Tetrahedron Letters 53 (2012) 4591–4594

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Intramolecular C–C coupling of 2,6-disubstituted-1-bromoaryls for dihydrophenanthridines

Vijay P. Singh [a], Puspendra Singh [a], Harkesh B. Singh [a,*], Ray J. Butcher [b]

[a] Department of Chemistry, Indian Institute of Technology Bombay, Mumbai 400076, India
[b] Department of Chemistry, Howard University, Washington, DC 20059, USA

ARTICLE INFO

Article history:
Received 10 May 2012
Revised 12 June 2012
Accepted 15 June 2012
Available online 23 June 2012

Keywords:
Intramolecular C–C coupling
Phenanthridine
Dihydrophenanthridine

ABSTRACT

The reaction of 2,6-disubstituted-1-bromoaryl imines with sodium borohydride under reflux condition leads to an intramolecular cyclization through C–Br and C–H coupling without any transition-metal catalyst, furnishing 5,6-dihydrophenanthridine and phenanthridine derivatives.

Phenanthridines are important structural motifs in several natural products and alkaloids.[1,2] Phenanthridine alkaloids including nitidine and sanguinarine have been attractive molecules to synthetic organic chemists and biochemists over the last few decades due to their interesting biological properties.[3–6] To date, the reported phenanthridines are obtained by multistep synthetic sequences, which are constructed by intramolecular ring cyclization methods.[7,8] Phenanthridine (**1**) was obtained from phenanthridone by reduction with lithium aluminum hydride (Fig. 1).[1b] Haloanils when treated with potassium amides in liquid ammonia, afforded phenanthridines via the formation of benzyne intermediate in the cyclization step.[9]

Phenanthridines (**1**–**3**) have been further used to obtain highly functionalized phenanthridines.[10] Leardini and co-workers reported an efficient method for the synthesis of phenanthridines by intramolecular addition of aryl radicals to the C–N double bond.[11] Another class of biologically important phenanthridines, such as phenanthridinone (**4**) has been accessed via palladium-catalyzed aryl C–H activation.[12]

Among phenanthridines, dihydrophenanthridines' (**5**–**6**) skeleton is also found in several natural products and alkaloids.[13] Generally, dihydrophenanthridines are obtained by the reduction of phenanthridines.[14] Functionalized dihydrophenanthridines have also been obtained from amines by treatment with electrophile.[15] A highly convergent route for the synthesis of a variety of dihydrophenanthridines (**7**) has been developed by ring expansion of 4-alkylnyl-4-hydroxycyclobutenones.[13a]

Recently, we have investigated the addition/elimination reactions (S_NAr) of 2,6-disubstituted-1-bromoaryls with selenium nucleophiles.[16] The selenium compounds show unusual reactivity and undergo facile cyclization to give selenium heterocycles **8** and **9** (Fig. 2).[16b,17] In continuation, while attempting to prepare precursors, such as *sec*-amines by the reduction of imines for the synthesis of desired isoselenazolines (**10**)[18] we obtained some functionalized 5,6-dihydrophenanthridines (vide infra). We report our findings in this article.

2-Bromo-3-nitrobenzaldehyde[19] and 2-bromo-3-methylbenzaldehyde[20] were treated with respective amines to prepare imines; **11a**,[16a] **11b**,[18] **11c**,[17] **11d**,[18] and **11e–11h**. Attempted reduction of

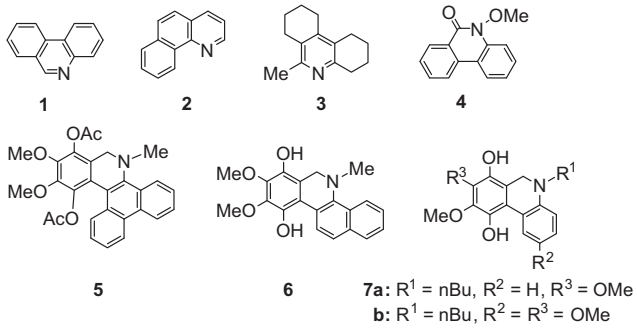


Figure 1. Some phenanthridines (**1**–**4**) and dihydrophenanthridines (**5**–**7**).

