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Enamine Precursors of 1-Substituted-1,2,3,4-Tetrahydro-ß-carbolines by way of a Peterson Reaction

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Abstract: Enamines, prepared by way of a Peterson reaction between N^b-formyl-N^a, N^b-dimethyltryptamine and lithio derivatives of aromatic nitrogen heterocycles bearing a trimethylsilylmethyl group α- or γ- to the nitrogen atom, cyclize readily to ß-carbolines.

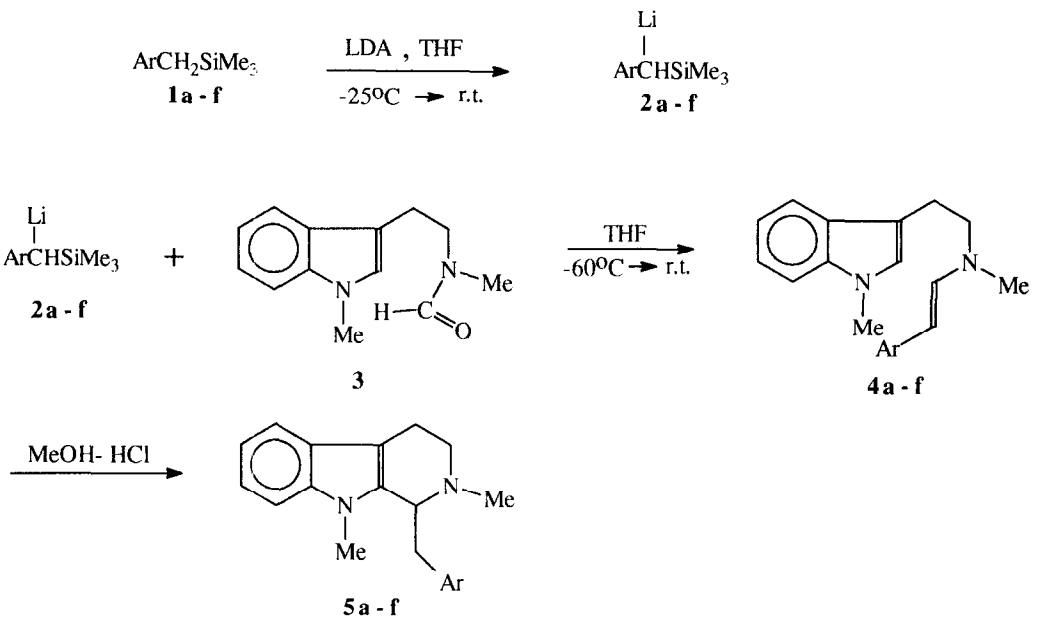
Acyclic enamines derived from N^b-alkyltryptamines[1-3] and N^b-alkyltryptophans[4] are useful precursors of 1-substituted-1,2,3,4-tetrahydro-ß-carbolines and 1,3-disubstituted-1,2,3,4-tetrahydro-ß-carbolines, respectively. The enamines have been prepared by a variety of methods, for example, the addition of N^b-alkyltryptamines[1] and N^b-alkyltryptophans[4] to activated alkynes, an exchange reaction between the dimethylamino group of an *N,N*-dimethylaminoethenamine and N^b-methyltryptamine,[2] and a reaction between an enolate and N^b-methyltryptamine.[3] We report here a method, involving a Peterson reaction,[5] in which lithio derivatives of aromatic nitrogen heterocycles bearing a trimethylsilymethyl group α- or γ- to the nitrogen are treated with N^b-formyl-N^a, N^b-dimethyltryptamine **3**[6] to afford enamines. Cyclization of the enamines to 1,2,3,4-tetrahydro-ß-carbolines was effected by treatment with a saturated solution of hydrogen chloride in methanol. The general reaction, illustrated in Scheme 1, has been applied successfully to 3-ethyl-4-trimethylsilylmethylpyridine, 2- and 4-trimethylsilylmethyl pyridines and quinolines, and 6,7-dimethoxy-1-trimethylsilylmethylisoquinoline. In all cases the intermediate enamines cyclized readily to 1-arylmethyl-1,2,3,4-tetrahydro-ß-carbolines.

The trimethylsilylmethyl compounds, **1a** - **1f**, were prepared from the parent methylated heterocycles, using conditions similar to those reported for the preparation of the **1c**[7] and were converted into their lithio derivatives by treatment with lithium diisopropylamine (LDA) in tetrahydrofuran (THF). Compounds **1a**, **1b**, and **1c** were isolated and fully characterized but **1d**, **1e**, and **1f** were not isolated but were converted *in situ* into the corresponding lithio derivatives.

