A Novel Microwave-Assisted Green Synthesis of Condensed 2-Substituted-pyrimidin-4(3*H*)-ones Under Solvent-Free Conditions

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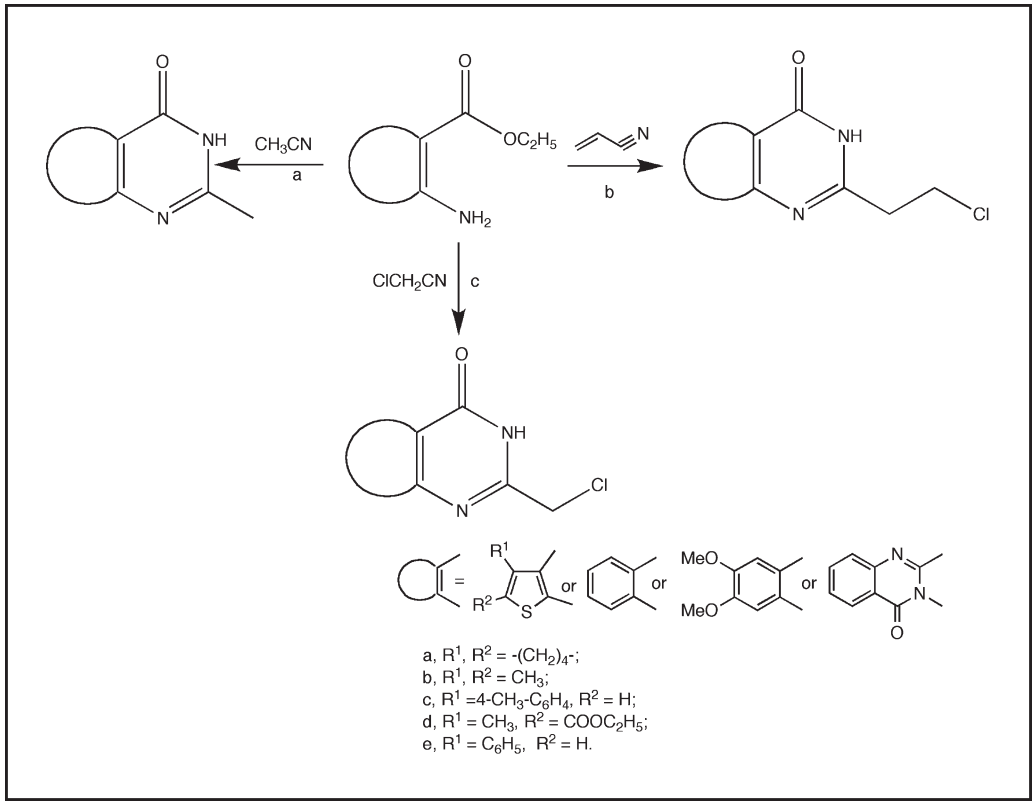

A rapid microwave-assisted green chemical synthesis of condensed 2-substituted-pyrimidin-4(3*H*)-ones **3, 4,** and **5** involving the condensation of a variety of nitriles with *o*-aminoesters of thiophene **2a–e**, benzene **2f**, dimethoxybenzene **2g** and quinazolinone **2h** in the presence of catalytic amount of HCl alone or with the Lewis acid $AlCl_3$ under solvent-free conditions, is described for the first time. This novel and clean one-pot methodology, which is characterized by very short reaction times and easy workup procedures, can be exploited to generate a diverse library of condensed pyrimidine heterocycles.

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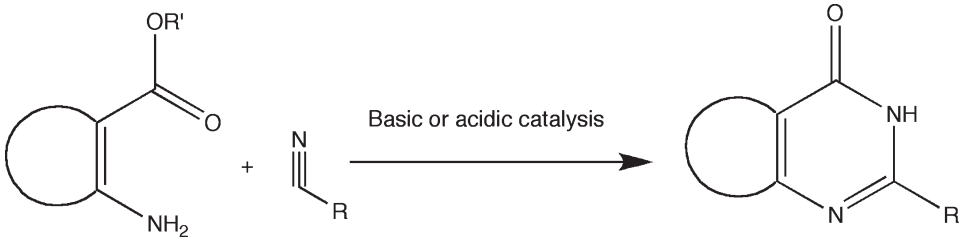
INTRODUCTION

Pyrimidines and condensed pyrimidines have a long and distinguished history of their numerous biological and medicinal applications [1]. The synthesis and biological evaluation [2] of potentially bioactive condensed pyrimidines, appropriately functionalized, especially at the 2- and 4-positions have attracted considerable attention of medicinal chemists worldwide. Therefore, the synthesis of condensed pyrimidines has been a very important process, subject to improvement, from time to time. The regularly employed synthetic methodologies involve annelation of the pyrimidine ring on an appropriately substituted carbocycle or heterocycle [3].

