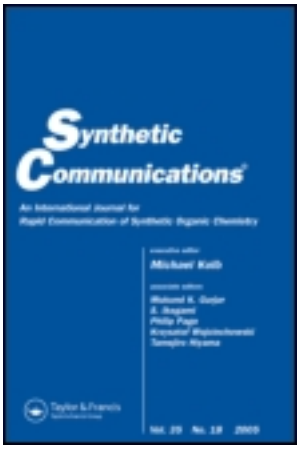


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Synthesis of Hexahydrocarbazoles

Sharada S. Labadie [a] & Christa Parmer [a]

[a] Department of Medicinal Chemistry, Roche Palo Alto LLC, Palo Alto, California, USA

Published online: 29 Apr 2011.

To cite this article: Sharada S. Labadie & Christa Parmer (2011) Efficient Synthesis of Hexahydrocarbazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:12, 1752-1758, DOI: 10.1080/00397911.2010.492080

To link to this article: http://dx.doi.org/10.1080/00397911.2010.492080

Synthetic Communications®, 41: 1752–1758, 2011

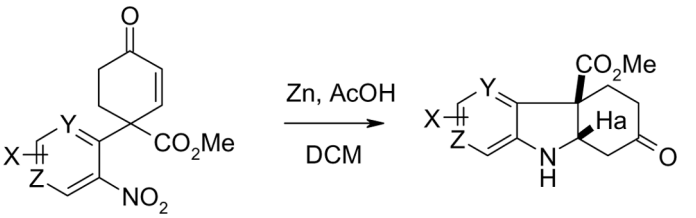
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.492080

Taylor & Francis
Taylor & Francis Group

EFFICIENT SYNTHESIS OF HEXAHYDROCARBAZOLES

Sharada S. Labadie and Christa Parmer
Department of Medicinal Chemistry, Roche Palo Alto LLC, Palo Alto, California, USA

GRAPHICAL ABSTRACT



Abstract *Selective reduction of the nitro group in methyl 1-(2-nitrophenyl)-4-oxo-cyclohex-2-enecarboxylates with zinc-acetic acid forms hexahydrocarbazoles. The reaction is applicable to the corresponding pyridyl analogs to generate azahexahydrocarbazoles. This provides an efficient method for the generation of tricyclic framework.*

Keywords Azahexahydrocarbazoles; Diels–Alder reaction; hexahydrocarbazoles; zinc-acetic acid reduction

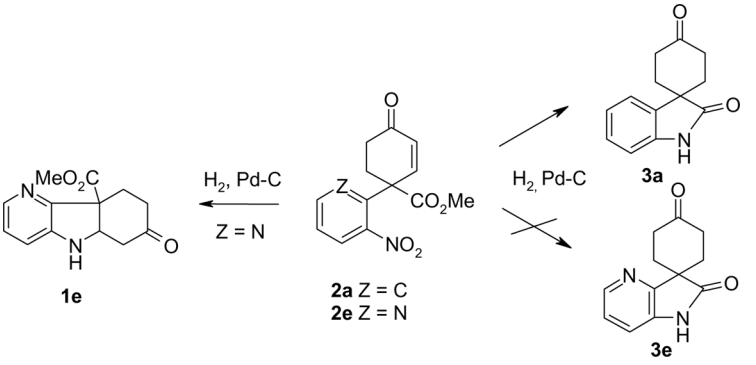
The hexahydrocarbazole framework occurs in a number of biologically active natural products, the syntheses of which have been studied extensively.[1,2] Recently reported syntheses of the hexahydrocarbazole framework indicate that there still is a need for new, preferably simple, methods for the generation of such entities.[3] As described in the previous paper,[4] the hexahydrocarbazole **1e** was formed unexpectedly from methyl 1-(3-nitropyridin-2-yl)-4-oxo-cyclohex-2-enecarboxylate **2e** in an attempt to form the spirocycle **3e** (Scheme 1). Given this constitutes a simple two-step synthesis of the tricyclic framework, the scope of this process was further investigated.

The cyclohexenonecarboxylates **2a–h**, the required precursors for this synthetic study, were prepared as described in the previous paper,[4] by a Diels–Alder reaction of methyl 2-(2-nitroaryl)acrylates **4a–h** with *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene **5** (Table 1). Whereas the palladium-catalyzed hydrogenation of the pyridyl compound **2e** produced hexahydrocarbazole **1e**, catalytic reduction of **2a**

Received January 29, 2010.

