An Efficient Selective Reduction of Aromatic Azides to Amines Employing BF_3·OEt_2/NaI: Synthesis of Pyrrolobenzodiazepines

Ahmed Kamal,*[a] N. Shankaraiah,[a] N. Markandeya,[b] Ch. Sanjeeva Reddy*[b]

[a] Chemical Biology, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India
Fax +91(40)927193189; E-mail: ahmedkamal@iict.res.in

[b] Department of Chemistry, Kakatiya University, Warangal 506009, A.P., India
Fax +91(870)2439600; E-mail: chsrkue@yahoo.in

Received 20 November 2007

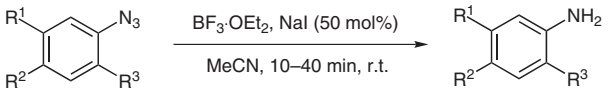
Abstract: A selective and facile method for the reduction of aromatic azides to amines by employing borontrifluoride diethyl etherate and sodium iodide. This methodology has been applied towards the preparation of biologically important imine-containing pyrrolobenzodiazepines and their dilactams through intramolecular reductive–cyclization process. In this protocol the reagent systems are amenable for the generation of solution-phase combinatorial synthesis.

Key words: pyrrolo[2,1-*c*][1,4]benzodiazepines, boron trifluoride diethyl etherate, sodium iodide, intramoleculor reductive–cyclization

In recent years, azides[1] have attracted much attention as key intermediates for the synthesis of a large number of organic compounds such as nucleosides, carbohydrates,[2] and nitrogen-containing heterocycles[3] – such as pyrrolobenzodiazepines, quinolines, lactams, and cyclic imides. The conversion of aromatic azides into amines has been a desirable strategy in various synthetic sequences and for this purpose a variety of reagents has been reported in the literature.[4a–h] However, in terms of their practical applicability, selectivity, commercial availability, and reaction conditions, most of these methods have certain disadvantages, prompting considerable demand for the development of novel, more efficient, mild, and selective methodologies.[5]

Recently, we have reported[6] a versatile method for the reduction of aromatic azides to amines in solution as well as on solid phase employing BF_3·OEt_2 and EtSH in anhydrous CH_2Cl_2. This new methodology is applicable for the synthesis of naturally occurring DC-81 and also for resin cleavage. Ethanethiol used in this methodology is a reagent of highly volatile nature, malodorous, and requiring safety precautions for carrying out the reaction. In this connection, we herein report a mild, efficient, and selective method for the reduction of aromatic azides **1a–j** to their corresponding amines **2a–j** by employing boron trifluoride diethyl etherate and sodium iodide in acetonitrile at room temperature to give excellent yields as shown in Table 1.

Table 1 Selective Reduction of Aromatic Azides **1a–j** to Amines **2a–j** by Employing BF_3·OEt_2 and NaI



1a–j **2a–j**

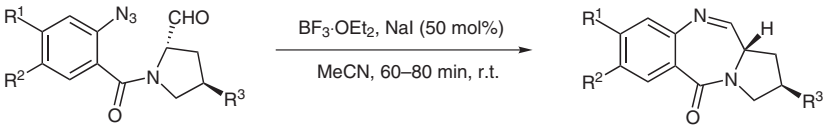
Entry	R^1	R^2	R^3	Time (min)	Yield (%)[a,b]	EIMS
2a	H	H	COOH	30	85	137
2b	H	Me	COOH	40	80	151
2c	H	Cl	COOH	35	92	171
2d	OH	OMe	COOH	40	86	183
2e	OBn	OMe	COOH	35	88	273
2f	H	Me	COOMe	10	90	165
2g	H	Cl	COOMe	15	96	185
2h	OH	OMe	COOMe	25	84	197
2i	OMe	OMe	COOMe	20	94	211
2j	OBn	OMe	COOMe	30	96	287

[a] Isolated yields.
[b] Compounds characterized by ^{1}H NMR, IR, and EIMS.

This method is an efficient and convenient alternative to the aza-Wittig route by employing TPP or Bu_3P as it does not require any anhydrous conditions and furthermore, this reagent system is inexpensive. In continuation of these efforts, this methodology has been applied for the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines (PBD) through an intramolecular azido-reductive cyclization approach. Pyrrolo[2,1-*c*][1,4]benzodiazepines are a family of naturally occurring antitumor antibiotics that usually interact with DNA covalently in a sequence-selective manner preferentially at Pu-G-Pu motifs.[7] The development of viable synthetic pathways[8] has allowed many analogues of PBD monomers to be explored. The substituted azidobenzoyl prolinaldehydes[9] **3a–f** have been reduced with BF_3·OEt_2 and NaI to afford the reductive-cyclized products **4a–f** in good yields, which are illustrated in Table 2. However, in our previous studies[9] employing BF_3·OEt_2 and EtSH for the reduction of azido to amino functionality, an additional cyclization step is necessary to

