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Article

Lewis Acid Promoted Friedländer Condensation Reactions between Anthranilonitrile and Ketones for the Synthesis of Tacrine and its Analogues

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Nesse trabalho estudou-se a reação de ciclodesidratação entre antranilonitrila e várias cetonas na presença de diferentes ácidos de Lewis não reportados na literatura, para a obtenção de 9-amino-1,2,3,4-tetrahidroacridinas. As reações de ciclodesidratação foram realizadas em condições térmicas empregando-se diferentes solventes e também na ausência de solvente, seguidas de hidrólise alcalina, levando à obtenção dos produtos em bons a excelentes rendimentos após isolamento.

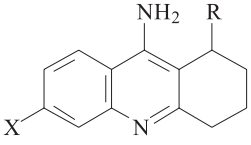
The scope of Lewis acid-promoted cyclodehydratation reactions between anthranilonitrile and several ketones, to afford tacrine and its derivatives, was expanded to include the use of various metal chloride salts not reported in the literature. The ability of the Lewis acids to effectively promote the cyclodehydratation between anthranilonitrile and cyclohexanone as the ketone was found to be the following order: $InCl_3$ > $AlCl_3$ ~ $BF_3.Et_2O$ > $FeCl_3$ > $BiCl_3$ ~ $SbCl_3$ ~ $SnCl_2.2H_2O$. The reactions were performed under both solvent and solvent-free conditions in good to excellent yields. Other Lewis acids screened, such as $RuCl_3$, $CeCl_3$, $NiCl_2$, $CoCl_2.2H_2O$ and CsCl were not effective.

Keywords: tacrine analogues, Lewis acid, Friedländer reaction, Alzheimer's disease

Introduction

Tacrine (**1a**, 9-amino-1,2,3,4-tetrahydroacridine or THA) is a reversible inhibitor of acetylcholinesterase (AChE), and was launched in 1993 as the first drug for the symptomatic treatment of Alzheimer's disease (AD).[1-2] However, the use of tacrine in AD has been limited by serious side effects such as hepatotoxicity, which often forces patients to discontinue treatment.[3-5] Tacrine has also been shown to possess a much broader pharmacological profile than cholinesterase inhibition: blockage of potassium channels,[6,7] inhibition of neuronal monoamine uptake processes,[8] and inhibition of monoamine oxidase[9] have all been reported (Figure 1).

A recent contribution to the development of tacrine related agents showed that tacrin-1-ol (**1b**, velnacrine),[10,11] an active metabolite of tacrine, has been chosen for clinical trial. Compared to tacrine, 6-fluoro-tacrin-1-ol (**1c**) has been reported to be slightly more potent, and 6-chlorotacrin-1-ol (**1d**), 30 times more potent.[12] In particular, 6-chlorotacrine (**1e**) has been found to be more potent than other substituted analogues (Figure 1).[2, 11, 13]



1a, X = R = H
1b, X = H, R = OH
1c, X = F, R = OH
1d, X = Cl, R = OH
1e, X = Cl, R = H

Figure 1.

The importance of these compounds has led to the development of various methods for their synthesis. The Friedländer reaction is a well-known method for preparing quinolines and polypyridyl bridging ligands,[14,15,16] and is still considered to be one of the most useful methods for preparing quinolines and related bicyclic azaaromatic compounds. In its original form, the Friedländer reaction is the reaction between an aromatic ortho-aminoaldehyde and an aldehyde or ketone bearing α-methylene functionality. Since Friedländer's initial discovery, the reaction has been extended to a wide range of substrates, including aromatic ortho-aminoketones and nitrogen-containing heterocycles.[16,17,18] In this regard, condensation reactions

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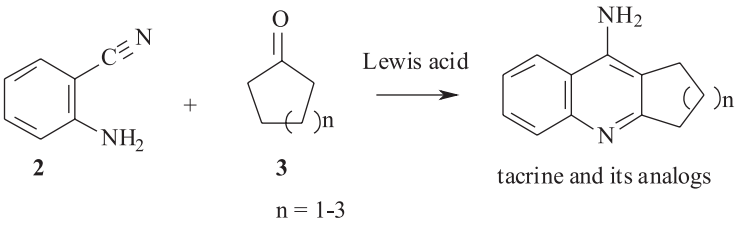


Scheme 1.

between anthranilonitrile (**2**) and ketones **3** (also classified as Friedländer reaction), have been recognized as an important and general approach to the synthesis of tacrine and its analogues (Scheme 1).[18]

