Chemistry of Heterocyclic Compounds, Vol. 39, No. 2, 2003

NEW METHOD FOR THE SYNTHESIS OF 1,2,3,6,7,11b-HEXAHYDRO-4H-PYRIMIDO-[6,1-*a*]ISOQUINOLINE-4-THIONES AND 2,3,6,7,12,12b-HEXAHYDROPYRIMIDO-[6,1-*a*]-β-CARBOLINE-4(1H)-THIONES

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Keywords: pyrimido[6,1-*a*]isoquinoline, pyrimido[6,1-*a*]-β-carboline, intramolecular amidoalkylation.

Pyrimido[6,1-*a*]isoquinolines hold interest as physiologically active compounds [1]. The structural fragment of pyrimido[6,1-*a*]-β-carbolines is found in several alkaloids such as elaeocapridine [2]. The methods reported for the preparation of such compounds involve multiple steps and have proved inefficient. As a rule, the synthesis of such compounds requires not readily available isoquinoline and β-carboline precursors. The pyrimidine ring is subsequently completed [3]. On the other hand, intramolecular amidoalkylation of heterocyclic acyliminium is often used for the preparation of isoquinolines and β-carbolines fused with other heterocycles [4]. Such an approach to the synthesis of pyrimido[6,1-*a*]isoquinolines and pyrimido[6,1-*a*]-β-carbolines has not yet been employed.

We have shown that 6-hydroxytetrahydropyrimidine-2-thiones **5**, obtained according to Unkovskii et al. [5] by the reaction of the corresponding isothiocyanatocarbonyl derivatives **1a** and **1b** [6] with homoveratrylamine **3** or tryptamine **4**, are converted upon heating in acetic acid to 1,2,3,6,7,11b-hexahydro-4H-pyrimido[6,1-*a*]isoquinoline-4-thiones **8a** and **8b** and 2,3,6,7,12,12b-hexahydropyrimido[6,1-*a*]-β-carboline-4(1H)-thiones **9a** and **9b** with satisfactory yields (method A). Thione **8b** is formed as a 10:9 2,11b-*cis/trans* isomer mixture while thione **9b** is formed as a 1:4 1,12b-*cis/trans* isomer mixture. Heterocyclic cation **6** may also be obtained from 3,4-dihydropyrimidine-2(1H)-thione **7** in acid medium. The use of amines **3** and **4** in reported methods for the synthesis of **7** based on the condensation of isothiocyanato ketones and amines [7] (method B) or of α,β-unsaturated ketones, thiocyanic acid, and amines [8] (method C) also leads to heterocyclic thiones **8** and **9** (Scheme 1).

The yields of **8a** relative to amine **3** obtained by methods A (overall yield in two steps), B, and C are 73, 65, and 64%, respectively. The reaction proceeds as an intramolecular amidoalkylation of the aryl or hetaryl fragment by heterocyclic cation **6** formed in acid medium from **5** or **7**.

General Method for the Synthesis of 8 and 9 (Method B). A mixture of isothiocyanatocarbonyl derivative (72.3 mmol) and 3,4-dimethoxyphenylethylamine (60.5 mmol) in glacial acetic acid (50 ml) was heated at reflux for 1.5 h. The reaction mixture was cooled to room temperature and poured onto ice. The crystals formed were filtered off, dried, and recrystallized from absolute ethanol.