SYNLETT 2008, No. 9, pp 1297–1300
Advanced online publication: 07.05.2008
DOI: 10.1055/s-2008-1072742; Art ID: D37407ST

Table 2 Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepines **4a–h** via Azido-Reductive Cyclization Approach by Employing $BF_3{\cdot}OEt_2$ and NaI



3a–h **4a–h**

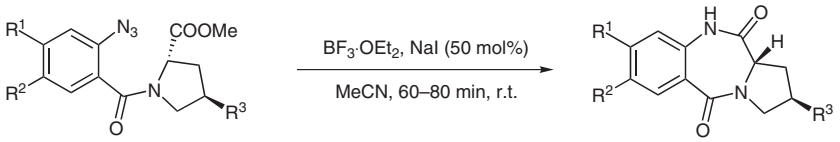
Entry	R^1	R^2	R^3	Time (min)	Yield (%)[a,b]	EIMS
4a	H	H	H	60	92	200
4b	H	Me	H	65	90	214
4c	OBn	OMe	H	70	90	336
4d	OMe	OMe	H	68	88	260
4e	H	H	OH	75	75	216
4f	H	Me	OH	80	78	230
4g	OBn	OMe	OH	80	82	352
4h	OMe	OMe	OH	80	80	276

[a] Isolated yields.
[b] Compounds characterized by ^{1}H NMR, IR, and EIMS.

obtain this product as the aldehyde intermediate is protected by the ethanethiol, which is present in the reaction medium. In contrast the present methodology using $BF_3{\cdot}OEt_2$ and NaI results in the reduction of azide to amine followed by cyclization in a single step.

This reagent system has also been employed towards the preparation of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones. Some of these dilactams have been reported to possess significant in vivo antitumor activity in the P388 rat model.[10] This tricyclic ring system has been used for a number of pharmaceutical applications, including as a template for design and assembly of peptidomimetic agents,[11] anxiolytic drugs,[12] anticonvulsants,[13] and herbicides.[14] Pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones

Table 3 An Efficient Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones **6a–j** via Azido-Reductive Cyclization Approach by Employing $BF_3{\cdot}OEt_2$ and NaI[19,20]



5a–j **6a–j**

Entry	R^1	R^2	R^3	Time (min)	Yield (%)[a,b]	EIMS
6a	H	H	H	60	90	216
6b	H	Me	H	60	96	230
6c	H	Cl	H	65	95	250
6d	OMe	OMe	H	68	90	276
6e	OBn	OMe	H	70	96	352
6f	H	H	OH	68	95	232
6g	H	Me	OH	75	85	246
6h	H	Cl	OH	75	86	266
6i	OMe	OMe	OH	72	78	292
6j	OBn	OMe	OH	80	85	368

[a] Isolated yields.
[b] Compounds characterized by ^{1}H NMR, IR, and EIMS.

have been employed as intermediates in the synthesis of naturally occurring and synthetically modified PBD imines such as tomaymycin and chicamycin.[15] They are also useful precursors for the PBD cyclic secondary amines[16] which can be converted into PBD imines by mild oxidation.[17] Their importance as intermediates for a wide range of biologically active compounds, such as psychomotor depressant activity[18a–c] and sedative activity[18d] has been extensively investigated. The substrates **5a–j** have been converted into its lactams **6a–j** in the presence of $BF_3{\cdot}OEt_2$ and NaI by intramolecular azido-reductive cyclization process to give excellent yields as shown in Table 3.

In summary, we have demonstrated an efficient, mild, cost-effective, and ecofriendly protocol for the reduction of azido functionality. Additionally, this method has been successfully applied to the efficient synthesis of pharmacologically important nitrogen-containing heterocycles, such as pyrrolobenzodiazepine analogues through the intramolecular azido-reductive cyclization process employing this reagent system.

Acknowledgment

The authors N.S. and N.M.K. are grateful to CSIR, New Delhi, for the award of Research Fellowships.