Of these the most popularly used synthetic methodology is the ''Principal Pyrimidine Synthesis'', which involves mainly the cyclocondensation of *o*-aminocarbonyl substrates with reagents like amidines, ureas, thiourea or imidates [3]. Alternatively use of nitriles as reagents for cyclocondensation with *o*-aminocarbonyl substrates is relatively less exploited and is reported under basic [4,5] as well as

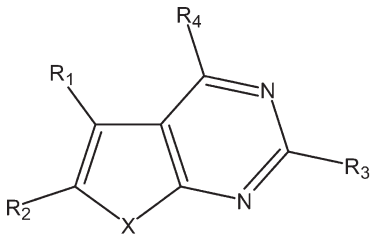
Scheme 1



acidic [6,7] conditions. The direct use of nitriles in these cyclocondensations is attractive as it offers more flexibility and generates a variety of 2-substituents in the resultant condensed pyrimidines. Nitriles often being the precursors for amidines are also more economical than the amidines (Scheme 1).

It would be very interesting to adopt this reaction for high throughput synthesis in order to generate diverse libraries of condensed pyrimidines of type **1** with four diverse points for further functionalization.

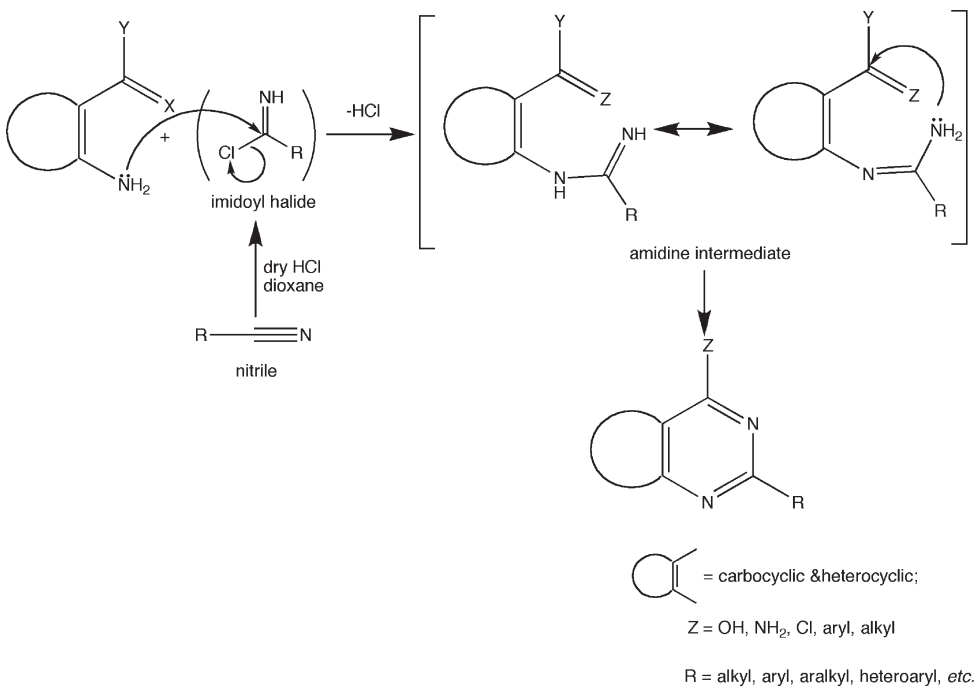
The direct use of the electrophilic properties of nitriles in such syntheses, though previously reported [8], has received only scant attention. Shishoo and coworkers [6,7,9–15] have exploited the reactions of a variety of nitriles with a host of *o*-aminocarbonyl substrates, under the influence of dry HCl gas under conventional conditions to obtain a wide range of 2-substituted-4-oxo/4-amino/4-chloro and 4-aryl condensed pyrimidines (Scheme 2). These reactions are known to proceed *via* the imidoyl halide intermediate, whose carbon is highly electrophilic. The cyclocondensation proceeds *via* the transient amidine intermediate. This interesting reaction has been developed as a synthetic method of general applicability to obtain a variety of condensed 2-substituted-4-functionalized pyrimidines. The reaction generally takes 8–12 h for completion and typically involves bubbling of dry HCl gas through the reaction mixture in dioxane (Scheme 2).



