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AN EASY ACCESS TO THE EXOCYCLIC LACTAMS ANALOGOUS OF THE CENTRAL NERVOUS SYSTEM ACTIVE TRICYCLIC NITROXAPINE, MIANSERINE AND CHLOTHIAPINE AGENTS USING *N*-ACYLIMINIUM CHEMISTRY

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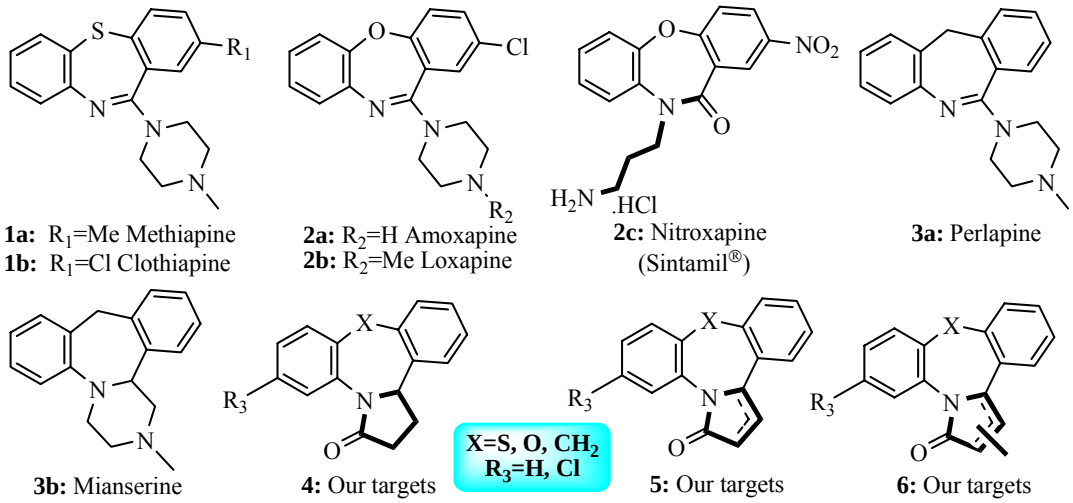
Abstract – The conformationally restrained dibenzothia(oxa)zepines and dibenz-azepines **4-6** analogous to the antidepressant Sintamil® were prepared easily by π-cationic cyclization of the *N*-acyliminium ions **9A-C** precursors with neat trifluoroacetic acid in three step-sequence starting from available amines and anhydrides. The regioselectivity in the reduction of imides especially in the maleimide derivatives as well as in the cyclization step was also discussed.

INTRODUCTION

Dibenzothia(oxa)zepines are important and widely used scaffolds in medicinal chemistry. For example, Methiapine (**1a**) and Clothiapine (**1b**) are reported as anti-psychoneurotics[1] and their oxygenated derivatives Defanyl® (**2a**),[2] Sintamil® (**2c**)[3] and Loxpine (**2b**)[4] are also efficient as antidepressants and antipsychotics, respectively. In addition, other analogous have also shown remarkable activities as a non-nucleoside type inhibitors of wild type HIV-1 replication.[5] The dibenzothiazepine Seroguel related to products **1a,b**, exerts and increasing 5-HT_2 affinity relative to the so popular Clozapine and possibly a lower potential for causing agranulocytosis,[6] constitutes also another interesting example. Also, dibenzodiazepines Perlapine (**3a**) and Mianserine (**3b**), as the carbon-analogous of the latter structures, were used for their hypnotic and sedative properties and for the treatment of depressions associated or not with the anxiety. As a consequence, new methods enabling the efficient preparation of libraries based on these scaffolds should be useful for lead generation of various drug discovery programs.

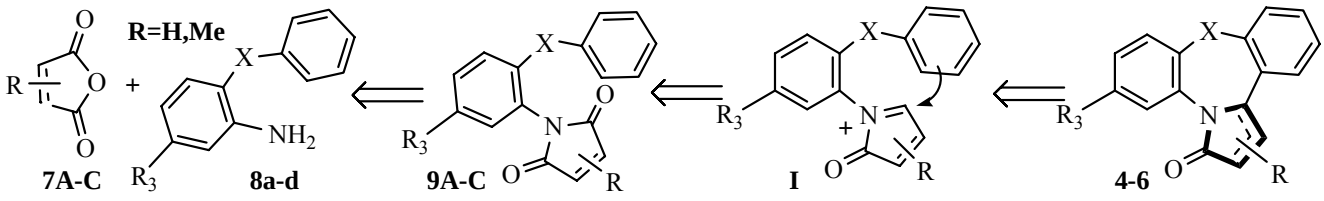
Chart 1. Representative active dibenzothiazepines **1a,b**, dibenzoxazepines **2a-c**, dibenzazepines **3a,b** and our targets **4-6**.



