HETEROCYCLES, Vol. 55, No. 8, pp. 1519 - 1526, Received, 7th May, 2001

# SYNTHESIS OF TETRACYCLIC DIBENZO[*c,f*]AZEPINE AND BENZO[*f*]THIENO[3,2-*c*]AZEPINE DERIVATIVES *VIA N*-ACYLIMINIUM ION CYCLIZATION

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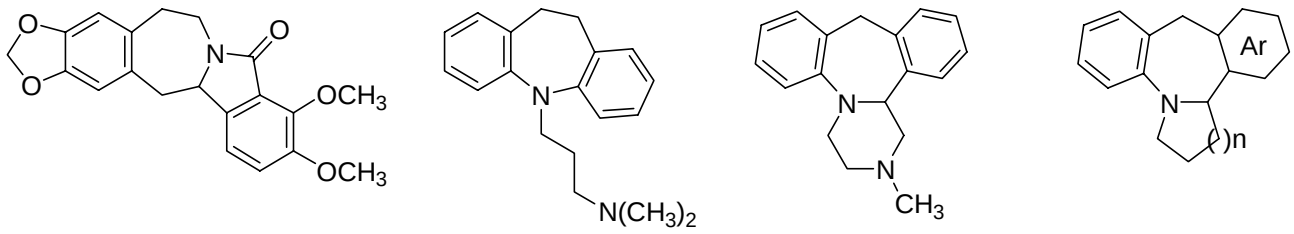
**Abstract-** Tetracyclic dibenzo[*c,f*]-4-oxopyrrolo[1,2-*c*]azepine (**2a**), dibenzo[*c,f*]-5-oxopiperido[1,2-*c*]azepine (**2b**), benzo[*f*]-4-oxopyrrolo[1,2-*a*]thieno[3,2-*c*]azepine (**2c**), and benzo[*f*]-5-oxopiperido[1,2-*a*]thieno[3,2-*c*]azepine (**2d**) were prepared through intramolecular *N*-acyliminium ion cyclization of hydroxylactams (**3a-d)** with aromatic or heteroaromatic rings such as benzene and thiophene as a π-nucleophile. In the case of furan ring, the hydroxylactams (**3e**, **f**) were completely decomposed under the acidic conditions (formic acid or methanesulfonic acid). Subsequent reduction of **2a-d** with $BF_3{\cdot}O(C_2H_5)_2$ and $BH_3{\cdot}S(CH_3)_2$ finally provided the tetracyclic dibenzo[*c,f*]pyrrolo[1,2-*c*]azepine (**1a**), dibenzo[*c,f*]piperido[1,2-*c*]azepine (**1b**), benzo[*f*]pyrrolo[1,2-*a*]thieno[3,2-*c*]azepine (**1c**), and benzo[*f*]piperido[1,2-*a*]thieno[3,2-*c*]azepine derivatives (**1d**) as analogues of mianserin.

The benzoazepine unit is present in a large number of natural alkaloids, including lennoxamine,[1]

