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# Synthesis of partially reduced ferrocenylphenanthrenes from 2-oxobenzo[*h*]chromenes through C–C insertion[☆]

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**Abstract**—An efficient and concise de novo synthesis of ferrocenyl tethered partially reduced phenanthrenes is described through base-catalyzed ring transformation of 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles with acetylferrocene.

The chemistry of ferrocene is highly significant because of its use as a building block for the synthesis of organomaterials[1] displaying unusual solid state properties by virtue of their electron donating nature and fixed intranuclear spacing. The ability of organoferrocenes to form charge transfer complexes and radical ion salts with a wide range of organic and inorganic acceptors makes them highly suitable as components of molecular wires,[2] anion sensors[3] and potential organic ferromagnets.[4] Various ferrocenyl derivatives are reported to display antimalarial,[5] antitumor,[6] and DNA cleaving[7] properties. Phenanthrenes also represent an important class of compounds abundantly distributed in nature, which exhibit a broad spectrum of biological activities.[8–13] The therapeutic importance of both these ring systems inspired us to develop a synthetic strategy by which compounds possessing both ring systems in the same molecule could be prepared efficiently.

Aromatic compounds with covalently linked ferrocene are also of great interest due to their unusual solid state properties and limited synthetic approaches.[14,15] It was apparent from a comprehensive literature survey that partially reduced ferrocenylphenanthrenes have not been reported so far because of the difficulty in introducing the ferrocenyl moiety onto a phenanthrene ring.

Cyclotrimerization of alkynes in the presence of transition metal catalysts is a general approach for the construction of arenes,[16] either in a stepwise or concerted manner. Highly functionalized ferrocenylarenes are conveniently obtained from the reaction of ferrocenyl alkynes and zirconium cyclopentadiene using CuCl or $NiCl_2(PPh_3)_2$ as catalyst.[17,18] The size of the substituent linked to the alkyne enhances the rate of cyclization and yield of the product. The limitations of accessibility of precursors, multistep processes, harsh reaction conditions, low tolerance of functional groups, and use of expensive catalysts, prompted us to develop a novel approach, which could overcome the shortcomings of the earlier procedures and also provide an option for varying the substituent on the aryl ring.

Herein, we report a novel approach for the synthesis of various 3-ferrocenyl-9,10-dihydrophenanthrenes, tethered with an electron-withdrawing and donating substituent through base-catalyzed ring transformation of 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** with acetylferrocene **5** in the presence of powdered KOH in DMF.

The 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitriles **4** were prepared by reaction of methyl 2-cyano-3,3-dimethylthioacrylate **1** and 1-tetralone **2** in DMSO using KOH as base followed by amination of the intermediate 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **3**, with a secondary amine in refluxing ethanol as described earlier[19] (Scheme 1).

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*Keywords*: Acetylferrocene; Ferrocenylphenanthrenes; 2-Oxobenzo[*h*]-chromene; Ring transformation.

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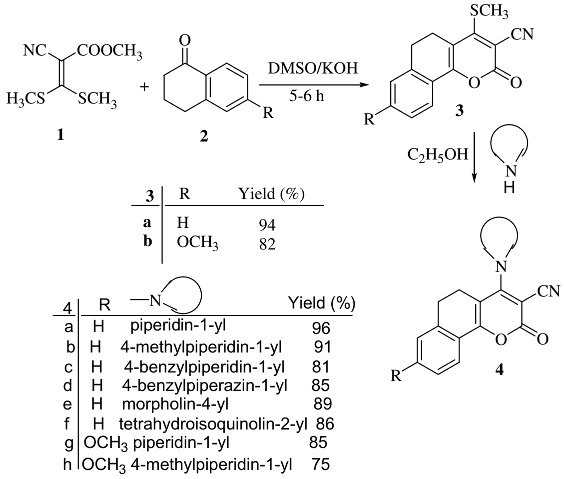