Compound **3** was prepared previously by treatment of N^a, N^b-dimethyltryptamine with ethyl formate; however, we found it more convenient to prepare **3** from N^b-formyltryptamine.[8] A solution of dimsylsodium (2.25 equivalents) in dimethylsulfoxide (DMSO) was added to a solution of N^b-formyltryptamine in DMSO and the red solution was stirred for 3 h at 20 °C before quenching with 3 equivalents of iodomethane. The resulting mixture was stirred for 30 min, water was added, and the solution was extracted with dichloromethane. The extract was evaporated to dryness and the residue purified by preparative-layer, radial

chromatography [silica gel 60 PF_{254}, ethyl acetate–hexane, 2:1 (v/v)] to afford **3** as an oil in ~ 90% yield. The ^1H NMR spectrum of **3** agreed with that in the literature[6] and the ^{13}C NMR spectrum confirmed the earlier finding that **3** is a mixture of rotamers.

The enamines were prepared by dropwise addition of a solution of **3** in THF to stirred solutions of **2a - f** in THF at –60 °C in an argon atmosphere. The mixtures were kept at –60 °C for 1 h after which time the temperature was allowed to rise to 20 °C where it was maintained for 1 h more. The reaction mixtures were quenched with water and the solutions extracted with dichloromethane. The crude residues obtained upon evaporation of solvent were purified by preparative-layer, radial chromatography (silica gel 60 PF_{254}, ethyl acetate) in the cases of **4a**, **4b**, and **4c** but **4d**, **4e**, and **4f** were not purified further because they were sensitive to decomposition on chromatography. Compounds **4a - 4f** have the (*E*)–configuration about the enamine double bond as evidenced by the large coupling constants ($J \approx 13.0$ - 13.5 Hz) between the vinylic protons. Treatment of compounds **4a - 4f** with a saturated solution of hydrogen chloride in methanol afforded compounds **5a - 5f**, respectively. The yields of **5a - 5f** are based on Compound **3**: **5a** (mp 118 - 119 °C, 45%); **5b** (mp 155 - 156 °C, 44%); **5c** (oil, 52%); **5d** (mp 171 - 172 °C, 34%); **5e** (oil, 42%); **5f** (oil, 61%).



Ar = **a**, 3-ethylpyridin-4-yl ; **b**, pyridin-4-yl ; **c**, pyridin-2-yl ; **d**, quinolin-4-yl ; **e**, quinolin-2-yl ; **f**, 6,7-dimethoxyisoquinolin-1-yl .

Scheme 1

The structures of all compounds are supported by ^{1}H NMR and mass spectra and for the ß-carbolines by ^{13}C NMR as well. All compounds gave single spots on tlc analysis; exact masses, determined by hrms, agreed with calculated values within $\pm$ 0.003 Daltons. Spectroscopic data[9] are given for **3**, **4a** and **5a**; space limitation did not permit inclusion of data for all compounds. Spin decoupling and nOe experiments were used to assign signals in the ^{1}H NMR spectra in the case of **3** and **5a**; selective proton decoupling was used to assign signals in the ^{13}C NMR spectra.

This method of preparation of ß-carbolines may be considered a variant of the classical Pictet-Spengler reaction,[10] in that the same intermediate is deemed to be involved in the cyclization step. This approach will be preferred in those cases where the aldehydes required for a Pictet-Spengler reaction are unstable or difficult to access. The utility of this approach to the synthesis of other heterocyclic systems is under investigation.

We have developed a simple method for the preparation of **3**, and have demonstrated that formamide **3**, by way of a Peterson reaction, may be converted into enamines that cyclize readily to ß-carbolines.

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REFERENCES AND NOTES

1. Vercauteren, J.; Lavaud, C.; Lévy, J.; Massiot, G. *J. Org. Chem.* **1984**, *49*, 2278 - 2279.
2. McGee, L.R.; Reddy, G.S.; Confalone, P.N. *Tetrahedron Lett.* **1984**, *25*, 2115 - 2118.
3. Onanga, M.; Khuong-Huu, F. *Tetrahedron Lett.* **1983**, *24*, 3627 - 3630.
4. Bailey, P.D.; Hollinshead, S.P.; Dauter, Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1507 - 1509.
5. Peterson, D.J. *J. Org. Chem.* **1968**, *33*, 780 - 784.
6. Nakagawa, M.; Kaneko, T.; Yamaguchi, H.; Kawashima, T.; Hino, T. *Tetrahedron*, **1974**, *30*, 2591 - 2600.
7. Konakahara, T.; Takagi, Y. *Heterocycles*, **1980**, *14*, 393 - 396.
8. Schöpf, C.; Steuer, H. *Ann.* **1947**, *558*, 124 - 136.
9. In **4a** and **5a** the protons and carbon atoms of the pyridine ring are designated by a single prime, those on the indole ring of **4a** by a double prime.

