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A simple and efficient separation of the Hofmann degradation mixture of 2-amino-4-bromobenzoic acid and 2-amino-5-bromobenzoic acid

Yingxin Zou and Yuge Zhang*

Jinling High School Hexi Campus, Nanjing City, Jiangsu province, PR China
Email: zygjlhx@sina.com

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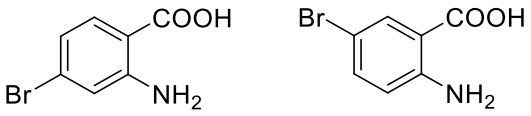
Abstract

A practical method for separating 2-amino-4-bromobenzoic acid (4-BrABA) and 2-amino-5-bromobenzoic acid (5-BrABA) from their mixtures was developed. By exploiting solubility differences under pH-controlled conditions, selective crystallization was achieved using aqueous ammonia and ammonium dihydrogen phosphate as key reagents. The optimized protocol afforded 2-amino-4-bromobenzoic acid with >88% purity and ~~2~~ 2-amino-5-bromobenzoic acid with 91% purity, demonstrating significant improvement over prior separation attempts.



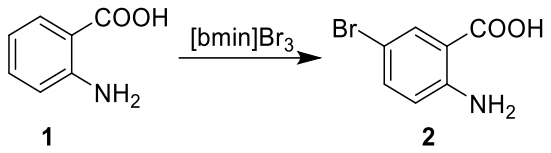
Separation by way of pH-controlled selective crystallization

Keywords: Separation, 2-amino-4-bromobenzoic acid, 2-amino-5-bromobenzoic acid, Hofmann degradation

Introduction

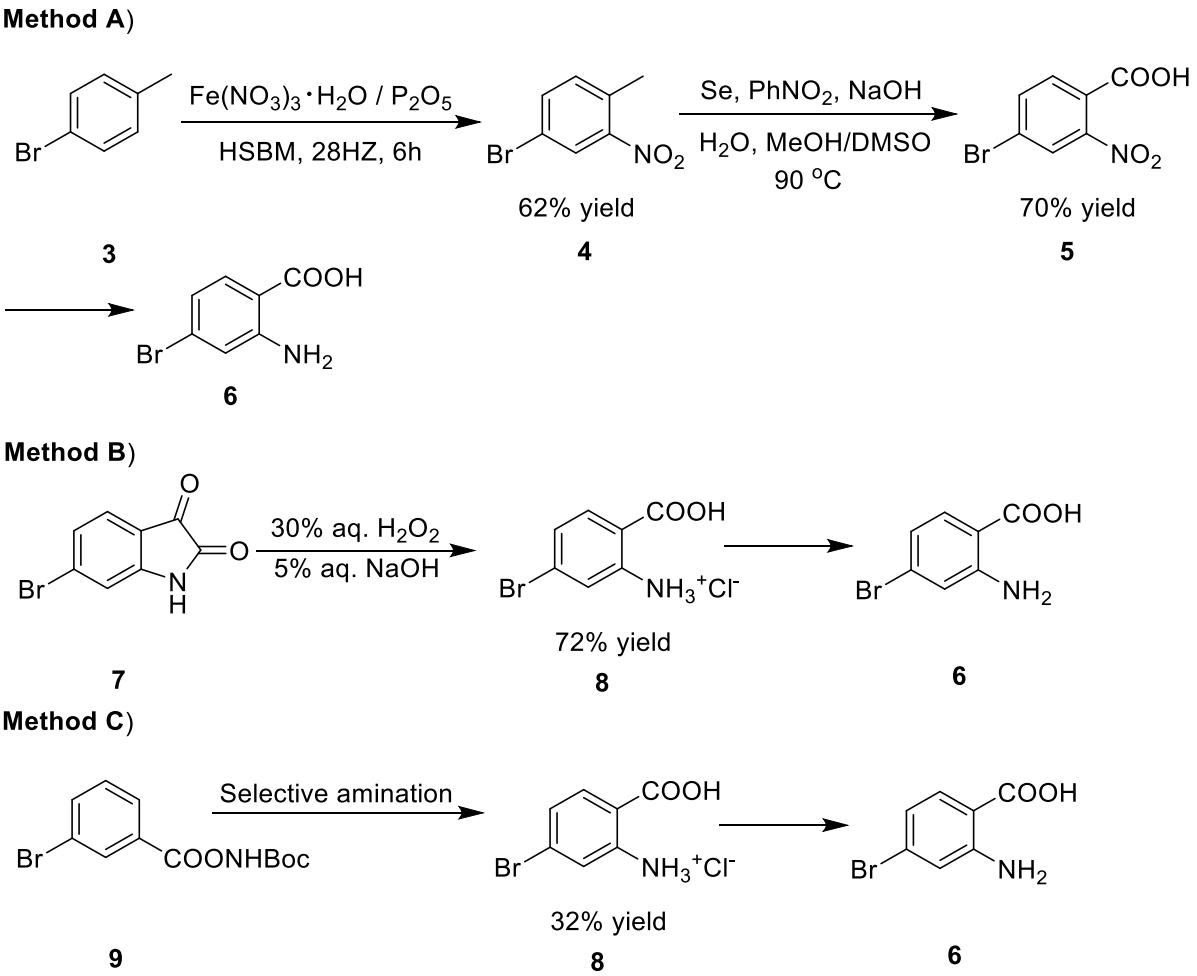
2-Aminobromobenzoic acids bearing a bromo substituent, particularly the isomeric 2-amino-4-bromobenzoic acid **6** and 2-amino-5-bromobenzoic acid **2**, serve as pivotal intermediates in synthesizing bioactive molecules, including antitumor agents, antimicrobial compounds, therapeutic agents for Alzheimer's disease and agrochemicals.[1-4] Despite their structural similarity, the positional isomerism of the bromine substituent significantly influences their reactivity and application scope. For instance, compound **2** is a key precursor for synthesizing brominated heterocycles with enhanced bioactivity,[5] while derivatives of compound **6** exhibit unique electronic properties valuable in material science.[6] However, the efficient separation of these isomers remains a persistent challenge, limiting their large-scale application.