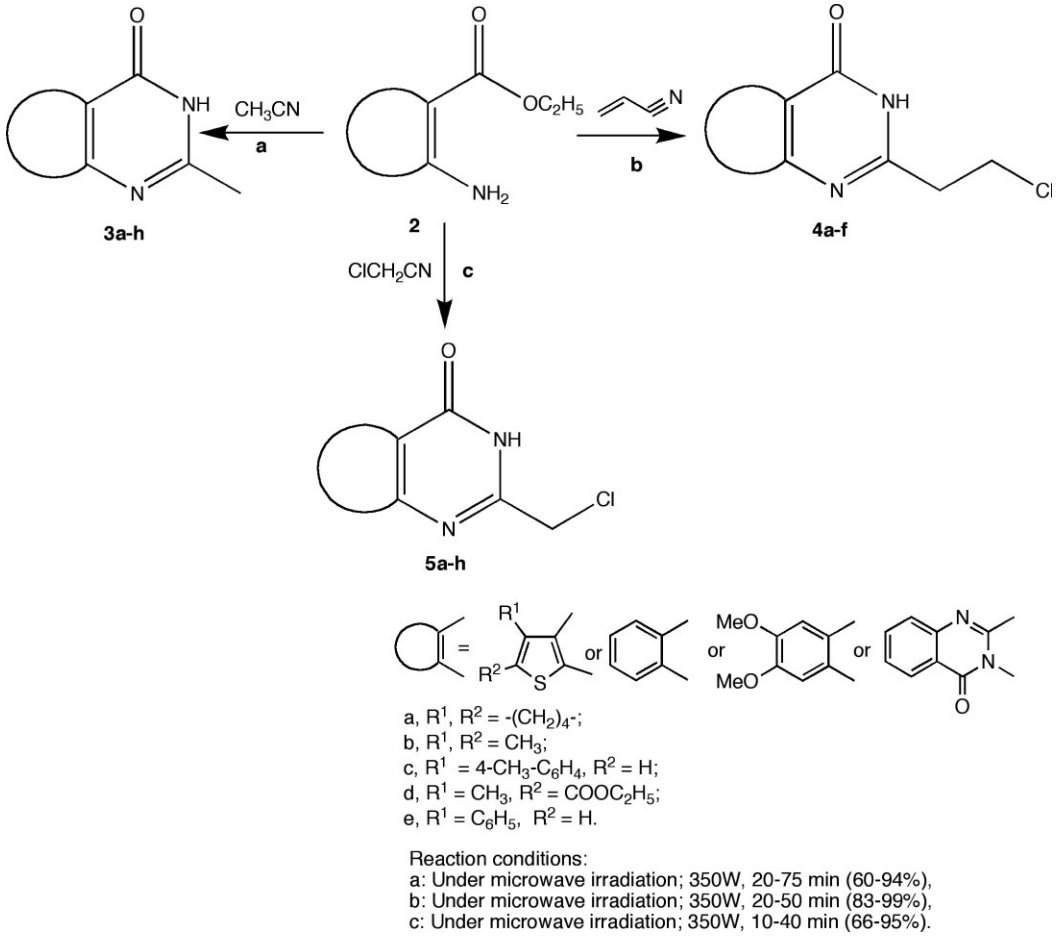
1

X = S, -CH=CH-, N, O, *etc*
R^1, R^2 = H, alkyl, aryl, cycloalkyl, carboalkoxy, carbocyclic, heterocyclic, *etc*
R^3 = alkyl, aryl, arylalkyl, heteroaryl, substituted amino, heteroalkyl,aryl, *etc*
R^4 = OH, alkyl, aryl, Cl, NH_2

Scheme 2



Scheme 3



Reactions that are adaptable for high speed throughput syntheses have become an important component of the modern medicinal chemist's armory, as a great number of compounds can be produced through such rapid parallel synthetic programs [16]. Synthetic methods that enable the rapid production of an array of heterocycles, useful for the identification of new lead structures are of critical importance from the point of new drug discovery. Moreover, quinazolines, thienopyrimidines and other condensed pyrimidine scaffolds are important heterocyclic building blocks and have been shown to possess significant pharmacological activity against a variety of molecular targets [17].

Our encouraging results in the MWI-based syntheses of thiophene *o*-aminoesters involving Gewald reaction [18], as well as, thienopyrimidine bioisosteres of gefitinib [19] under microwave irradiation conditions, motivated us to assess whether the use of MWI could be extended to the single pot cyclocondensation of the nitriles with various *o*-aminoester substrates under solvent-free conditions for generating compound libraries of condensed pyrimidines of type **1**.

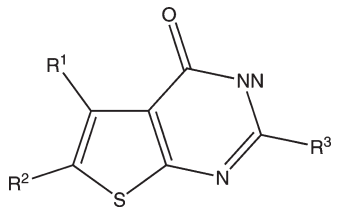
Herein, we report for the first time a rapid microwave-assisted green synthesis of condensed 2-substitutedpyrimidin-4(3*H*)-ones, **3**, **4**, and **5** involving the condensation of a variety of nitriles with *o*-aminoesters of thiophene **2a–e**, benzene **2f**, dimethoxybenzene **2g** and quinazolinone **2h** in the presence of catalytic amount of HCl alone or with the Lewis acid, $AlCl_3$ under solvent-free conditions (Scheme 3).

