Synthesis of 10-Amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[\(f\)]inden-8-one Derivatives using Schmit Reaction

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Alzheimer’s disease (AD) is neurodegenerative disease characterized by a low concentration of acetylcholine (ACh) in the hippocampus and cortex.\(^1\) The deficiency in cholinergic neurotransmission is also believed to be one of the major causes of the decline in cognitive and mental functions associated with AD.\(^2\) Acetylcholinesterase (AChE) inhibitors, which inhibit the enzyme responsible for ACh hydrolysis in order to increase the level of brain ACh, have been used for years in treatment of AD.\(^5\)

![Chemical Structures](image)

To date only tacrine (1a, the first AChE inhibitor), donepezil, rivastigmine, and galanthamine are available for AD treatment. However, the use of AChE inhibitors is sometimes limited mainly due to serious adverse effects such as hepatotoxicity and modest benefits to AD patients. Efforts to search for more potent and selective inhibitors of AChE without side effects still remain highly significant in AD treatment.

Recently, we have reported the synthesis of new thienopyridine derivatives 2 and 3 as potential AChE inhibitors.\(^6\) In continuation of our works for biologically active heterocyclic compounds\(^7\) we describe herein the synthesis of 10-amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[\(f\)]inden-8-one derivatives (4). Since it is widely recognized that thiophene is a biososeter of benzene, our synthetic plan is based on the replacement of benzene and cyclohexane moiety in tacrine 1 by thiophene and azepanone scaffold.

The synthetic route to 4 is, as shown in Scheme 1, similar in many respects to the one used for the synthesis of compound 11\(^6\) except the starting material 5. The condensation of 3-aminothiophene-2-carbonitrile 5 with 5-substituted cyclohexane-1,3-diones 6 in refluxing toluene in the
presence of $p$-TsOH gave the corresponding enaminoketone 7. The latter ones were then cyclized with potassium carbonate and cuprous chloride in refluxing THF to produce tricyclic ketones 8.12 The ring expansion of 8 by Schmit reaction with sodium azide in a mixture of concentrated sulfuric acid and chloroform at room temperature for 5-6 h afforded one lactam, 6-substituted-10-amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohept[a]inden-8-one 4 and 4-substituted-1,3,4,5-tetrahydro-9-thia-1,2,6-triazacyclopenta[f]acenaphthylene 9 with the ratio of 4:1 in yield ranging from 44 to 65%. Another isomeric lactam 12 was not formed.

The structure of 4 was characterized by their spectral data and chemical evidence. For instance, IR carbonyl absorption peak of 4a appeared at 1670 cm$^{-1}$ as carbonyl value of anide but 9a showed no carbonyl band. The $^1$H NMR spectrum of 4a showed NH$_2$ and NH at $\delta$ 8.71 and 6.18, respectively, while the broad NH signal in 9a was shifted at lower field to $\delta$ 13.50. The mass and elemental analysis data for 4a and 9a also matched the proposed structures and formulas, respectively (in Experimental). And, the chemical shift of C-7 methylene group next to carbonyl in 4a was $\delta$ 2.13. Its value is in agreement with the fact that a methylene of 4a absorbs at higher field when compared to a methylene next to NH group of 12a. The structure of compound 4a compared to 12a was further supported by the result that cyclization of 4a with triethylthioformate gave imidazole derivative 10a whose NMR spectrum showed a sharp singlet for one proton at $\delta$ 9.13 as an imine proton.

In conclusion, we reported the synthesis of new 10-amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohept[a]inden-8-one derivatives (4), as potential AChE inhibitors, from 8 using Schmit reaction.