The synthesis of compound **2** is relatively straightforward, yielding a pure product with a sharp melting range (Scheme 1).[7] In contrast, the preparation of compound **6** is hampered by low yields and intricate purification requirements (Scheme 2), such as method A (multistep nitration, oxidation, and reduction sequences), [8-9] method B (Treating 6-Bromo-isatin with hydrogen peroxide under strongly basic conditions to produce compound **8** and then adjusted pH to obtain **6**),[10-11] and method C (ortho-selective amination of arene carboxylic acids that proceeds via a facile rearrangement of acyl *O*-hydroxylamine derivatives), [12] Hofmann degradation of substituted phthalimides offers a promising alternative for regioselective synthesis of 2-aminobenzoic acid derivatives (Scheme 3). For example, 3-nitro- and 4-chlorophthalimides undergo Hoffmann degradation to yield single isomers of nitro- or chloro-substituted 2-aminobenzoic acids.[13-14] However, Hoffmann degradation of 4-nitrophthalimide produces a near-equimolar mixture of 2-amino-4-nitrobenzoic acid and 2-amino-5-nitrobenzoic acid. These isomers can be separated by recrystallization in nitric acid or sulfuric acid.[15-16] Analogous degradation of 4-bromophthalimide **14** produces compounds **6** and **2** in a 44:56 ratio. For these brominated derivatives, analogous separation strategies fail due to inadequate solubility contrasts in common solvents. Prior attempts to resolve the bromo isomers via recrystallization or extraction were unsuccessful, necessitating innovative separation approaches.[17]