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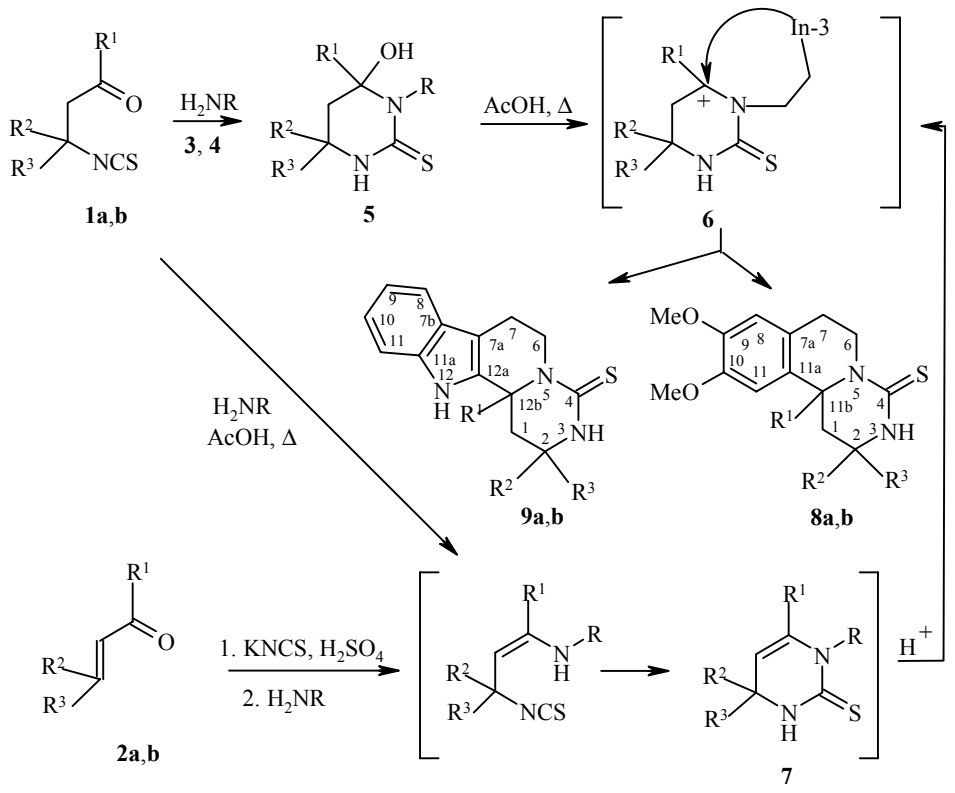
0009-3122/03/3902-0277$25.00

Scheme 1



9,10-Dimethoxy-2,2,11b-trimethyl-1,2,3,6,7,11b-hexahydro-4H-pyrimido[6,1-*a*]isoquinoline-4-thione (8a) was obtained in 65% yield; mp 166-167°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.18 (3H, s, 2-CH_3); 1.46 (3H, s, 2-CH_3); 1.72 (3H, s, 11b-CH_3); 2.12 (1H, d, ^2J = 14, 1-H_e); 2.35 (1H, d, ^2J = 14, 1-H_a); 2.65 (1H, m, ^2J = 14, $^3J_{67e}$ = 3, 6-H_e); 3.05 (1H, m, ^2J = 15, $^3J_{6e7e}$ = 3, 7-H_e); 3.35 (1H, m, ^2J = 14, $^3J_{6a7a}$ = 3, 7-H_a); 3.87 (3H, s, 9-O$\underline{CH_3}$); 3.89 (3H, s, 10-O$\underline{CH_3}$); 5.63 (1H, dd, ^2J = 14, $^3J_{7a6a}$ = 3, 6-H_a); 6.62 (2H, s, 8-H, 11-H); 7.13 (1H, br. s, NH). Found, %: C 63.93; H 7.60; N 8.09. $C_{17}H_{24}N_2O_2S$. Calculated, %: C 63.72; H 7.55; N 8.74.

9,10-Dimethoxy-2-methyl-1,2,3,6,7,11b-hexahydro-4H-pyrimido[6,1-*a*]isoquinoline-4-thione (8b) was obtained in 49% yield; mp 197-198°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2,11b-*cis*-**8b**: 1.28 (3H, d, ^3J = 6.5, 2-CH_3); 1.65 (1H, m, ^2J = 13.3, $^3J_{1a11b}$ = 11.9, J_{1a2} = 11.5, 1-H_a); 2.51 (1H, m, ^2J = 13.3, $^3J_{1a11b}$ = $^3J_{1a2}$ = 3.3, 1-H_e); 2.60-2.75 (1H, m, 7-H_e); 2.92-3.12 (1H, m, 7-H_a); 3.25 (1H, m, ^2J = $^3J_{7a6a}$ = 12.1, $^3J_{7e6a}$ = 3.1, 6-H_a); 3.71 (1H, m, $^3J_{1a2a}$ = 11.5, $^3J_{2aCH_3}$ = 6.5, $^3J_{1e2a}$ = 3.3, 2-H_a); 3.87 (6H, s, 2OCH_3); 4.62-4.78 (1H, m, 11b-H); 5.45-5.61 (1H, m, 6-H_e); 6.64, 6.61 (2H, s, Ar); 6.58 (1H, br. s, NH); 2,11b-*trans*-**8b**: 1.35 (3H, d, $^3J_{2CH_3}$ = 6.5, 2-CH_3); 1.87-2.17 (2H, m, 1-H_2); 2.60-2.75 (1H, m, 7-H_e); 2.92-3.12 (1H, m, 7-H_a); 3.14 (1H, m, ^2J = $^3J_{7a6a}$ = 12.1, $^3J_{7e6a}$ = 2.2, 6-H_a); 3.50-3.66 (1H, m, 2-H_e); 3.73 (6H, s, 2OCH_3); 4.62-4.78 (1H, m, 11b-H); 5.45-5.61 (1H, m, 6-H_e); 6.64, 6.61 (2H, s, Ar); 6.93 (1H, br. s, NH). Found, %: C 62.05; H 6.76; N 9.51. $C_{15}H_{20}N_2O_2S$. Calculated, %: C 61.62; H 6.89; N 9.58.

