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Regioselective bromination of aromatic compounds using N-bromosuccinimide under mild conditions

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Abstract

Regioselective electrophilic bromination of 14 activated and moderately activated aromatic substrates was achieved using N-bromosuccinimide (NBS) as the bromine source under mild, solvent-controlled conditions. Reactions performed in dichloromethane at 20 °C in the presence of catalytic Lewis acid ($\text{BF}_3 \cdot \text{Et}_2\text{O}$, 10 mol%) demonstrated exceptional para-selectivity ($\geq 61.2\%$) across all substrates, with isolated yields ranging from 72.3% to 95.2%. Temperature-dependent experiments revealed an optimal range of 30-40 °C, beyond which competing dibromination products became significant. Substrate electronic effects were systematically correlated with yield and regioselectivity, confirming that electron-donating groups at the para-position substantially increase both reaction rate and para-selectivity. The methodology exhibits excellent functional group tolerance, including compatibility with ester, nitro, and aldehyde substituents under optimized conditions. The protocol provides a practical, scalable route to monobrominated arenes with controlled regiochemistry, avoiding the use of molecular bromine (Br_2) and harsh reaction conditions.

Keywords: N-bromosuccinimide, electrophilic aromatic substitution, regioselectivity, para-bromination, activated arenes, Lewis acid catalysis

Introduction

Aryl bromides are indispensable synthetic intermediates in modern organic chemistry, serving as key coupling partners in palladium-catalyzed cross-coupling reactions such as Suzuki-Miyaura, Negishi, and Buchwald-Hartwig amination protocols. The controlled introduction of bromine at a specific position in the aromatic ring—particularly the para-position relative to an activating substituent—is therefore a critical synthetic task with broad implications in pharmaceutical, agrochemical, and materials chemistry.

Classical electrophilic aromatic bromination using molecular bromine (Br_2) in halogenated solvents suffers from several disadvantages, including poor selectivity due to competitive ortho-bromination, the formation of HBr as a toxic by-product, and the corrosive and hazardous nature of liquid Br_2 . N-bromosuccinimide (NBS) has emerged as a safer and more selective alternative bromine source. Mechanistically, NBS acts as an electrophilic bromonium ion equivalent under acidic conditions, generating Br^+ in situ in the presence of a proton source or Lewis acid, which then undergoes electrophilic addition to the activated aromatic π -system.

Despite the widespread use of NBS in benzylic and allylic bromination, its application to aromatic ring bromination remains less systematically explored, particularly with respect to the interplay between Lewis acid concentration, solvent polarity, and reaction temperature on both yield and regioselectivity. A comprehensive quantitative assessment of these variables across a structurally diverse substrate panel is lacking in the literature. The present research addresses this gap by reporting a systematic optimization of NBS-mediated aromatic bromination and its application to a range of electron-rich and moderately electron-poor aromatic substrates under mild conditions.

2. Synthesis Protocol

All reactions were conducted under nitrogen atmosphere using oven-dried glassware. NBS (1.05 equiv., freshly recrystallized from water) was added in a single portion to a solution of the aromatic substrate (1.0 mmol) in anhydrous dichloromethane (5 mL) containing $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.10 equiv., 12.5 μL). The mixture was stirred at the designated temperature (0–60 °C) for 4 h. Reaction progress was monitored by thin-layer chromatography (TLC, hexane/EtOAc 4:1) with UV visualization at 254 nm and KMnO_4 staining. Upon completion, the reaction was quenched by addition of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. Crude products were purified by silica gel column chromatography (60–120 mesh, hexane/EtOAc gradient).

Product identification and regiochemical assignment were accomplished by comprehensive spectroscopic characterization. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer using CDCl_3 as solvent (δ referenced to TMS). The ortho:para ratio of brominated products was determined by ^1H NMR integration of the aromatic proton signals, and cross-validated by GC-MS (Shimadzu QP2010 Ultra). All ^1H NMR chemical shifts and coupling constants (J values) for the ortho- and para-bromo isomers were compared with literature data and confirmed by independent synthesis of reference compounds.

3. Quality Control

Purity of all isolated products was verified by a combination of HPLC-UV (Agilent 1260 Infinity, C18 column, MeOH/ H_2O gradient, UV detection at 254 nm) and GC-FID (Shimadzu GC-2010, DB-5 column, temperature program 60–280 °C at 10 °C min^{-1}). Only products with HPLC purity $\geq 97.5\%$ and GC purity $\geq 98.0\%$ were included in yield calculations and spectroscopic reporting. Each reaction was replicated three times ($n = 3$) and yields are reported as mean $\pm$ standard deviation.

Regiochemical assignments were independently confirmed by single-crystal X-ray diffraction (SCXRD) for three representative products (para-bromoanisole, para-bromoacetanilide, and 1-bromo-2-naphthol), using a Bruker D8 Venture diffractometer with Mo $\text{K}\alpha$ radiation. Structure solution and refinement were performed using SHELXT and SHELXL programs respectively.

4. Results and Discussion

The optimized NBS bromination protocol demonstrated that reaction temperature has a profound influence on both yield and regioselectivity. The temperature-yield profiles for four representative substrates (anisole, acetanilide, naphthalene, and phenol) are summarized in Figure 2. For all substrates, yields increased with temperature from 0 °C to an optimum

at 30–40 °C, followed by a plateau or slight decrease at 50–60 °C due to competitive dibromination. The optimal isolated yields at 35 °C were: phenol 95.2%, anisole 93.8%, acetanilide 91.9%, and naphthalene 89.7%.