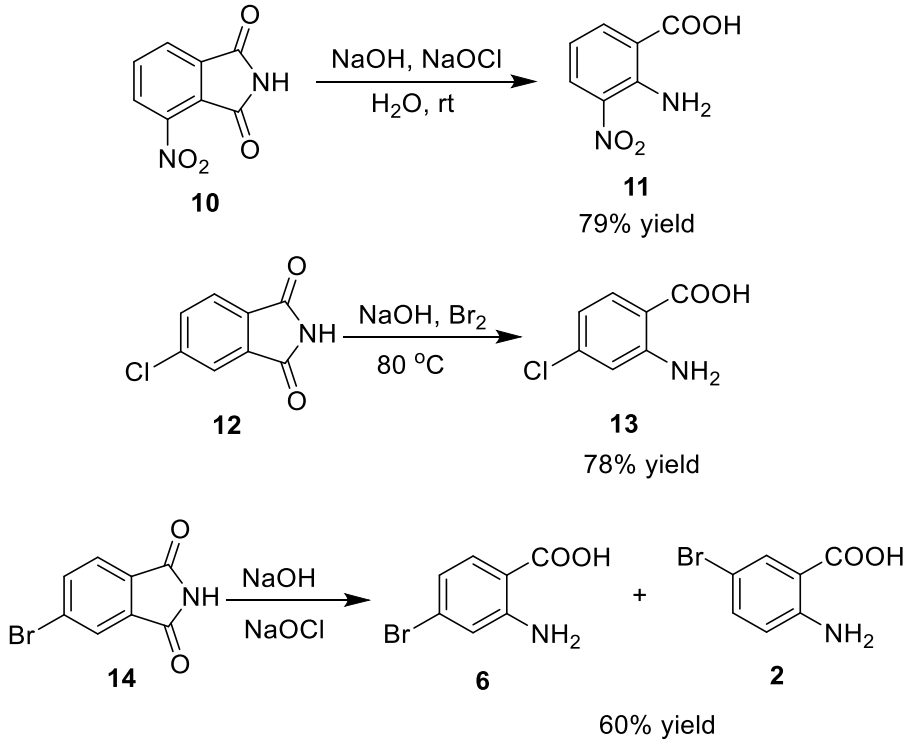


1 **2**

Scheme 1. Synthesis route of 2-amino-5-bromobenzoic acid **2**.



Scheme 2. Synthesis route of 2-amino-4-bromobenzoic acid **6**.



Scheme 3. Hofmann degradation strategy for preparation of 2-aminobenzoic acids.

This study addresses this unresolved challenge by leveraging pH-dependent solubility differences between the sodium salts of compounds **6** and **2**. Inspired by the distinct solubility profiles of these isomers at pH 1 and 7, we systematically evaluated weak acids to selectively precipitate one isomer while maintaining the other in solution. Our optimized protocol employs ammonia water and ammonium dihydrogen phosphate,–taking advantage of mild pH modulation, and recrystallization to achieve reasonably well-separated compounds **6** (98.15%) and **2** (99.71%) without the need for chromatography. This method overcomes the limitations of prior separation strategies and provides a scalable route for the industrial production of these valuable intermediates.

Results and Discussion

The separation efficiency of **6** and **2** was systematically evaluated using pH-controlled crystallization (Table 1). Initial attempts with carboxylic acids (acetic or propionic acid) yielded limited selectivity (Entries 1–2), affording fractions A and B with modest compound **6** enrichment (54–58% in A, 33–34% in B, which were determined by HPLC, see Supporting Information for details). In contrast, phosphate-based proton donors (Entries 3–6) significantly improved separation. For instance, ammonium dihydrogen phosphate combined with ammonia water (Entry 5) produced fraction A (7.95 g) with an 93:6 ratio of compound **6**: compound **2**, while fraction B (10.8 g) have an 18:81 ratio of compound **6**: compound **2**, after EDTA-mediated neutralization. Similarly, trisodium phosphate with ammonium dihydrogen phosphate (Entry 6) achieved 88:9 selectivity in composition of A.

The superior performance of phosphate systems likely arises from their buffering capacity, which enables precise pH control during salt protonation. In contrast, strong acids (e.g., HCl in Runs 1–4) induced rapid precipitation, reducing selectivity. Notably, CO_2 acidification (Entry 7) failed to isolate 4-BrABA effectively, yielding only 10% recovery despite prolonged bubbling, possibly due to insufficient solubility modulation.

Post-treatment refinement further enhanced purity. Ethanol recrystallization of solids from composition A of Runs 3, 5, 6, 7) consistently provided **6** with sharp melting ranges (228-233°C), consistent with literature values.[4] For compound **2**, fractional crystallization from 50% DMF/water (Purified solid from composition B of ~~Run~~ Entry 5) removed residual compound **6**, achieving 99.71% purity.

Table 1. Separation of Brominated 2-Aminobenzoic Acid Isomers (Mix) Using Base-Acid Combinations

Entry	Mix(g)	Base	Acid	Composition of A[a]	Composition of B[a]
1	21.00	NaOH (4.00 g)	CH_3COOH (3.00 g)	9.10 g (58/38[a])	10.50 g (33/61)
2	21.00	NaOH (4.00 g)	C_2H_5COOH (3.70 g)	9.80 g (54/41)	9.10 g (34/59)
3	21.00	NaOH (4.00 g)	NaH_2PO_4 (6.00 g)	5.70 g (86/8)	14.40 g (30/67)
4	21.00	NaOH (4.00 g)	KH_2PO_4 (7.00 g)	9.04 g (77/20)	9.07 g (40/55)
5	21.00	NH_4OH (6.36 g)	$NH_4H_2PO_4$ (6.00 g)	7.95 g (93/6)	10.80 g (18/81)
6	18.50	$(NH_4)_3PO_4$ (35.00 g)	$NH_4H_2PO_4$ (5.20 g)	6.00 g (88/9)	9.10 g (33/63)
7[b]	100.00	NaOH (18.52 g)	CO_2	10.00 g (93/2)	0.00

a. The ratio of **6** and **2**.

