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Novel Dual Use of Formamide-$POCl_3$ Mixture for the Efficient, One-Pot Synthesis of Condensed 2H-Pyrimidin-4-amine Libraries Under Microwave Irradiation

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NOVEL DUAL USE OF FORMAMIDE-$POCl_3$ MIXTURE FOR THE EFFICIENT, ONE-POT SYNTHESIS OF CONDENSED 2*H*-PYRIMIDIN-4-AMINE LIBRARIES UNDER MICROWAVE IRRADIATION

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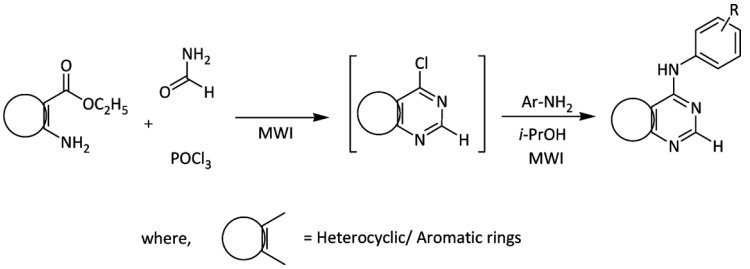
GRAPHICAL ABSTRACT



Abstract *The novel dual use of formamide-$POCl_3$ mixture for the incorporation of a C-N fragment to form the pyrimidine nucleus and its subsequent chlorination in an efficient, one-pot synthesis of potentially bioactive condensed 2*H*-pyrimidin-4-amine libraries under microwave irradiation (MWI) is reported. The one-pot microwave-assisted synthetic protocol is high-yielding, ecofriendly, rapid, and novel as well as eliminates intermittent work-ups. The protocol can be adapted for the library synthesis of series of a condensed pyrimidines.*

Keywords Condensed 2*H*-pyrimidin-4-amines; MWI; one-pot synthesis

INTRODUCTION

Organic synthesis by microwave irradiation (MWI) is an invaluable technology for drug discovery applications as it reduces reaction time, which makes it ideal for rapid reaction scouting and optimization, allowing rapid synthesis of large number of new chemical entities (NCEs) and their libraries.[1–3] Pyrimidines and condensed pyrimidines have exhibited diverse biological activites.[4] A variety of condensed

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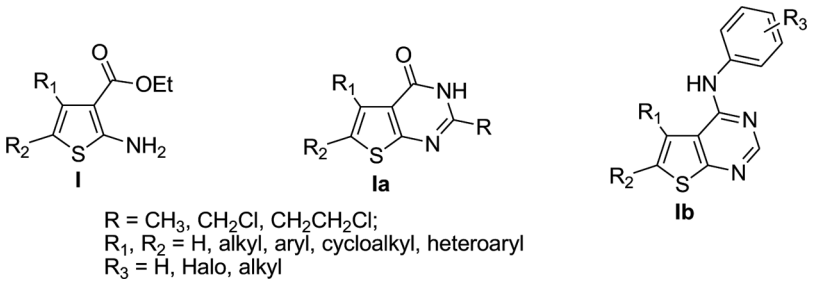


Figure 1. Microwave-assisted synthesis of 2-amino-3-carbethoxy-4,5-disubstitutedthiophenes **I**, 2-substituted condensedthieno{2,3-*d*]pyrimidines **Ia**, and 2*H*-4-substituted anilinothieno[2,3-*d*] pyrimidines **Ib**.

2*H*-pyrimidin-4-amines have been reported[5–10] to exhibit receptor tyrosine kinase inhibitory activity and hold potential for the development of antiproliferative and antitumour drugs.

