A Simple Key for Benzylic Mono- and *gem*-Dibromination of Primary Aromatic Amine Derivatives Using Molecular Bromine[1]

Anirban Kar, Narshinha P. Argade*

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India
Fax +91(20)5893153; E-mail: argade@dalton.ncl.res.in

Received 25 September 2001; revised 12 November 2001

Dedicated to Honourable Professor Kenji Mori, Science University of Tokyo, Tokyo, Japan

Abstract: Quantitative benzylic mono- and *gem*-dibromination on primary aromatic amine derivatives have been achieved using molecular bromine and by protecting the amino group as a succinimide moiety. The reactions of *N*-(*o*/*m*/*p*-tolyl)succinimides **5a**–**c** with 1.25 equivalents of molecular bromine in CCl_4 at room temperature furnished the corresponding benzylic monobrominated products **6a**–**c** in 92–94% yields, while with 2.5 equivalents of molecular bromine in refluxing CCl_4 *gem*-dibromo products **7a**–**c** were obtained in 94–96% yields. It is also possible to carry out nuclear bromination in these *N*-protected primary aromatic amines at an alternate site by using suitably substituted aniline derivatives. Thus the reaction of **3** with 1.25 equivalents of molecular bromine in acetic acid gave the desired monobrominated product **4** in nearly 100% yield.

Key words: primary aromatic amines, succinimide derivatives, molecular bromine, benzylic mono-/*gem*-dibromination

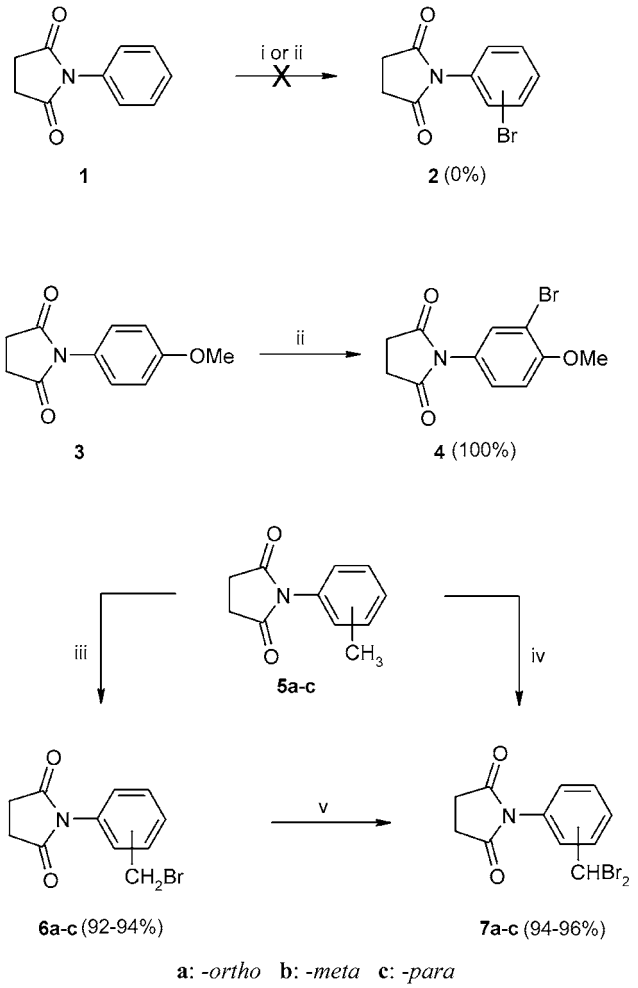
Large numbers of primary aromatic amine derivatives (aniline derivatives) with a variety of substituents and substituent patterns are well known in the literature and their utilities have been also well proved in practice.[2] They are generally obtained by electrophilic or nucleophilic aromatic substitution reactions and these synthetic operations are performed directly on free aniline derivatives,[2c] *N*-nitrosoaniline derivatives,[2c] *N*-haloaniline derivatives,[3] *N*-hydroxyaniline derivatives[4] or *N*-protected aniline derivatives.[2c] The free NH_2 group protections are generally done by converting it into (a) *N*-acyl derivatives (b) *N*-protonated salts (c) carbamates, and (d) phthalimides. The latter two protecting groups have been mostly used in the chemistry of amino acids.[2c] There is no direct method to obtain aniline derivatives, wherein the electrophilic substitutions are directed by a secondary activating group on the phenyl ring, and also for benzylic halogenations on aniline derivatives. To date, both these aims have been achieved in a stepwise fashion by carrying out the various reactions on the corresponding less reactive nitro derivatives, followed by reduction of the nitro group to an amino group.[5] This process is quite cumbersome and may not be feasible for all the cases. For the past several years we have been using cyclic anhydrides and imides as potential starting materials for the synthesis of structurally interesting and biologically important heterocycles[6] and bioactive natural products.[7] During these studies,[6–9] we noticed that the lone pair of electrons on nitrogen atom in *N*-aryl cyclic imides has no influence on the aryl ring. We reasoned and planned to take advantage of this futuristic observation to add a new useful concept in the chemistry of primary aromatic amines.