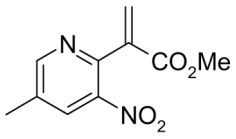
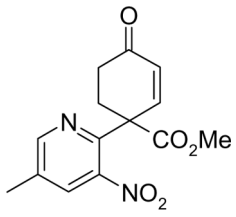
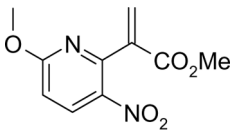
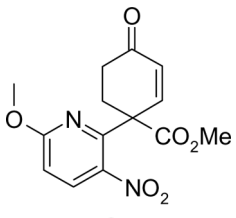
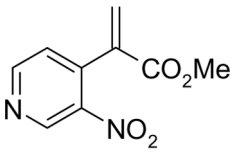
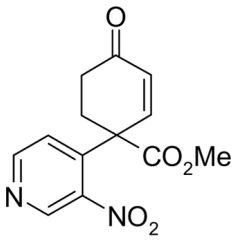
Current name and affiliation for Christa Parmer: Christa Tatyosian, Bio-Rad Laboratories, Hercules, California, USA.

Address correspondence to Sharada S. Labadie, Genentech, MS: 18B, 1 DNA Way, So. San Francisco, CA 94080-4990, USA. E-mail: labadie.sharada@gene.com

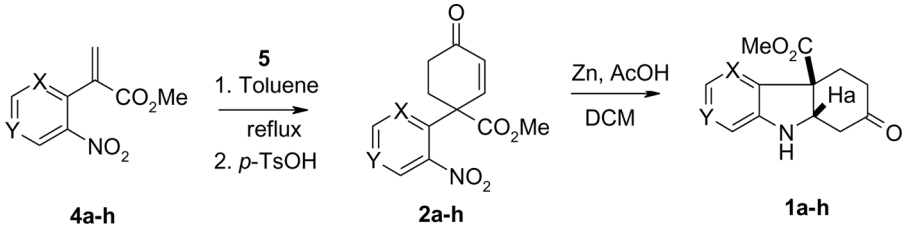


Scheme 1. Results of hydrogenation of **2a** and **2e**.

Table 1. Formation of cyclohexenones as in Scheme 2[a]

Entry	Acrylate	Cyclohexenone	Yield %
1	 **4f**	 **2f**	87
2	 **4g**	 **2g**	85
3	 **4h**	 **2h**	75

[a]All are isolated yields and are not optimized. Synthesis of cyclohexenones **2a–e** are described in the previous paper.[4]

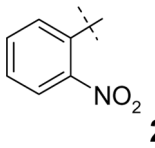
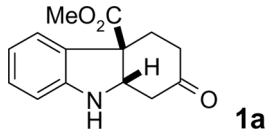
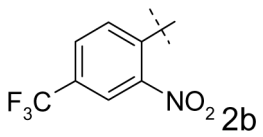
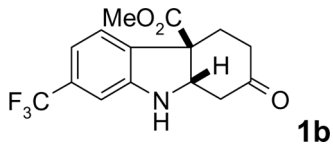
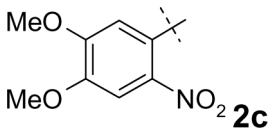
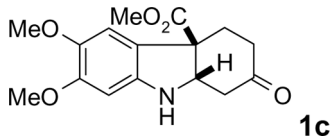
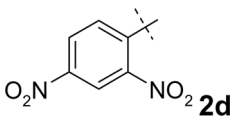
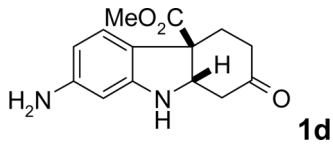


Scheme 2. Synthesis of hexahydrocarbazoles.

gave the spirocyclic oxindole compound **3a**. It was therefore essential to effect selective reduction of the nitro group to ensure exclusive formation of hexahydrocarbazoles. This was readily achieved by reduction of **2a–h** with zinc in acetic acid solution (Scheme 2). Under these conditions, the desired hexahydrocarbazoles **1a–d** were obtained in poor (**1d**) to moderate yields, whereas the corresponding aza compounds **1e–h** were all produced in good yields (Table 2).

