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A facile synthesis of bis-tacrine isosteres

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Abstract

An efficient synthesis of highly potent and selective acetylcholinesterase (AChE) inhibitors, bis-tacrines and their isosteres **2**–**4**, has been accomplished by bis-amination of 9-chloro-tetrahydroacridine (**9a**) and its analogs. The critical intermediates were concisely prepared in situ by heating the corresponding *ortho*-amino aromatic acids and cycloketones in the presence of phosphorus oxychloride. © 2000 Elsevier Science Ltd. All rights reserved.

Alzheimer's disease is critical and may be life threatening for humans, especially the elderly. Demographic data indicate that the percentage of the elderly in the population is increasing.[1] Therefore, much attention has recently been paid to the treatment of Alzheimer's disease. Tacrine (**1**, tetrahydroaminoacridine or THA), is currently one of the major approved drugs for use in Alzheimer's disease.[2] It functions as an acetylcholinesterase (AChE) inhibitor for treating the disease. However, there are considerable debates over some drawbacks of tacrine due to its many actions in the CNS and its serious toxicity.[3] Therefore, it is very important to design and develop more selective inhibitors of AChE as opposed to tacrine. [4]

Very recently, a series of bis-tacrines (e.g. **3b**,**c**) were reported as highly potent and selective inhibitors of AChE.[5] These compounds were up to 10 000-fold more selective and 1000-fold more potent than tacrine in inhibiting rat AChE. As a part of our program aimed at developing suitable prodrugs and derivatives of tacrine, we are interested in the development of an efficient procedure for preparation of 9-chlorotetrahydroacridine (**9a**) and its isosteres as critical intermediates toward a series of bis-tacrine analogs. In this paper, we report the results of our work in detail.

Sargent and others have reported the synthesis of **9a** from chlorination of the corresponding tetrahydroacridone, which was obtained according to Tiedtke by treatment of anthranilic acid (**6a**) and cyclohexanone (**7b**) under Dean–Stark conditions.[6] Here, we disclose that **9a** could be concisely synthesized with high efficiency (94% yield) by directly heating the mixture of **6a** and **7b** in $POCl_3$ without isolation of dehydrated adduct or tetrahydroacridone (Table 1).[7] The method was applied to furnish the corresponding chloride isosteres **8**–**10** by direct condensation of acids **6a**–**d** and cycloketones **7a**–**c**. When reacting with cycloketones, acids **6a**,**c** showed higher transformations to give **8a**, **9a**, and **9c** whereas isosteric acid

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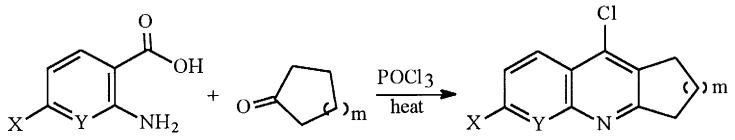
6b resulted in decreased yields (54–67%) of **8b**, **9d**, and **10b**. The electron-withdrawing effect from the pyridyl ring of **6b** was supposed to be responsible for the reduced nucleophilicity of the amino group and resulted in lower yields. The successful one-pot reactions were thought to proceed via rapid dehydration followed by cyclization and chlorosubstitution in situ in the presence of the chlorinating agent. Compared with the method previously described, this discovery provided a quite simple way toward the synthesis of isosteres of chloride **9a**, which could be economically utilized to prepare tacrine and its related derivatives.[6c,8]

Table 1
Preparation of chlorides **8**–**10** from acids and cycloketones



6a-c X = H, F, Cl, Y = CH **7a-c m = 1-3** **8-10**
d X = H, Y =N

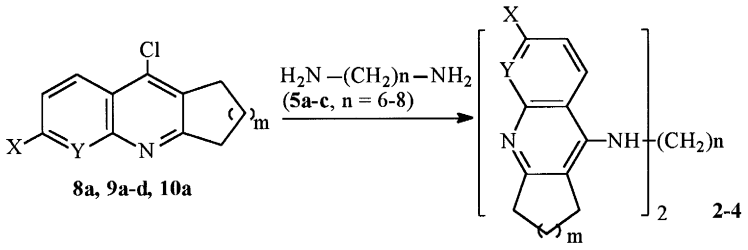
Product	X	Y	m	Yield (%)	Product	X	Y	m	Yield (%)
8a	H	CH	1	90	**9c**	Cl	CH	2	93
8b	H	N	1	67	**9d**	H	N	2	65
9a	H	CH	2	94	**10a**	H	CH	3	63
9b	F	CH	2	54	**10b**	H	N	3	59

Although Pang and co-workers reported the synthesis of bis-tacrines beginning with tacrine itself,[5a] this method proved to be much less reproducible after numerous attempts by variation of the base, reaction temperature, concentration, and solvent. In fact, Michalson and co-workers have reported similar difficulties when preparing 9-(1-azetidinyl)-tetrahydroacridine by using tacrine and 1,3-diiodopropane.[9] These results implied that the amino group of tacrine is apparently quite unreactive as a nucleophile. An alternative method might be considered toward the synthesis of a series of bis-tacrine analogs.