The *N*-phenylsuccinimide (**1**)[10] on reaction with molecular bromine in refluxing CCl_4 and with bromine in acetic acid at room temperature remained completely unreacted proving that the lone pair of electrons on nitrogen atom in phenyl succinimide **1** is fully engaged with two imide carbonyls and loses its mesomeric connectivity with aromatic ring and the phenyl ring behaves like benzene (Scheme). The reaction of the corresponding *p*-methoxy derivative **3** with bromine in acetic acid at room temperature exclusively furnished the desired nuclear brominated product **4** in ~100% yield (Scheme), thus rendering the electrophilic substitution at an alternate site, dictated by a secondary activating OCH_3 group (as compared to NH_2). With suitable manipulations in substrate structures and reaction conditions, several electrophilic substitution reactions will be possible to generate an avenue of new and useful aniline derivatives. Like toluene,[2c] the *N*-(*o*/*m*/*p*)-tolylsuccinimides **5a**–**c** on treatment with 1.25 equivalents of molecular bromine in CCl_4 at room temperature, underwent a smooth monobenzylic bromination to yield the products **6a**–**c** respectively, in 92–94% yields, while in refluxing CCl_4 with 2.50 equivalents of bromine they furnished the corresponding *gem*-dibromo derivatives **7a**–**c** respectively, in 94–96% yields (Scheme). Both these mono- and *gem*-dibenzylic bromination reactions must be following a radical pathway and the *ortho*-, *meta*- and *para*-isomers reacted in a similar manner revealing that only the benzylic relay may be operational at the reaction sites. Moreover these compounds **6a**–**c** and **7a**–**c** are clean solid materials and do not show any noticeable lachrymal properties. Thus for the first time benzylic monobrominations and *gem*-dibrominations have been achieved on the toluidine nucleus by using molecular bromine and protecting the free amino group as succinimide moiety and this concept will be amply useful for benzylic mono/*gem*-dihalogenations of several other primary aromatic amine derivatives. The monobrominated products **6a**–**c** will provide a new simple, clean and efficient approach to *ortho*-, *meta*- and *para*-aminobenzyl nitrile,[11,12] benzyl amine,[13] benzyl alcohol,[14] benzyl thiol[15] derivatives and several other products, while *gem*-dibromo products **7a**–**c**

Synthesis 2002, No. 2, 01 02 2002. Article Identifier:
1437-210X,E;2002,0,02,0221,0224,ftx,en;Z11001SS.pdf.

ISSN 0039-7881

will be potential starting materials for corresponding *o*/*m*/*p*-amino *gem*-diamine/imine,[2d] *gem*-diol,[16] *gem*-dithiol,[17] benzaldehyde,[18] acetal,[19] 1,3-dithiane[20] derivatives and several other products. These new potential approaches to the above mentioned compounds will be highly useful in practice and depending on the substrate structure, the protecting group can be detached by using hydrazine or acidic/basic reaction conditions.



Scheme *Reagents and conditions*: (i) Br_2 (1.25 mmol), CCl_4, reflux, 24 h; (ii) Br_2 (1.25 mmol), HOAc, r.t., 6 h (aqueous workup); (iii) Br_2 (1.25 mmol), CCl_4, r.t., 4 h; (iv) Br_2 (2.50 mmol), CCl_4, reflux, 8 h; (v) Br_2 (1.25 mmol), CCl_4, reflux, 8 h

In summary, for the first time *N*-arylsuccinimides have been treated as an aniline derivatives rather than succinic anhydride derivatives to demonstrate the simple method for nuclear bromination at an alternate site and benzylic mono/*gem*-dibrominations using molecular bromine. In future this concept will be highly useful to demonstrate plenty of new applications in the subject. Starting from compound **6a** and **7a**, we plan to develop new synthetic routes to mitomycins[21] and their congeners via reactivity umpolung.

Melting points are uncorrected. Ac_2O was obtained from Aldrich Chemical Co. Freshly prepared succinic anhydride and freshly purified amines were used.

