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RESEARCH ARTICLE

Solid supported synthesis of new thieno[2,3-d]pyrimidines

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A new and practical procedure for the synthesis of novel thieno[2,3-d]pyrimidines is described here. A series of thieno[2,3-d]pyrimidines was readily obtained from the corresponding aromatic and heterocyclic carboxylic acids using Montmorillonite K-10 dry media under microwave irradiation and solvent less conditions.

Keywords: Thiophene; Thienopyrimidine; Dry Media; Solvent less; Microwave

1. Introduction

Owing to present environmental awareness, attempts are being made towards the evolution of environmentally benign processes which meet the concepts of "Green Chemistry" [1]. Recently, microwaves [2, 3] have proved to be a very important tool for environmental protection [4]. "Dry media reaction" [5, 6] and solvent less synthesis [7] with microwaves represents a step forward in this direction. Dry media have shown synthetic utility for the synthesis of biodynamic heterocycles [8], and for many reductions [9], condensations [10], and organometallic reactions [11]. Using solid supported reagents, many reactions has been carried out cleanly and rapidly, realizing higher yield under milder reactions conditions, often due to an increase in the effective surface area available for reaction. Furthermore, this methodology provides: a) solvent less condition, b) experimental simplicity and c) enhanced selectivity.

The chemistry of pyrimidines and its derivatives has been studied for over a century due to their diverse biological activities [12–15]. Due to formal isoelectronic relationship with purines, the thieno[2,3-d]pyrimidine ring system is of special biological interest. It has numerous pharmacological and medicinal [16] applications viz, antitumour [17, 18], immunodilator [19], tuberculosis [20], antiallergic [21, 22] and radioprotective [23, 24].

Thienopyrimidines are formed by the fusion of thiophene ring with pyrimidine moiety. The continuous efforts directed towards the preparation of biological active compound has led to the development of a number of syntheses of thienopyrimidines. Of the numerous strategies

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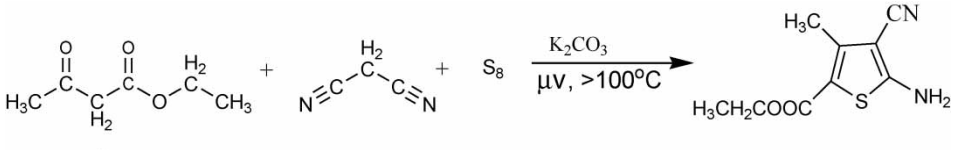
[25–30] that have been reported for the preparation of thienopyrimidine derivatives, many include use of expensive, commercially unavailable reagents, drastic reaction conditions, long reaction times and difficult workups. Propelled by environmental protection awareness, ecofriendly role of dry media and microwave irradiation under solvent less condition, the biopotential of thieno pyrimidines and our ongoing endeavor towards green synthesis, we have developed a rapid facile synthesis of novel thieno[2,3-d]pyrimidines using solid support under microwave irradiation.

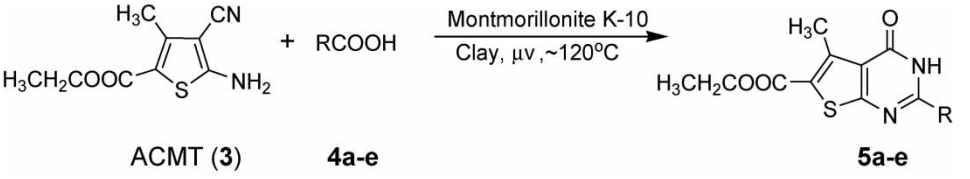
2. Results and discussion

An interesting multi component reaction is a Gewald synthesis of 5-amino-4-cyano-3-methyl-thiophene-2-carboxylic acid ethyl ester, ACMT (**3**). Earlier reports of classical synthesis [31, 32] of thiophene by conventional heating requires longer reaction time, laborious purification techniques, use of hazardous bases [33] such as morpholine, pyridine, carcinogenic solvent toluene [34] and result in a mixture of product. In order to greenify the classical methodology, the synthesis of ACMT (**3**) was performed using K_2CO_3 as a green base by cyclocondensation of the commercially available ethyl acetoacetate (**1**), malononitrile (**2**) with elemental sulphur S_8, employing microwave "Neat Reaction Technology [35]". Excellent yields of the product were obtained within just few minutes of microwave irradiation. (scheme 1)

This technique was further extended for the synthesis of novel thieno[2,3-d]pyrimidines **5a–e** by cyclisation of ACMT (**3**) with various aromatic and heterocyclic acids **4a–e** using Montmorillonite K-10 clay as solid support (scheme 2). Best yields of product were obtained within 3–6 minutes of microwave irradiation (table 1). The excellent results obtained for the synthesis of **5a–e** provoked us to synthesize 2-oxothieno[2,3-d]pyrimidine **7a** and 2-thioxothieno[2,3-d]pyrimidine **7b** using phenylisocyanate (**PhCNO**) and phenylisothiocyanate (**PhNCS**), respectively (scheme 3). However satisfactory results were not obtained with Montmorillonite K-10 clay, which implies that cyclization of **PhNCO** and **PhNCS** with ACMT (**3**) requires strong basic conditions. Hence the reaction was tried on basic Al_2O_3 as solid support to provide 80–90% yields without much compromise in the reaction time (table 2).