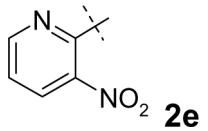
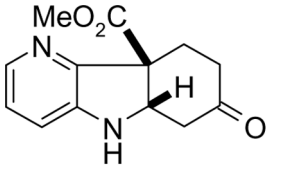
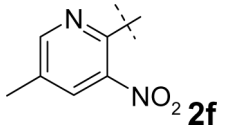
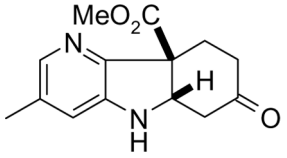
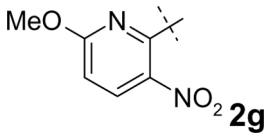
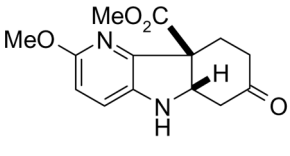
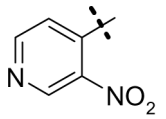
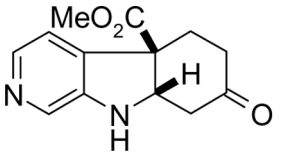
It should be noted that ring closure occurred with the formation of a *cis*-fused framework, a result for which there is ample literature precedent.[5] This was confirmed for compound **1b** by observation of a strong nuclear Overhauser effect (NOE) between H_a and the ester methyl group.

Table 2. Formation of hexahydrocarbazoles as in Scheme 2

Entry	Cyclohexenone	Hexahydrocarbazole	Yield[a] (%)
1	 **2a**	 **1a**	67
2	 **2b**	 **1b**	47
3	 **2c**	 **1c**	66
4	 **2d**	 **1d**	20[b]

(*Continued*)

Table 2. Continued

Entry	Cyclohexenone	Hexahydrocarbazole	Yield[a] (%)
5	 **2e**	 **1e**	80
6	 **2f**	 **1f**	69
7	 **2g**	 **1g**	66
8	 **2h**	 **1h**	75

[a]All are isolated yields and are not optimized.
[b]Isolated as an HCl salt.

In summary, a simple two-step synthesis of highly functionalized hexahydrocarbazoles is described. The method tolerates a variety of functionalities and uses readily accessible starting materials. To our knowledge, this is the first reported synthesis of azahexahydrocarbazoles.

EXPERIMENTAL

Cyclohexenonecarboxylates **2a–h** were synthesiszed as described in the previous paper.[4] The analytical data for those not reported earlier are as follows.

Methyl 1-(5-Methyl-3-nitropyridin-2-yl)-4-oxo-cyclohex-2-enecarboxylate 2f

Mp 101–103 (hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.62$ (d, $J = 1.5$ Hz, 1 H), 8.12 (d, $J = 1.5$ Hz, 1 H), 7.04 (d, $J = 10.2$ Hz, 1 H), 6.20 (d, $J = 10.2$ Hz, 1 H), 3.72 (s, 3 H), 3.0–2.57 (m, 4 H), 2.48 (s, 3 H). Anal. calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.98; H, 4.73; N, 9.63.

Methyl 1-(6-Methoxy-2-nitropyridin-2-yl)-4-oxocyclohexen-2-enecarboxylate 2g

Mp 89–90 (hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.34$ (d, $J = 9.0$ z, 1 H), 7.06 (d, $J = 10.2$ Hz, 1 H), 6.83 (d, $J = 9.0$ Hz, 1 H), 6.20 (d, $J = 10.2$ Hz, 1 H), 3.99 (s, 3 H), 3.73 (s, 3 H), 3.02–2.50 (m, 4 H). Anal. calcd. for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.76; H, 4.37; N, 9.15.

Methyl 1-(3-Nitropyrid-4-yl)-4-oxo-cyclohexen-2-enecarboxylate 2h

Mp 85–87 °C (hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 9.21$ (s, 1 H), 8.81–8.79 (m, 0 H), 7.41 (d, $J = 4.9$ Hz, 1 H), 6.75 (d, $J = 10.2$ Hz, 1 H), 6.39 (d, $J = 10.2$ Hz, 1 H), 3.73 (s, 3 H), 3.34–3.16 (m, 1 H), 3.07–2.90 (m, 1 H), 2.39 (d, $J = 4.5$ Hz, 2 H). Anal. calcd. for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.21; H, 4.22; N, 9.97.

Synthesis of Hexahydrocarbazoles 1a–h

Hexahydrocarbazole 1a. Acetic acid (0.6 mL) was added to a vigorously stirred mixture of **2a** (0.1 g, 0.36 mmol) and zinc dust (0.6 g) in dichloromethane (10 mL), and the heterogeneous mixture was stirred for 18 h. Solids were removed by filtration through a Celite washing well with dichloromethane. The filtrate was stirred over aqueous $NaHCO_3$ solution (20 mL), and the organic layer was separated. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, 20–60% EtOAc/hexane) to obtain **1a** as an off-white solid (0.07 g): mp 109–110 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$–7.29 (m, 1 H), 7.18–7.03 (m, 1 H), 6.83–6.70 (m, 1 H), 6.66–6.52 (m, 1 H), 4.94–4.84 (m, 1 H), 3.82 (s, 3 H), 2.84–2.56 (m, 2 H), 2.28 (d, 4 H). Anal. calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.48; N, 6.11; N, 5.78.