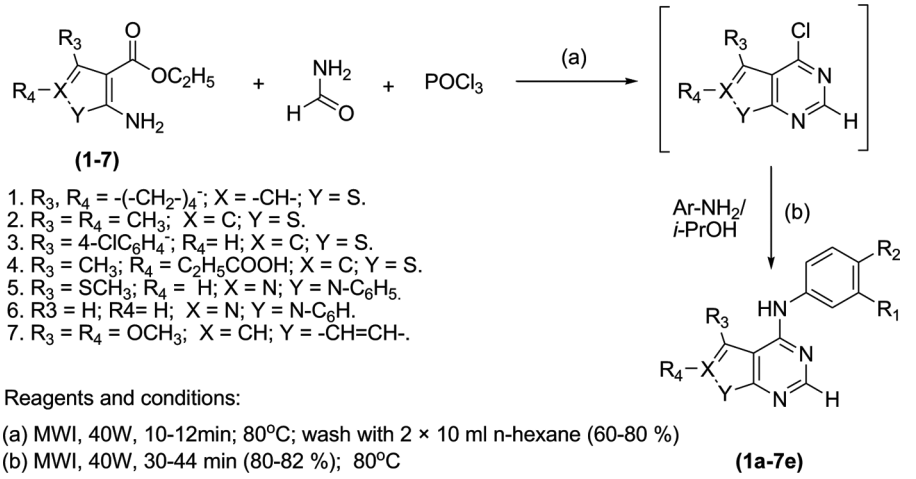
Earlier, we reported a novel methodology for the microwave-assisted synthesis of 2-amino-3-carbethoxy-4,5-disubstitutedthiophenes I[11] and rapid cyclocondensation of these derivatives with various aliphatic nitriles under MWI (Ia).[12] Further, we have also reported a MWI-based three-step synthesis of condensed 2*H*-4-substitutedanilinothieno[2,3-*d*] pyrimidines Ib.[13] (Fig. 1) Our recent endeavors involving green chemical techniques of synthesis are focused on converting multistep syntheses into simple one-pot multicomponent reactions (MCRs).

In the present study we report a MWI-based, rapid, and one-pot protocol adaptable to the parallel synthesis of this type of condensed 2*H*-pyrimidin-4-amines (**Ib**) with improved yields. In all we report the one-pot synthesis of thirty-five such derivatives. The main attraction of this protocol is short reaction time and elimination of the intermittent workup procedures to isolate the intermediates, thus directly leading to the target compounds.

RESULTS AND DISCUSSION

The starting materials, thiophene *o*-aminoesters **1-4**[11] and pyrazole *o*-aminoesters **5,6**[14] were synthesized as per reported methods. In the next step the *o*-aminoester substrate was cyclocondensed with formamide either through conventional heating under reflux or under MWI to afford the corresponding condensed 2*H*-4-hydroxypyrimidine. The subsequent steps involve the chlorination of the 4-hydroxy function with $POCl_3$ to form the corresponding condensed 4-chloropyrimidine and finally the nucleophilic displacement of 4-chloro substituent with various amines using *iso*-propanol as the solvent. The latter two steps of the synthesis can be done through the conventional protocol or under MWI. The drawback of this methodology as far as high-throughtput parallel library synthesis is concerned is that it involves intermittent workup and isolation of the intermediates. This affects the speed and overall yield of the throughput.

Our aim was to develop a protocol by which both cyclocondensation of formamide with the *o*-aminoester substrate as well as subsequent chlorination of the condensed pyrimidin-4-one could be coupled in a single step (Scheme 1).



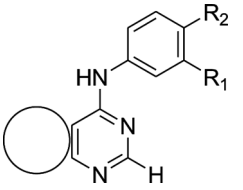
Scheme 1. Protocol for one-pot synthesis of condensed 2*H*-4-anilinopyrimidines.