**EXPERIMENTAL**

All products were characterized by IR, $^1$H NMR, MS and elemental analysis. Melting points were measured by using the capillary tubes on Buchi apparatus and are uncorrected. Each compound of the reactions was checked on thin-layer chromatography of Merck Kieselgel 60F$_{254}$ and purified by column chromatography using Merck silica gel (70-230 mesh). IR spectra were recorded on the FT-IR Bruker Tensor 27. The $^1$H NMR spectra were recorded on Bruker DRX-300 FT-NMR spectrometer (300 MHz) with Me$_4$Si as internal standard and chemical shifts are given in ppm (δ). Electron ionization mass spectra were recorded on a HP 59580 B spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.
To a solution of 8 (0.01 mole) in concentrated H$_2$SO$_4$ (10 mL) and CHCl$_3$ (10 mL), sodium azide (0.03 mole) was slowly added over 1 h. The solution was stirred for 5 h at room temperature. The reaction mixture was basified with dilute NH$_4$OH and extracted with CHCl$_3$. After evaporation the precipitate was filtered and recrystallized from EtOH.

10-Amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[7]inden-8-one (4a):
Yield 58%; mp 231 °C (dec); IR (KBr): 1670 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): $\delta$ 7.81 (s, 1H, NH). 7.78 (d, $J = 5.9$ Hz, 1H, thiophene H-2), 7.24 (d, $J = 5.9$ Hz, 1H, H-3), 6.18 (s, 2H, NH$_2$), 2.78 (m, 2H, H-5), 2.13-2.07 (m, 4H, H-6 and H-7); MS: (m/z) 233 (M$^+$), 204, 190. Anal. Calcd. for C$_{11}$H$_9$N$_3$: C, 56.63; H, 3.14; N, 18.01. Found: C, 56.50; H, 3.30; N, 18.22.

1,3,4,5-Tetrahydro-9-thia-1,2,6-triazacyclopen
tal[acenaphthylen (9a):
Yield 14%; mp 283-284 °C; $^1$H NMR (DMSO-d$_6$): $\delta$ 13.30 (s, 1H, NH). 7.91 (d, $J = 5.9$ Hz, 1H, thiophene H-8), 7.59 (d, $J = 5.9$ Hz, 1H, H-9), 3.60-2.94 (m, 4H, H-3 and H-5), 2.19 (q, 2H, H-4); MS: (m/z) 215 (M$^+$), 186, 160. Anal. Calcd. for C$_{11}$H$_9$N$_3$: C, 61.37; H, 4.21; N, 19.52. Found: C, 61.49; H, 4.10; N, 19.70.

10-Amino-6,6-dimethyl-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[7]inden-8-one (4b):
Yield 52%; mp 227-228 °C (dec); $^1$H NMR (DMSO-d$_6$): $\delta$ 8.77 (s, 1H, NH). 7.61 (d, $J = 5.9$ Hz, 1H, thiophene H-2), 7.29 (d, $J = 5.9$ Hz, 1H, H-3), 6.18 (s, 2H, NH$_2$), 2.90 (s, 2H, H-5), 2.58 (m, 2H, H-7), 1.00 (s, 6H, dMe); MS: (m/z) 261 (M$^+$), 246, 218, 178, 135. Anal. Calcd. for C$_{13}$H$_{15}$N$_3$: C, 59.75; H, 5.78; N, 16.08. Found: C, 59.90; H, 5.59; N, 16.20.

10-Amino-6-phenyl-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[7]inden-8-one (4c):
Yield 62%; mp 196-197 °C; $^1$H NMR (DMSO-d$_6$): $\delta$ 8.94 (s, 1H, NH). 7.81 (d, $J = 6.0$ Hz, 1H, thiophene H-2), 7.29-7.22 (m, 6H, H-3 and phenyl), 6.27 (s, 2H, NH$_2$), 3.65 (m, 1H, H-6), 3.15 (m, 1H, H-5a), 2.98 (m, 1H, H-5b), 2.49 (m, 1H, H-7a), 2.29 (m, 1H, H-7b); MS: (m/z) 309 (M$^+$), 284, 179. Anal. Calcd. for C$_{17}$H$_{15}$N$_3$: C, 66.00; H, 4.89; N, 13.58. Found: C, 65.84; H, 4.73; N, 13.70.