These reactions are usually performed in the presence of a protic acid such as *p*-toluenesulfonic acid (PTSA) or a Lewis acid,[18,19] including $AlCl_3$,[20] $ZnCl_2$,[21] $BF_3.Et_2O$,[7] $SnCl_4$,[22] CuCl, $CuCl_2$, $TiCl_4$, P_2O_5.[23,24] However, these methods suffer from low yield and long reaction time, and are limited in terms of substrate applicability.[7,18-24] As part of our interest in the development of synthetically useful methods by combining Lewis acid-mediated organic transformations,[25] we investigated the cyclodehydratation reactions between several ketones and anthranilonitrile to afford the corresponding 9-amino-1,2,3,4-tetrahydroacridines, employing various Lewis acids not reported in the literature. The condensation reactions were investigated under solvent-free and solvent-reflux conditions.

Results and Discussion

In order to extend the scope of Lewis acids in the cyclodehydratation reactions between anthranilonitrile and ketones, cyclohexanone was chosen as the substrate, the aim being to examine some of the general features of these reactions, such as stoichiometry, solvent, temperature and product conversion. The remarkable utility of indium trihalides in various reported organic transformations,[26] along with our own contribution in this field,[25] motivated us to initially test the use of $InCl_3$ as catalyst in the Friedländer reaction. In fact, we found that the use of 1.0 equiv. of $InCl_3$ under toluene reflux for 24 h, followed by an additional 24 h of alkaline hydrolysis work up, afforded tacrine (**1a**) in a quantitative yield as depicted in Table 1 (entry 1). However, attempts to use a substoichiometric amount of $InCl_3$ (0.5 and 0.8 equiv.), shortening the reaction or hydrolysis work up time, led to lower yields. The influence and the nature of the solvent are noteworthy. Other solvents such as acetonitrile and *n*-nonane, under solvent reflux for 24 h, provided lower yields (entries 4 and 6). The excellent result achieved using nonpolar toluene and $InCl_3$ (1.0 equiv.) could be explained by the efficient coordination of catalyst and reactants. It was also observed that the use of toluene as the reaction solvent increased the solubility of the reaction solution, compared with the nonpolar *n*-nonane. In protic solvents such as anhydrous ethanol and *n*-propanol, a complex mixture of products was observed (entries 7 and 8). In the latter solvents, coordination of the Lewis acid with reactants was less favorable, as a result of the strong solvent interaction which has to be disrupted. To compare the efficiency of the solution *vs*. solvent-free system, a mixture of anthranilonitrile and cyclohexanone was heated at 120 °C for 24 h in the presence of 1.0 equiv. of $InCl_3$, affording tacrine in 80% yield (entry 9). Despite varying the reaction time, it was observed that changing the reflux time from 24 to 48 h (entry 5) or 60 h (entry 3) led to comparable yields of **1a**. It is also noteworthy that shorter reaction times under solvent-free conditions at 120 °C (entries 10 and 11) led to similar yield.

Table 1. $InCl_3$ promoted condensation reactions of anthranilonitrile and cyclohexanone under different conditions

Entry	Solvent[a]	Reaction Time (h)	Tacrine Yield[b] (%)
1	toluene	24	50[c], 80[d], 100[e]
2	toluene	6	40[e]
3	toluene	60	80[d]
4	acetonitrile	24	50[e]
5	acetonitrile	48	50[e]
6	*n*-nonane	24	80[e]
7	ethanol	24	complex mixture[e]
8	*n*-propanol	24	complex mixture[e]
9	without solvent	24	80[e,f]
10	without solvent	6	79[e,f]
11	without solvent	1	75[e,f]

[a]The reactions were performed under solvent reflux and additional 24 h of alkaline hydrolysis work up was required. [b]All yields refer to isolated product. [c]0.5 equiv. [d]0.8 equiv. [e]1.0 equiv. [f]The reactions were performed at 120 °C followed by additional 24 h of alkaline hydrolysis work up.

Our next series of experiments examined the use of various metal chloride salts as Lewis acid promoters in the cyclodehydratation reactions between anthranilonitrile and cyclohexanone, as depicted in the Table 2. Among these,

$AlCl_3$[20,27,28] and $BF_3.Et_2O$ complex[7] have previously been applied in the Friedländer reaction and were included in our set of experiments for comparative purposes.