* Corresponding author.
E-mail address: chhbsia@chem.iitb.ac.in (H.B. Singh).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.06.087

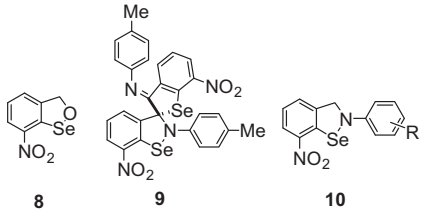
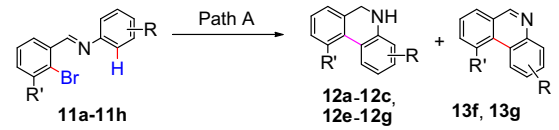


Figure 2. Some selenium heterocycles **8**–**10**.

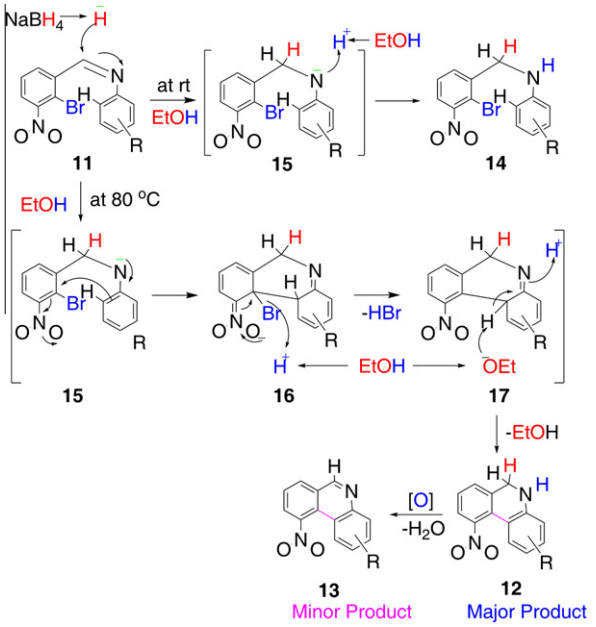


R	R'	11	12	13	14
H	NO_2	**11a**	**12a**	_	**14a**
4-Me	NO_2	**11b**	**12b**	_	**14b**
4-OMe	NO_2	**11c**	**12c**	_	**14c**
4-NO_2	NO_2	**11d**	_	_	**14d**
4-Et	NO_2	**11e**	**12e**	_	**14e**
3,4-Me_2	NO_2	**11f**	**12f**	**13f**	**14f**
2,3-	NO_2	**11g**	**12g**	**13g**	**14g**
4-Me	Me	**11h**	_	_	**14h**

Scheme 1. Synthesis of phenanthridine, dihydrophenanthridines, and *sec*-amines in the presence of $NaBH_4$ and ethanol. Path A; reflux for 5–12 h, Path B; at room temperature for 5 h or reflux 12 h (for **14h**).

imines (**11**) with $NaBH_4$ in ethanol under reflux condition afforded, unexpectedly, 5,6-dihydrophenanthridines **12** in major and (**13**) in minor yield (Scheme 1 and Table 1) via intramolecular C–C coupling. We were able to isolate the minor products along with the major product in two cases. Imine **11f** yielded **12f** (50%) along with **13f** (34%) and **11g** afforded **12g** (47%) and **13g** (15%).

However, the reaction of **11d** containing an electron-withdrawing $–NO_2$ group at the *para*-position of the *N*-phenyl ring gave only **14d**. When the reduction of (**11**) with $NaBH_4$ in ethanol was carried out at the room temperature, the reaction afforded expected **14**. Interestingly, further reaction of *sec*-amine **14e**, under reflux did not yield the expected dihydrophenanthridine **12e**. To find out the role of *ortho*-NO_2 group in the cyclization reaction, when **11h** having an electron-donating methyl group in the place of $–NO_2$ group, was treated with $NaBH_4$, the reaction afforded only the *sec*-amine based bromide (**14h**).



Scheme 2. Plausible mechanism for the formation of compounds **12** and **13**.