The following were obtained in a similar fashion.

Compound 1b. Mp 75–76 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.42$ (d, $J = 7.9$ Hz, 1 H), 7.02 (d, $J = 7.9$ Hz, 1 H), 6.78 (s, 1 H), 4.93 (d, $J = 3.4$ Hz, 1 H), 4.14 (d, $J = 2.3$ Hz, 1 H), 3.83 (s, 3 H), 2.87–2.56 (m, 2 H), 2.53–1.98 (m, 4 H). Anal. calcd. for $C_{15}H_{14}F_3NO_3$: C, 57.51; H, 4.50; N, 4.47. Found: C, 57.41; H, 4.31; N. 4.58.

Compound 1c. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 6.90$ (s, 1 H), 6.25 (s, 1 H), 4.87 (t, $J = 3.6$ Hz, 1 H), 3.94–3.71 (m, 9 H), 2.83–2.55 (m, 2 H), 2.46–2.00 (m, 4 H); MS (ESI): $m/z = 306$ (M + 1).

Compound 1d. ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 6.84$–6.68 (m, 1 H), 5.90–5.78 (m, 1 H), 5.78–5.67 (m, 1 H), 5.70–5.60 (m, 1 H), 4.89–4.71 (m, 2 H), 4.71–4.51 (m, 1 H), 3.69 (s, 3 H), 2.50 (d, $J = 1.9$ Hz, 6 H); MS (ESI): $m/z = 261$ (M + 1).

Compound 1e. Mp 149–150 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.99$ (dd, $J = 1.5$, 4.9 Hz, 1 H), 7.00 (dd, $J = 4.9$, 7.9 Hz, 1 H),

6.93–6.79 (m, 1 H), 4.96–4.83 (m, 1 H), 4.01–3.94 (m, 1 H), 3.83 (s, 3 H), 2.78 (d, $J = 3.8$ Hz, 1 H), 2.66–2.52 (m, 3 H), 2.41–2.31 (m, 1 H), 1.98 (m, 1 H). Anal. calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40, H, 5.73; N, 11.38. Found: C, 63.50; H, 5.68; N, 11.43.

Compound 1f. Mp 128–129 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.82$ (s, 1 H), 6.69 (s, 1 H), 4.88 (t, $J = 3.6$ Hz, 1 H), 3.81 (s, 3 H), 2.86–2.27 (m, 5 H), 2.88–2.27 (m, 5 H), 2.24 (s, 3 H), 2.23 (s, 3 H), 1.97 (s, 1 H). Anal. calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.22; H, 6.06; N, 10.72.

Compound 1g. Mp 140–141 °C (EtOAc/hexane).^{1}H NMR (300 MHz $CDCl_3$) $\delta = 6.92$ (d, $J = 8.3$ Hz, 1 H), 6.50 (d, $J = 8.7$ Hz, 1 H), 4.80 (t, $J = 3.8$ Hz, 1 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 2.80–2.28 (m, 5 H), 2.07–1.91 (m, 1 H). Anal. calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.86; H, 5.79; N, 10.17.

Compound 1h. Mp 218–220 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 7.86$ (d, $J = 4.5$ Hz, 1 H), 7.82 (s, 1 H), 7.25 (d, $J = 4.9$ Hz, 1 H), 6.33 (d, $J = 3.0$ Hz, 1 H), 4.70–4.65 (m, 1 H), 3.73 (s, 3 H), 2.84 (dd, $J = 3.8$, 15.9 Hz, 1 H), 2.56–2.39 (m, 3 H), 2.25–2.08 (m, 2 H); MS (ESI) $m/z = 247$ (M + 1).

ACKNOWLEDGMENTS

The authors acknowledge Dr. Francisco Talamas and Dr. Josh Taygerly for their valuable input and the analytical department for providing the spectroscopic and physical data.