RESULTS AND DISCUSSION

We started the experiments using different nitriles such as acetonitrile, chloroacetonitrile and acrylonitrile. The conventional methods for the synthesis of the target condensed 2-substitutedpyrimidin-4(3*H*)-ones are through the cyclization of appropriate *o*-amino esters **2** with these nitriles under acidic conditions in the solvent, 1,4-dioxane at 0–5°C. This particular reaction requires

Table 1

Physical data of 2-substituted-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **3a–e**, **4a–e**, and **5a–e**



				Conventional method			Microwave-assisted method		
	R^1	R^2	R^3	Yield (%)	mp (°C)	Time (h)	Yield (%)	mp (°C)	Time (min)
3a	—$(CH_2)_4$—		—CH_3	66	300–302[a]	8–10	68	298	75
3b	—CH_3	—CH_3	—CH_3	76	286–288[b]	10–12	89	286	60
3c	4-$CH_3C_6H_4$—	—H	—CH_3	93	243–245	8–10	94	248	55
3d	—CH_3	—$COOC_2H_5$	—CH_3	71	260–262[c]	8–10	85	262	40
3e	—C_6H_5	—H	—CH_3	69	262–264[d]	8–10	75	264	65
4a	—$(CH_2)_4$—		—CH_2CH_2Cl	84	218–220	8–10	96[e]	218	45
4b	CH_3	—CH_3	—CH_2CH_2Cl	85	199–200	20–24	99	201	50
4c	4-$CH_3C_6H_4$—	—H	—CH_2CH_2Cl	91	167–168	10–12	92[e]	169	35
4d	—CH_3	—$COOC_2H_5$	—CH_2CH_2Cl	85	165–167	8–10	88	167	20
4e	—C_6H_5	—H	—CH_2CH_2Cl	94	267–268	8–10	96	267	45
5a	—$(CH_2)_4$—		—CH_2Cl	77	257–259[f]	6–8	90	258	30
5b	—CH_3	—CH_3	—CH_2Cl	83	246–247[g]	8–10	91	256	25
5c	4-$CH_3C_6H_4$—	—H	—CH_2Cl	88	246–248	6–8	93	249	40
5d	CH_3	—$COOC_2H_5$	—CH_2Cl	86	243–245[h]	6–8	95	225	10
5e	—C_6H_5	—H	—CH_2Cl	90	208–210[i]	6–8	91	214	35

[a] Reported m.p. 300–302°C [10].
[b] Reported m.p. 286–288°C [10].
[c] Reported m.p. 260–262°C [6].
[d] Reported m.p. 262–264°C [20].
[e] Catalytic amount of anhydrous. $AlCl_3$ was added to the reaction mixture as per General Procedure B (experimental section).
[f] Reported m.p. 257–259°C [21].
[g] Reported m.p. 246–247°C [9].
[h] Reported m.p. 243–245°C [12].
[i] Reported m.p. 208–210°C [12].

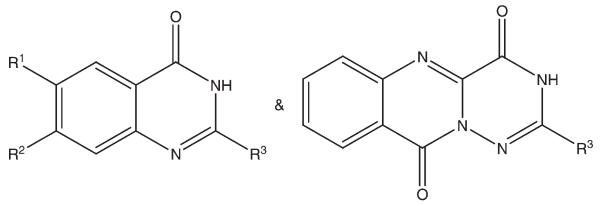
bubbling of dry HCl gas in the reaction mixture for 8–12 h, which is the time taken to complete the reaction depending upon the nature of nitrile used. Interestingly, these same reactions under microwave irradiation at 350 W were accomplished by using catalytic amount of concentrated HCl (33% w/v, 5.0 mL) in very short time periods. The physical data for the 2-substituted-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **3a–e**, **4a–e**, **5a–e** synthesized under MWI is presented in Table 1 and that for the 2-substitutedquinazolines **3f–h**, **4f,** and **5f–h** is recorded in Table 2. The reaction time varied depending upon the type of nitrile used. The reactions with acetonitrile were completed in 40–75 min to obtain the condensed 2-methylpyrimidin-4(3*H*)-ones **3a–h** with isolated yields ranging from 68–94%. The reactions with acrylonitrile were completed in 20–50 min and afforded the condensed 2-chloroethylpyrimidin-4(3*H*)-ones **4a-f** in 85–96% yields (Scheme 3).

Interestingly, when the reactive nitrile, chloroacetonitrile was used, the reaction went to completion in just 10–40 min and afforded the corresponding 2-chloromethylpyrimidin-4(3*H*)-ones **5a–h** in generally excellent isolated yields (>90%). Thus, in all the aforementioned cases, there is considerable reduction in the reaction times, when conventional heating is replaced by microwave-assisted heating, *i.e*., from 6–12 h to 10–75 min, respectively. Considerable improvement in yields was also observed.