Succinanilic acids

To a stirred solution of succinic anhydride (5 g, 50 mmol) in a mixture of benzene and 1,4-dioxane (60 mL, 2:1) was added a solution of primary aromatic amine (50 mmol) in Et_2O (40 mL) in a dropwise fashion at r.t. over a period of 20 min and the mixture was further stirred for 2 h. The formed solid product was filtered, washed with Et_2O (25 mL) and vacuum dried to obtain succinanilic acids in quantitative yield, which were used for the next step without any further purification.

***N*-Arylsuccinimides 1, 3 and 5; General Procedure**

A mixture of succinanilic acid (45 mmol), Ac_2O (30 mL) and fused NaOAc (500 mg) was heated on a water bath at 60 °C for 2 h. The mixture was cooled to r.t. and poured into ice-cold water. The precipitated product was filtered, washed with H_2O and dried in vacuo to obtain succinimides **1**, **3** and **5** in 90–95% yield.

1

Mp 158–159 °C.

IR (Nujol): 1776, 1709, 1595 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.91 (s, 4 H), 7.20–7.60 (m, 5 H).

3

Mp 165–167 °C.

IR (Nujol): 1770, 1705, 1607 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.88 (s, 4 H), 3.82 (s, 3 H), 6.99 (d, *J* = 10 Hz, 2 H), 7.20 (d, *J* = 10 Hz, 2 H).

5a

Mp 99–102 °C.

IR (Nujol): 1770, 1705, 1600 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.15 (s, 3 H), 2.93 (s, 4 H), 7.08 (d, *J* = 6 Hz, 1 H), 7.25–7.45 (m, 3 H).

5b

Mp 103–105 °C.

IR (Nujol): 1767, 1705, 1607 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.39 (s, 3 H), 2.88 (s, 4 H), 7.00–7.50 (m, 4 H).

5c

Mp 158-160 °C.

IR (Nujol): 1770, 1705, 1600 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.38 (s, 3 H), 2.87 (s, 4 H), 7.15 (d, *J* = 6 Hz, 2 H), 7.28 (d, *J* = 6 Hz, 2 H).

***N*-(3-Bromo-4-methoxy)phenylsuccinimide (4)**

To a stirred solution of imide **3** (2.84 g, 10 mmol) in HOAc (20 mL) was added Br_2 (2.00 g, 12.5 mmol) and the mixture was stirred at r.t. for 6 h. Aqueous workup, followed by filtration of the formed precipitate and vacuum drying gave pure **4** (3.62 g, ~100%); mp 178–180 °C (CCl_4).

IR ($CHCl_3$): 1782, 1717, 1603 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.89 (s, 4 H), 3.93 (s, 3 H), 6.99 (d, *J* = 10 Hz, 1 H), 7.24 (dd, *J* = 10, 2 Hz, 1 H), 7.51 (d, *J* = 4 Hz, 1 H).

MS: *m/z* = 285, 283, 270, 268, 257, 255, 240, 239, 214, 212, 204, 186, 158, 140, 132, 106, 90, 76, 63.

Anal. Calcd for $C_{11}H_{10}BrNO_3$ (284.1): C, 46.50; H, 3.55; N, 4.93. Found: C, 46.62; H, 3.41; N, 5.01.

Benzylic Monobromination and *gem*-Dibromination of 5a–c

To a stirred solution of the appropriate succinimide **5a–c** (5 mmol) in CCl_4 (40 mL) was added dropwise a solution of Br_2 (6.25 mmol) in CCl_4 (10 mL) at r.t. over a period of 10 min to 15 min and the mixture was further stirred for 4 h at r.t. The mixture was concentrated in vacuo and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with H_2O, 5% aq $NaHSO_3$, H_2O, brine and dried (Na_2SO_4). Concentration of the organic layer in vacuo furnished the desired monobromo products **6a–c** in 92–94% yields. Similarly the starting materials **5a–c** (5 mmol) with Br_2 (12.5 mmol) on refluxing in CCl_4 (50 mL) for 8 h gave the *gem*-dibromo compounds **7a–c** in 94–96% yields. The ^{1}H NMR spectra of isolated monobromo products **6a–c** revealed that 2–3% of starting materials remain unreacted and/or the formation of corresponding *gem*-dibromo products. The analytically pure products were obtained by further recrystallisation.

6a

Mp 126–128 °C (CCl_4).

IR (Nujol): 1782, 1717, 1595 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.96 (d, *J* = 2 Hz, 4 H), 4.38 (s, 2 H), 7.17 (d, *J* = 6 Hz, 1 H), 7.30–7.65 (m, 3 H).