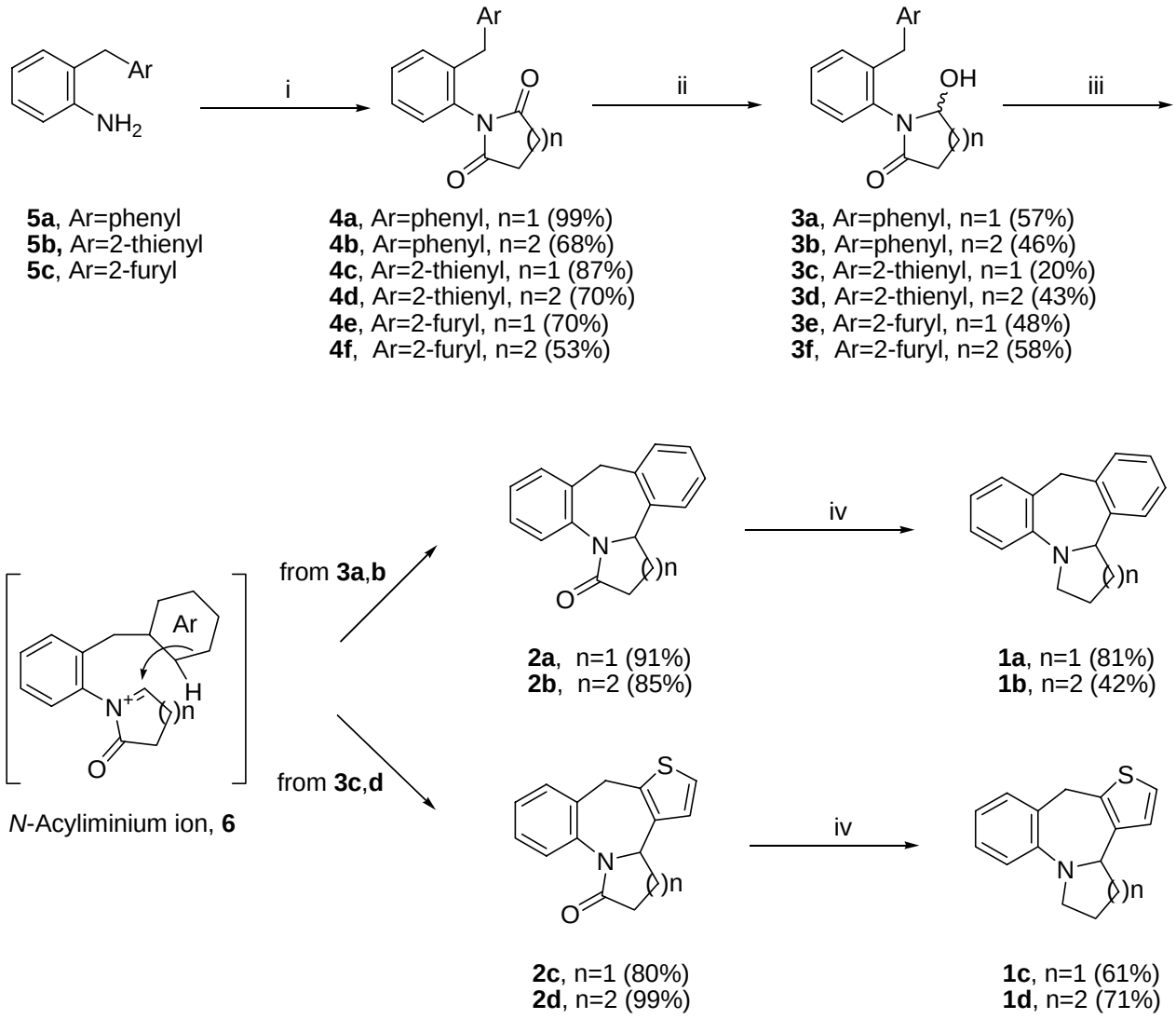
cephalotaxine[2] and chilenine.[3] Dibenzo[*b,f*]azepine, in particular, forms the skeleton of tricyclic antidepressant such as desipramine, imipramine and lofepramine.[4] The mianserin, antidepressant agent as a selective 5-$HT_2$ receptor antagonist, also contains dibenzo[*c,f*]azepine annelated to piperazine ring (Figure 1).[5] In this regard, many synthetic efforts have been directed toward synthesis of benzoazepine derivatives because of their unique structural features and potential biological activities.[6] We have also reported the synthesis of azepino[5,4,3-*cd*]indole derivatives in the course of searching the pharmacologically active compound.[7]




**Lennoxamine** **Imipramine** **Mianserin** **1**

**Figure 1.**

In connection with our interest in the synthesis of diverse polycyclic alkaloids, we wish to report herein the synthesis of tetracyclic dibenzo[*c,f*]azepine and benzo[*f*]thieno[3,2-*c*]azepine derivatives (**1**) from 2-arylmethylanilines (**5**) through *N*-acyliminium ion cyclization. Our synthesis is based on the hydroxylactams (**3**) as key intermediates for *N*-acyliminium ion cyclization. These hydroxylactams (**3**) would be obtained by reduction of imides (**4**), which would be prepared from the condensation reaction of 2-arylmethylaniline (**5**) with cyclic anhydride. The cyclization of hydroxylactams (**3**) having aromatic rings as a π-nucleophile[8] and subsequent reduction of tetracyclic lactams (**2**) should complete the synthesis of the target tetracyclic dibenzo[*c,f*]azepine and benzo[*f*]thieno[3,2-*c*]azepine (**1**) respectively. The 2-thienyl and 2-furylmethylanilines (**5b**, **c**) if not commercially available, could be readily prepared by known procedures.[9] The condensation of anilines (**5a-c)** with cyclic anhydrides [succinic anhydride (n=1) or glutaric anhydide (n=2) ] followed by treatment with excess of AcCl in refluxing xylene gave the