A very important and noteworthy fact is that all the reactions depicted in Scheme 3 failed to proceed in the absence of HCl. This indicates that these reactions under MWI, may also be involving the imidoyl chloride intermediates [22,23]. Further, in a few typical cases, only catalytic amount of HCl failed to bring about the completion of the reaction. This was observed in the reaction of **2a** and **2c** with acrylonitrile to prepare

Table 2

Physical data of other 2-substitutedpyrimidin-4(3*H*)-ones **3f–h**, **4f**, and **5f–h**



				Conventional method			Microwave-assisted method		
	R^1	R^2	R^3	Yield (%)	mp (°C)	Time (h)	Yield (%)	mp (°C)	Time (min)
3f	—H	—H	$-CH_3$	70	240–242[a]	8–10	80	240	45
3g	$-OCH_3$	$-OCH_3$	$-CH_3$	62	239–241	8–10	70	240	45
3h	–		$-CH_3$	52	243–245	8–10	71	243	20
4f	—H	—H	$-CH_2CH_2Cl$	80	200–202	8–10	83	202	30
5f	—H	—H	$-CH_2Cl$	90	246–248[b]	6–8	94	241	30
5g	$-OCH_3$	$-OCH_3$	$-CH_2Cl$	65	242–244	6–8	70	242	25
5h	–		$-CH_2Cl$	53	240–242	8–10	66	241	20

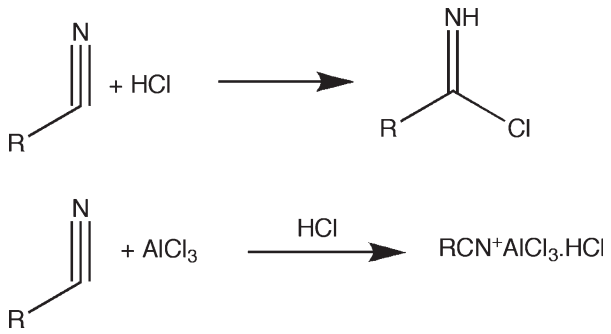
[a] Reported m.p. 240–242°C [10].
[b] Reported m.p. 246–248°C [10].

compounds **4a** and **4c,** respectively. However, addition of catalytic amount of a Lewis acid, anhydrous $AlCl_3$ along with conc. HCl, accomplished the successful completion of the aforementioned reactions to afford the target condensed 2-substitutedpyrimidin-4(3*H*)-ones **4a** and **4c** in excellent isolated yields (Table 1). Thus, the Lewis acid $AlCl_3$, has forwarded the reactions, probably by way of forming the electrophilic nitrile-metal halide, hydrohalide complex as shown below (Scheme 4) [24].

CONCLUSION

A novel microwave-assisted green synthesis of the condensed 2-substitutedpyrimidin-4(3*H*)-ones **3**, **4**, and **5** under solvent-free conditions has been reported for the first time. The unusually rapid synthetic methodology involves the cyclocondensation of a variety of nitriles with *o*-aminoesters of thiophene **2a-e**, benzene **2f**, dimethoxybenzene **2g** and quinazolinone **2h** in the presence of catalytic amount of conc. HCl alone or with the Lewis acid, $AlCl_3$. This novel synthesis involving nitriles as the building blocks, under microwave irradiation for these condensed 2-substitutedpyrimidin-4(3*H*)-ones requires only 10–75 min as compared to the conventional heating protocols requiring 6–12 h, thereby showing a significant acceleration in reaction rates (Tables 1 and 2). The reaction proceeds through the same activated electrophilic nitrile derivatives, the imidoyl halide intermediate and affords the products in yields superior to that by the conventional protocols. Coupled with simple workup procedures and superior yields the methodology is eminently suitable for the generation of diverse libraries of condensed 2-substitutedpyrimidin-4(3*H*)-ones employing parallel synthesis procedures.

Scheme 4



EXPERIMENTAL

Microwave synthesizer (Questron Technologies, Canada; model: Q-Pro M) having monomode open-vessel was used for the synthesis. All the chemicals used in the synthesis were of laboratory grade. The melting points were determined in open capillary on Veego (VMP-D) electronic apparatus and are uncorrected. The IR spectra of synthesized compounds were recorded on Perkin Elmer BX_2 FT-IR Spectrophotometer in KBr and reported in cm^{-1}. ^1H NMR spectra were measured

on a Varian Mercury YH-300 FT NMR spectrometer in DMSO-d_6 with chemical shifts (δ) given in ppm relative to TMS as internal standard. Thin layer chromatography was performed on precoated silica plates (Merck Silicagel F_{254}) using hexane-ethyl acetate-glacial acetic acid (4.5 mL:0.5 mL:2drops), chloroform-methanol (4.5 mL:0.5 mL) as the solvent systems and the spots were visualized by exposure to iodine vapors or under ultra violet (UV) light. The HCl used was 33% w/v aqueous and was of LR grade.