b. $CO_2$was bubbled below the liquid surface for 8 h (no precipitation observed). After storage at 5°C overnight, a solid precipitated. The filter cake (washed with water and dried) afforded purified solid from composition A of Run 7. The filtrate was further treated with CO_2 for 72 h, yielding no solid.

These results underscore the critical role of mild, buffered pH adjustment in resolving structurally similar brominated isomers—a challenge unresolved by prior methods.[9] The protocol is a practical solution for large-scale applications.

Conclusions

A pH-mediated crystallization strategy enables the separation of 2-amino-4-bromobenzoic acid and 2-amino-5-bromobenzoic acid from Hofmann degradation mixtures. Selective precipitation using ammonia water and ammonium dihydrogen phosphate achieves 98.15% purity for 2-amino-4-bromobenzoic acid after ethanol recrystallization, while 2-amino-5-bromobenzoic acid is recovered at 99.71% purity via DMF/water fractional crystallization.

The method's efficacy originates from buffered pH control, which exploits solubility differences between the isomers' sodium salts. Unlike prior failed approaches employing strong acids or CO_2, this approach aligns with industrial scalability requirements. The protocol's simplicity and reproducibility address a critical bottleneck in accessing high-purity brominated intermediates for pharmaceutical synthesis.

Experimental Section

General. All reagents used were of analytical purity. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification. The Hofmann degradation reaction mixture, a grey powder (designated as **Mix**) with the melting point at 170–200°C, was provided by chemistry department of Nanjing University.

General procedure for the Separation Procedure for 2-amino-4-bromobenzoic acid 6 and 2-amino-5-bromobenzoic acid 2 Mix was dissolved in an equimolar amount of 4% aqueous base solution with stirring. Subsequently, 0.5 equiv of the first acid was added. The mixture was filtered, and the filter cake was washed with water and dried to yield **A**. The combined filtrate and washings were acidified to pH 1 with HCl or neutralized with stoichiometric EDTA-2Na. The precipitated solid was filtered, washed with water, and dried to afford fraction **B**.

Purified solids from composition A of Entry 3. The Fraction A of Entry 3 (5.7 g) was suspended in 95% ethanol (36 mL) and heated under reflux. After complete dissolution, the solution was then cooled to room temperature. The resultant suspension was filtered and the solid was dried under reduced pressure to afford 4.3 g of 2-amino-4-bromobenzoic acid as a grey powder (The purity was 98.15 % detected by HPLC).
Purified solids from composition A of Entries 5, 6 and 7 were purified via the same procedure of Entry 3.

Purified solid from composition B of Entry 5 was added to 12 mL of 50% aqueous DMF, heated to 100°C until fully dissolved, then cooled to 80°C. The precipitated solid was filtered at 80°C, washed with methanol, and dried to afford 2-amino-5-bromobenzoic acid (The purity was 99.71 % detected by HPLC). Water (20 mL) was added to the filtrate to precipitate an additional solid (yield: 50%).

2-amino-5-bromobenzoic acid (2). Grey solid, mp 220-225 °C. ^{1}H-NMR (500MHz, DMSO-d_6): δ7.76 (d, *J*. 2.5 Hz, 1H), 7.33 (dd, *J*. 8.9, 2.5 Hz, 1H), 6.72 (d, *J*. 8.9 Hz, 1H). NMR result agrees well with that of literature data[17].

2-amino-4-bromobenzoic acid (6). Grey solid, mp 228-233 °C. ^{1}H-NMR (500MHz, DMSO-d_6): δ 7.59 (d, *J*. 7.5 Hz, 1H), 6.98 (s, 1H), 6.64 (d, *J*. 7.0 Hz, 1H). NMR result agrees well with literature data.[17]

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Supplementary Material

The ^{1}H NMR and HPLC spectra are given in the Supplementary Material file associated with this manuscript.