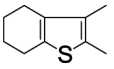
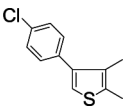
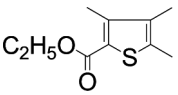
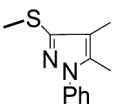
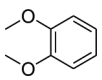
Combination of dimethylformamide (DMF) with $POCl_3$, $SOCl_2$, and SO_2Cl_2 under varying conditions from ice cold (0–5 °C) to 60 °C leads to a complex, referred as Vilsmier–Hack reagent.[15–17] Any group or site susceptible to formylation in the substrate is the limiting factor for chlorination under these conditions. Because, the transient 2*H*-pyrimidin-4(3*H*)-one intermediate did not have any such site susceptible to formylation, the adaptation of Vilsmier-Hack conditions appeared to be attractive. We have replaced DMF with formamide in this reagent. Thus, use of the combination of formamide–$POCl_3$ appeared to be more attractive. This has been achieved by a novel dual use of formamide-$POCl_3$ mixture in proper stoichiometry and under suitable reaction conditions. This mixture, besides serving as a variant of Vilsmier–Hack reagent, also can provide the C-N component from $HCONH_2$ for the cyclocondensation reaction to form the condensed 2*H*-pyrimidin-4-one. Further, the stoichiometry of $POCl_3$ can be manipulated to afford the subsequent chlorination. The $HCONH_2$-$POCl_3$ mixture was prepared under ice-cold conditions and added to the reaction flask containing the *o*-aminoester substrate, and then the reaction mixture was subjected to MWI. After the formation of condensed 2*H*-4-chloropyrimidine, the reaction mixture was washed with *n*-hexane. The residue was further treated in the same flask with a solution of appropriate aromatic amine in *i*-PrOH, without isolation, and subjected to MWI afford the target compounds (**1a–e** to **7a–e**) in good yield (Table 1).

This protocol provides some distinct advantages over the conventional method: reducing the reaction time from 2–12 h to just a few minutes, employing very mild reaction conditions (40 W), and using minimal quantity of the chlorinating agent, due to which the intermediate, condensed 4-chloro-2-substitutedpyrimidine, is formed in good yield and purity. Further, the intermediate 4-chloropyrimidine is not isolated but is directly converted to the final product, thus avoiding intermittent workup and isolation, as well as leading to improved overall yields.

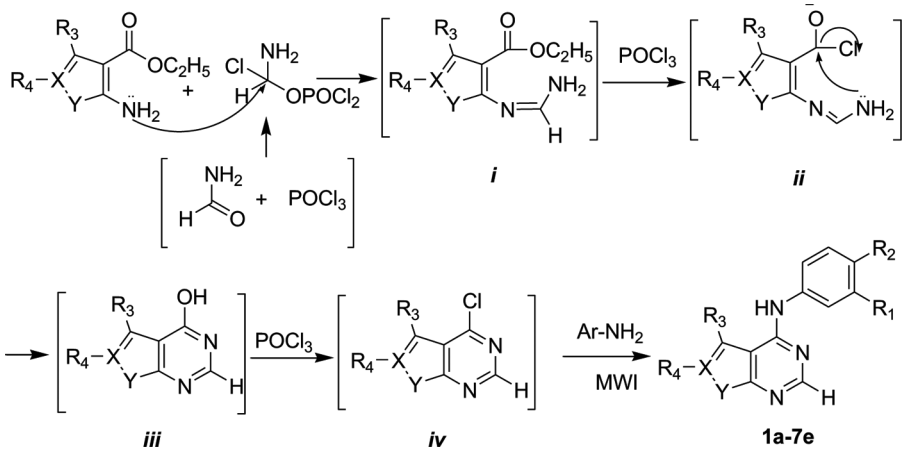
The protocol was explored for the synthesis of a library of compounds (**1a–e** to **7a–e**). (Table 1). It has been observed that aniline underwent the nucleophilic

Table 1. Physical data of condensed 2*H*-pyrimidin-4-amines (**1a–e** to **7a–e**)