General procedure A.

Reaction of 2-amino-3-carbethoxysubstrates 2 with nitriles (in presence of only conc. HCl). A mixture of the appropriate 2-amino-3-carbethoxy substrate **2** (0.02 moles), nitrile (0.022 moles) and catalytic amount of HCl (33% w/v, 5.0 mL) was irradiated at 350 W for 10–75 min in a microwave synthesizer. The progress of reaction was monitored (using TLC) after 5-min intervals. The reaction mixture was allowed to cool to room temperature, and after completion of the reaction poured into ice-water. The resulting precipitated solid was collected by filtration, washed with chilled water and dried. The crude product on recrystallization from methanol-chloroform mixture yielded the appropriate condensed 2-substitutedpyrimidin-4-(3*H*)-ones **3a–h, 4b, 4d–f,** and **5a–h.**

2-Methyl-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (3a). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1659 cm^{-1}; ^1H NMR: δ 1.77 (s, 4H, 6- and 7-CH_2), 2.30 (s, 3H, 2-CH_3), 2.70 (s, 2H, 5-CH_2), 2.83 (s, 2H, 8-CH_2). Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.90; H, 5.47. Found: C, 59.66; H, 5.38.

2,5,6-Trimethylthieno[2,3-d]pyrimidin-4(3H)-one (3b). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1665 cm^{-1}; ^1H NMR: δ 2.37 (s, 3H, 2-CH_3), 2.46 (s, 3H, 5-CH_3), 2.51 (s, 3H, 6-CH_3), 12.04 (s, br, 1H, 3-NH). Anal. Calcd. for $C_9H_{10}N_2OS$: C, 55.64; H, 5.15. Found: C, 55.81; H, 5.52.

2-Methyl-5-(4-methylphenyl)thieno[2,3-d]pyrimidin-4(3H)-one (3c). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1670 cm^{-1}; ^1H NMR: δ 2.39 (s, 3H, 2-CH_3), 2.47 (s, 3H, Ar—CH_3), 7.04 (s, 1H, 6-H), 7.16–7.48 (m, 4H, phenyl protons), 11.90 (s, 1H, 3-NH). Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.66; H, 4.73. Found: C, 65.76; H, 4.52.

Ethyl 3,4-dihydro-2,5-dimethyl-4-oxothieno[2,3-d]pyrimidin 6-carboxylate (3d). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1718, 1667 cm^{-1}; ^1H NMR: δ 1.40 (t, 3H, 6-$COOCH_2CH_3$, J = 7.3 Hz), 2.55 (s, 3H, 2-CH_3), 2.94 (s, 3H, 5-CH_3), 4.36(q, 2H, 6-$COOCH_2CH_3$, J = 7.1 Hz,); 10.95 (1H, s, 3-NH). Anal. Calcd. for $C_{10}H_{11}N_2O_2S$: C, 52.37; H, 4.74. Found: C, 52.56; H, 4.97.

2-Methyl-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one (3e). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1671 cm^{-1}; ^1H NMR: δ 3.36 (s, 3H, 2-CH_3), 7.31–7.50 (m, 5H, phenyl protons and 6-H), 12.28(s, 1H, 3-NH). Anal. Calcd. for $C_{13}H_{10}N_2OS$: C, 64.46; H, 4.12. Found: C, 64.15; H, 4.46.

2-Methylquinazolin-4(3H)-one (3f). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1666 cm^{-1}; ^1H NMR: δ 2.50 (s, 2H, 2-CH_3), 7.38–7.74 (m, 4H, phenyl protons), 12.13 (s, br, 1H, 3-NH). Anal. Calcd. for $C_9H_8N_2O$: C, 67.44; H, 5.02. Found: C, 67.63; H, 5.42.

6,7-Dimethoxy-2-methylquinazolin-4(3H)-one (3g). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1669 cm^{-1}; ^1H NMR: δ 2.55 (s, 3H, 2-CH_3), 3.99 (s, 6H, 6- and 7-OCH_3), 7.02–7.55 (m, 2H, phenyl protons), 10.87 (s, 1H, 3-NH). Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.90; H, 5.41. Found: C, 58.99; H, 5.72.

2-Methyl-3H-[1,2,4]triazino[6,1-b]quinazolin-4,10-dione (3h). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1680 cm^{-1}; ^1H NMR: δ 2.37 (s, 3H, 2-CH_3), 7.72–8.22 (m, 4H, phenyl protons). Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.90; H, 3.51. Found: C, 57.69; H, 3.71.