RESULTS AND DISCUSSION

In our group we are interested in the development of simple approaches towards aza-heterocyclic systems containing benzo(thia and oxa)azepines moieties with promising pharmaceutical activities. Our objective herein was to construct the conformationally restrained products **4-6** analogous to Sintamil® (**2c**) and the use of *N*-acyliminium chemistry to provide these targets in an efficient and concise manner seemed to be a valuable strategy. In fact, in association with our recent reports using *N*-acyliminium cyclization in tandem with Grignard reaction[7] and heterocyclization processes,[8] we reasoned that a suitably substituted *N*-acyliminium precursor of type **I** could allow a facile approach to the title targets **4-6** (Scheme 1).

Scheme 1. Retrosynthetic scheme leading to the tetracyclic targets **4-6**.



First, the synthesis of the required *N*-acyliminium ions precursors of type **10** was accomplished by a two-step sequence as outlined in Scheme 2. The *N*-alkylated imides **9** as starting materials are not commercially available but were prepared easily according to known procedures from anhydrides **7A-C** and amines **8a-d** by thermal amino-anhydride condensation in refluxing acetic acid for 48 h (40-99%). Reduction of imides **9Aa** (X=O) and **9Ab** (X=S) was performed with a large excess of $NaBH_4$ (3-6 equiv.) in dry EtOH at 0 °C for a short time (1 h). Under these conditions, only the opened alcohol-amides **10A(a,b)U** were isolated in excellent yields (Table 1). Interestingly, the reaction profile was inverted giving the expected hydroxyl-lactams **10A(a,b)V** when $Zn(BH_4)_2$ was used instead of $NaBH_4$ under

conditions ii (Scheme 2).[9] The yields were however lower (61 and 66%, respectively) than those obtained for **10A(a,b)U** under conditions i. Further, all attempts of reduction of imides **9B(a,b)** to access hydroxyl-lactams **10B(a,b)** by using conditions i but at 0-5 °C failed since only succinimide derivatives **9A(a,b)** were isolated in high yields average 90% in both cases. The regioselective reduction of one function of the imides **9B(a-d)** was ultimately accomplished under mild conditions with $NaBH_4$ in MeOH at 0 °C for 1-2 h (monitored by TLC using a silica gel plate and cyclohexane/AcOEt as the eluting mixture) in the presence of $CeCl_3.7H_2O$ (40-99% yield).[10] By using the same protocol, the imides **9C(a-d)** provided only α-hydroxy-lactams **10C(a-d)** in yields ranging from 40 to 83%. In all cases no opened alcohol-amides were detected in the crude reaction mixture but we observe the formation of two regioisomers in 9:1 (**10CaU,V**; 60% yield) and 8:2 (**10CdU,V**; 40% yield) ratios in favor of **10C(a,d)V** in which the hydroxyl function is near the methyl group at C4-position of the 1,5-dihydropyrrol-2-one nuclei. These results are in accordance with those published by us[11] and others[12] for related structures.

Scheme 2. Scheme leading to α-hydroxy-lactams **10** precursors of the tetracyclic systems.

