# Regioselective Synthesis of para-Bromo Aromatic Compounds

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Reaction of substituted benzene rings with N-bromophthalimide, under neutral conditions, gave the corresponding bromo derivatives with a preference for the formation of the para bromo isomer over the ortho isomer. The simple work-up procedure minimizes loss of product and the yields are good.

**Keywords:** Aromatic compounds; Electrophilic bromination; Regioselective; Steric effect.

## INTRODUCTION

In recent years we have been actively searching for new and more powerful methods of aromatic bromination. Bromination of organic substrates, particularly aromatics, has garnered a significant amount of attention in recent years[1-8,14-17] owing to the considerable commercial importance of such compounds as potent antitumor, antibacterial, antifungal, antineoplastic, antiviral, and antioxidizing agents[9] and also as industrial intermediates for the manufacture of speciality chemicals, pharmaceuticals, and agrochemicals. Unfortunately, the hazards associated with traditional bromination are not trivial and cannot be ignored.[7] Environmental problems caused by the use of detrimental chemicals and solvents[10-11] in classical bromination and the anticipated legislations against their use are some of the major concerns. Consequently, what is needed is a methodology that would be environmentally friendly and clean and yet efficient, site-selective, operationally simple, and cost-effective. Selective bromination of aromatics, which is of great commercial importance, has also been a case in point. So, we have now developed a new and simple method for the selective bromination of activated aromatic rings using N-bromophthalimide (**1**), that involves all of the advantages indicated above. Simple reaction of activated aromatic compounds with N-bromophthalimide in diethyl ether at room temperature, gave para bromo isomer in good yields (Scheme I).

## RESULTS AND DISCUSSION

Table 1 shows the results of reactions of N-bromophthalimide with different aromatic compounds.

The results showed that N-bromophthalimide is an effective brominating agent. When an ortho-para directing group is on a ring, it is usually difficult to predict how much of the product will be the ortho isomer and how much the para isomer. Indeed, these proportions may depend greatly on the reaction conditions,[12] but as indicated in Table 1, by this method, only para bromo isomer was produced (entries 1, 2, 4, 5, 6, 8, and 10). The proposed mechanism is shown in Scheme II.

One of the main factors of this reagent is releasing $Br^+$ easily. The reason is the resonance effect of anion with the

**Scheme I**

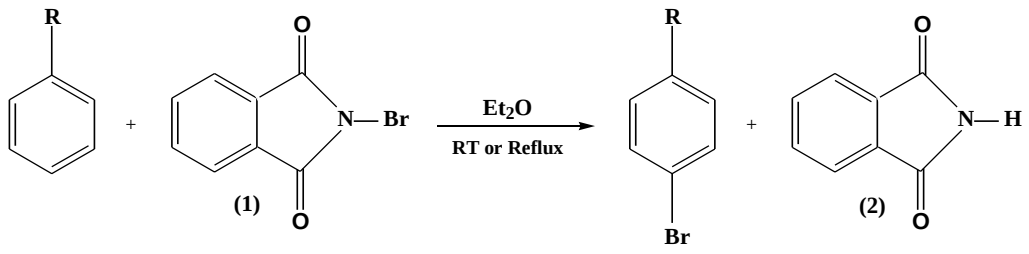


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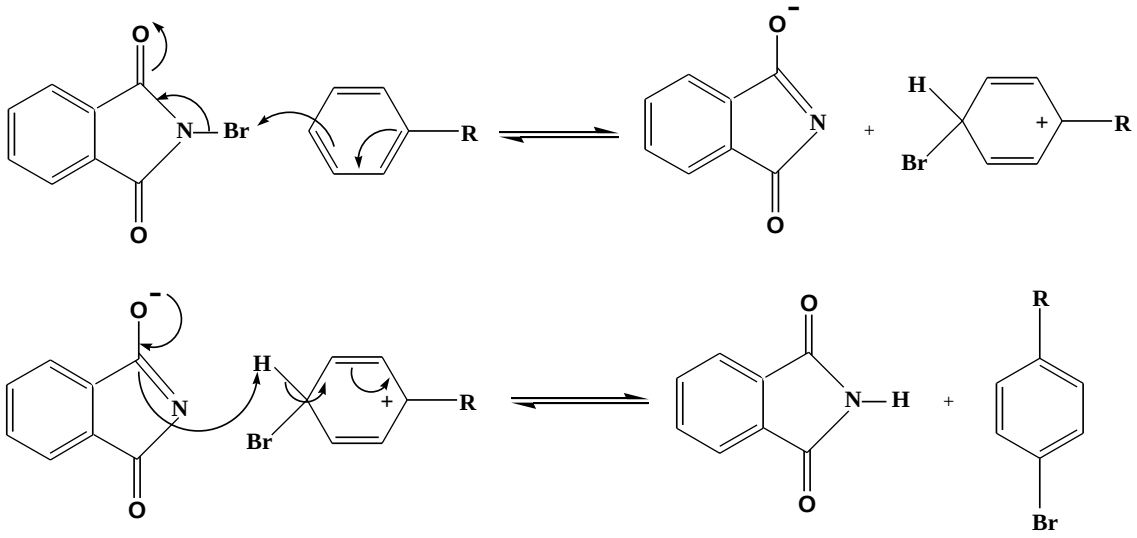
Table 1. Bromination of aromatic compounds with NBPI

