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Rapid access to novel 2-alkylthiopyrimidine derivatives and attempt of their Tacrine analogs synthesis

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ABSTRACT

A variety of novel 2-alkylthiopyrimidines were synthesized through simple condensation of arylidenemalononitriles with different 2-alkylthiouronium halide derivatives catalyzed by anhydrous potassium carbonate (K_2CO_3). The reactions have been carried out under mild conditions in *i*-PrOH, and the products were obtained in moderate to good yields with a simple work-up method. Subsequently, some examples of these compounds have been converted into Tacrine analogs by applying the Friedländer reaction.

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KEYWORDS
Friedländer reaction; pyrimidine-based heterocycles; S-substituted thiopyrimidines; Tacrine analogs

Introduction

Pyrimidines are important structural units found in a wide variety of molecules, including natural products,[1] substances of biological and pharmaceutical importance,[2] as well in therapeutics such as Voriconazole,[3] Crestor, Gleevec[4] and Avitriptan[5] (Fig. 1). Especially, pyrimidines have also been utilized as means intermediates in medicinal chemistry to produce new chemical entities with a wide range of pharmacological activities.[6] Also, this exceptional structure has been developed as chemotherapeutic agents in the treatment of various types of cancer,[7,8] and found to be effective as antimicrobial[9] and antioxidant[10] agents. Extension of various approaches to pyrimidines is of great interest and many methods for the synthesis of substituted pyrimidines have been reported.[11–19]

Recently, the oxidative dehydrogenation of 2-alkylthiodihydropyrimidines was found to produce 2-alkylthiopyrimidines in the presence of a Cu catalyst with no additional reagents.[20] This procedure was then applied to generate 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs) and 2-arylthiopyrimidines via Cu-catalyzed C–S cross-coupling and concomitant oxidative dehydrogenation.[21]

However, the development of simple, facile and efficient methodologies to get six-membered heterocycles is one of the major aspects in organic synthesis. This stimulated

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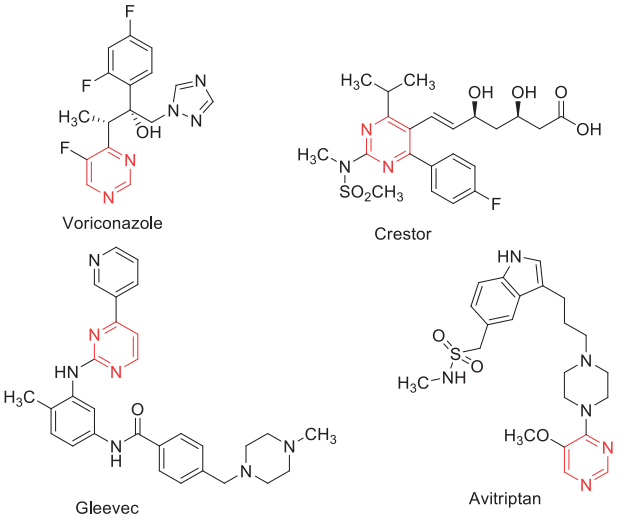


Figure 1. Different drugs containing pyrimidine nucleus.

our interest for the synthesis of new fused pyrimidines from simple condensation of arylidenemalononitrile with different 2-alkylthiouronium halide derivatives.

In our continuous interest for the development of new efficient catalytic synthesis of biologically important heterocycles,[22] as only few general and highly methods for the synthesis of S-substituted thiopyrimidines have been reported, in this paper we further report a simple and effective method for synthesis of 2-alkylthiol-substituted pyrimidines in good yields, employing *i*-PrOH as solvent and using easily available anhydrous potassium carbonate, subsequently some examples of these products will be converted to Tacrine analogs applying the Friedländer reaction.