10-Amino-6-p-tolyl-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[7]inden-8-one (4d):
Yield 44%; mp 169-171 °C; $^1$H NMR (DMSO-d$_6$): $\delta$ 8.92 (s, 1H, NH). 7.81 (d, $J = 6.0$ Hz, 1H, thiophene H-2), 7.29 (d, $J = 5.9$ Hz, 1H, H-3), 7.25 (d, 2H, phenyl H-2 and H-6'), 7.09 (d, 2H, phenyl H-3' and H-5'), 6.26 (s, 2H, NH$_2$), 3.57 (m, 1H, H-6), 3.12 (m, 1H, H-5a), 2.96 (m, 1H, H-5b), 2.50 (m, 1H, H-7a), 2.27-2.20 (m, 4H, H-7b and Me); MS: (m/z) 323 (M$^+$), 295, 280, 179, 145. Anal. Calcd. for C$_{19}$H$_{17}$N$_3$: C, 68.85; H, 5.30; N, 12.99. Found: C, 66.99; H, 5.48; N, 13.19.

4-p-Tolyl-1,3,4,5-tetrahydro-9-thia-1,2,6-triaza
cyclopentad[acenaphthylen (9d):
Yield 10%; mp 246-247 °C; $^1$H NMR (DMSO-d$_6$): $\delta$ 13.60 (s, 1H, NH). 7.95 (d, $J = 5.9$ Hz, 1H, thiophene H-8), 7.34 (d, $J = 5.9$ Hz, 1H, H-9), 7.24 (d, 2H, phenyl H-2 and H-6'), 7.07 (d, 2H, phenyl H-3' and H-5'), 3.40 (m, 1H, H-4), 3.11-2.95 (m, 4H, H-3 and H-5), 2.22 (s, 3H, Me); MS: (m/z) 305 (M$^+$), 299, 286. Anal. Calcd. for C$_{17}$H$_{15}$N$_3$: C, 70.79; H, 4.95; N, 13.76. Found: C, 70.62; H, 4.76; N, 13.90.

10-Amino-6-(4-chlorophenyl)-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[7]inden-8-one (4e):
Yield 65%; mp 189-190 °C; $^1$H NMR (DMSO-d$_6$): $\delta$ 8.97 (s, 1H, NH). 7.83 (d, $J = 5.9$ Hz, 1H, thiophene H-2). 7.48 (d, 2H, phenyl H-3' and H-5'), 7.31 (d, 2H, phenyl H-2' and H-6'). 7.28 (d, $J = 5.9$ Hz, 1H, H-3), 6.35 (s, 2H, NH$_2$), 3.67 (m, 1H, H-6), 3.16 (m, 1H, H-5a), 2.98 (m, 1H, H-5b), 2.49 (m, 1H, H-7a), 2.28 (m, 1H, H-7b); MS: (m/z) 344 (M$^+$), 316, 300, 219, 180, 165. Anal. Calcd. for C$_{17}$H$_{17}$ClN$_3$: C, 59.79; H, 4.10; N, 12.22. Found: C, 59.22; H, 4.28; N, 12.10.

10-Amino-6-(4-bromophenyl)-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[7]inden-8-one (4f):
Yield 56%; mp 252-254 °C; $^1$H NMR (DMSO-d$_6$): $\delta$ 8.96 (s, 1H, NH). 7.82 (d, $J = 5.9$ Hz, 1H, }
thiophene H-2). 7.47 (d, 2H, phenyl H-3' and H-5'). 7.31 (d, 2H, phenyl H-2' and H-6'). 7.27 (d, J = 5.9 Hz, 1H, H-3). 6.30 (s, 2H, NH2). 3.66 (m, 1H, H-6). 2.96 (m, 1H, H-5a). 2.49 (m, 1H, H-7a). 2.26 (m, 1H, H-7b); MS: (m/z) 388 (M+), 360, 218, 190, 179. Anal. Calcd. for C17H14BN3OS: C, 52.59; H, 3.63; N, 10.82. Found: C, 52.75; H, 3.48; N, 11.01.

REFERENCES

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