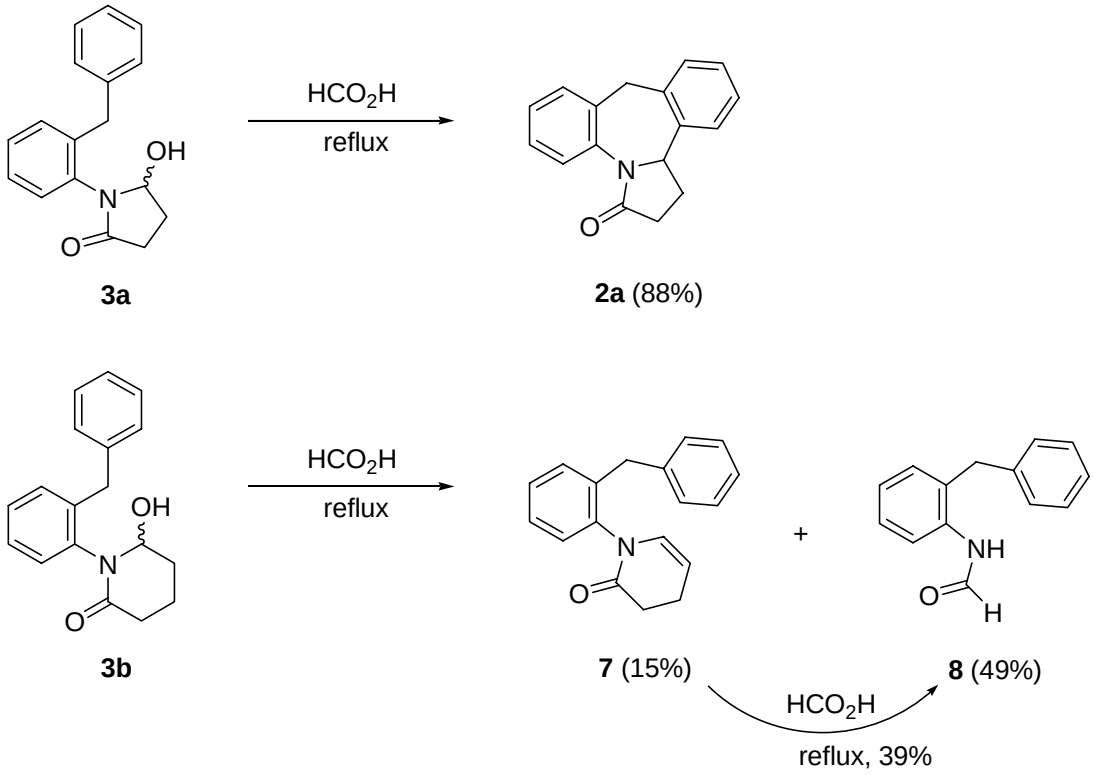



(i) succinic anhydride (n=1) or glutaric anhydride (n=2), xylene, reflux; then AcCl, reflux; (ii) DIBAL-H, THF, -78 ℃ ~ rt; (iii) $CH_3SO_3H$, $CH_2Cl_2$, reflux; (iv) $BF_3{\cdot}O(C_2H_5)_2$ and $BH_3{\cdot}S(CH_3)_2$, THF, reflux

**Scheme 1.**

cyclic imides (**4a-f**) in 53-99% yield (Scheme 1).[10] In the case of reduction of imides (**4a-f**) for hydroxyimides (**3a-f**), the use of $NaBH_4$ as a reducing agent gave over-reduced compounds (hydroxyamide) or imide ring-opened compounds (methyl ester) in the presence of 1M $H_2SO_4$/ MeOH. This result was totally unexpected as many research groups and we have previously performed the exact reduction of cyclic imides by using the same condition.[11] Therefore, the intended hydroxylactams (**3a-f**),

precursors for *N*-acyliminium ion (**6**), were successfully obtained by the reduction of imides (**4a-f**) with DIBAL-H in THF at -78 ℃ to room temperature without over-reduction.[12]