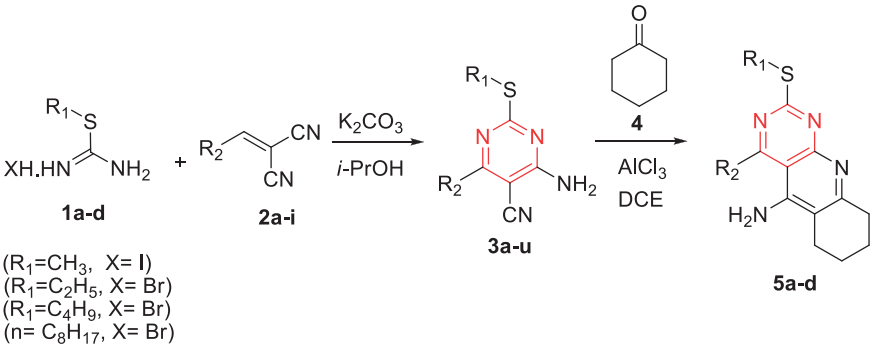
Results and discussion

Herein, we are interested in the synthesis of new 4-amino-2-(alkylthio)-6-arylpyrimidine-5-carbonitriles **3a–u.** In fact, the reactivity of 2-arylidenemalononitriles with different 2-alkylthiouronium halides has been studied, relying on the utility of the catalyst in the reaction. For this purpose, we first synthesized 2-alkylthiouronium halides **1a–d** from the condensation between thiourea and different alkyl halides using the method described by Masquelin et al.[23] (Scheme 1)

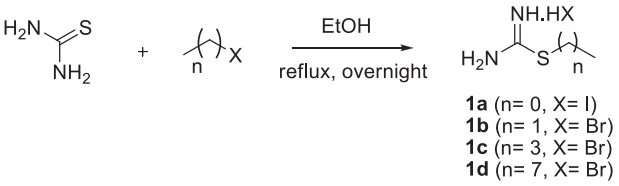
Furthermore, the condensation between various substituted aromatic or heterocyclic aldehydes and malononitrile in the presence of piperidine as catalyst in ethanol at room temperature, give rise to the formation of variety of 2-arylidenemalononitriles **2** (Scheme 2).

The optimization of the reaction conditions was carried out on the condensation of S-methylthiouronium iodide **1a** with 2-benzylidenemalononitrile **2a** (Scheme 3).

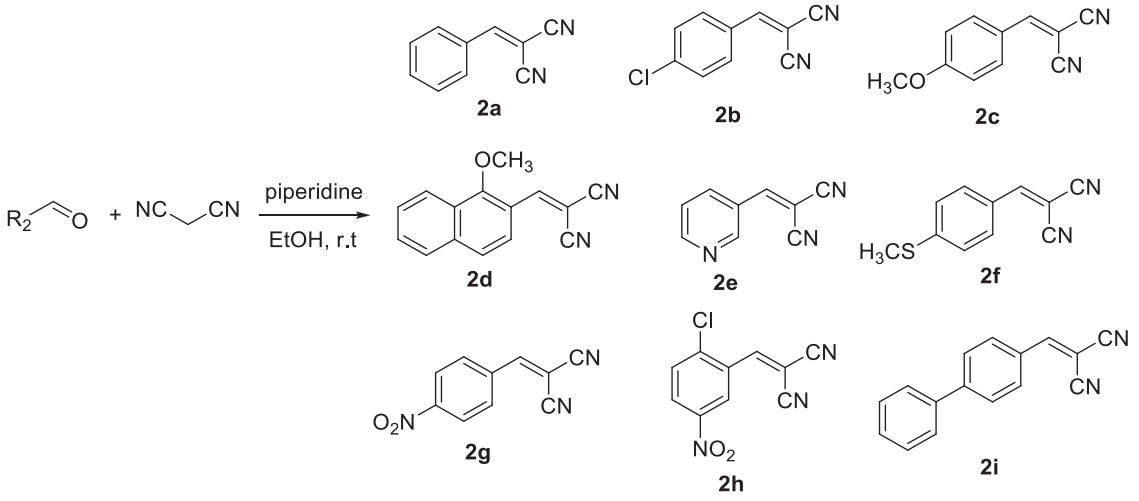
In an initial experiment, a reaction has been performed in ethanol at room temperature for 24 h. After simple workup, the corresponding product was isolated in very low



Scheme 1. Synthetic layout for the synthesis of 4-amino-2-(alkylthio)-6-arylpyrimidine-5-carbonitrile derivatives **3a-u** and some of their Tacrine analogs **5a-d**.



Scheme 2. Synthesis of 2-alkylthiouronium halides **1a-d.**



Scheme 3. Synthesis of arylidenemalonitriles **2a-i.**

yield (Table 1, entry 1). Running the same reaction at room temperature in other solvents such as *i*-PrOH (Entry 2), MeOH (Entry 3), and CH_3CN (Entry 4) did not improve the reaction yields.

From these initial results, we further optimized the reaction conditions by employing various catalysts. The results are listed in Table 1. When the same reaction was

Table 1. Optimization of the reaction conditions.