| No. | Substrates | Products | Total Yield (%)[a] | Time/Min | Temperature (°C) |
|---|---|---|---|---|---|
| 1 | Anisole | p-Bromo Anisole | 82 | 45 | 25 |
| 2 | Acetanilide | p-Bromo Acetanilide | 80[b] | 60 | 62 |
| 3 | Orthoanisaldehyde | 5-Bromo orthoanisaldehyde | 72 | 60 | 25 |
| 4 | N,N-Dimethyl Aniline | p-Bromo-N,N-dimethyl Aniline | 90 | 10 | 25 |
| 5 | N,N-Diethyl Aniline | p-Bromo N,N-diethyl Aniline | 85 | 10 | 25 |
| 6 | Phenol | p-Bromo Phenol | 80[b] | 15 | 62 |
| 7 | Para-N,N-Dimethyl-Amino benzaldehyde | 3-Bromo Para-N,N-Dimethyl-Amino benzaldehyde | 78 | 30 | 25 |
| 8 | Benzamide | p-Bromo Benzamide | 70 | 150 | 25 |
| 9 | Naphthalene | 1-Bromo Naphthalene | 75 | 45 | 25 |
| 10 | 1-Naphthylamine | 4-Bromo-1-Naphthylamine | 90 | 10 | 25 |
| 11 | Anthracene | 9-Bromo Anthracene | 80 | 30 | 25 |

[a] Isolated yields.
[b] Chloroform as the reaction solvent and under reflux conditions.

**Scheme II**




C=O groups, which makes them very stable. One of the advantages of this method is that, (according to Scheme I), after the reaction was completed, N-bromophthalimide (**1**), converted to the phthalimide (**2**), which can be isolated, brominated and reused as a new brominating agent.

## CONCLUSIONS

The advantages of this method of the bromination are as follows:

1) The brominating reagent is solid and the reaction's procedure is very simple (does not need special safety).

2) The reagent is acting selectively.

3) Reaction time is very short.

4) Work-up procedure is very simple.

5) The yields are good.

6) If other functional groups are present in the aromatic ring of the substrates, they do not react with this reagent (entries 3, 7 in Table 1), eg. aldehyde groups attached to the sub-

strate ring do not oxidize with this reagent, whereas a $Br_2$ molecule can oxidize this group.

7) Aromatic rings containing the $–NH_2$, -NHR, or $-NR_2$ group do not undergo classical bromination, partly because the strongly basic nitrogen ties up the Lewis acid needed for ionization of the bromine molecule, whereas by our method, these types of compounds are brominated selectively.

8) The starting material is recovered easily and can be reused many times without reducing the yield.

## EXPERIMENTAL SECTION

IR and $^1$H-NMR spectra were recorded using a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and a 90 MHz Jeol FT-NMR spectrometer, respectively. $^1$H-NMR chemical shifts were measured relative to TMS (int; 1H).

### Regioselective Synthesis of para Bromo-N,N-dimethyl-aniline; Typical Procedure

In a 250 mL round-bottomed flask, 6.55 g (29 mmol) of N-bromophthalimide and 30 mL of $Et_2O$ were placed. The flask was cooled in ice-water and added, with stirring, 3.68 mL (29 mmol) of N,N-dimethylaniline dropwise. The mixture was stirred for 10 minutes at room temperature. Then the flask was cooled; by this time all of the solid should have risen to the surface of the liquid. The phthalimide was filtered under suction. The solvent was removed on a water bath, and the para bromo-N,N-dimethylaniline was collected as a single product. The yield of product, m.p. 53-54 °C, was 5.22 g (90%).