**Scheme 2.**

The hydroxylactams (**3a-f**) were subjected to the general *N*-acyliminium ion cyclization condition (formic acid, reflux).[13] The compound (**3a**) only was cyclized to afford the target compound (**2a**) in 88% yield. In the case of six-membered hydroxylactam (**3b**), however, this same condition did not provide the cyclized lactam (**2a**) but the enamide compound (**7**) (15%) resulting from the dehydration of hydroxylactam (**3b**) and formamido compound (**8**) (49%), which was identified with NMR, MS, IR, and $^{1}$H-$^{1}$H COSY. The isolated enamide (**7**) was converted to formamido compound (**8**) (39%) under the reflux condition of formic acid (Scheme 2). The thienyl compounds (**3c**, **d**) were not cyclized and the furyl compounds (**3e**, **f**) were completely decomposed under this condition. However, the application of more acidic condition (methanesulfonic acid, reflux) to hydroxylactams (**3a-d**) gave successfully tetracyclic lactam (**2a-d**) in 80-99% yield,[14] while furyl compounds (**3e**, **f**) were not cyclized but decomposed again in this condition due

to the cyclization difficulty of furan 2-to-3 closure.[15] Finally, reduction of lactams (**2a-d**) with $BH_3 \cdot S(CH_3)_2$ in the presence of $BF_3 \cdot O(C_2H_5)_2$ afforded tetracyclic dibenzo[*c,f*]azepine (**1a**, **b**) and benzo[*f*]thieno[3,2-*c*]azepine (**1c, d**) respectively in good yield (42-81%).[16,17]

In conclusion, we have accomplished the synthesis of tetracyclic dibenzo[*c,f*]azepine and benzo[*f*]thieno[3,2-*c*]azepine derivatives (**1a-d**) annelated to pyrrolidine or piperidine moiety through *N*-acyliminium ion cyclization by using aromatic rings such as benzene and thiophene as a π-nucleophile, followed by subsequent reduction. In the *N*-acyliminium ion cyclization, the five-membered benzyl compound (**3a)** was easily cyclized under both of formic acid and methanesulfonic acid. The six-membered benzyl compound (**3b**) and thienyl compounds (**3c**, **d**) were cyclized only under the more acidic condition (methanesulfonic acid), while the furyl compounds (**3e**, **f**) were completely decomposed under both of acids.

**ACKNOWLEDGEMENTS**

This work was supported by grants from The Ministry of Health and Welfare (2M10170)