Entry	Solvent	Time (h)	Catalyst	Amount of catalyst (mol %)	T (°C)	Yield[a] (%)
1	EtOH	24	–	–	25	Traces
2	*i*-PrOH	24	–	–	25	Traces
3	MeOH	24	–	–	25	Traces
4	CH_3CN	24	–	–	25	–
5	EtOH	24	HCl	2–3 drops	25	–
6	EtOH	24	HCl	2–3 drops	Reflux	–
7	EtOH	24	$ZnCl_2.H_2O$	10	Reflux	–
8	EtOH	5	DABCO	10	Reflux	51
9	EtOH	5	DMAP	10	Reflux	54
10	EtOH	2	Et_3N	2–3 drops	Reflux	55
11	EtOH	5	P_2O_5	20	Reflux	23
12	EtOH	2	NaOH (1N)	2–3 drops	Reflux	42
13	EtOH	2	K_2CO_3	100	Reflux	50
14	*i*-PrOH	1	K_2CO_3	100	Reflux	68

[a]Yields of pure isolated product.

performed at room temperature in EtOH in the presence of a few drops of HCl as catalyst, only a trace amount of the corresponding product **7a** was observed, even when the reaction was carried out under reflux (Entry 6). Similarly, the use of $ZnCl_2.H_2O$ was not able to afford the desired product (Entry 7). Other catalysts such as DABCO, DMAP, Et_3N, P_2O_5 and NaOH (1N) were also screened. However, all of them gave the final product in low to moderate yields (entries 8–12).

The use of K_2CO_3 as catalyst in refluxed ethanol facilitated the reaction to some extent but did not exceed the yield of 50% (Entry 13). However, this reaction was most efficient when using K_2CO_3 (1 equiv) in *i*-PrOH under reflux (Entry 14).

These results show the advantage of using K_2CO_3 as catalyst with notable improvement in the reaction giving rise to 4-amino-2-(methylthio)-6-phenylpyrimidine-5-carbonitrile **3a**. This method was subsequently generalized to various other 2-arylidenemalononitriles and different 2-alkylthiouronium halides, thus allowing the synthesis of a series of products **3a–u** bearing electron donating or withdrawing groups with moderate to good yields varying between 56 and 68% within 1–2 h in refluxed *i*-PrOH (Table 2, entries 1–21). The reactions were remarkably cleans, and no chromatographic separation were required. The use of aromatic or heterocyclic 2-arylidenemalononitriles has no significant impact on the conversions. Similarly, various other 2-alkylthiouronium halides have been used with success.

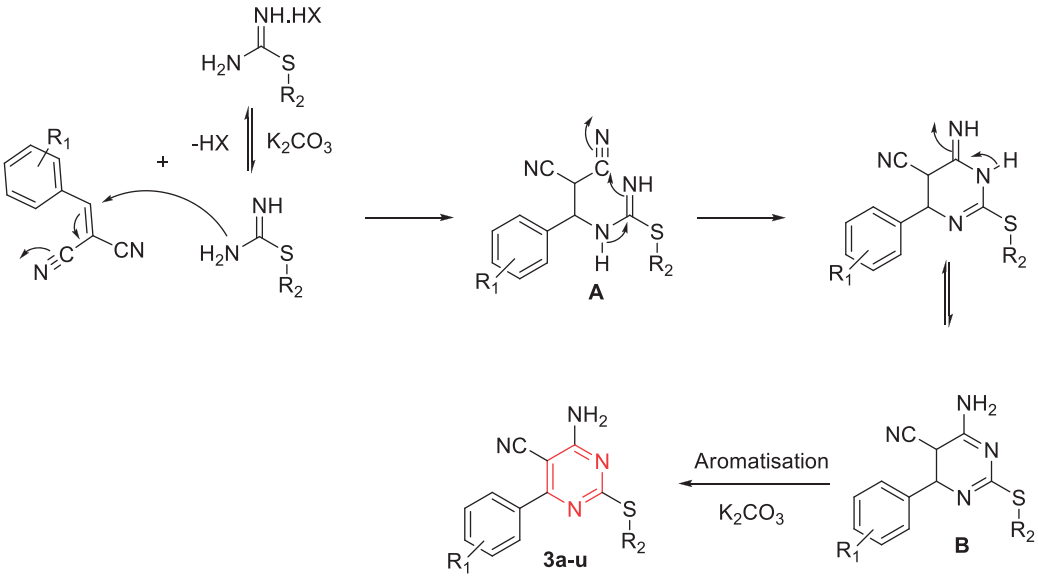
The proposed mechanistic path for this reaction can be suggested first by a condensation of 2-alkylthiouronium halides with 2-arylidenemalononitriles according to a Michael type 1,4-addition. Then, intermediate **A** cyclizes to give rise to a second intermediate **B** obtained *in situ* from the reaction, finally complete aromatization in the presence of K_2CO_3 provide the desired products (Scheme 4).