Table 2. Condensation reactions of anthranilonitrile and cyclohexanone using different Lewis acids

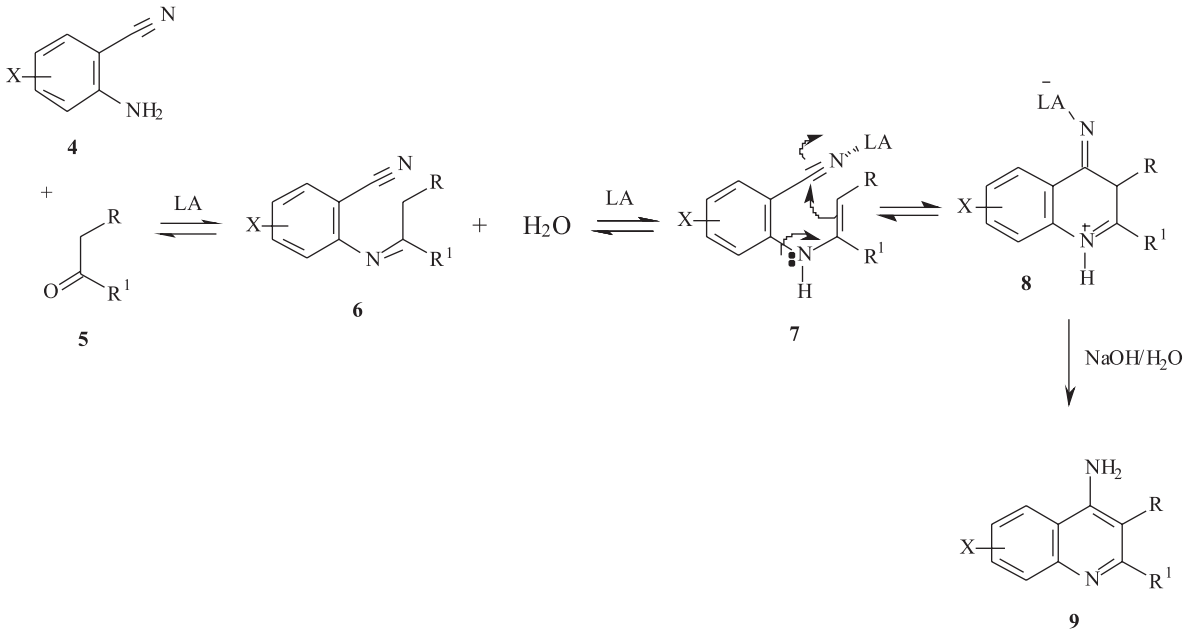
Entry	Lewis acid[a]	Solvent	Tacrine Yield[b] (%)
1	$FeCl_3$	toluene	73[c]
2	$AlCl_3$	toluene	85[c]
3	$BiCl_3$	toluene	70[c]
4	$SbCl_3$	toluene	68[c]
5	$SnCl_2.2H_2O$	toluene	71[c]
6	$BF_3.Et_2O$	toluene	85[c]
7	$RuCl_3$	toluene	10[c]
8	$NiCl_2$	toluene	0[c]
9	$CeCl_3$	toluene	0[c]
10	$CoCl_2.2H_2O$	toluene	11[c]
11	CsCl	toluene	0[c]
12	$FeCl_3$	without solvent	76[d], 78[e]
13	$AlCl_3$	without solvent	70[d], 87[e]
14	$BiCl_3$	without solvent	51[d], 49[e]
15	$SbCl_3$	without solvent	62[d], 61[e]
16	$SnCl_2.2H_2O$	without solvent	67[d], 55[e]
17	$BF_3.Et_2O$	without solvent	75[d], 83[e]

[a]1.0 equiv. [b]All yields refer to isolated product. [c]The reactions were performed under solvent reflux for 24 h and additional 24 h of alkaline hydrolysis. [d]Heating for 24 h at 120 °C and additional 24 h of alkaline hydrolysis. [e]Heating for 6 h at 120 °C and additional 24 h of alkaline hydrolysis.

In the screening, the chloride salts of Fe(III), Al(III), Bi(III), Sb(III), Sn(II), and the $BF_3.Et_2O$ complex gave tacrine **1a** with good yields under toluene reflux at 120 °C (entries 1-6). Under similar conditions, other Lewis acids such as the chloride salts of Ru(III), Ce(III), Co(II), Ni(II) and Cs(I) were not effective for the above reaction (entries 7-11). In the case of solvent-free conditions (entries 12-17), tacrine **1a** was obtained with good yield using Fe(III), Al(III), Sb(III), Sn(II) and $BF_3.Et_2O$ complex.