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14. **Typical procedure of cyclization:** To a solution of **3a** (695 mg, 2.60 mmol) in dry $CH_2Cl_2$ (20 mL) was added methanesulfonic acid (2.02 mL, 31.2 mmol). The reaction mixture was heated under reflux for 24 h, cooled to rt, and neutralized with 10% $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (EtOAc/hexane=3:2) to afford **2a** (588 mg, 91%).
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17. Selected data for: **dibenzo[*c,f*]pyrrolo[1,2-*a*]azepine (1a)**: mp 104 ℃(EtOAc-hexane); MS *m*/*z*: 235 ($M^+$); IR (KBr) 2964, 1596, 1498, 746 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.21-7.16 (m, 4H, Ph), 7.04-6.97 (m, 2H, Ph), 6.55 (t, *J*=7.3 Hz, 1H, Ph), 6.45 (d, *J*=8.0 Hz, 1H, Ph), 5.35 (t, *J*=6.6 Hz, 1H, N-C<u>H</u>-Ph), 4.80 and 3.58 (ABq, *J*=14.8 Hz, 2H, Ph-C<u>H</u>$_2$-Ph), 3.34-3.29 (m, 2H, N-C<u>H</u>$_2$-CH$_2$-), 2.41 (m, 1H, N-CH$_2$-C<u>H</u>-), 2.26 (m, 1H, N-CH$_2$-C<u>H</u>-), 2.10-2.01 (m, 2H, N-CH$_2$-CH$_2$-C<u>H</u>$_2$-); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 146.7, 140.4, 138.7, 130.1, 128.4, 128.1, 128.0, 127.1, 124.3, 117.2, 114.2, 60.2, 50.7, 41.2, 30.8, 23.8; HRMS (EI) Calcd for $C_{17}H_{17}N$ ($M^+$) m/z 235.1361, Found 235.1351. *Anal.* Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.74; H, 7.27; N, 5.86. **dibenzo[*c,f*]piperido[1,2-*a*]azepine** (**1b)**: mp 245-248 ℃ (EtOAc-hexane); MS *m*/*z*: 249 ($M^+$); IR (KBr) 3220, 1452, 1048, 610 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.57-6.87 (m, 8H, Ph), 4.85 and 3.32 (ABq, *J*=12.4 Hz, 2H, Ph-C<u>H</u>$_2$-Ph), 3.88 (dd, *J*=10.5, 2.1 Hz, 1H, N-C<u>H</u>-Ph), 3.43 (m 1H, N-C<u>H</u>-CH$_2$-), 3.30 (m, 1H, N-C<u>H</u>-CH$_2$-), 2.00-1.66 (m, 6H, -C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 141.3, 140.7, 139.5, 129.6, 128.2, 127.5, 126.8, 126.6, 122.1, 119.6, 69.1, 53.6, 39.2, 39.0, 27.29, 26.4; HRMS (EI) Calcd for $C_{18}H_{19}N$ ($M^+$) m/z 249.1517, Found 249.1516. **benzo[*f*]pyrrolo[1,2-*a*]thieno[3,2-*c*]azepine** (**1c**): mp 148 ℃ (EtOAc-hexane, decomp); MS *m*/*z*: 241($M^+$); IR (KBr) 3420, 1450, 1084, 745 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.12-7.02 (m, 2H, Ph), 6.96 (d, *J*=7.8 Hz, 1H, Ph), 6.82 (d, 1H, *J*=5.2 Hz, thienyl-H$_5$), 6.77 (t, *J*=7.8 Hz, 1H, Ph), 6.58 (d, 1H, *J*=5.2 Hz, thienyl-H$_4$), 4.30 and 3.65 (ABq, *J*=15.2 Hz, 2H, Ar-C<u>H</u>$_2$-thienyl), 3.92 (dd, *J*= 8.1, 7.2 Hz, 1H, N-C<u>H</u>-Ph), 3.24-3.10 (m, 2H, N-C<u>H</u>$_2$-), 2.29 (m, 1H, N-CH-C<u>H</u>-), 1.93-1.78 (m, 3H, N-CH-C<u>H</u>- and N-CH$_2$-CH$_2$-C<u>H</u>$_2$-); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 148.6, 138.4, 134.1, 133.8, 128.9, 128.1, 127.9, 122.2, 121.6, 118.2, 63.9, 51.3, 33.9, 33.6, 22.3; HRMS (EI) Calcd for $C_{15}H_{15}NS$ ($M^+$) m/z 241.0925, Found 241.0922. *Anal.* Calcd for $C_{15}H_{15}NS$: C, 74.65; H, 6.26; N, 5.80. Found: C, 74.64; H, 6.33; N, 5.73. **benzo[*f*]piperido[1,2-*a*]thieno[3,2-*c*]azepine** (**1d**): mp 178 ℃ (EtOAc-hexane, decomp); MS *m*/*z*: 255($M^+$); IR (KBr) 3424, 3126, 1458, 1084, 750 $cm^{-1}$; $^1H$ NMR (300 MHz, pyridine-$d_5$ and $CDCl_3$) δ 7.32-7.25 (m, 3H, Ph), 7.20 (d, 1H, *J*= 5.2 Hz, thienyl-H$_5$), 7.18 (m, 1H, Ph), 6.95 (m, 1H, Ph), 6.91(d, 1H, *J*= 5.2 Hz, thienyl-H$_4$), 4.77 and 3.44 (ABq, 2H, *J*= 15.7 Hz, Ph-C<u>H</u>$_2$-thienyl), 3.87(dd, 1H,

*J*=10.5, 2.0 Hz, N-C<u>H</u>-thieny-), 3.31 (m, 1H, N-C<u>H</u>-$CH_2$-), 3.15 (m, 1H, N-C<u>H</u>-$CH_2$-), 1.99-1.54 (m, 6H, N-C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-); $^{13}$C NMR (75 MHz, pyridine-$d_5$ and $CDCl_3$) δ 151.3, 141.1, 139.2, 135.7, 128.8, 127.9, 126.7, 122.7, 121.0, 65.5, 53.9, 37.8, 32.2, 27.2, 25.7 (one of aromatic carbons was overlapped with solvent peaks); HRMS (EI) Calcd for $C_{16}H_{17}NS$ ($M^+$) m/z 255.1082, Found 255.1089.