2-(2-Chloroethyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (4b). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1669 cm^{-1}; ^1H NMR: δ 2.38 (s, 3H, 5-CH_3), 2.47 (s, 3H, 6-CH_3), 3.19 (t, 2H, 2-CH_2CH_2Cl, J = 7.5 Hz), 3.97 (t, 2H, 2-CH_2CH_2Cl , J = 7.2 Hz), 12.34 (s, br, 1H, 3-NH). Anal. Calcd. for $C_{10}H_{11}ClN_2OS$: C, 49.40; H, 4.53. Found: C, 49.14; H, 4.35.

Ethyl 2-(2-chloroethyl)-3,4-dihydro-5-methyl-4-oxothieno [2,3-d]pyrimidin 6-carb-oxylate (4d). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1719, 1670 cm^{-1}; ^1H NMR: δ 1.41 (t, 3H, 6-$COOCH_2CH_3$, J = 7.3 Hz), 2.9 (s, 3H, 5-CH_3), 3.24 (t, 2H, 2-CH_2CH_2Cl, J = 6.7 Hz), 4.29 (t, 2H, 2-CH_2CH_2Cl, J = 7.3 Hz CH_2), 4.3 (q, 2H, 6-$COOCH_2CH_3$, J = 7.1 Hz), 12.30 (s, 1H, 3-NH). Anal. Calcd. for $C_{11}H_{13}ClN_2O_2S$: C, 47.93; H, 4.35. Found: C, 47.97; H, 4.42.

2-(2-Chloroethyl)-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one (4e). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1685cm^{-1}; ^1H NMR: δ 3.19 (t, 2H, 2-CH_2CH_2Cl, J = 7.2 Hz), 4.02 (t, 2H, 2-CH_2CH_2Cl, J = 7.5 Hz), 7.30–7.50 (m, 6H, phenyl protons and 6-H), 12.40 (s, br, 1H, 3-NH). Anal. Calcd. for $C_{14}H_{11}ClN_2OS$: C, 57.83; H, 3.81. Found: C, 57.74; H, 3.89.

2-(2-Chloroethyl)quinazolin-4(3H)-one (4f). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1678 cm^{-1}; ^1H NMR: δ 3.18 (t, 2H, 2-CH_2CH_2Cl, J = 6.3, 7.2 Hz), 4.06 (t, 2H, 2-CH_2CH_2Cl, J = 6.3, 7.2 Hz), 7.44–8.07 (m, 4H, phenyl protons), 10.25 (s, 1H, 3-NH). Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 57.55; H, 4.37. Found: C, 57.49; H, 4.80.

2-Chloromethyl-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (5a). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1663 cm^{-1}; ^1H NMR: δ 1.86 (s, 4H, 6- and 7-CH_2), 2.79 (s, 2H, 5-CH_2), 3.02 (s, 2H, 8-CH_2), 4.55 (s, 2H, 2-CH_2Cl), 10.65 (s, br, 1H, 3-NH). Anal. Calcd. for $C_{11}H_{11}ClN_2OS$: C, 51.87; H, 4.30. Found: C, 57.69; H, 4.25.

2-Chloromethyl-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (5b). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1662 cm^{-1}; ^1H NMR: δ 2.39 (s, 3H, 5-CH_3), 2.47 (s, 3H, 6-CH_3), 4.51 (s, 2H, 2-CH_2Cl), 10.03(s, br, 1H, 3-N*H*). Anal. Calcd. for $C_9H_9ClN_2OS$: C, 47.20; H, 3.95. Found: C, 47.30; H, 3.40.

2-Chloromethyl-5-(4-methylphenyl)thieno[2,3-d]pyrimidin-4(3H)-one (5c). This compound was obtained according to the

aforementioned general procedure; IR (potassium bromide): CO 1651 cm^{-1}; ^1H NMR: δ 2.39 (s, 3H, Ar-CH_3), 4.53 (s, 2H, 2-CH_2Cl), 7.13 (s, 1H, 6-H), 7.19–7.46 (m, 4H, phenyl protons), 10.43 (s, 1H, 3-NH). Anal. Calcd. for $C_{14}H_{13}ClN_2OS$: C, 57.89; H, 3.80. Found: C, 57.79; H, 3.87.

Ethyl 2-chloromethyl-3,4-dihydro-5-methyl-4-oxothieno [2,3-d]pyrimidine 6-carboxylate (5d). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1725, 1670 cm^{-1}; ^1H NMR: δ 1.41 (t, 3H, 6-COOCH$_2CH_3$ J = 7.0 Hz,), 2.95 (s, 3H, 5-CH_3), 4.38 (q, 2H, 6-COOCH_2CH$_3$, J = 7.0 Hz), 4.57 (s, 2H, 2-CH_2Cl), 10.62 (s, 1H, 3-NH). Anal. Calcd. for $C_{10}H_{11}ClN_2O_2S$: C, 46.04; H, 3.86. Found: C, 46.10; H, 3.92.