References and Notes

(1) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.
(2) Smith, S. C.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 6379.
(3) McDonald, F. E.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 7001.
(4) (a) Ito, M.; Koyakumaru, K.; Takaya, T. H. *Synthesis* **1995**, 376. (b) Rao, H. S. P.; Siva, P. *Synth. Commun.* **1994**, *24*, 549. (c) Alverez, S. G.; Fisher, G. B.; Singavam, B. *Tetrahedron Lett.* **1995**, *36*, 2567. (d) Molina, P.; Diaz, I.; Tarraga, A. *Tetrahedron* **1995**, *51*, 5617. (e) Ramesha, A. R.; Bhat, S.; Chandrasekaran, S. *J. Org. Chem.* **1995**, *60*, 7682. (f) Capperucci, A.; Degl'Innocenti, A.; Funicello, M.; Mauriello, G.; Scafato, P.; Spagnolo, P. *J. Org. Chem.* **1995**, *60*, 2254. (g) Kamal, A.; Reddy, B. S. P.; Reddy, B. S. N. *Tetrahedron Lett.* **1996**, *37*, 6803. (h) Huang, Y.; Zhang, Y.; Wang, Y. *Tetrahedron Lett.* **1997**, *38*, 1065.
(5) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.
(6) (a) Kamal, A.; Rao, M. V.; Laxman, N.; Ramesh, G.; Reddy, G. S. K. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 215. (b) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Reddy, D. R. *Mini-Rev. Med. Chem.* **2006**, *6*, 53. (c) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Rao, M. V. *Mini-Rev. Med. Chem.* **2006**, *6*, 71.
(7) Thurston, D. E. In *Molecular Aspects of Anticancer Drug-DNA Interactions*, Vol. 1; Neidle, S.; Waring, M. J., Eds.; The Macmillan Press Ltd: London, **1993**, 54.
(8) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433.
(9) Kamal, A.; Shankaraiah, N.; Reddy, K. L.; Devaiah, V. *Tetrahedron Lett.* **2006**, *47*, 4253.
(10) Kneko, T.; Wong, H.; Doyle, T. W.; Rose, W. C.; Brander, W. T. *J. Med. Chem.* **1985**, *28*, 388.
(11) Blackburn, B. K.; Lee, A.; Baier, M.; Kohl, B.; Olivero, A. G.; Matamoros, R.; Robarge, K. D.; McDowell, R. S. *J. Med. Chem.* **1997**, *40*, 717.
(12) Wright, W. B.; Brabander, H. J.; Greenblatt, E. N.; Day, I. P.; Hardy, R. A. *J. Med. Chem.* **1978**, *21*, 1087.
(13) Di Martino, G.; Massa, S.; Corelli, F.; Pantaleoni, G.; Fanini, D.; Palumbo, G. *Eur. J. Med. Chem.* **1983**, *18*, 347.
(14) Karp, G. M.; Manfredi, M. C.; Guaciaro, M. A.; Ortlip, C. L.; Marc, P.; Szamosi, I. T. *J. Agric. Food Chem.* **1997**, *45*, 493.
(15) (a) Kaneko, T.; Wong, H.; Doyle, T. W. *J. Antibiotics* **1984**, *37*, 300. (b) Kamal, A.; Reddy, B. S. P.; Reddy, B. S. N. *Tetrahedron Lett.* **1996**, *37*, 2281. (c) Jones, G. B.; Davey, C. L.; Jenkins, T. C.; Kamal, A.; Kneale, G.; Neidle, S.; Webster, G. D.; Thurston, D. E. *Anti-Cancer Drug Des.* **1990**, *5*, 249. (d) Kaneko, T.; Wong, H.; Doyle, T. W. *Tetrahedron Lett.* **1983**, *24*, 5165.
(16) Kamal, A.; Howard, P. W.; Reddy, B. S. N.; Reddy, B. S. P.; Thurston, D. E. *Tetrahedron* **1997**, *53*, 3223.
(17) (a) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433. (b) Kamal, A.; Rao, M. V.; Reddy, B. S. N. *Khim. Geterotsikl. Soedin.* (*Chem. Heterocycl. Compd.*) **1998**, 1588. (c) Kamal, A.; Rao, N. V. *Chem. Commun.* **1996**, 385.
(18) (a) Carbateas, P. M. US 3,732,212, **1973**; *Chem. Abstr.* **1973**, *79*, P42570x. (b) Carbateas, P. M. US 3,763,183, **1973**; *Chem. Abstr.* **1973**, *79*, P146567t. (c) Carbateas, P. M. US 3,860,600, **1975**; *Chem. Abstr.* **1975**, 83, P58892x. (d) Reddy, B. S. P. *PhD Thesis*; Osmania University: India, **1995**.
(19) General Procedure for Azido Reductions
The substituted aromatic azides were dissolved in MeCN (15 mL), $BF_3{\cdot}OEt_2$ (2.0 equiv), NaI (50 mol%) was added and then solvent stirred at r.t. for 10–80 min to afford reductively cyclized products. The reaction mixture was quenched with aq $Na_2S_2O_3$ followed by neutralization with aq $NaHCO_3$ soln. The mixture was extracted with EtOAc (3 × 35 mL) and the combined organic extracts dried over anhyd Na_2SO_4. The solvent was evaporated under vacuum and the residue purified by column chromatography through SiO_2 (60–120 mesh) eluting with EtOAc–hexane (yields as shown in Tables 1–3).
(20) Selected Data
Compound **2h**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.45 (m, 5 H), 7.22 (s, 1 H), 6.15 (s, 1 H), 5.47–5.90 (br s, 2 H), 5.20 (s, 2 H), 3.84 (s, 3 H), 3.83 (s, 3 H). MS (EI): *m*/*z* = 287 [M$^+$].
Compound **4a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.43 Hz, 1 H), 7.79 (d, *J* = 4.46 Hz, 1 H), 7.53 (t, *J* = 6.69 Hz, 1 H), 7.28–7.38 (m, 2 H), 3.36–3.94 (m, 3 H), 2.26–2.38, (m, 2 H), 2.02–2.16 (m, 2 H). MS (EI): *m*/*z* = 200 [M$^+$]. $[\alpha]_D^{26}$ +343 (*c* 0.4, $CHCl_3$).
Compound **4b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–8.05 (m, 1 H), 7.00–7.80 (m, 1 H), 7.40–7.60 (m, 1 H), 7.20–7.30 (m, 1 H), 3.40–3.90 (m, 3 H), 1.90–2.50 (m, 7 H). MS (EI): *m*/*z* = 214 [M$^+$].
Compound **4e**: ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.84 (d, 1 H, *J* = 7.32), 7.12–7.26 (m, 1 H), 6.95 (d, 1 H, *J* = 5.01 Hz), 6.70–7.80 (m, 2 H), 4.92 (d, 1 H, *J* = 4.81 Hz), 4.17–4.26 (m, 1 H), 4.02 (m, 1 H), 3.50–3.75 (m, 2 H), 1.95–2.10 (m, 1 H), 1.70–1.80 (m, 1 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 166.5, 150.2, 144.6, 133.5, 131.7, 131.4, 128.6, 125.2, 71.0, 56.6, 52.0, 39.5. MS (EI): *m*/*z* 216 [M$^+$]. HRMS: *m*/*z* calcd for $C_{12}H_{12}N_2O_2$: 216.2358; found: 216.2361.
Compound **6a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.22 (br s, 1 H), 7.96–8.08 (d, 1 H, *J* = 8.03 Hz), 7.42–7.58 (t, 1 H, *J* = 8.03, 7.03 Hz), 7.21–7.28 (m, 1 H), 7.03–7.07 (d, 1 H, *J* = 8.03 Hz), 4.05–4.09 (d, 1 H, *J* = 6.57 Hz), 3.75–3.86 (m, 1 H), 3.51–3.65 (m, 1 H), 2.71–2.82 (m, 1 H), 1.85–2.15 (m, 3 H). MS (EI): *m*/*z* = 216 [M$^+$]. HRMS: *m*/*z* calcd for $C_{12}H_{12}N_2O_2$: 216.2358; found: 216.2363.