Compound	Target compounds	R_1	R_2	Yield (%)	Melting point (°C)	Reaction time (min)
1a		H	H	89	176–178	40
1b		H	Cl	83	136–138	45
1c		H	Br	81	154–156	45
1d		H	F	87	167–169	50
1e		Cl	F	81	136–138	45
2a		H	H	83	173–174	35
2b		H	Cl	81	145–147	40
2c		H	Br	84	162–164	50
2d		H	F	86	168–170	50
2e		Cl	F	83	146–148	45
3a		H	H	97	184–186	40
3b		H	Cl	88	160–162	45
3c		H	Br	94	190–192	50
3d		H	F	82	183–185	45
3e		Cl	F	88	193–195	50
4a		H	H	87	242–244	40
4b		H	Cl	85	145–147	45
4c		H	Br	83	139–140	45
4d		H	F	92	180–182	40
4e		Cl	F	80	130–132	50
5a		H	H	86	170–172	40
5b		H	Cl	81	142–144	45
5c		H	Br	88	158–160	50
5d		H	F	89	152–154	55
5e		Cl	F	84	162–163	45
6a		H	H	81	181–183	50
6b		H	Cl	87	156–158	45
6c		H	Br	81	169–171	55
6d		H	F	82	174–176	55
6e		Cl	F	83	169–171	45
7a		H	Cl	89	248–250	40
7b		Cl	H	87	253–257	45
7c		H	F	90	255–258	40
7d		Cl	F	92	250–252	50
7e		CH_3	H	87	247–248	35

displacement reaction at a faster rate than the amines bearing an electron-withdrawing group(EWG). The reaction, however, tolerates a variety of functional groups and is applicable to amines containing EWG. The increase in



Scheme 2. Plausible mechanism for the one-pot reaction.

bulkiness of the substituents in the *o*-aminoesters substrate has no significant effect on the rate of reaction. The overall yield is better than those reported so far (80–97%) in a shorter time (35–55 min). The process is amenable to scale up and can be gainfully employed to synthesize a library of condensed pyrimidine analogs.

A plausible mechanism of the one-pot reaction is as follows: initially the first mole of $POCl_3$ reacts with formamide and results in the formation of Vilsmier–Hack-type reagent. $POCl_3$ acts as a Lewis acid and results in the formation of imidyl halide, which facilitates nucleophilic attack of amine to give intermediate ***i***. The second mole of $POCl_3$ reacts with ester and converts it into acid chloride ***ii***, increasing the electrophility of the carbonyl carbon. The intramolecular cyclization reaction between the acid chloride and amidine amino group results in the formation of the condensed 2*H*-pyrimidin-4(3*H*)-one ***iii***. The third mole of $POCl_3$ converts the 4-hydroxy into the 4-chloro derivative ***iv***. The mechanism is depicted in Scheme 2.

EXPERIMENTAL

All reagents and chemicals were of LR grade, purchased from standard vendors, and used as received. Microwave synthesizer (Qustron Technologies Corp., Canada; model-Pro M) with monomode open vessel was used for the synthesis. The ^{1}H NMR spectra were recorded in $CDCl_3$ using a NMR Varian Mercury YH 300-MHz spectrometer, and chemical shifts are given in units as per million, downfield from tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a Shimadzu GCMS-QP2010 spectrometer. Elemental analyses were obtained using a flash EA 1112 Thermofinnigan instrument. The ultraviolet absorption spectra were determined in methanol on a Jasco V-530, UV-visible double-beam spectrophotometer. The infrared (IR) spectra of the synthesized compounds were recorded on Perkin-Elmer Spectrum BX Fourier transform (FT-IR) in potassium bromide discs.

Synthesis of Starting Materials

The starting material *o*-aminoester substrates were prepared as per reported methods.[11–13] To synthesize the variant of the Vilsmier–Hack reagent, 2.8 ml of $POCl_3$ was added to an ice-cold stirred solution of 1.2 ml formamide dropwise over 10 min. After stirring for 30 min, the reagent was used for further study.