On the other hand, we attempted to extend the process we have taken four randomly selected derivatives of the previously synthesized 3-amino-2-cyanopyrimidines for use in the Friedländer reaction. We therefore performed the reaction by applying standard conditions described in our previous work.[24c] The structures of all the products were confirmed on the basis of their spectroscopic data, particularly nuclear magnetic resonance (^1H and ^{13}C NMR) spectroscopy, high-resolution mass spectroscopy (HRMS) and elemental analysis (Table 3).

Table 2. Synthesis of 4-amino-6-aryl-2-methylthio pyrimidine-5-carbonitrile in ethanol catalyzed with K_2CO_3.

Entry	Product	R^1	R^2	Yield[a](%)	m.p. (°C)	Lit. Mp (°C)
1	**3a**	C_6H_5	CH_3	68	202–204	210[23a]
2	**3b**	4-ClC_6H_4	CH_3	65	215–217	225.5[23a]
3	**3c**	4-(MeO)C_6H_4	CH_3	63	207–209	211.5[23a]
4	**3d**	2-(MeO)-1-Naphthyl	CH_3	53	250	–
5	**3e**	C_6H_5	C_2H_5	61	177–179	170–171[23b]
6	**3f**	4-ClC_6H_4	C_2H_5	62	175–177	191–192[23b]
7	**3g**	4-(MeO)C_6H_4	C_2H_5	59	166–168	–
8	**3h**	2-(MeO)-1-Naphthyl	C_2H_5	54	218–220	–
9	**3i**	C_6H_5	C_4H_9	56	132–134	128–129[23b]
10	**3j**	4-ClC_6H_4	C_4H_9	54	159–161	158–159[23b]
11	**3k**	4-(MeO)C_6H_4	C_4H_9	61	151–153	–
12	**3l**	3-Pyridin-C_6H_4	C_4H_9	52	106–108	–
13	**3m**	2-(MeO)-1-Naphthyl	C_4H_9	51	195–197	–
14	**3n**	C_6H_5	C_8H_{17}	70	105–107	–
15	**3o**	4-ClC_6H_4	C_8H_{17}	68	120–122	–
16	**3p**	4-(MeO)C_6H_4	C_8H_{17}	66	107–109	–
17	**3q**	4-(MeS)C_6H_4	C_8H_{17}	65	116–118	–
18	**3r**	4-(NO_2)C_6H_4	C_8H_{17}	60	147–149	–
19	**3s**	2-(Cl)-5-(NO_2)C_6H_3	C_8H_{17}	69	190–192	–
20	**3t**	C_6H_5-C_6H_4	C_8H_{17}	62	146–148	–
21	**3u**	2-(MeO)-1-Naphthyl	C_8H_{17}	64	172–174	–

[a]Isolated yield.



Scheme 4. Proposed mechanism for the S-substituted thiopyrimidines **3**.

Table 3. Synthesis of pyrimidine analogs of Tacrine.

Product	R^1	R^2	Yield (%)	m.p. (°C)
5a	4-ClC_6H_4	C_2H_5	47	219–220
5b	4-ClC_6H_4	C_2H_5	51	232–234
5c	4-(MeO)C_6H_4	C_4H_9	43	190–192
5d	4-(MeO)C_6H_4	C_4H_9	40	224–226

[a]Isolated yield.

Conclusions

We reported in this paper the synthesis of 4-amino-6-aryl-2-alkylthiopyrimidine-5-carbonitrile derivatives from the condensation of 2-benzylidenemalononitriles with different 2-alkylthiouronium halides. Because of the easy work-up procedure, low cost, and, especially, good product yields, this method is a useful and attractive procedure for synthesis of S-substituted thiopyrimidines compounds. An attempt to convert some 2-amino-6-aryl-2-alkylthiopyrimidine-5-carbonitriles to the corresponding Tacrine analogs applying the Friedländer reaction has been accomplished with success. The continuation of this project as well as the biological evaluation of these compounds will be the subject of another paper.

Experimental section

Instruments and materials

All the chemicals were purchased from the Sigma-Aldrich and used without further purification. All solvents used for spectroscopic and synthesis studies were reagent grade and were further purified by literature methods. Melting points were determined on an Electrothermal capillary fine control apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Brüker Avance 400 instrument at 400 and 100 MHz, respectively, and Brüker advance DPX 250 (250 MHz for the ^{1}H, 62.5 for the ^{13}C), in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are given in part per million downfield from TMS as an internal standard and J values in Hz. High-Resolution Mass spectra were recorded with a MicroTof-Q 98. Elemental analyses were carried out on a Microanalyzer Flash EA1112 CHNS/O Thermo Electron.