MS: *m/z* = 269, 267, 188, 160, 142, 132, 118, 104, 91, 77, 63.

Anal. Calcd for $C_{11}H_{10}BrNO_2$ (268.1): C, 49.28; H, 3.76; N, 5.23. Found: C, 49.11; H, 3.58; N, 5.08.

6b

Mp 97–100 °C ($CHCl_3$).

IR ($CHCl_3$): 1782, 1718, 1610 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.90 (s, 4 H), 4.50 (s, 2 H), 7.20–7.55 (m, 4 H).

MS: *m/z* = 269, 267, 188, 160, 146, 132, 106, 91, 77, 65.

Anal. Calcd for $C_{11}H_{10}BrNO_2$ (268.1): C, 49.28; H, 3.76; N, 5.23. Found: C, 49.15; H, 3.82; N, 5.36.

6c

Mp 186-187 °C (EtOAc).

IR (Nujol): 1778, 1700, 1600 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.90 (s, 4 H), 4.50 (s, 2 H), 7.29 (d, *J* = 8 Hz, 2 H), 7.51 (d, *J* = 8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 28.4, 32.3, 126.7, 129.8, 131.8, 138.1, 175.9.

MS: *m/z* = 269, 267, 188, 132, 106, 89, 77.

Anal. Calcd for $C_{11}H_{10}BrNO_2$ (268.1): C, 49.28; H, 3.76; N, 5.23. Found: C, 49.16; H, 3.70; N, 5.19.

7a

Mp 200–203 °C ($CHCl_3$).

IR (Nujol): 1771, 1709, 1595 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.99 (d, *J* = 2 Hz, 4 H), 6.55 (s, 1 H), 7.05 (dd, *J* = 8, 2 Hz, 1 H), 7.45 (dt, *J* = 8, 2 Hz, 1 H), 7.57 (dt, *J* = 8, 2 Hz, 1 H), 8.12 (dd, *J* = 10, 2 Hz, 1 H).

MS: *m/z* = 349, 347, 345, 268, 266, 186, 158, 130, 103, 76.

Anal. Calcd for $C_{11}H_9Br_2NO_2$ (347.0): C, 38.07; H, 2.61; N, 4.04. Found: C, 37.93; H, 2.55; N, 3.81.

7b

Waxy solid.

IR (Nujol): 1780, 1715, 1607 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.93 (s, 4 H), 6.65 (s, 1 H), 7.29 (d, *J* = 8 Hz, 1 H), 7.40–7.70 (m, 3 H).

MS: *m/z* = 349, 347, 345, 268, 266, 210, 187, 158, 130, 117, 103, 89.

Anal. Calcd for $C_{11}H_9Br_2NO_2$ (347.0): C, 38.07; H, 2.61; N, 4.04. Found: C, 37.88; H, 2.43; N, 4.02.

7c

Mp 212–213 °C (EtOAc).

IR (Nujol): 1774, 1707, 1603 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.93 (s, 4 H), 6.65 (s, 1 H), 7.35 (d, *J* = 8 Hz, 2 H), 7.69 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (acetone-d_6, 50 MHz): δ = 29.2, 41.6, 127.8, 127.9, 135.2, 142.8, 177.0.

MS: *m/z* = 349, 347, 345, 268, 266, 210, 184, 158, 130, 104, 77, 63.

Anal. Calcd for $C_{11}H_9Br_2NO_2$ (347.0): C, 38.07; H, 2.61; N, 4.04. Found: C, 37.97; H, 2.58; N, 3.76.

Acknowledgements

A. K. thanks CSIR, New Delhi, for the award of a research fellowship. N. P. A. thanks Department of Science and Technology, New Delhi, for financial support. We thank Dr. K. N. Ganesh, Head, Division of Organic Chemistry (Synthesis), for constant encouragement.