2,2,12b-Trimethyl-2,3,6,7,12,12b-hexahydropyrimido[6,1-*a*]-β-carboline-4(1H)-thione (9a) was obtained in 52% yield; mp 250-251°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.08 (3H, s, 2-CH_3); 1.39 (3H, s, 2-CH_3); 1.73 (3H, s, 12b-CH_3); 2.25 (1H, d, ^2J = 13.8, 1-H_a); 2.46 (1H, d, ^2J = 13.8, 1-H_e); 2.70 (1H, m, ^2J = 15.4, $^3J_{6a7a}$ = 3.4, $^3J_{6e7a}$ = 0.9, 7-H_e); 2.92 (1H, m, ^2J = 15.4, $^3J_{6a7a}$ = 11.9, $^3J_{6e7a}$ = 4.7, 7-H_a); 3.44 (1H, m, ^2J = 12.4, $^3J_{7a6a}$ = 11.9, $^3J_{7e6a}$ = 3.4, 6-H_a); 5.72 (1H, m, ^2J = 12.4, $^3J_{7a6e}$ = 4.7, $^3J_{7e6e}$ = 0.9, 6-H_e); 6.95-7.12, 7.24-7.48 (4H, m, Ar); 8.11 (1H, br. s, $N_{(4)}H$); 10.63 (1H, br. s, $N_{(12)}H$). Found, %: C 68.46; H 6.98; N 14.26. $C_{17}H_{21}N_3S$. Calculated, %: C 68.19; H 7.07; N 14.03.

2-Methyl-2,3,6,7,12,12b-hexahydropyrimido[6,1-*a*]-β-carboline-4(1H)-thione (9b) was obtained in 23% yield; mp 266-267°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2,12b-*trans*-**9b**: 1.27 (3H, d, $^3J_{2CH_3}$ = 6.6, 2-CH_3); 2.08 (1H, m, ^2J = 13.3, $^3J_{12b1a}$ = 9.1, $^3J_{1a2}$ = 4.6, 1-H_a); 2.38 (1H, m, ^2J = 13.3, $^3J_{12ba1e}$ = 4.6, $^3J_{1e2}$ = 4.2, 1-H_e); 2.67 (1H, br. d, ^2J = 15.2, 7-H_e); 2.88 (1H, m, ^2J = 15.2, $^3J_{6a7a}$ = 11.7, $^3J_{6e7a}$ = 3.7, 7-H_a); 3.22 (1H, m, ^2J = 12.2, $^3J_{7a6a}$ = 11.7, $^3J_{7e6a}$ = 3.0, 6-H_a); 3.40-3.60 (1H, m, 2-H); 4.83 (1H, m, $^3J_{1a12b}$ = 9.1, $^3J_{1e12b}$ = 4.6, 12b-H); 5.69 (1H, m, ^2J = 12.2, $^3J_{7a6e}$ = 3.7, $^3J_{7e6e}$ = 1.0, 6-H_e); 7.01-7.10, 7.29-7.42 (4H, m, Ar); 8.12 (1H, br. d, $^3J_{23}$ = 2.9, $N_{(3)}H$); 10.68 (1H, br. s, $N_{(12)}H$); 2,12b-*cis*-**9b**: 1.21 (3H, d, $^3J_{2CH_3}$ = 6.6, 2-CH_3); 1.50 (1H, m, ^2J = 12.7, $^3J_{12b1a}$ = $^3J_{21a}$ = 11.5, 1-H_a); 2.49-2.58 (1H, m, 1-H_e); 2.59-3.00 (2H, m, 7-H_e, 7-H_a); 3.15 (1H, m, 6-H_a); 3.40-3.60 (1H, m, 2-H); 4.80-4.90 (1H, m, 12b-H); 5.70-5.80 (1H, m, 6-H_e); 7.01-7.10, 7.24-7.48 (4H, m, Ar); 7.84 (1H, s, $N_{(3)}H$); 10.66 (1H, br. s, $N_{(12)}H$). Found, %: C 66.34; H 6.21; N 15.34. $C_{15}H_{17}N_3S$. Calculated, %: C 66.39; H 6.31; N 15.48.

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