General procedure for the preparation of 2-alkylthiouronium *halides* 1a-d [22]

A mixture of thiourea (1 mmol) and alkyl halides (1.2 mmol) in EtOH (5 mL) was stirred overnight under reflux, the mixture was cooled to room temperature and evaporated. The residue was suspended in Et_2O and filtered. The final product was used in the next step without any additional purification.

2 -Octylthiouronium bromide (1d)

Yield: >95%; white solid; m.p.: 98–100 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.48 (s, 2H, NH_2), 3.29 (t, $J = 7.2$ Hz, 2H, S–CH_2), 1.71 (qt, $J = 7.4$ Hz, 2H, CH_2), 1.46–1.28 (m, 10 H), 0.89 (t, $J = 6.8$ Hz, 3H).^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 172.2, 119.9, 32.3, 31.9, 29.2, 28.7, 28.4, 22.8, 14.3.

General procedure for the preparation of 4-amino-6-aryl-2-methylthio pyrimidine-5-carbonitrile 3a–u

In a 100 mL flask was introduced 2-alkylthiouronium halides **1** (1 mmol) and 2-benzylidenemalononitriles derivatives **2** (1 mmol) with 1 mmol of K_2CO_3 in refluxed *i*-PrOH (10 mL). The mixture was cooled to room temperature (the progress of the reaction was

monitored by TLC). Then the mixture was poured onto 100 mL of water. The obtained precipitate was filtered on Büchner and the resulting solid was recrystallized from ethanol.

4 -Amino-2-(butylthio)-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile (3k)

Yield: 61%; white solid; m.p.: 151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.98 (dd, $J = 8.8$, 2.0 Hz, 2H), 6.94 (dd, $J = 8.8$, 2.0 Hz, 2H), 5.54 (br s, 2H, NH_2), 3.81 (s, 3H, O–CH_3), 3.10 (t, $J = 7.6$ Hz, 2 H, S–CH_2), 1.65 (qt, $J = 7.6$ Hz, 2H, CH_2), 1.42 (qt, $J = 7.6$ Hz, 2H, CH_2), 0.89 (t, $J = 7.2$ Hz, 3H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.1, 166.2, 163.6, 162.4, 130.5, 128.1, 117.0, 114,0, 81.9, 55.5, 31.3, 30.8, 22.0, 13.7. HRMS (ESI^+) *m/z* 337.1101 $[M + Na]^{+\cdot}$, Calcd for $C_{16}H_{18}N_4ONaS$: 337.1099.

General procedure for the preparation of compounds 5a-d

In a 100 mL round bottom flask, aluminum chloride (2 mmol) were added into adequate volume of dry 1,2-dichloroethane (DCE) and stirred at reflux for few minutes. Then, a mixture of 4-amino-6-aryl-2-methylthio pyrimidine-5-carbonitrile **3** (1 mmol), and cyclohexanone **4** (2 mmol) were added into the reaction. The mixture was continuously stirred for 24 h (monitored by TLC) at constant temperature. After completion, solvent was evaporated and water was added and the mixture was basified with 10% sodium hydroxide solution to pH = 8–9. After stirring for 30 min, the precipitate was filtered and washed with water. Purification by column chromatography on silica gel (ethyl acetate:cyclohexane = 3:1, v/v) afforded the title compounds **5a–d**.

2 -(Butylthio)-4-(4-chlorophenyl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-5-amine (5b)

Yield: 51%; yellow solid; m.p.: 232–234 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 (m, 4H), 4.56 (br s, 2H, NH_2), 3.28 (t, $J = 7.2$ Hz, 2H),2.98 (t, $J = 6.0$ Hz, 2H), 2.33 (t, $J = 6.0$ Hz, 2H), 1.84–1.81 (m, 4H),1.68 (qt, $J = 6.0$ Hz, 2H), 1.41 (qt, $J = 6.0$ Hz, 2H), 0.86 (t, $J = 7.2$ Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.0, 165.9, 165.6, 158.4, 149.2, 137.5, 136.7, 130.1, 129.5, 111.9, 104.0, 33.8, 30.9, 23.5, 22.3, 22.2, 22.0, 13.8. HRMS (ESI^+) *m/z* 399.1437 $[M + H]^{+\cdot}$, calcd for $C_{21}H_{24}ClN_4S$: 399.1410.

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