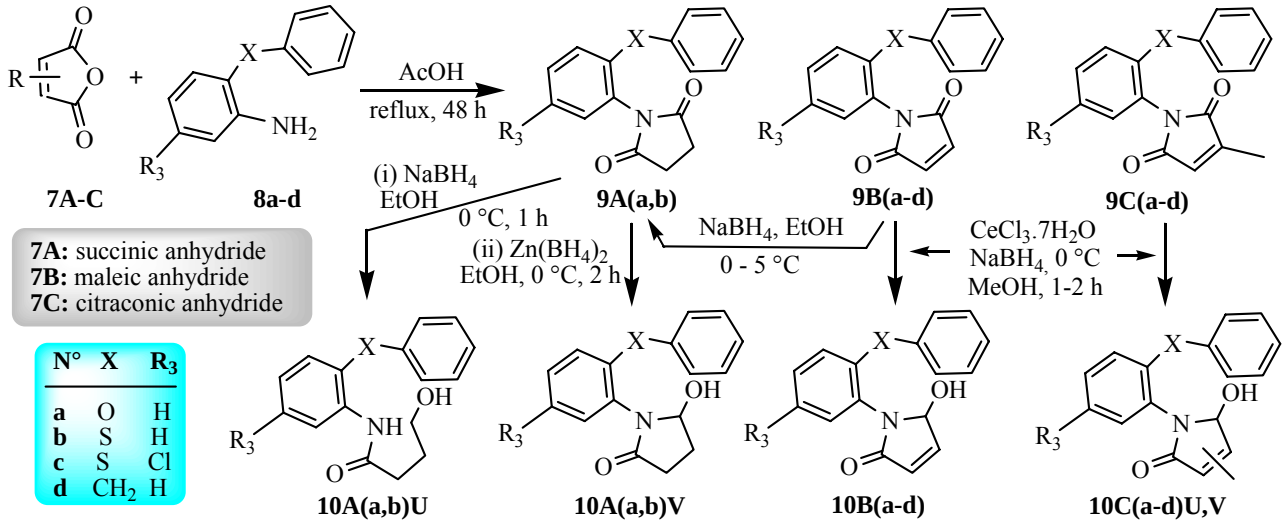


Table 1. Imides **10** and corresponding α-hydroxy-lactams **10**.

Product	Imide **9A** Yield (%)	Alcool-amide **10AU**[b] Yield (%)	Hydroxy-lactam **10AV**[b] Yield (%)	Imide **9B** Yield (%)	Hydroxy-lactam **10B** Yield (%)	Imide **9C** Yield (%)	Hydroxy-lactams **10CU**[c,d] and **10CV**[c,d] Yield (%), Ratio	
a (X=O)	93	89 (**0**)	0 (**61**)	61	81	93	68	(80/20)
b (X=S)	95	93 (**0**)	0 (**66**)	64	69	90	47	(100/0)
c (X=S)	-[a]	-[a]	-[a]	58	47	40	83	(100/0)
d (X=CH_2)	-[a]	-[a]	-[a]	65	74	99	40	(90/10)

[a] The reaction was not performed in this case. [b] Conditions i lead only to alcohol-amides **10A(a,b)U** while conditions ii provided exclusively α-hydroxy-lactams **10A(a,b)V**. [c] The ratio of products was determined by ^{1}H NMR spectroscopy. [d] Yields of the reaction are in % and the ratios are given in parentheses.

Having established earlier the capacity of trifluoroacetic acid to promote the capture of an *N*-acyliminium ion in an intramolecular manner with an array of nucleophiles,[7,8] *o*-phenyoxy(thio)-*N*-phenylamidals and *o*-benzyl-*N*-phenylamidals of type **10** (Scheme 3) were subjected to this general π-cyclization protocol (neat TFA, room temperature).[13] Under these conditions, α-hydroxy-lactams **10A,B** provided a cyclized lactams **4a,b**[14] and **5a-d**[15] with the intermediacy of species **I** (Scheme 1). In the tetracyclic system **5a-d**, the double bond of the dihydropyrrole ring is in conjugation with the benzene ring in accordance with our own earlier observations.[11] Interestingly, under same conditions a mixture of **10C(a-d)U** and **10C(a-d)V** led to the expected products **6U** and **6V** in moderate to very good yields (Table 2). These products, which in case of **6(a,b)U**[16] and **6(a,b)V** were separable easily by flush chromatography on silica gel column, were obtained in yields ranging from 46 to 84% (Table 2). The structure of these products as well as all reported in this paper was supported by NMR (^{1}H, ^{13}C, Dept) spectroscopic analysis. In fact, the NMR studies demonstrate that lactams **6(a,c,d)U** appeared in less conjugated form (proved by the presence of an angular proton in the ^{1}H NMR spectra) except in the case of **6bU (form L)** while lactams **6(a,b)V** exist only in the more conjugated form as mentioned above for the corresponding lactams **5a-d**.