References

(1) NCL Communication No. 6615.
(2) (a) *Kirk–Othmer Encyclopedia of Chemical Technology*, 4th ed., Vol.2; Kirk, R. E.; Othmer, D. F., Eds.; Wiley: New York, **1991**, 426. (b) *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed., Vol. A2; Ullmann, F.; Gerhartz, W.; Yamamoto, Y. S.; Campbell, F. T.; Pfefferkorn, R.; Rounsaville, J. F., Eds.; VCH: Weinheim, **1985**, 303. (c) Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Furniss, B. S.; Stanley, B., Eds.; Longman: Harlow, **1989**, Chap. 6, 824. (d) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, **1992**, Chap. 11, 501. (e) Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 6th ed.; Prentice-Hall: New Delhi, **1996**, Chap. 15, 517. (f) Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 6th ed.; Prentice Hall: New Delhi, **1996**, Chap. 22, 821. (g) Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 6th ed.; Prentice-Hall: New Delhi, **1996**, Chap. 23, 845.
(3) Gassman, P. G.; Drewes, H. R. *J. Am. Chem. Soc.* **1978**, *100*, 7600.
(4) Ayyangar, N. R.; Kalkote, U. R.; Nikrad, P. V. *Tetrahedron Lett.* **1982**, *23*, 1099.
(5) Ref.,[2a] see page 437.
(6) Argade, N. P.; Balasubramaniyan, V. *Heterocycles* **2000**, *53*, 475; and references cited therein.
(7) (a) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2002**, 67. (b) Mangaleswaran, S.; Argade, N. P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1764. (c) Mangaleswaran, S.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 5259. (d) Deshpande, A. M.; Natu,

A. A.; Argade, N. P. *Synthesis* **2001**, 702. (e) Mangaleswaran, S.; Argade, N. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3290. (f) Deshpande, A. M.; Natu, A. A.; Argade, N. P. *J. Org. Chem.* **1998**, *63*, 9557. (g) Desai, S. B.; Argade, N. P. *J. Org. Chem.* **1997**, *62*, 4862. (h) Argade, N. P.; Naik, R. H. *Bioorg. Med. Chem.* **1996**, *4*, 881.

(8) Balasubramaniyan, V.; Argade, N. P. *Tetrahedron* **1989**, *45*, 835.

(9) Balasubramaniyan, V.; Argade, N. P. *Tetrahedron Lett.* **1986**, *27*, 2487.

(10) Ref.,[2c] see page 1265.

(11) Sheng, W. *Zhongguo Yiyao Gongye Zazhi* **1993**, *24*, 276; *Chem. Abstr*. **1994**, *120*, 54281.

(12) Orlemans, E. O. M.; Schreuder, A. H.; Conti, P. G. M.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1987**, *43*, 3817.

(13) (a) Kornblum, N.; Iffland, D. C. *J. Am. Chem. Soc*. **1949**, *71*, 2137. (b) Georgiev, V. S.; Bennett, G. A.; Radov, L. A.; Kamp, D. K.; Trusso, L. A. *J. Heterocycl. Chem.* **1986**, *23*, 1359.

(14) (a) Coleman, G. H.; Johnson, H. L. *Org. Synth. Coll. Vol. 3*; Wiley: New York, **1955**, 60. (b) Conover, L. H.; Tarbell, D. S. *J. Am. Chem. Soc.* **1950**, *72*, 3586.

(15) Abraham, D. J.; Kennedy, P. E.; Mehanna, A. S.; Patwa, D. C.; Williams, F. L. *J. Med. Chem.* **1984**, *27*, 967.

(16) Le Henaff, P. *Bull. Soc. Chim. Fr*. **1968**, 4687.

(17) Mayer, R.; Hiller, G.; Nitzschke, M.; Jentzsch, D. C. J. *Angew. Chem., Int. Ed. Engl*. **1963**, *2*, 370.

(18) (a) Smith, L. I.; Opie, J. W. *Org. Synth. Coll. Vol. 3*; Wiley: New York, **1955**, 56. (b) Foy, B. D.; Smudde, R. A.; Wood, W. F. *J. Chem. Educ.* **1993**, *70*, 322. (c) Anderson, W. K.; Dalvie, D. K. *J. Heterocycl. Chem.* **1993**, *30*, 1533. (d) Icke, R. N.; Redemann, C. E.; Wisegarver, B. B.; Alles, G. A. *Org. Synth.* **1955**, *Coll. Vol. 3*, 59. (e) Campaigne, E.; Budde, W. M.; Schaefer, G. F. *Org. Synth.* **1963**, *Coll. Vol.4*, 31.

(19) (a) Yoon, N. M.; Choi, J. *Synlett* **1993**, 135. (b) Joshi, M. V.; Narasimhan, C. S. *J. Catal.* **1989**, *120*, 282.

(20) (a) Blickenstaff, R. T.; Brandstadter, S. M.; Foster, E.; Reddy, S.; Witt, R. *Ind. Eng. Chem. Res.* **1993**, *32*, 2455. (b) Tzeng, Y. L.; Yang, P. F.; Mei, N. W.; Yuan, T. M.; Yu, C. C.; Luh, T. Y. *J. Org. Chem.* **1991**, *56*, 5289.

(21) Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475; and references cited therein.