A fair number of ketones are known participants in the Friedländer cyclodehydratation reaction with *ortho*-amino-substituted benzonitriles promoted by a Lewis acid.[18] Its mechanism, however, has not been thoroughly studied.

In this regard, some mechanistic considerations have been offered.[16,18,19,21] We believe that the reaction may proceed through an initial imine-enamine tautomerism (whose preparation or isolation has been reported in some cases, depending upon the structure of the imine and enamine), activated by Lewis acid coordination under equilibrium conditions.[7,12,18,19] Next, we propose that the weakly basic nitrile of **7** is activated by Lewis acid coordination, followed by the intramolecular addition of the enamine carbon to the nitrile group to afford the intermediate **8**. Next, an imine-enamine tautomerism should take place, during or prior to the alkaline hydrolysis work up, to afford **9**. The proposed mechanism shows a delicate balance, where the ability of the Lewis acid to coordinate with the starting materials intermediates and product, in an interchangeable manner through the reaction pathway, should play an important and critical role in the reaction course. In this sense, we believe that the Lewis



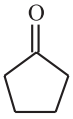
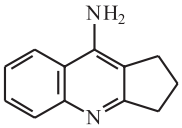
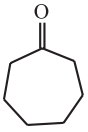
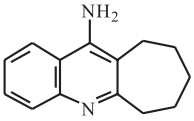
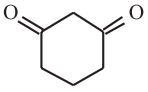
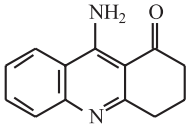
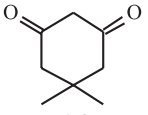
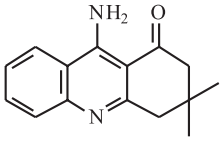
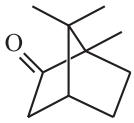
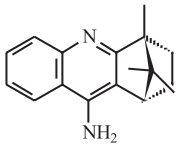
Scheme 2.

acid activation of the nitrile group followed by cyclization should be the rate-limiting step in the above reaction.

Next, under optimized conditions, the cyclodehydratation reaction under toluene reflux was further evaluated with several ketones and anthranilonitrile in the presence of different Lewis acids. As depicted in Table 3 (entries 1 and 2), cyclopentanone (**10**) and cycloheptanone (**12**), delivered a lower yield of products **11** and **13**, comparative to the six-membered ring substrate cyclohexanone (Tables 1 and 2). In this regard, there was no difference with the results reported in the literature. This feature can presumably be ascribed to the ring strain in the cyclization step, along with a slower rate reaction. Even so, it is evident from the results that $InCl_3$ proved to be an efficient promoter for the cyclodehydratation reaction in the cases of ketones **10** and **12**, to afford higher yields in comparison with results in the literature.[7] In the case of diketones **14** and **16** (entries 3 and 4), the tacrine analogues **15** and **17** were observed in good yields restrictively for $InCl_3$ and $FeCl_3$. Next, (+/-)-camphor was examined as the ketone, and shown to be a highly acid sensitive substrate under the screened metal chloride salts (entry 5). A reasonable yield (45%) of **19** was achieved using $AlCl_3$. In comparison with a precedent in the literature, $BF_3.Et_2O$ under similar reaction conditions led to only 3.8% yield of **19**.[7]

In summary, this work has extended the use of Lewis acid promoters in cyclodehydratation reactions between anthranilonitrile and cycloketones to afford tacrine and its analogs with good to excellent yields, employing both organic solvent and solvent-free conditions. The ability of the Lewis acids to effectively promote the cyclodehydratation between anthranilonitrile and cyclohexanone as the ketone was found to be the following order: $InCl_3 > AlCl_3 \sim BF_3.Et_2O > FeCl_3 > BiCl_3 \sim SbCl_3 \sim SnCl_2.2H_2O$. Other Lewis acids screened, such as $RuCl_3$, $CeCl_3$, $NiCl_2$, $CoCl_2.2H_2O$ and CsCl were not effective.