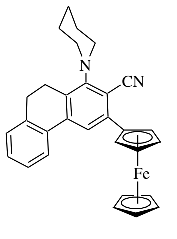
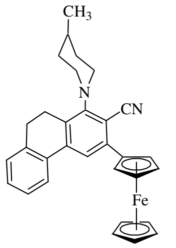
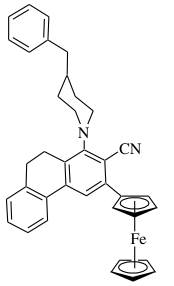
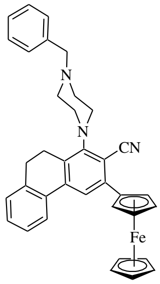
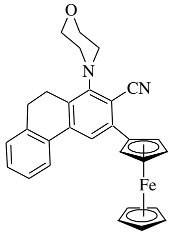
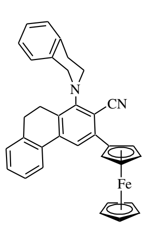
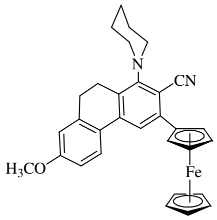
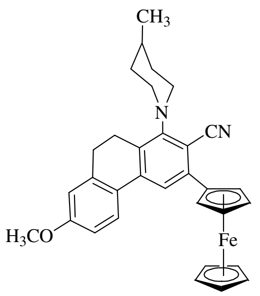
| 3 | R | Yield (%) |
|---|---|---|
| a | H | 94 |
| b | OCH$_3$ | 82 |

| 4 | R | —N | Yield (%) |
|---|---|---|---|
| a | H | piperidin-1-yl | 96 |
| b | H | 4-methylpiperidin-1-yl | 91 |
| c | H | 4-benzylpiperidin-1-yl | 81 |
| d | H | 4-benzylpiperazin-1-yl | 85 |
| e | H | morpholin-4-yl | 89 |
| f | H | tetrahydroisoquinolin-2-yl | 86 |
| g | OCH$_3$ | piperidin-1-yl | 85 |
| h | OCH$_3$ | 4-methylpiperidin-1-yl | 75 |

**Scheme 1.** Synthesis of 2-oxobenzo[*h*]chromene.

As is evident from the structures of 4-*sec*-amino-2-oxo-5,6-dihydrobenzo[*h*]chromene-3-carbonitriles **4**, they posses three electrophilic centers at C-2, C-4, and C-10b in which the latter is highly electrophilic and prone to nucleophilic attack due to extended conjugation and the presence of a electron-withdrawing substituent at position 3 of the chromene ring. The nucleophile used in the present study is the carbanion generated in situ from acetylferrocene in the presence of a base.

**Table 1.** Ferrocenylphenanthrenes **6** synthesized[a]

| 6 | Product | Yields (%) |
|---|---|---|
| **a** |  | 25 |
| **b** |  | 19 |
| **c** |  | 22 |
| **d** |  | 15 |
| **e** |  | 27 |
| **f** |  | 22 |
| **g** |  | 15 |
| **h** |  | 18 |

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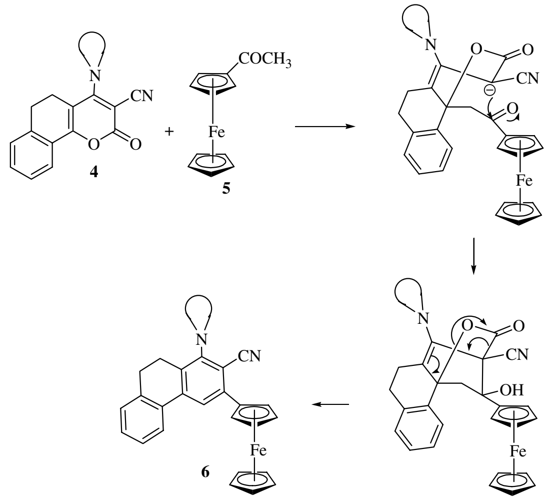
[a] All the compounds synthesized were characterized[20] by spectroscopic techniques.

Thus, a mixture of **4** and acetylferrocene **5** in DMF in the presence of powdered KOH was stirred for 6–7 h at room temperature and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10% HCl. The precipitate obtained was filtered, washed with water several



**Scheme 2.** A plausible mechanism for the formation of 3-ferrocenylphenanthrenes **6**.

times and dried. The crude product was purified by neutral alumina column chromatography in 15–30% yields and characterized as a 3-ferrocenyl-1-*sec.*amino-5,6-dihydrophenanthrene-2-carbonitrile **6** (Table 1). Possibly the initial step in the formation of **6** is the Michael addition of acetylferrocene to 2-oxobenzo[*h*]chromene **4** followed by ring closure with loss of carbon dioxide and water as shown in Scheme 2.

In summary, the synthesis of various ferrocenylphenanthrenes possessing electron-withdrawing and donating substituents has been reported for the first time through base-catalyzed ring transformation of suitably functionalized 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromene with acetylferrocene under very mild reaction conditions through C–C insertion. The procedure is efficient and provides a new avenue for the construction of new ferrocenyl pendant partially reduced phenanthrenes.