Related intramolecular C–C coupling via borohydride reduction of dienone in THF has been reported.[21] The intramolecular C–C coupling takes place due to hydride attack and alkoxide attack on the β-carbon atom of the enone.[22] A similar intramolecular cyclization through C_{Ar}–Cl and C_{Ar}–H coupling by iron or photo-assisted intermolecular electron transfer led to the formation of 9*H*-carbazole and phenanthridine.[23] Based on the literature reports and our own experimental observations, a plausible mechanism (Scheme 2) for the formation of **12**, **13**, and **14** is proposed via the common intermediate **15**. At room temperature reduction, the amide anion generated from the attack of the hydride ion abstracts proton from the protic solvent ethanol to give the *sec*-amine. However, the reaction of $NaBH_4$ and ethanol at high temperature results in the formation of side products $NaB(OEt)_4$ and H^+ in significant quantities.[24] The electrophilic attack of the proton on the carbon bonded to Br (intermediate **15**) leads to the forma-

Table 1
Precursors, products, and their yields in (%)

Entry	R	R′	**11** Yield (%)	**12** Yield[a] (%)	**13** Yield[a] (%)	**14** Yield[b] (%)
1	H	NO_2	**11a** (83)	**12a** (63)	–	**14a** (80)
2	4-Me	NO_2	**11b** (65)	**12b** (60)	–	**14b** (78)
3	4-OMe	NO_2	**11c** (64)	**12c** (47)	–	**14c** (82)
4	4-NO_2	NO_2	**11d** (53)	–	–	**14d** (61)
5	4-Ethyl	NO_2	**11e** (78)	**12e** (75)	–	**14e** (85)
6	3,4-Me_2	NO_2	**11f** (67)	**12f** (50)	**13f** (34)	**14f** (87)
7	2,3-	NO_2	**11g** (73)	**12g** (47)	**13g** (15)	**14g** (70)
8	4-Me	Me	**11h** (60)	–	–	**14h** (76)

[a] The products **12** and **13** were isolated at high temperature in ethanol via Path A shown in Scheme 1.
[b] The product **14** were isolated at room temperature in ethanol via Path B shown in Scheme 1.

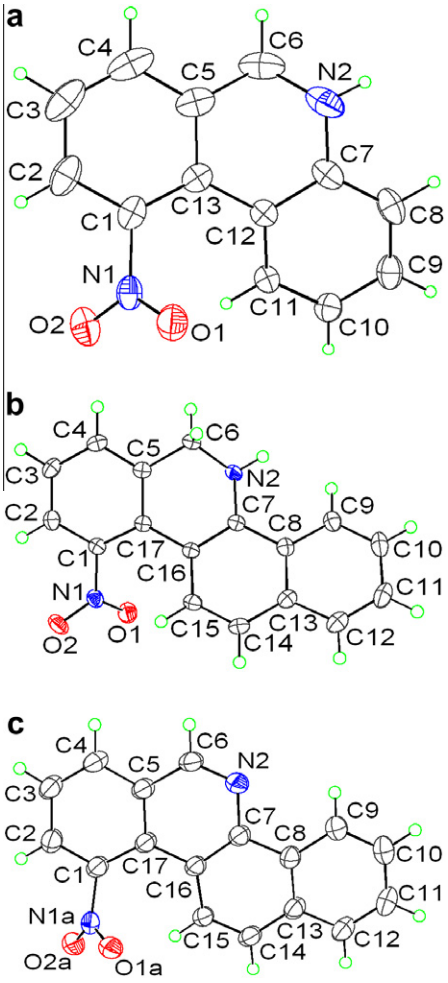


Figure 3. Molecular structures of **12a** (a), **12g** (b), and **13g** (c) shown with 25% (for **12a**) or 50% (for **12g** and **13g**) probability displacement ellipsoids drawn from ORTEP. The disordered NO_2 group (for **13g**) is omitted for clarity.

tion of dihydrophenanthridines via intermediates **16** and **17**. The reducing reagent, $NaBH_4$, and solvent ethanol play crucial roles in the cyclization reaction. The role played by $NaBH_4/NaB(OEt)_4$ is corroborated by attempting the cyclization in the absence of $NaBH_4$. When **14e** was refluxed in ethanol in the absence of $NaBH_4$, no cyclization was observed. Since $NaBH_4$ is the source of hydride ion and which also acts as a base, the cyclization reaction of *sec*-amine was attempted with NaH. The reaction gave a red intractable mixture, which could not be purified and characterized. Also when the *sec*-amine was refluxed with bases Et_3N/NaOH, only the starting material was recovered. Attempted catalytic cyclization of **14e** with $Pd(OAc)_2/Ag_2SO_4$ in AcOH under reflux condition did not lead to the corresponding dihydrophenanthridine.