Scheme 3. π-Cyclization of α-hydroxy-lactams **10** into the tetracyclic systems **4-6**.

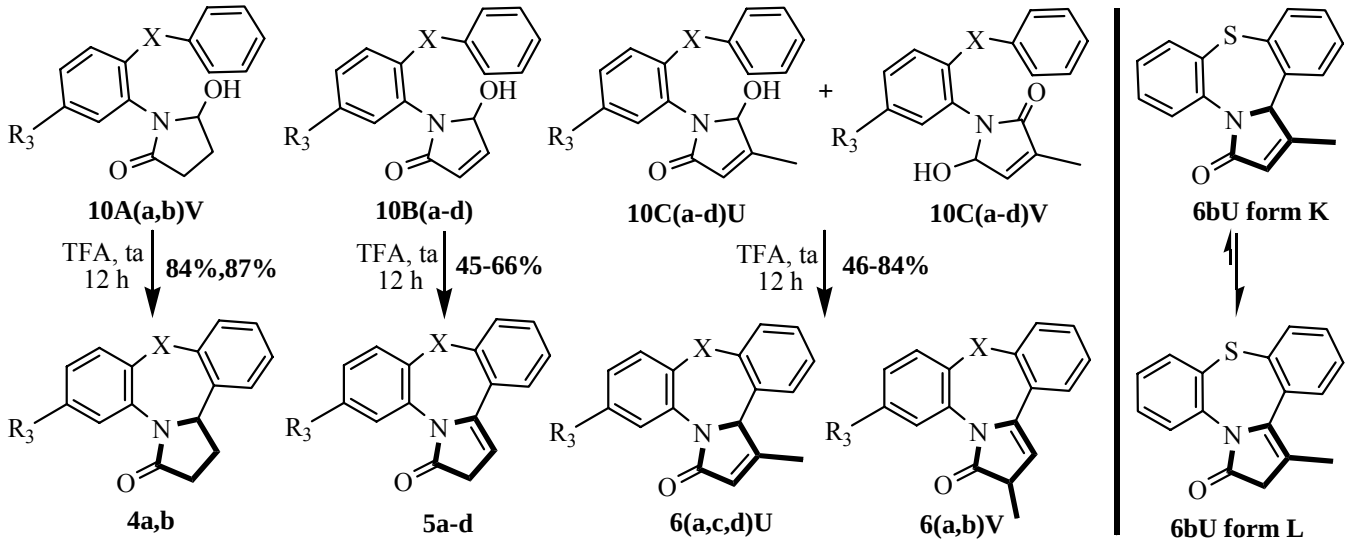


Table 2. Yields and melting points of the tetracyclic systems **4-6**.

Product index	Cyclic product **4** Yield (%), mp (°C)	Cyclic product **5** Yield (%), mp (°C)	Cyclic product **6U** Yield (%), mp (°C)	Cyclic product **6V** Yield (%), mp (°C)
a (X=O)	84 , 127	64 , 115	65[b] , 159	65[b] , 172
b (X=S)	87 , 144	57 , 207	84[c] , 207	84[c] , 170
c (X=S)	-[a]	66 , 172	71 , 129	-[d]
d (X=CH_2)	-[a]	45 , 181	46 , 155	-[d]

[a] No reaction was performed in this case. [b] The separable regioisomers were obtained in 9/1 ratio in favor of **6aU**. [c] The separable regioisomers were obtained in 8/2 ratio in favor of **6bU**. [d] Products not obtained.

In summary, we have developed efficient and versatile method for the synthesis of conformationally constrained **4-6** analogous to the antidepressant Sintamil® in three step-sequence starting from easily available substrates. The key step of this sequence was the trifluoroacetic acid-catalyzed intramolecular π-cationic cyclization and significant structural variation via the heteroelement (X=O, S, CH_2) as an *N*-acyliminium source was also realized.