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## References and notes

1. *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, 1995.
2. Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304–1319.
3. Beer, P. D.; Dickson, C. A. P.; Fletcher, N.; Goulden, A. J.; Grieve, A.; Hodacora, J.; Wear, T. *J. Chem. Soc., Chem. Commun.* **1993**, 828–830.
4. Miller, J. S.; Epstein, A. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 385–415.
5. (a) Biot, C.; Glorian, G.; Maciejewski, L. A.; Brocard, J. S. *J. Med. Chem.* **1997**, *40*, 3715–3718; (b) Itoh, T.; Shirakami, S.; Ishida, N.; Yamashita, Y.; Yoshida, T.; Kim, H.-S.; Wataya, Y. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1657–1659.
6. Köpf-Maier, P.; Köpf, H. *Drugs Future* **1986**, *11*, 297–319; (b) Köpf-Maier, P.; Köpf, H.; Neuse, E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 456–457.
7. Fruhauf, H.-H. *Chem. Rev.* **1997**, *97*, 523–596; (b) Lautens, M.; Tam, W. *Chem. Rev.* **1996**, *96*, 49; (c) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539–556; (d) Dell, C. P. *Curr. Med. Chem.* **1998**, *5*, 179–194; (e) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2915.
8. Huffmann, C. W.; Traxler, J. T.; Krbechek, L.; Riter, R. R.; Wagner, R. G. *J. Med. Chem.* **1971**, *14*, 90.
9. Wilson, S.; Ruenitz, P. C. *J. Pharm. Sci.* **1992**, *82*, 571.
10. Fisch, M. H.; Flick, B. H.; Arditti, J. *Phytochemistry* **1973**, *12*, 437.
11. Kelly, T. R.; Li, Q.; Bhushan, V. *Tetrahedron Lett.* **1990**, *31*, 161.
12. (a) Tanabe, A.; Nakashima, H.; Yoshida, O.; Yamamoto, N.; Tenmyo, O.; Oki, T. *J. Antibiot.* **1988**, *41*, 1708; (b) Hoshino, H.; Seki, J.-I.; Takeuchi, T. *J. Antibiot.* **1989**, *42*, 344.
13. Cannon, J. G.; Khonji, R. R. *J. Med. Chem.* **1975**, *18*, 110.
14. Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organometallics* **1995**, *14*, 5486.
15. Egger, H.; Schlogl, K. *Monatsh. Chem.* **1964**, *96*, 1750.
16. (a) Negishi, E.; Holmes, S. J.; Tour, J.; Miller, J. A.; Cedebaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336–3346; (b) Buchwald, S. I.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870–2874; (c) Negishi, E.; Cedebaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829–2832.
17. Takahashi, T.; Tsai, F. Y.; Li, Y. Z.; Nakazima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093.
18. Dufkova, L.; Matsumura, H.; Necas, D.; Stepnicka, P.; Uhlik, F.; Kotora, M. *Collect. Czech. Chem. Commun.* **2004**, *69*, 351–364.
19. Pratap, R.; Ram, V. J. *Tetrahedron Lett.* **2007**, *48*, 2755.
20. *1-sec-Amino-3-ferrocenyl-9,10-dihydro-phenanthrene-2-carbonitriles* (**6**): A mixture of 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile (0.5 mmol), acetylferrocene and KOH in DMF was stirred for 6–7 h. The reaction was monitored by TLC. Excess DMF was removed under reduced pressure and the reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10% aqueous HCl. The crude product thus obtained was filtered, washed with water, dried, and purified by neutral alumina column chromatography using 20% chloroform in hexane as eluent. Compound **6d**: Viscous oil; yield: 15%; IR (KBr): 2209 (CN) $\text{cm}^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.65–2.75 (br s, 4H, $CH_2$), 2.87–2.89 (m, 4H, $CH_2$), 3.45–3.55 (m, 4H, $CH_2$), 3.64 (s, 2H, $CH_2$), 4.20 (s, 5H, FcH), 4.43 (t, $J = 1.83$ Hz, 2H, ArH), 4.92 (t, $J = 1.86$ Hz, 2H, FcH), 7.32–7.41 (m, 8H, ArH), 7.74–7.78 (m, 1H, ArH), 7.82 (s, 1H, ArH); MS *m*/*z* 564 ($M^+$+1); HRMS: (EI, 70 eV) calcd for $C_{36}H_{33}FeN_3$, 563.20239 ($M^+$), found *m*/*z* 563.20353.