Compound **6f**: ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.84 (d, 1 H, *J* = 7.3 Hz), 7.12–7.26 (m, 1 H), 6.95 (d, 1 H, *J* = 5.0 Hz), 6.70–6.80 (m, 2 H), 4.92 (d, 1 H, J = 4.8 Hz), 4.17–4.26 (m, 1 H), 4.02–4.10 (m, 1 H), 3.50–3.75 (m, 2 H), 1.95–2.10 (m, 1 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 166.5, 150.2, 144.6, 133.5, 131.7, 131.4, 128.6, 125.2, 71.0, 56.6, 52.0, 39.5. MS (EI): *m*/*z* = 232 [M$^+$]. HRMS: *m*/*z* calcd for $C_{12}H_{12}N_2O_3$: 232.2352; found: 232.2358.

Compound **6j**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.10 (s, 1 H), 7.26–7.40 (m, 6 H), 6.49 (s, 1 H), 5.10 (s, 2 H), 3.98–4.01 (d, 1 H, *J* = 6.44 Hz), 3.91 (s, 3 H), 3.65–3.75 (m, 1 H), 3.42–3.50 (m, 2 H), 2.65–2.75 (m, 1 H), 1.90–2.00 (m, 2 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 171.2, 166.5, 152.2, 146.6, 137.2, 131.4, 129.5, 128.6, 118.3, 113.4, 106.8, 71.0, 68.5, 56.6, 54.0, 35.8. MS (EI): *m*/*z* = 368 [M$^+$]. HRMS: *m*/*z* calcd for $C_{20}H_{20}N_2O_5$: 368.3824; found: 368.3831.