2-Chloromethyl-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one (5e). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1663 cm^{-1}; ^1H NMR: δ 4.58 (s, 2H, 2-CH_2Cl), 7.31–7.52 (m, 5H, aryl protons and 6-H), 12.69 (s, br, 1H, 3-NH). Anal. Calcd. for $C_{13}H_9ClN_2OS$: C, 56.49; H, 3.23. Found: C, 56.62; H, 3.33.

2-Chloromethylquinazolin-4(3H)-one (5f). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1697 cm^{-1}; ^1H NMR: δ 4.53 (s, 2H, 2-CH_2Cl), 7.49–7.82 (m, 4H, aryl protons), 12.56 (s, br, 1H, 3-NH). Anal. Calcd. for $C_9H_7ClN_2O$: C, 55.50; H, 3.64. Found: C, 55.62; H, 3.24.

2-Chloromethyl-6,7-dimethoxyquinazolin-4(3H)-one (5g). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1668 cm^{-1}; ^1H NMR: δ 4.0 (s, 6H, 6- and 7-OCH_3), 4.57 (s, 2H, 2-CH_2Cl), 7.01–7.59 (m, 2H, aryl protons) 9.75 (s, 1H, 3-NH). Anal. Calcd. for $C_{11}H_{11}ClN_2O_3$: C, 51.85; H, 4.36. Found: C, 51.66; H, 4.20.

2-Chloromethyl-3H-[1,2,4]triazino[6,1-b]quinazoline-4,10-dione (5h). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1690 cm^{-1}; ^1H NMR: δ 4.59 (s, 2H, 2-CH_2Cl), 7.53–7.79 (m, 4H, aryl protons), 9.48 (s, br, 1H, 3-NH). Anal. Calcd. for $C_{11}H_7ClN_4O_2$: C, 50.35; H, 2.66. Found: C, 50.29; H, 2.81.

General procedure B.

Reaction of 2-amino-3-carbethoxythiophenes 2a and 2c with acrylonitrile (in presence of conc. HCl and $AlCl_3$). A mixture of appropriate 2-amino-3-carbethoxythiophene **2a** or **2c** (0.02 moles), acrylonitrile (0.022 moles), aq. HCl (33% w/v, 5.0 mL) and anhydrous $AlCl_3$ (0.1–0.25 g) was irradiated at 350 W for 35–45 min in a microwave synthesizer. After completion of reaction, the reaction mixture was allowed to cool to room temperature then was poured into ice-water. The resulting precipitated solid was collected by filtration, washed with chilled water and dried. The crude product on recrystallization from methanol–chloroform mixture yielded the appropriate condensed 2-chloroethylthieno[2,3-*d*]pyrimidin-4-(3*H*)-ones **4a** or **4c**.

2-(2-Chloroethyl)-5,6,7,8-tetrahydro-3H-benzo[b]thieno[2,3-d]pyrimidin-4-one (4a). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1665 cm^{-1}; ^1H NMR: δ 1.90 (4H, s, 6- and 7-CH_2), 2.81 (s, 2H, 5-CH_2), 3.02 (s, 2H, 8-CH_2), 3.23 (t, 2H, 2-CH_2CH_2Cl, J = 7.0 Hz), 4.02 (t, 2H, 2-CH_2CH_2Cl, J = 6.2 Hz), 11.90 (s, 1H, br, 3-NH); Anal. Calcd. for $C_{11}H_7ClN_4O_2$: C, 53.66; H, 4.83. Found: C, 53.44; H, 4.60.

2-(2-Chloroethyl)-5-(4-methylphenyl)thieno[2,3-d]pyrimidin-4(3H)-one (4c). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1672 cm^{-1}; ^1H NMR: δ 2.40 (3H, s, Ar-CH_3), 3.06 (2H, t, 2-CH_2CH_2Cl, J = 7.0 Hz,), 3.87 (t, 2H, 2-CH_2CH_2Cl, J = 7.0 Hz, 7.06 (s, 1H, 6-H), 7.15–7.45 (m, 4H, aryl protons), 12.99 (s, 1H, 3-NH). Anal. Calcd. for $C_{15}H_{15}ClN_2OS$: C, 59.10; H, 4.33; Found: C, 59.25; H, 4.20.

General procedure C: Conventional method. A stream of dry hydrogen chloride gas was bubbled through an ice-cold mixture of the appropriate 2-amino-3-carbethoxysubstrate, **2a–h** (0.06 mole) and appropriate nitrile (0.09 mole) in dry dioxane (60 mL) for 8–12 h while maintaining the temperature below 10°C. The reaction mixture was allowed to stand thereafter at room temperature for 12 h. The reaction was then heated on a water bath for 2–3 h, cooled to room temperature and poured onto ice-water mixture (150–200 mL) and neutralized with strong ammonium hydroxide solution (50%v/v). The solid that separated was collected by filtration, washed with water, dried and recrystallized from appropriate solvent.

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