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13. General procedure for cyclization of hydroxy-lactams **10**. Neat TFA (10 mL) was added to a stirred solution of the hydroxyl-lactam (**10**, 10 mmol), obtained by standard borohydride reduction of the imide **9** as indicated above in the text. After 4–12 h of reaction at rt whilst stirring, the reaction mixture was diluted with water (45 mL) and neutralized on cooling with 5% NaOH aqueous solution. The solution was extracted twice with CH_2Cl_2 (25 mL) and separated. The organic layer was washed with water, brine, separated, dried with $MgSO_4$, and the solvents evaporated *in vacuo*. The resulting crude residue was purified by chromatography [SiO_2, AcOEt/cyclohexane (4:1)] and recrystallized from the indicated solvents to give the expected tricyclic product.
14. Selected data for 1,2,3,13*b*-tetrahydropyrrolo[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-3-one (**4a**). This compound was isolated as a white solid in 84% yield after recrystallization from Et_2O and melted at 127 °C; IR (KBr) ν 1711 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.22-2.44 (m, 1H, $H_{pyrrolidine}$), 2.47-2.71 (m, 3H, $H_{pyrrolidine}$), 5.28-5.39 (m, 1H, CH), 7.07-7.28 (m, 7H, $H_{aromatic}$), 7.72 (d, 1H, *J*=8.3 Hz, $H_{aromatic}$); ^{13}C-NMR ($CDCl_3$) δ 27.1 (CH_2), 31.3 (CH_2), 60.4 (CH), 121.8 (CH), 125.0 (CH), 125.1 (CH), 125.2 (CH), 126.6 (CH), 127.0 (CH), 127.6 (CH), 129.5 (CH), 130.4 (Cq), 130.9 (Cq), 151.6 (Cq), 155.7 (Cq), 174.1 (CO); MS (EI, 70 ev) *m/z*: 251 (M+); *Anal.* Calcd for $C_{16}H_{13}NO_2$ (251.28): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.31; H, 5.09; N, 5.48.
15. Selected data for 1,2-dihydropyrrolo[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-3-one (**5a**). This product was isolated as a white solid in 64% yield after recrystallization from Et_2O/cyclohexane and melted at 115 °C; IR (KBr) ν 1712 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.40 (s, 2H, CH_2-C=), 5.60 (s, 1H, CH=C), 7.13-7.42 (m, 6H, $H_{aromatic}$), 7.52 (d, 1H, *J*=7.6 Hz, $H_{aromatic}$), 7.87 (d, 1H, *J*=7.6 Hz, $H_{aromatic}$); ^{13}C-NMR ($CDCl_3$) δ 37.5 (CH_2), 102.3 (CH=), 121.0 (CH), 121.8 (CH), 125.5 (CH), 125.6 (CH), 125.7 (CH), 127.0 (Cq), 127.3 (CH), 128.6 (CH), 129.0 (Cq), 131.2 (CH), 142.5 (Cq), 151.5 (Cq), 156.6 (Cq), 176.1 (CO); MS (EI, 70 ev) *m/z*: 249 (M+); *Anal.* Calcd for $C_{16}H_{11}NO_2$ (249.27): C 77.10; H 4.45; N 5.62. Found: C 76.92; H 4.30; N 5.48.
16. Selected data for 1-methyl-3,13*b*-dihydropyrrolo[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-3-one (**6Ua**). This product was isolated as a white solid in 65% yield after recrystallization from Et_2O/hexane and melted at 159 °C; IR (KBr) ν 1687 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.07 (d, 3H, *J*=1.3 Hz, CH_3(CH)), 6.11 (q, 1H, *J*=1.3 Hz, CH(CH_3)), 6.96-7.17 (q, 4H, $H_{aromatic}$+CH=C), 7.20-7.35 (m, 4H, $H_{aromatic}$), 8.85 (d, 1H, *J*=7.6 Hz, $H_{aromatic}$); ^{13}C-NMR ($CDCl_3$) δ 11.6 (CH_3), 60.7 (CH), 120.7 (CH), 121.3 (CH), 122.0 (CH), 125.0 (CH), 125.2 (CH), 125.3 (CH), 126.8 (CH), 129.5 (Cq), 130.6 (CH), 131.2 (Cq), 137.5 (CH), 137.7 (Cq), 146.1 (Cq), 156.6 (Cq), 169.9 (CO); MS (EI, 70 ev) *m/z*: 263 (M+); *Anal.* Calcd for $C_{17}H_{13}NO_2$ (263.29): C 77.55; H 4.98; N 5.32. Found: C 77.33; H 4.76; N 5.16.