   3. ^{1}H nmr (500 Mz, $CDCl_3$) δ: 2.85 and 2.91 (3 H, 2s, N ^{b}Me), 2.96 and 2.99 (2 H, 2 t, $J \approx 6.9$ and 7.6 Hz, CH_2CH_2N), 3.49 and 3.62 (2 H, 2 t, $J \approx 6.9$ and 7.6 Hz CH_2CH_2N), 3.70 (3 H, s, N ^{a}Me), 6.80 and 6.89 (1 H, 2 s, H-2) 7.10 - 7.13 (1H, t, H-5), 7.20 - 7.24 (1H, m, H-6), 7.26 - 7.29 (1H,

overlapping d, H-7) 7.51 and 7.53 (1H, 2 d J, ≈ 7.5 and 7.9 Hz, H-4), 7.78 and 8.03 (1 H, 2 s, C*H*=O);[13]C nmr (125.8 MHz, $CDCl_3$) δ: 22.56 and 24.21 (CH_2CH_2N), 29.47 and 34.79 (N ^{b}Me), 32.45 (N ^{a}Me), 44.91 and 50.04 (CH_2CH_2N), 109.12 and 109.35 (C-7), 110.00 and 111.09 (C-3), 118.23, 118.60, 118.74 and 118.91 (C-4 and C-5), 121.49 and 121.68 (C-6), 126.59 and 126.96 (C-2) 127.30 and 127.71 (C-3a), 136.91 and 137.01 (C-7a) 162.29 and 162.53 (*C*H=O); MS *m/z* (EI): 216 (17), 157 (46), 144 (100), 115 (10), 44 (20); MS *m/z* (CI-NH_3): 234 $[M+NH_4]^+$ (100); Exact mass (hrms) calcd for $C_{13}H_{16}N_2O$: 216.1263; found 216.1278.

4a. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.58 (2H, q, J = 7.5 Hz, CH_2CH_3), 2.89 (3H, s, N ^{b}Me), 3.00 (2H, apparent t, J ≈ 7.0 Hz, CH_2CH_2N), 3.49 (2 H, apparent t, J = 7.0 Hz, CH_2CH_2N), 3.70 (3H, s, N ^{a}Me), 5.05 (1H, d, J = 13.5 Hz, C*H*=CHN), 6.60–7.80 (6H, m, H-2″, H-5″, H-6″, H-7″, H-5′,CH=C*H*N), 7.60 (1H, d, J = 7.6 Hz, H-4″), 8.09 (1H, d, J = 5.4 Hz, H-6′), 8.15 (1H, s, H-2′); MS *m/z* (EI): 319(12), 175(46), 157(56), 144(100), 117(13.6). Exact mass (hrms) calcd for $C_{21}H_{25}N_3$: 319.2048; found: 319.2034.

5a. ^{1}H nmr (500 MHz, $CDCl_3$) δ: 1.19 (3 H, t, J ≈ 7.6 Hz, CH_2CH_3), 2.44 (3 H, s, N ^{b}Me), 2.60 - 2.65, 2.93 -3.02, 3.11-3.16, 3.31-3.39 (8 H, 4 m, CH_2CH_3, 2 H-7′, 2 H-3, 2 H-4), 3.35 (3 H, s, N ^{a}Me), 3.92 - 3.96 (1H, dd, H-1), 7.10 (1H, t, J = 7.8 Hz, H-6), 7.16 (1H, d, J = 5.0 Hz, H-5′) 7.19 (1H, t, J = 7.8 Hz, H - 7), 7.23 (1H, d, J = 8.1 Hz, H - 8), 7.52 (1H, d, J = 7.8 Hz, H - 5), 8.36 (1H, d, J = 5.0 Hz, H - 6′), 8.40 (1H, s, H - 2′). ^{13}C nmr (125.8 MHz, $CDCl_3$) δ: 15.09 (CH_2CH_3), 16.76 (C-4), 23.30 (CH_2CH_3), 29.59 (N ^{a}Me), 36.25 (C-7′), 41.81 (N ^{b}Me), 44.29 (C-3), 58.18 (C-1), 106.78 (C-4a), 108.86 (C-8), 118.24 (C-5), 119.10 (C-6), 121.42 (C-7), 124.21 (C-5′), 126.85 (C-4b), 135.23 (C-3′) 137.27 (C-9a), 137.98 (C-8a), 146.02 (C-4′), 147.34 (C-6′), 149.94 (C-2′); MS *m/z* (EI): 319(1), 199(100); MS *m/z* (CI-NH_3): 320 $[M + H]^+$ (20), 199(100), 122(20); Exact mass (hrms) calcd for $C_{21}H_{25}N_3$: 319.2048; found: 319.2051.

10. Whaley, W.M.; Govindachari, T.R. *Org. React.* **1951**, *6*, 74 - 150.

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