All of the bromo products were characterized by their physical constants, comparison with authentic samples, and by their IR and NMR spectra.[13]

## DATA OF THE PRODUCTS

1: **p-Bromo Anisole**, b.p. 217 °C, IR (neat): 3107, 1713, 1591, 1490, 1356, 1218, 1092, 1013, 968, 908, 832 cm$^{-1,}$ $^1$H-NMR (acetone-$d_6$ / TMS): δ 3.64 (s, 3H), 6.74- 7.26 (dd, 4H).

2: **p-Bromo Acetanilide**, m.p. 173 °C, IR (paraffin): 3304, 3192, 2855, 1670, 1603, 1536, 1465, 1372, 1313, 1259, 1041, 966, 825 cm$^{-1}$, $^1$H-NMR (acetone-$d_6$ / TMS): δ 2.08 (s, 3H), 7.47 (q, 4H), 9.31 (br, 1H).

3: **5-Bromo orthoanisaldehyde**, m.p. 120 °C, IR (paraffin): 3076, 2843, 1732, 1599, 1483, 1393, 1287, 1246, 1162, 1022, 903, 834 cm$^{-1}$, $^1$H-NMR (acetone-$d_6$ / TMS): δ 3.90 (s, 3H), 7.07 (d, 1H), 7.78 (t, 2H), 10.38 (s, 1H).

4: **p-Bromo-N,N-dimethyl Aniline**, m.p. 52 °C, IR (paraffin): 2926, 2853, 1864, 1716, 1597, 1501, 1457, 1353, 1311, 1226, 1190, 1165, 1125, 1063, 947, 816 cm$^{-1}$, $^1$H-NMR (acetone-$d_6$ / TMS): δ 2.78 (s, 6H), 6.67-7.19 (dd, 4H).

5: **p-Bromo-N,N-diethyl Aniline**, b.p. 215 °C, IR (neat): 2971, 2892, 1718, 1591, 1499, 1396, 1355, 1266, 1194, 1156, 1078, 1011, 920, 804 cm$^{-1,}$ $^1$H-NMR (acetone-$d_6$ / TMS): δ 1.07 (t, 6H), 3.27 (q, 4H), 6.63-7.16 (dd, 4H).

6: **p-Bromo Phenol**, m.p. 70 °C, IR (paraffin): 3454, 3207, 2888, 1770, 1728, 1606, 1434, 1372, 1306, 1231, 1174, 1139, 1089, 1059, 968, 860, 817 cm$^{-1}$, $^1$H-NMR (acetone-$d_6$ / TMS): δ 6.86-7.22 (dd, 4H), 8.40 (br, 1H).

7: **3-Bromo Para-N,N-Dimethyl-Amino benzaldehyde**, m.p. 70 °C, IR (paraffin): 2923, 2853, 1749, 1661, 1601, 1530, 1457, 1375, 1231, 1164, 1065, 937, 812 cm$^{-1}$, $^1$H-NMR (acetone-$d_6$ / TMS): δ 3.05 (s, 6H), 6.70- 6.80 (d, 1H), 7.61-7.80 (t, 2H), 9.68 (s, 1H).

8: **p-Bromo Benzamide**, m.p. 191 °C, IR (NUJOL MULL): 3480, 3000, 1690, 1400, 1200, 1100, 1050, 840 cm$^{-1}$, $^1$H-NMR (DMSO-$d_6$ / $D_2O$): δ 7.51-7.94 (q, 4H).

9: **1-Bromo Naphthalene**, m.p. 50 °C, IR (paraffin): 3190, 2925, 2855, 1774, 1728, 1604, 1463, 1377, 1307, 1289, 1141, 1093, 1052, 903, 863 cm$^{-1}$, $^1$H-NMR (acetone-$d_6$ / TMS): δ 7.18-7.71 (m, 6H).

10: **4-Bromo-1-Naphthylamine**, m.p. 101 °C, IR (NUJOL MULL): 3300, 1720, 1530, 1480, 1330, 1050, 920, 810 cm$^{-1}$, $^1$H-NMR (acetone-$d_6$ / TMS): δ 3.90 (br, 2H), 6.43-8.35 (m, 6H).

11: **9-Bromo Anthracene**, m.p. 97 °C, IR (paraffin): 3049, 2964, 2861, 1678, 1623, 1525, 1454, 1378, 1310, 1260, 1151, 1012, 952, 920, 884, 838, 808 cm$^{-1}$, $^1$H-NMR (acetone-$d_6$ / TMS): δ 7.59-8.49 (m, 9H).

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