General Procedure for One-Pot Synthesis of Condensed 2h-Pyrimidin-4-amine Derivatives (1a–e to 7a–e)

Appropriate *o*-aminoester (**1–7**) (0.01 mol) was taken in the reaction vessel, to which an ice-cold mixture of $POCl_3$-formamide was added. The reaction vessel was removed from the ice bath, allowed to attain room temperature (rt), and subjected to MWI at 40 W for 10–12 min. The formation of the corresponding condensed 2*H*-4-chloropyrimidine intermediate was confirmed by thin-layer chromatography (TLC). The reaction mixture was washed with *n*-hexane (2×10 mL). Thereafter, a solution of the appropriate aniline (0.02 mol) in isopropyl alcohol (20 mL) was added to the reaction mixture, and the reaction mixture was further subjected to MWI at 40 W for 30–44 min. After the completion of the reaction (by TLC), the reaction mixture was poured onto an ice-cold water mixture (50 mL). The precipitated solid was filtered and air dried. The crude product was purified by crystallization to give the desired products (**1a–e** to **7a–e**). (Table 1)

Representative Data

Compound 1a. Mp 176–178 °C; yield: 89%; UV (MeOH)/nm: 304.6, IR KBr, υ/cm^{-1}: 3430.60 (NH), 2925 (C–H), 1598 (N=N); ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm = 1.91 (d, 4*H*, $J = 9.31$ Hz, CH_2 at 6 & 7), 2.82 (s, 2*H*, CH_2 at 5), 3.03 (s, 2*H*, CH_2 at 8), 7.07–7.37 (m, 3*H*, Ar–*H*), 7.24 (s, 1*H*, N*H* at 4), 7.61 (d, 2*H*, $J = 9.0$ Hz, Ar–*H*), 8.41 (s, 1*H*, C*H* at 2); EIMS (70 eV, m/z) 281 (M^+), 266, 252, 236, 204, 190. Anal. calcd. for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37. Found: C, 68.11; H, 5.18.

Compound 1e. Mp 136–138 °C; yield: 81%; UV (MeOH)/nm: 303; IR KBr, cm^{-1} 3385 (NH), 2942 (C–H), 1491 (N=N), 722 (C–Cl); ^{1}H NMR ($CDCl_3$, 300 MHz,): δ ppm 1.92 (d, 4*H*, $J = 9.28$ Hz, CH_2 at 6 & 7), 2.83 (s, 2*H*, CH_2 at 5), 3.01 (s, 2*H*, CH_2 at 8), 7.01–7.11 (m, 1*H*, Ar–*H*), 7.60 (s, 1*H*, N*H* at 4), 7.86–7.95 (m, 2*H*, Ar–*H*), 8.45 (s, 1*H*, C*H* at 2); EIMS (70 eV, m/z) 333 (M^+), 318, 304, 288, 204, 190. Anal. calcd. for $C_{16}H_{13}ClFN_3S$: C, 57.57; H, 3.93. Found: C, 57.31; H, 3.81.

Compound 2c. Mp 162–164 °C; yield: 84%; UV (MeOH)/nm: 308; IR KBr, cm^{-1}: 3412 (NH), 2915 (C–H), 1558 (C–H): ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.46 (s, 3*H*, CH_3 at 5), 2.58 (s, 3*H*, CH_3 at 6), 7.08–7.47 (m, 3*H*, Ar–*H*), 7.50–7.67 (m, 2*H*, Ar–*H*), 8.48 (s, 1*H*, C*H* at 2); EIMS (70 eV, m/z) 334 (M^+), 318, 302, 178, 163. Anal. calcd. for $C_{14}H_{12}BrN_3S$: C, 50.31; H, 3.62. Found: C, 50.00; H, 3.50.

Compound 3b. Mp 160–162 °C; yield: 88%; UV (MeOH)/nm: 248; IR KBr, cm^{-1}: 3448 (NH), 2925 (C–H), 765 (C–Cl); ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.18 (s, 1*H*, C*H* at 6), 7.26–7.52 (m, 8*H*, Ar–*H*), 7.41 (s, 1*H*, N*H* at 4), 7.97 (s, 1*H*, C*H* at

2); EIMS (70 eV, *m/z*): 372 (M^+), 262, 245, 226, 172. Anal. calcd for $C_{18}H_{11}Cl_2N_3S$: C, 58.07; H, 2.98. Found: C, 57.91; H, 2.97.