It has been reported that most alkyl derivatives of tacrine can be made by heating **9a** with appropriate amines either in sealed tubes or in phenol.[6a,8] The similar fashion was therefore optimized here to prepare bis-tacrines and their isosteres. First, heating the mixture of **9a** and 1,7-diaminoheptane (**5b**, 0.5 equiv.) in the presence of phenol and catalytic amounts of sodium iodide at 100°C only gave the mono-aminated product, 9-(7-aminoheptylamino)-tetrahydroacridine (**11**), in 38% yield accompanied by unreacted **9a** after silica gel chromatography. Extending the reaction time to 6 h or increasing the amount of sodium iodide did not drive the second amination for **5b**. These results proved the fact that the chlorine atom in **9a** is rather less reactive than that in corresponding fused aromatic ring systems such as 9-chloroacridine.[10] Noting the previous report for the preparation of alkyltacrines at high temperature in sealed tubes,[6a] we therefore raised the reaction temperature of the bis-amination to 180°C under an argon atmosphere (Table 2).[11] As expected, bis-amination of **9a** effectively occurred within 2 h to furnish the desired bis-tacrinyl alkanes **3a**–**c** in 47–56% yields. Bis-(6-fluoro)tacrinyl alkanes **3g**–**i** and *N*,*N*′-bis(cycloheptylquinolinyl)-diamino alkanes **4a**–**c** were obtained in lower yields (22–28%) together with undesired mono-aminated products from the corresponding chlorides **9c** and **10a**. The lower transformations might attribute to the electronic effects of the fluoro group and steric effects of the fused heptyl ring, respectively. The resulting

bis-tacrines and their isosteres were characterized by their satisfactory spectra (^{1}H NMR, MS, and HR-FABMS). The 6-fluoro and 6-chloro group on the aromatic ring of chlorides **9c**, **9d** proved to be stable under the bis-amination conditions.

Table 2
Synthesis of bis-tacrines and their isosteres



product	X	Y	m	n	Yield (%)	product	X	Y	m	n	Yield (%)
2a	H	CH	1	6	34	**3g**	Cl	CH	2	6	31
2b	H	CH	1	7	36	**3h**	Cl	CH	2	7	56
2c	H	CH	1	8	31	**3i**	Cl	CH	2	8	46
3a	H	CH	2	6	56	**3j**	H	N	2	6	25
3b	H	CH	2	7	47	**3k**	H	N	2	7	36
3c	H	CH	2	8	51	**3m**	H	N	2	8	51
3d	F	CH	2	6	56	**4a**	H	CH	3	6	26
3e	F	CH	2	7	47	**4b**	H	CH	3	7	22
3f	F	CH	2	8	51	**4c**	H	CH	3	8	28

In brief, direct $POCl_3$-mediated cyclocondensation as well as chlorination in situ proves to be applicable to the preparation of the critical chloride **9a** and its analogs. This method allows the efficient synthesis of the target bis-tacrines and their isosteres.

Acknowledgements

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7. Typical procedure (for the preparation of **9a**): To a mixture of **6a** (7.4 g, 53.9 mmol) and **7b** (5.36 mL, 51.7 mmol) was carefully added 50 mL of $POCl_3$ in an ice bath. The mixture was heated under reflux for 2 h, then cooled at room temperature, and concentrated to give a slurry. The residue was diluted with EtOAc, neutralized with aqueous K_2CO_3, and washed with brine. The organic layer was dried over anhydrous K_2CO_3 and concentrated in vacuo to furnish a pale brown solid. It was recrystallized from acetone to give **9a** (11.4 g, 94%): mp 68–70°C (lit.[6a] mp 66–68°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J=7.5 Hz, 1H, ArH), 8.00 (d, J=8.3 Hz, 1H, ArH), 7.63 (dd, J=9.2, 7.5 Hz, 1H, ArH), 7.51 (dd, J=9.2, 8.3 Hz, 1H, ArH), 3.10 (t, J=6.3 Hz, 2H, CH_2), 2.97 (t, J=4.8 Hz, 2H, CH_2), 1.91 (s br, 4H, CH_2-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 147.2, 129.9, 129.5, 129.1, 127.1, 124.3, 34.7, 28.1, 23.2, 23.0; EIMS: 217 (M^+, 100), 219 ($M+2^+$, 33); HR-EIMS: exact mass calcd for $C_{13}H_{12}NCl$: $[M]^+$ 217.0659, found: 217.0648.
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11. Typical procedure (for the preparation of **3a**): A mixture of **9a** (0.75 g, 3.5 mmol), **5a** (0.25 g, 1.75 mmol), phenol (1.5 g), and NaI (0.07 g) were carefully heated at 180°C under an inert system for 2 h and then cooled at room temperature. The mixture was diluted with EtOAc and made basic with 10% KOH solution. The organic layer was washed with water and brine, and then dried over anhydrous $MgSO_4$. After concentration, the resulting residue was purified on silica gel chromatography (CH_2Cl_2 to CH_2Cl_2:MeOH=10:1) to give **3a** (0.47 g, 56%) as amber glass foam: mp 94–96°C; R_f 0.42 (CH_2Cl_2:MeOH:NH_4OH=10:1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J=4.1 Hz, 2H, Ar-H), 7.91 (d, J=4.1 Hz, 2H, Ar-H), 7.54 (t, J=7.0 Hz, 2H, Ar-H), 7.32 (t, J=7.0 Hz, 2H, Ar-H), 4.00 (s br, 2H, 2 NH), 3.47 (t, J=7.1 Hz, 4H, 2 N-CH_2), 3.06 (s br, 4H, 2 CH_2), 2.68 (s br, 4H, 2 CH_2), 1.89 (s br, 8H, 2 CH_2CH_2), 1.65 (s br, 4H, CH_2CH_2), 1.41 (s br, 4H, CH_2CH_2); FABMS (NBA as matrix): *m/z* $[M+H]^+$ 479.2; HR-FABMS: exact mass calcd for $C_{32}H_{39}N_4$: [M+H]+479.3173, found: 479.3187.