Table 3. Lewis acids promoted condensation reactions of anthranilonitrile and several cycloketones[a]

Entry	Ketones	Product	Lewis acid[b]	Yield[c] (%)
1	 **10**	 **11**	$InCl_3$	83
			$BiCl_3$	36
			$FeCl_3$	39
			$SbCl_3$	40
			$SnCl_2.2H_2O$	33
			$AlCl_3$	57
2	 **12**	 **13**	$InCl_3$	87
			$BiCl_3$	64
			$FeCl_3$	65
			$SbCl_3$	31
			$SnCl_2.2H_2O$	59
			$AlCl_3$	95
3	 **14**	 **15**	$InCl_3$	67
			$BiCl_3$	35
			$FeCl_3$	60
			$SbCl_3$	24
			$SnCl_2.2H_2O$	25
			$AlCl_3$	Complex mixture
4	 **16**	 **17**	$InCl_3$	80
			$BiCl_3$	51
			$FeCl_3$	63
			$SbCl_3$	58
			$SnCl_2.2H_2O$	42
			$AlCl_3$	0
5	 **18**	 **19**	$InCl_3$	Complex mixture
			$BiCl_3$	15
			$FeCl_3$	27
			$SbCl_3$	0
			$SnCl_2.2H_2O$	Complex mixture
			$AlCl_3$	45

[a]The reactions were performed under toluene reflux for 24 h and additional 24 h of alkaline hydrolysis; [b]1.0 equiv.; [c]Isolated yield.

This general trend was observed by employing different ketones as substrates. We also found that lower reaction time is required under solvent-free conditions.

Experimental

Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. IR spectra were measured on a Mattson Galaxy Series FT-IR 3000 (model 3020). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. The chemical shifts are expressed as δ (ppm) relative to TMS as an internal standard and *J* standard values are given in Hz.

*Cyclodehydratation reaction of 2-aminobenzonitrile (**2**) with ketones under solvent reflux*

To a mixture of 2-aminobenzonitrile (1.0 mmol) and ketone (1.0 mmol) in toluene (8 mL) placed in a round bottom flask connected to a Dean-Stark water separator, was added Lewis acid (1.0 mmol). The mixture was heated at reflux for 24 h under stirring. After cooling to rt, the toluene was decanted, the remaining solids were treated with NaOH solution (2 mol L^{-1}, 8 mL) and this mixture was heated at reflux for 24 h. On cooling to rt, the reaction mixture were extracted with $CHCl_3$ (3 × 8 mL), the organic layers were combined and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the desired product.

*Cyclodehydratation reaction of 2-aminobenzonitrile (**2**) with ketones under solvent-free*

To a mixture of 2-aminobenzonitrile (1.0 mmol) and ketone (1.0 mmol) placed in a round bottom flask connected to a reflux condenser, was added Lewis acid (1.0 mmol). The mixture was heated at 120 ºC for 24 h under stirring. After cooling to rt, the remaining solids were treated with NaOH solution (2 mol L^{-1}, 8 mL) and this mixture was heated at reflux for 24 h. On cooling to rt, the reaction mixture were extracted with $CHCl_3$ (3 × 8 mL), the organic layers were combined and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the desired product.

Both procedures were performed under an argon atmosphere in the cases of $AlCl_3$ and $BF_3.Et_2O$. The isolated products showed to be sufficiently clean and no further purifications were runned. ^{1}H and, ^{13}C NMR, IR analysis and melting point were consistent with the literature data. (See NMR spectra of isolated products at Supplementary Information).

*9-amino-1,2,3,4-tetrahydroacridine (**1a**)*

IR (*KBr*) ν_{max}/cm^{-1}: 3478, 3302, 3050, 2933, 1646, 756; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J* 8.4 Hz, 1H), 7.72 (dd, *J* 8.4, 0.6 Hz, 1H), 7.57 (t, *J* 7.5 Hz, 1H), 7.37 (t, *J* 7.5 Hz, 1H), 4.66 (br s, 2H), 3.04 (t, *J* 6.0 Hz, 2H), 2.62 (t, *J* 6.0 Hz, 2H), 2.00-1.93 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 146.5, 146.3, 128.4, 128.3, 123.6, 119.8, 117.0, 110.1, 33.9, 23.5, 22.6, 22.5; mp = 175-177 ºC. For reported data of melting point, IR, and NMR, see reference.[7,29]