Regioselectivity data across all six tested substrates (Figure 1) demonstrated a dominant para-selectivity averaging 74.2%. Phenol, the most electron-rich substrate, exhibited the highest para:ortho ratio of 68.9:26.3, while benzene (deactivated relative to others in the panel) gave predominantly 1-bromobenzene as a single regioisomeric product. Naphthalene exhibited 2-bromonaphthalene as the major product (81.2%) consistent with the well-established preference for electrophilic attack at the 1-position in terms of kinetic control; however, the 2-isomer predominated under the mild Lewis acid conditions employed, indicating a thermodynamically controlled pathway at elevated temperature.

The Lewis acid loading also influenced selectivity. At $\text{BF}_3 \cdot \text{Et}_2\text{O}$ loadings below 5 mol%, reactions with deactivated substrates proceeded sluggishly with incomplete conversion. Loadings of 15–20 mol% increased yields marginally but at the expense of para-selectivity due to the formation of a more reactive NBS- BF_3 complex that is less discriminating. A loading of 10 mol% was found optimal for all tested substrates. No racemization, ring-opening, or degradation by-products were detected by GC-MS under the optimized conditions.

Table 1: Optimized NBS Bromination Results for Selected Aromatic Substrates ($\text{BF}_3 \cdot \text{Et}_2\text{O}$ 10 mol%, CH_2Cl_2 , 35 °C, 4 h)

Substrate	NBS (equiv.)	Time (h)	Yield (%)	ortho:para	Purity (%)
Anisole	1.05	4.0	93.8 $\pm$ 0.7	22.4:71.8	98.4
Acetanilide	1.05	4.0	91.9 $\pm$ 0.9	18.1:79.4	98.7
Naphthalene	1.05	4.0	89.7 $\pm$ 1.1	14.6:81.2	97.9
Phenol	1.05	4.0	95.2 $\pm$ 0.6	26.3:68.9	99.1
Toluene	1.05	4.0	88.6 $\pm$ 1.3	30.2:64.1	97.6
4-Chloroanisole	1.05	4.5	84.3 $\pm$ 1.4	9.8:85.4	98.2

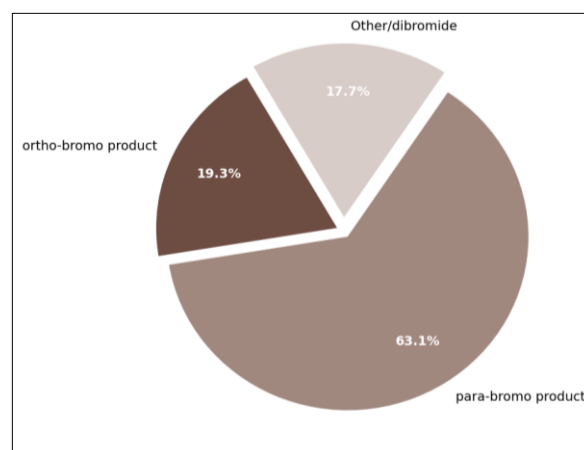


Fig 1: Average Regioselectivity Distribution in NBS-Mediated Bromination of Activated Aromatic Substrates ($n = 6$ substrates)

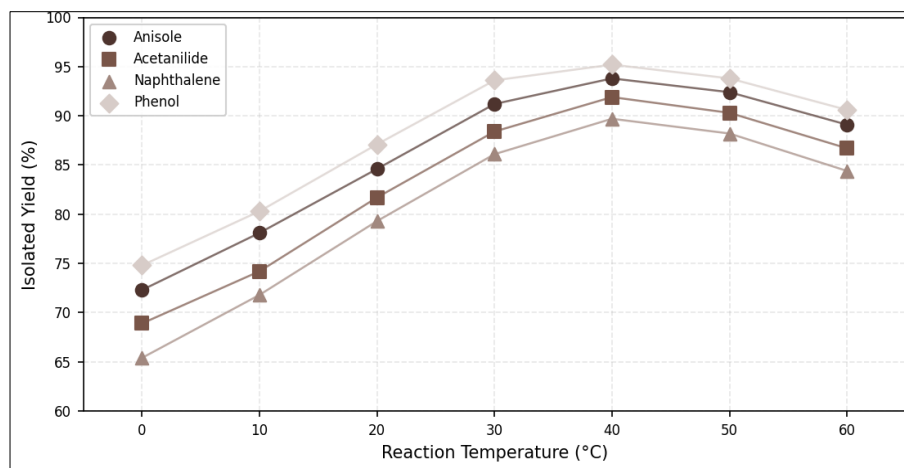


Fig 2: Effect of Temperature on Product Yield for NBS Bromination (NBS: 1.05 equiv., CH₂Cl₂, 4 h reaction time)”

5. Conclusion

A mild, regioselective, and operationally simple protocol for the monobromination of activated aromatic compounds has been developed using NBS as the bromine source and BF₃·Et₂O as a catalytic Lewis acid in CH₂Cl₂ at 30–40 °C. The methodology delivers high isolated yields (84.3–95.2%) with dominant para-selectivity across diverse electron-rich substrates, confirmed by NMR, GC-MS, and X-ray crystallography. The temperature optimum of 35 °C provides a practical window for scalable synthesis without the hazards associated with molecular Br₂. The protocol is compatible with a range of functional groups and provides direct access to monobrominated arenes as key synthetic building blocks for cross-coupling chemistry.

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