REFERENCES

1. (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. The total synthesis of strychnine. *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751; (b) Saxton, J. E. In *The Alkaloids of the Aspidospermine Group*; G. A. Cordell (Ed.); Academic Press: New York, 1998; vol. 51, p. 1; (c) Ando, M.; Büchi, G.; Ohnuma, T. The total synthesis of (±)-vindoline. *J. Am. Chem. Soc.* **1975**, *97*, 6880; (d) Zhou, S.-Z.; Bommezijn, S.; Murphy, J. A. Formal total synthesis of (±)-vindoline by tandem radical cyclization. *Org. Lett.* **2002**, *4*, 443, and references therein; (d) Choi, Y.; Ishikawa, H.; Velcicky, J.; Elliott, G. I.; Miller, M. M.; Boger, D. L. Total synthesis of (−)- and ent-(+)-vindoline. *Org. Lett.* **2005**, *20*, 4539–4542; (e) Benchekroun-Mounir, N.; Dugat, D.; Gramain, J. C. A short synthesis of (±)-N-benzyl aspidospermidine. *Tetrahedron Lett.* **1992**, *33*, 4001–4004.
2. (a) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. Organocatalytic asymmetric Diels–Alder reactions of 3-vinylindoles. *Angew. Chem., Int. Ed.* **2008**, *47*, 9236; (b) Fu, J.-M. Preparation of arylsulphonyl-substituted tetrahydro- and hexahydrocarbazolamines as 5-HT6 receptor ligands. WO Patent 2003030901, **2003**; (c) Fernandez, F.; Garcia-Mera, X.; Rodriguez, G.; Urrutia, A. New hexahydrocarbazoles and spiro indoles and their affinity for D2 dopamine and 5-HT2A serotonin receptors. *Chem. Pharm. Bull.* **1999**, *47*, 1006; (d) Rodriguez, J. G.; Urrutia, A. Synthesis of sterically hindered 4a,9a-disubstituted 1,2,3,4,4a,9a-hexahydrocarbazoles from 4a-methyl-1,2,3,4-tetrahydro-4aH-carbazole with organolithium reagents. *Tetrahedron* **1998**, *54*, 15613; (d) McCarthy, C.; Jones, K. Indole alkaloid synthesis: A stereospecific preparation of functionalized *cis*-hexahydrocarbazoles. *J. Chem. Soc., Chem. Comm.* **1989**, *22*, 1717; (e) Borch, R. F.; Newell, R. G. Novel synthesis of 2-oxo-1,2,3,4-tetrahydrocarbazoles. *J. Org. Chem.* **1973**, *38*, 2729–2730.

3. (a) Hyde, A. M.; Buchwald, S. L. Palladium-catalyzed γ-arylation of β,γ-unsaturated ketones: Application to a one-pot synthesis of tricyclic indolines. *Angew. Chem. Int. Ed.* **2008**, *47*, 177–180; (b) Beniazza, R.; Dunet, J.; Robert, F.; Schenk, K.; Landais, Y. Efficient synthetic approaches to common indole alkaloids. *Org. Lett.* **2007**, *9*, 3913–3916; (c) Heureux, N.; Wouters, J.; Mark, I. E. Sequential acid/base-catalyzed polycyclization of the tryptamine derivatives: A rapid access to Büchi's ketone. *Org. Lett.* **2005**, *7*, 5245–5248; (d) Marcos, I. S.; Moro, R. F.; Costales, I.; Escola, M. A.; Basabe, P.; Diez, D.; Urones, J. G. Synthesis of hexahydrocarbazoles by cyclisation of 3-(but-3-enyl) indole derivatives. *Tetrahedron* **2009**, *65*, 10235–10242; (e) Majumdar, K. C.; Kundu, U. K.; Das, U.; Jana, N. K.; Roy, B. N-Iodosuccinimide, an effective reagent for regioselective heterocyclization of o-cyclohex-2′-enylanilines for the synthesis of hexahydrocarbazoles. *Can. J. Chem.* **2005**, *83*, 63–67; (f) Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. Diethylphosphine oxide (DEPO): High-yielding and facile preparation of indolones in water. *Org. Lett.* **2003**, *5*, 2971–2974.
4. Labadie, S. S.; Parmer, C. Facile synthesis of spirocyclic oxindole, azaoxindole, and dihydroisoquinolone. *Synth. Commun.* **2011**, *41*, 1742–1751.
5. (a) Rupprecht, K. M.; Boger, J.; Hoogsteen, K.; Nachbar, R. B.; Springer, J. P. Controlling the stereochemistry of the ring junction in hexahydrodibenzofurans. *J. Org. Chem.* **1991**, *56*, 6180–6188; (b) Hamilton, C. J.; Fairlamb, A. H.; Egleston, I. M. Regiocontrolled synthesis of the macrocyclic polyamine alkaloid (±)-lunarine, a time-dependent inhibitor of trypanothione reductase. *J. Chem. Soc. Perkin Trans. I* **2002**, 1115–1123.