References

1. Yao, H.; Uras, G.; Zhang, P.-F.; Xu, S.-T.; Yin, Y.; Liu, J.; Qin, S.; Li, X.-N.; Allen, S.; Bai, R.-R.; Gong, Q.; Zhang, H.-Y.; Zhu, Z.-Y.; Xu, J.-Y. *J. Med. Chem.* **2021**, *64*, 7483-7506. https://doi.org/10.1021/acs.jmedchem.1c00160
2. Stiff, C.; Graber, D. R.; Thorarensen, A.; Wakefield, B. D.; Marotti, K. R.; Melchior, E. P.; Sweeney, M. T.; Han, F.-S.; Rohrer, D. C.; Zurenko, G. E.; Romero, D. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6293–6297. https://doi.org/10.1016/j.bmcl.2007.08.041
3. Liu, Y.-Y.; Ma, C.; Li, Y.-B.; Li, M.-Z.; Cui, T.; Zhao, X.-Q.; Li, Z.-L.; Jia, H.-W.; Wang, H.-X.; Xiu, X.-M.; Hu, D.-X.; Zhang, R.-W.; Wang, N.-W.; Liu, P.; Yang, H.-L.; Cheng, M.-S. *E. J. Med. Chem.* **2024**, *265*,116071. https://doi.org/10.1016/j.ejmech.2023.116071
4. Ma, Y.; Liu, F.; Yan, K.; Song, B.-A.; Yang, S.; Hu, D.-Y.; Jin, L.-H.; Xue, W. *Chin. J. Org. Chem*. **2008**, *28*, 1268-1272.

http://journal15.magtechjournal.com/Jwk3_hxs/yjhx/CN/article/article_332054.shtml

5. El-Hashash, M. A.; Azab, M. E., Morsy, J. M. *J*. *Heterocyclic*. *Chem*. **2016**, *53*, 95-101. https://doi.org/10.1002/jhet.2389
6. Chen, W.-C.; Yuan, Y.; Zhu, Z.-L.; Jiang, Z.-Q.; Liao, L.-S.; Lee, C.-S. *Adv*. *Opt*. *Mater*. **2018**, *6*, 1700855. https://doi.org/10.1002/adom.201700855
7. Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis*. **2004**, *17*, 2809-2812. https://doi.org/10.1055/s-2004-831239
8. Wu, J.-W.; Zhang, P.; Guo, Z.-X. *Tetrahedron*. *Lett*. **2021**, *72*, 153087. https://doi.org/10.1016/j.tetlet.2021.153087
9. Li, Y.-M.; Wang, Y.-H.; Yang, T.-L.; Lin, Z.-Y.; Jiang, X.-F. *Green*. *Chem*. **2021**, *23*, 2986-2991. https://doi.org/10.1039/D0GC04407E
10. Ligon, E. V.; Nawyn, J.; Jones, L. V.; Mckay Allred, B.; Reinhardt Jr, D. V.; France, S. *J. Org. Chem.* **2019**, *84*, 16, 10280–10291. https://doi.org/10.1021/acs.joc.9b01433
11. Stiff, C.; Graber, D. R.; Thorarensen, A.; Wakefield, B. D.; Marotti, K. R.; Melchior, E. P.; Sweeney, M. t., Han, F.-S.; Rohrer, D. C.; Zurenko, G. E.; Romero, D. L. *Bioorg*. *Med*. *Chem*. *Lett*. **2008**, *18*, 6293–6297 https://doi.org/10.1016/j.bmcl.2007.08.041
12. Gillespie, J. E.; Lam, N. Y. S.; Phipps, R. J. *Chem*. *Sci*. **2023**, *14*, 10103-10111. https://doi.org/10.1039/D3SC03293K
13. Bhowmik, S.; Pandey, G.; Batra, S. *Chem*. *Eur*. *J*. **2013**, *19*, 10487-0491. https://doi.org/10.1002/chem.201301705
14. Jyothsna, A. ; Padma Latha, K. *Int*. *J*. *Pharm*. *Biol*. *Sci*. **2022**, *12*, 197-204. https://doi.org/10.21276/ijpbs.2022.12.4.20
15. Yanagita, M. ; Kubota, M. *Yakugaku*. *Zasshi*. **1952**, *72*, 845-846 https://doi.org/10.1248/yakushi1947.72.6_845
16. Porter, Hardin, K. U.S. Patent 2 714 612, 1955; *Chem. Abstr.* **1956**, *50*, P 64788.
17. Wolk, J. L. ; Frimer, A. A. Molecules, 2010, 15, 5561-5580. https://doi.org/10.3390/molecules15085561