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[a008]

SYNTHESIS OF THIOPHENE ANALOGUES OF THE TACRINE SERIES

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Abstract :

Substitued 3-amino-2-cyanothiophenes condensed with cyclic ketones afforded in 2 or 3 steps analogues of velnacrine. Condensation under Friedländer conditions gave Tacine analogues in one step.

1. Introduction :

Alzheimer's disease (AD) is a neurodegenerative disorder. One of the therapeutic strategies is treating Alzheimer's disease patient using acetylcholinesterase inhibitors (AChEI). Tacrine (**Fig. 1**) was the first acetylcholinesterase inhibitor used in the United States. It is efficient but presents side effects for the patients.

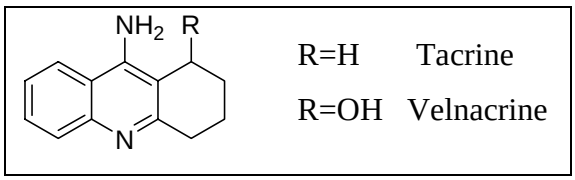


Fig. 1

We developped a synthesis of thiophene analogues of tacrine and velnacrine to have a look of the effect of structural modifications on the inhibition of acetylcholinesterase. (**Fig.2**)

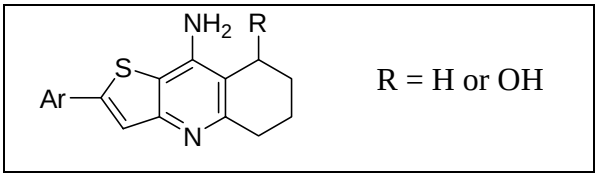
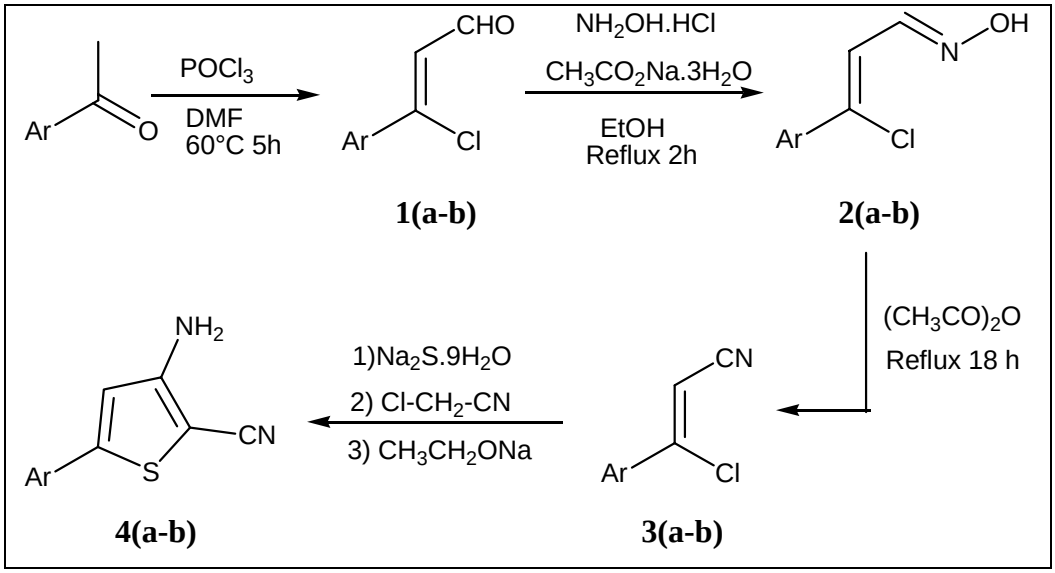


Fig.2

2. Results and discussions

First, we had to prepare substitued 3-amino-2-cyanothiophenes to have acces to the thiophene analogues of tacrine and velnacrine series. The synthesis of this kind of thiophene is very straightforward. The first step is the Vilsmeier Haack Arnold[1] reaction. We used acetophenones as starting material. The 3-aryl-3-chloroacroleins **1a-1b** were obtainded in goods yields. The next reaction was an oximation[2]. **1a** and **1b** were traited with hydroxylamine hydrochloride to get the corresponding oximes **2a** and **2b.** Then we prepared by dehydratation[2] 3-aryl-3-chloroacroleins **3a-3b** which are the precursors of the substitued 3-amino-2-cyanothiophenes **4a** and **4b.** (**Scheme 1**). The yields of these reaction are reported in the **Table 1**.