Compound 4d. Mp 180–182 °C; yield: 92%; UV(MeOH)/nm: 383; IR KBr, cm^{-1}: 2926 (C–H), 1689 (COO), 3173 (NH), 1372 (C–F); ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 1.41 (t, 3*H*, $COOCH_2CH_3$ at 6, $J = 7.0$ Hz), 2.96 (s, 3*H*, CH_3 at 5), 4.37–4.42 (m, 2*H*, $COOCH_2CH_3$ at 5), 7.27 (s, 1*H*, N*H* at 4), 8.07 (s, 1*H*, C*H* at 2); EIMS (70 eV, *m/z*) 331 (M^+), 239, 211. Anal. calcd. for $C_{15}H_{12}FN_3O_2S$: C, 56.77; H, 3.81. Found: C, 56.45; H, 3.74.

Compound 5e. Mp 162–163 °C; yield: 83%; UV (MeOH)/nm: 306; IR KBr, cm^{-1}: 3391 (NH), 2922 (C–H), 1585 (N=N); ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.45 (s, 3*H*, at 3), 7.02–7.82 (m, 5*H*, Ar–*H* at 1), 8.35 (d, 1*H*, Ar–*H*, $J = 7.2$ Hz), 8.61 (s, 1*H*, Ar–*H* at 2), 8.83 (s, 1*H*, N*H* at 4); EIMS (70 eV, *m/z*)385 (M^+), 370, 353, 338, 334, 256. Anal. calcd. for $C_{18}H_{13}ClFN_5S$: C, 56.03; H, 3.40. Found: C, 55.87; H, 3.25.

Compound 6d. Mp 174–176 °C; yield: 82%; UV (MeOH)/nm: 248; IR KBr, cm^{-1}: 3301 (NH), 2365 (C–H), 1584 (N=N), 975 (C–F); ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 7.21–8.23 (m, 9*H*, Ar–*H*), 8.61 (s, 1*H*, Ar–*H* at 5), 8.24 (s, 1*H*, Ar–*H* at 2), 12.22 (s, 1*H*, N*H* at 4); EIMS (70 eV, *m/z*): 304 (M^+), 304, 212. Anal. calcd. for $C_{17}H_{12}FN_5$: C, 66.88; H, 3.96. Found: C, 66.67; H, 3.69.

Compound 7d. Mp 250–252 °C; yield: 92%; UV (MeOH)/nm: 260; IR KBr, cm^{-1}: 3023(N–H); 2963 (C–H); 1556 (C=C), 804 (C–Cl); ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.45 (s, 6H, CH_3 at 6 & 7), 7.17 (s, 1H, Ar–H at 3) 8.20 (s, 1H, Ar–H), 8.57 (s, 1H, Ar–H at 2), 9.0 (s, 1H, Ar–H at 2), 9.8 (s, 1H, NH at 2); EIMS (70 eV, *m/z*) 333 (M^+), 316, 302, 188. Anal. calcd. for $C_{16}H_{13}ClFN_3O_2$: C, 57.58; H, 3.93. Found: C, 57.60; H, 4.02.

CONCLUSION

This synthetic protocol involves the MWI-assisted transformation of a variety of *o*-aminoester substrates (**1–7**), involving its cyclocondensation and further chlorination with formamide-$POCl_3$ mixture and subsequent nucleophilic displacement reaction with a substituted aniline, to afford the corresponding condensed 2*H*-pyrimidin-4-amines (**1a–e** to **7a–e**) in mere 35–55 min and in excellent yields and purity (Scheme 1). This novel synthetic protocol under MWI irradiation takes place one pot and can be adapted to rapid parallel library synthesis. Further, work is in progress employing substrates bearing a variety of *o*-aminoesters with aromatic as well as aliphatic amines containing electron donating groups and EWGs.

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Chemistry, Saurashtra University, Rajkot, Gujarat, India, and the Department of Chemistry University of Pune, India, respectively.

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