In order to understand the mechanism of the formation of phenanthridines **13f** and **13g**, the reduction of **11g** under reflux was monitored by TLC for 12 h. It was found that the reaction (for product **12**) was almost complete in 1 h and there was no significant change in the intensity of the red spot for **12** up to 12 h. However, the intensity of the minor product **13**, which appeared after 1 h (a faint yellow spot) increased with time up to 12 h. Therefore, we presume that the minor product is obtained by the aerial oxidation of **12**. The formation of **13** is favored in the cases where *N*-aryl ring is electron rich and also aromatization of phenanthridine ring may be the driving force for the oxidation. Recently, Zhou et al. reported that the conversion of phenanthridine into dihydrophenanthridine is a reversible reaction and in the presence of hydrogen gas it works like a NAD(P)H model for biomimetic asymmetric hydrogenation.[25]

The identities of dihydrophenanthridine derivatives **12** and phenanthridine **13** were established by spectroscopic methods such as IR, ^1H & ^{13}C NMR, and HRMS (please see Supplementary data). The molecular structures of **12a**, **12g**, and **13g** were unambiguously confirmed by single crystal X-ray crystallographic studies[26] (Fig. 3). The structure was solved by direct method and refined by a full-matrix least-squares procedure on F^2 for all reflections in SHELXL-97 software.[27] In summary, an efficient methodology for the high yield and facile synthesis of dihydrophenanthridines from Schiff's bases has been developed. The advantages of this methodology include easy access to the starting materials and one-pot procedure for the C–C bond formation without any transition-metal catalyst. The cyclization reactions of imines having electron-withdrawing *para*-substituents (e.g., NO_2) at the *N*-phenyl ring and electron-donating substituents (e.g., Me) in place of NO_2 in another ring are not viable.

Acknowledgments

HBS is grateful to the Department of Science and Technology (DST), New Delhi, for funding. P.S. thanks the Indian Institute of Technology, Bombay for a Post Doctoral Fellowship and V.P.S. wishes to thank IIT Bombay for a teaching assistantship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.087. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Theobald, R. S.; Schofield, K. *Chem. Rev.* **1950**, *46*, 171; (b) Taylor, E. C., Jr; Martin, A. E. *J. Am. Chem. Soc.* **1952**, *74*, 6295.
2. (a) Le, T. N.; Gang, S. G.; Cho, W.-J. *J. Org. Chem.* **2004**, *69*, 2768; (b) Ruchelman, A. L.; Houghton, P. J.; Zhou, N.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **2005**, *48*, 792.
3. Fleury, F.; Sukhanova, A.; Ianoul, A.; Devy, J.; Kudelina, I.; Duval, O.; Alix, A. J. P.; Jardillier, J. C.; Nabiev, I. *J. Biol. Chem.* **2000**, *275*, 3501.
4. Nakanishi, T.; Masuda, A.; Suwa, M.; Akiyama, Y.; Hoshino-Abe, N.; Suzuki, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2321.
5. Chang, Y.-C.; Hsieh, P.-W.; Chang, F.-R.; Wu, R.-R.; Liwa, C.-C.; Lee, K.-H.; Wu, Y.-C. *Planta Med.* **2003**, *69*, 148.
6. Ishikawa, T. *Med. Res. Rev.* **2001**, *21*, 61.
7. Le, T. N.; Gang, S. G.; Cho, W.-J. *Tetrahedron Lett.* **2004**, *45*, 2763.
8. (a) Nakanishi, T.; Suzuki, M. *Org. Lett.* **1999**, *1*, 985; (b) Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 523.
9. (a) Kesser, S. V.; Singh, M.; Jit, P.; Singh, G.; Lumb, A. K. *Tetrahedron Lett.* **1971**, 471; (b) Kesser, S. V.; Gopal, R.; Singh, M. *Tetrahedron* **1973**, *29*, 167.
10. Andriyankov, L. V.; Mal'kina, A. G.; Nikitina, L. P.; Belyaeva, K. V.; Ushakov, I. A.; Afonin, A. V.; Nikitin, M. V.; Trofimov, B. A. *Tetrahedron* **2005**, *61*, 8031.
11. Gioanola, M.; Leardini, R.; Nanni, D.; Pareschi, P.; Zanardi, G. *Tetrahedron* **1995**, *51*, 2039.
12. Wang, G.-W.; Yuan, T.-T.; Li, D.-D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1380.
13. (a) Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 9168; (b) Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1999**, *64*, 5979; (c) Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1999**, *64*, 6881.
14. (a) Wooten, W. C.; McKee, R. L. *J. Am. Chem. Soc.* **1949**, *71*, 2946; (b) Huttrer, C. P. *J. Am. Chem. Soc.* **1949**, *71*, 4147.
15. Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernán dez, Y. *Chem. Eur. J.* **2002**, *8*, 2034.
16. (a) Singh, V. P.; Singh, H. B.; Butcher, R. J. *Eur. J. Inorg. Chem.* **2010**, 637; (b) Singh, V. P.; Singh, H. B.; Butcher, R. J. *Chem. Asian J.* **2011**, *6*, 1431.
17. Singh, V. P.; Singh, H. B.; Butcher, R. J. *Chem. Commun.* **2011**, *47*, 7221.
18. Singh, V. P.; Singh, H. B.; Butcher, R. J. *Eur. J. Org. Chem.* **2011**, 5485.
19. (a) Rahman, L. K. A.; Scrowston, R. M. J. *Chem. Soc., Perkin. Trans. I* **1984**, 385; (b) Singh, V. P.; Singh, H. B.; Butcher, R. J. *Acta Cryst.* **2009**, *E65*, o2761.
20. (a) Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Text Book of Practical Organic Chemistry*, 4th ed.; Addison-Wesley: Reading, MA, 1978; (b) Miyano, S.; Fukushima, H.; Inagawa, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3285.
21. Kasturi, T. R.; Raju, G. J. *J. Chem. Soc., Chem. Commun.* **1982**, 167.