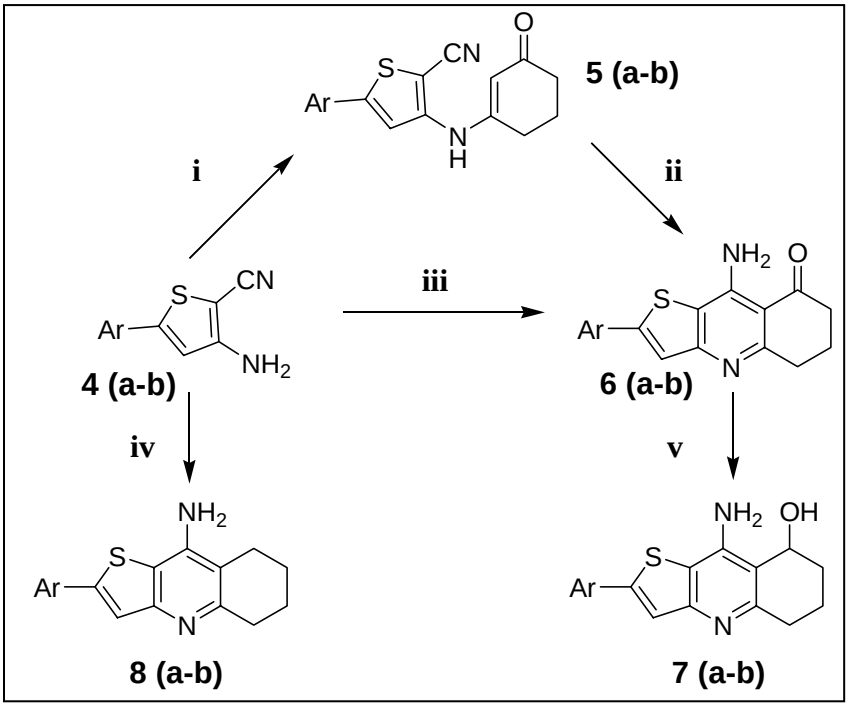
Scheme 1

	Vilsmeier Haack Arnold	Oximation	Dehydratation	Thiophene formation
Ar = p-CH_3-Ph	73 % **1 a**	>95 % **2 a**	67 % **3 a**	93 % **4 a**
Ar = p-CH_3O-Ph	>95 % **1 b**	>95 % **2 b**	90 % **3 b**	>95 % **4 b**

Table 1

4a and **4b** were used for the condensation's step with ketones to afford the corresponding enamines. The next step was the cyclisation to the cyclic coumpounds **5a** and **5b.**
The reduction with $LiAlH_4$ gave access to the thiophene analogues of velnacrine series.

These conditions only work with ketone as reactive as cyclohexan-1,3-dione. To have access to the thiophene analogues of tacrine, we used the Friedlander condition. We tried these conditons with cyclohexan-1,3-dione. We got the the coumpounds **6a** and **6b** with better yields and we shortened by one step the synthesis. (**Scheme 2**)



Conditions

i cyclohexan-1,3-dione, p-toluenesulfonic acid, toluene, reflux

ii CuCl, base, DMF, reflux

iii $AlCl_3$, cyclohexan-1,3-dione, $(CH_2)_2Cl_2$, reflux

iv $AlCl_3$, cyclohexanone, $(CH_2)_2Cl_2$, reflux

v $LiAlH_4$, THF, reflux

Scheme 2

The yields of these reactions are reported in the **Table 2.**

	Condensation i	Cyclisation ii	Friedländer iii	iv	Reduction v
Ar= p-CH_3-Ph	11 % **5a**	81 % 6a MeONa	80 % **6 a**	85 % **8 a**	75 % **7 a**
Ar= p-CH_3O-Ph	71 % **5b**	38 % 6b K_2CO_3	85 % **6 b**	> 95 % **8 b**	72 % **7 b**

Table 2

Conclusion

3-Amino- 5-aryl-2-cyanothiophenes were synthetised in four steps with good yields. The Friedländer reaction allowed a very rapid access to the target molecules with good yields.

Perspectives

Extension to other ketones are planned as well the synthesis of the selenium analogs. Biological tests using Ellman's procedure are underway.

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