 (in order of 2 to 5). This order of reactivity probably reflects the electron-withdrawing ability of the nitro group, compared to the aldehyde, wherein the former more effectively deactivates the 3 and 5 positions that would lead to formation of 3 and 4. The data for the reactions using 0.75 and 5.0 equivalents of NBS also suggest that compounds 3, 4, and 5 were brominated a second time at a much faster rate compared to 2, because a significant amount of the latter remains even at 5.0 equivalents of NBS. A rough order of reactivity for the second bromination can be calculated by comparing the ratios of monobrominated products at 0.75 and 5.0 equivalents of NBS. The reactivity order was 5 > 3 > 4 > 2.

In summary, we were unable to duplicate the reported selective bromination of 2-nitrobenzaldehyde (1) using NBS in sulfuric acid to give 4-bromo-2-nitrobenzaldehyde (2). Four monobrominated and three dibrominated products were isolated and identified and reduced to the corresponding benzyl alcohol. It should be noted that the methodology works very well for deactivated aromatic substrates wherein the directing effects of substituents do not conflict. Bromination of 2-nitrobenzaldehyde (1) using NaBr-NaIO₄ in sulfuric acid resulted only in the recovery of starting material.

EXPERIMENTAL

All NMR spectra were recorded in CDCl₃ at 600 MHz (¹H NMR) and 150 MHz (¹³C NMR). The chemical shifts are expressed in δ values relative to Me₄Si (0.0 ppm, ¹H and ¹³C) or CDCl₃ (77.0 ppm, ¹³C) internal standards. The yields and weights of compounds in the mixtures were calculated from ¹H NMR spectra.

N-Bromosuccinimide was recrystallized from water. All other reagents and solvents were obtained from commercial sources and used as received. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure.

Bromination of 1 Using 1.25 Equivalents of NBS

N-Bromosuccinimide (NBS) (1.48 g, 8.32 mmol) was added to a solution of 1 (1.01 g, 6.71 mmol) in H₂SO₄ (concentrated 5.0 mL). The resulting mixture was stirred at ambient temperature (3 h). The reaction was quenched with ice and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with saturated NaCl (aqueous, 30 mL), dried (MgSO₄), and filtered through a silica gel plug, and the solvents were evaporated under reduced pressure. The resulting brown oil was purified by column chromatography (hexanes/EtOAc, 8:2) to afford the following fractions in order of elution: (I) 7 (28 mg, 0.09 mmol, 1%) as an off-white solid; (II) 2 (328 mg, 21%), 4 (140 mg, 9%), and 3,4-dibromo-2-nitrobenzaldehyde

(6) (94 mg, 5%); (III) **5** (310 mg, 20%), **8** (65 mg, 3%), **1** (168 mg, 17%); (IV) **3** (54 mg, 0.23 mmol, 4%).

Data for **7**: mp = 105–106 °C (lit. mp = 105–107 °C^[4]); ¹H NMR δ 10.39 (s, 1H), 8.39 (s, 1H), 8.19 (s, 1H); ¹³C NMR δ 185.9, 147.7, 134.3, 132.5, 130.8, 130.4, 129.6; IR (ATR) 3088, 2890, 1687, 1525, 1338, 1178 cm⁻¹.

3-Bromo-2-nitrobenzylalcohol (**9**)^[5]

Sodium borohydride (37 mg, 0.98 mmol) was added to a solution of **3** (105 mg, 0.46 mmol) in THF (3 mL) and H₂O (1 mL). The resulting solution was stirred at ambient temperature (20 min), water was added (20 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (MgSO₄) and filtered, and the solvents were removed under reduced pressure to give **9** (87 mg, 0.37 mmol, 81%) as a pale yellow oil. No further purification was required. Spectral data were in accordance with literature data.

FUNDING

The C. Eugene Bennett Department of Chemistry at West Virginia University is gratefully acknowledged for financial support for this research project.

SUPPORTING INFORMATION

Full experimental details and ¹H and ¹³C NMR spectra for new compounds can be found via the “Supplementary Content” section of this article’s Web page.

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