22. Johnson, M. R.; Rickborn, B. J. *Org. Chem.* **1970**, *35*, 1041.
23. Guastavino, J. F.; Rossi, R. A. *J. Org. Chem.* **2012**, *77*, 460.
24. (a) Brown, H. C.; Mead, E. J.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1955**, *77*, 6209; (b) Davis, R. E.; Gottbrath, J. A. *J. Am. Chem. Soc.* **1962**, *84*, 895.
25. Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2012**, *134*, 2442.
26. *Crystal data for* ***12a***: $C_{13}H_{10}N_2O_2$; Mr = 226.23; orthorhombic; *P*bcn; a = 7.7355(2) Å; b = 13.8253(3) Å; c = 20.3291(4) Å; $\alpha = \beta = \gamma = 90^o$; V = 2174.11(8) Å^3; T = 295(2) K; ρ_{calcd} = 1.382 Mg/m^3; *GOF* = 1.063; R_1 = 0.0413, wR_2 = 0.1175 for [$I > 2\sigma(I)$]; R_1 = 0.0462, wR_2 = 0.1218 for all data. Of the 14911 reflections that were collected, 2288 were unique (R_{int} = 0.0321). Crystal data for **12g**: $C_{17}H_{12}N_2O_2$; Mr = 276.29; monoclinic; *P*21/c; a = 9.7183(3) Å; b = 7.3710(2) Å; c = 18.1991(5) Å; $\alpha = \gamma = 90^o$; β = 98.336(3)^o; V = 1289.90(6) Å^3; T = 123(2) K; ρ_{calcd} = 1.423 Mg/m^3; *GOF* = 1.034; R_1 = 0.0432, wR_2 = 0.1200 for [$I > 2\sigma(I)$]; R_1 = 0.0474, wR_2 = 0.1247 for all data. Of the 4429 reflections that were collected, 2591 were unique (*R*int = 0.0227). Crystal data for **13g**: $C_{17}H_{10}N_2O_2$; Mr = 274.27; monoclinic; *P*21/*n*; a = 8.7715(6) Å; b = 10.8310(6) Å; c = 13.1005(9) Å; $\alpha = \gamma = 90^o$; β = 93.581(6)^o; V = 1242.17(14) Å^3; T = 123(2) K; ρ_{calcd} = 1.467 Mg/m^3; *GOF* = 1.036; R_1 = 0.0705, wR_2 = 0.1969 for [$I > 2\sigma(I)$]; R_1 = 0.0814, wR_2 = 0.2162 for all data. Of the 7346 reflections that were collected, 2551 were unique (R_{int} = 0.0654).
27. Sheldrick, G. M. *SHELXL-97, Program for Crystal Structure Determination*; University of Göttingen: Germany, 1997.