*9-amino-2,3-dihydro-1H-cyclopenta[1,2-b]quinoline (**11**)*

IR (*KBr*) ν_{max}/cm^{-1}: 3342, 3241, 2960, 1659, 1568, 761; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, *J* 8.4 Hz, 1H), 7.71 (dd, *J* 8.4, 0.6 Hz, 1H), 7.56 (t, *J* 7.8 Hz, 1H), 7.35 (t, *J* 7.8 Hz, 1H), 4.68 (br s, 2H), 3.10 (t, *J* 7.8 Hz, 2H), 2.83 (t, *J* 7.5 Hz, 2H), 2.18 (quintet, *J* 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5 , 148.5, 144.5, 128.9, 128.2, 123.7, 119.8, 117.6, 115.0, 35.1, 27.3, 22.6; mp = 174-176 ºC. For reported data of melting point, IR, and NMR, see reference.[7]

*11-amino-2,3,4,5-tetrahydro-1H-cyclohepta[1,2-b]quinoline (**13**)*

IR (*KBr*) ν_{max}/cm^{-1}: 3487, 3310, 3162, 2908, 1648, 1579, 748; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J* 8.4 Hz, 1H), 7.68 (d, *J* 8.4 Hz, 1H), 7.55 (t, *J* 7.5 Hz, 1H), 7.36 (t, *J* 7.5 Hz, 1H), 4.77 (br s, 2H), 3.14-3.11 (m, 2H), 2.76-2.72 (m, 2H),1.89-1.63 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 146.1, 145.1, 128.9, 128.2, 124.2, 120.1, 117.9, 115.7, 39.7, 31.9, 27.5, 26.7, 26.3; mp = 170-172 ºC. For reported data of melting point, IR, and NMR, see reference.[7]

*9-amino-3,4-dihydroacridin-1(2H)-one (**15**)*

IR (*KBr*) ν_{max}/cm^{-1}: 3274, 3113, 2935, 1634, 1612, 1571, 1548, 1007, 755; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.27 (br, 1H, NH_2), 7.88-7.83 (m, 2H), 7.70 (t, *J* 8.1 Hz, 1H), 7.41 (t, *J* 7.8 Hz, 1H), 6.23 (br, 1H, NH_2), 3.12 (t, *J* 6.6 Hz, 2H), 2.74 (t, *J* 6.6 Hz, 2H), 2.15 (quintet, *J* 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.6, 163.7, 154.4, 148.1, 132.0, 129.0, 124.8, 120.9, 117.6, 106.5, 39.8, 34.5, 21.6; mp = 238-240 ºC. For reported data of melting point, IR, and NMR, see reference.[30]

*9-amino-3,4-dihydro-3,3-dimethylacridin-1(2H)-one (**17**)*

IR (*KBr*) ν_{max}/cm^{-1}: 3291, 3119, 2960, 2922, 1623, 1613, 1546, 760; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.26 (br, 1H, NH_2), 7.92-7.88 (m, 2H), 7.70 (t, *J* 7.5 Hz, 1H), 7.43 (t, *J* 7.5 Hz, 1H), 6.39 (br, 1H, NH_2), 3.01 (s, 2H), 2.58 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.2, 162.6, 154.1, 147.9, 132.1, 128.7, 125.0, 121.2, 117.6, 105.4, 53.2, 47.7, 32.1, 28.1; mp = 221-223 ºC. For reported data of melting point, IR, and NMR, see reference.[31,32]

*9-amino-1,4-methano-1,2,3,4-tetrahydro-4,11,11-trimethylacridine (**19**)*

IR (*KBr*) ν_{max}/cm^{-1}: 3327, 3143, 2956, 2869, 1643, 1594, 760; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, *J* 8.4 Hz, 1H), 7.64 (d, *J* 8.1 Hz, 1H), 7.48 (t, *J* 7.5 Hz, 1H), 7.32 (t, *J* 7.8 Hz, 1H), 4.47 (br s, 2H), 2.85 (d, *J* 3.9 Hz, 1H), 2.09-2.00 (m, 1H), 1.88-1.79 (m, 1H), 1.39 (s, 3H), 1.37-1.17 (m, 2H), 0.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 147.3, 140.8, 129.1, 127.7, 123.9, 120.0, 119.6, 119.2, 55.3, 54.5, 47.5, 32.5, 25.6, 20.1, 19.1, 10.6; mp = 160-162 ºC. For reported data of Melting point, IR, and NMR, see reference.[7,33]

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Supplementary Information

Supplementary data are available free of charge at http://jbcs.org.br, as PDF file.

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