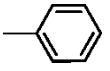
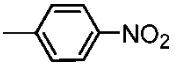
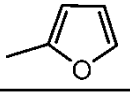


SCHEME 1 Synthesis of 5-amino-4-cyano thiophene is using K_2CO_3 as Green base under microwave irradiation.

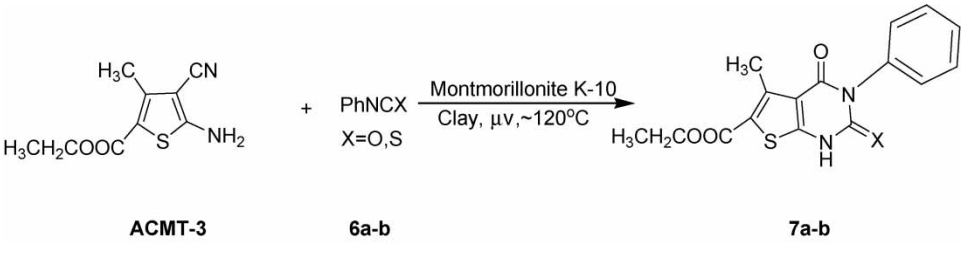


SCHEME 2 Synthesis of library of thieno[2,3-d]pyrimidines **5a–e**.

Table 1. Synthesis of library of thieno[2,3-d]pyrimidines **5a–e** using microwave irradiation (Montmorillonite K-10 adsorbed ACMT 0.01 mol, Aromatic/Aliphatic carboxylic acids 0.01 mmol).

		Microwave[b]		Conventional	
Comp. no.	R[a]	Time (min.)	Yield[c] (%)	Time (hrs)	Yield[c] (%)
5a	$-CH_3$	4.0	74	1.5	58
5b	$-CH_2CH_2CH_3$	5.5	82	3.0	65
5c		3.5	72	6.5	67
5d		3.0	68	2.5	44
5e		4.0	85	3.0	76

[a]All products were characterized by ^{1}H-NMR, Mass Spectroscopy, IR and Elemental Analysis.
[b]Kenstar microwave open model no. OM 9925E, operating at 800 W (2450 MHz).
[c]Isolated yields.



ACMT-3 **6a-b** **7a-b**

SCHEME 3 Synthesis of thieno[2,3-d]pyrimidines **7a–b**.

The isolated thieno[2,3-d]pyrimidines was confirmed on the basis of their analytical and spectral data. The IR spectra of cyclised product displayed bands at 1600 cm^{-1} due to the C=N group and at 1650 cm^{-1} due to the amide C=O and the absence of the C≡ N group at 2200 cm^{-1} was equally diagnostic. The ^{1}H NMR spectra showed a broad singlet at 7.2–8.0 δ for the amidic NH group in the pyrimidine ring in **5a–e** and the secondary amine singlet at

Table 2. Reaction time and yield for the compounds **7a–b**.

		Microwave[a]				Conventional			
		Basic Al_2O_3		Montmorillonite K-10 Clay		Basic Al_2O_3		Montmorillonite K-10 Clay	
Comp. no.	X	Time (hrs)	Yield[b] (%)	Time (%)	Yield[b] (hrs)	Time (%)	Yield[b] (hrs)	Time (%)	Yield[b] (%)
7a	O	5.5	91	8.2	62	2.5	72	3.5	65
7b	S	6.0	87	7.0	58	3.0	64	4.0	55

[a]Kenstar microwave open model no. OM 9925E, operating at 800 W (2450 MHz).
[b]Isolated Yields.

6.0–4.0 δ in **7a–b** confirmed the formation of product. Further structure identification of **5a–e** and **7a–b** was confirmed using EI-M^+ values.

3. Conclusion

Thus we have shown that the combination of dry media and microwave irradiation is a practical and mild synthetic methodology for obtaining thieno[2,3-d]pyrimidines in good yields. The strategy is simple, rapid, ecofriendly and the work-up is clean and not time-consuming. This procedure can be employed for a 'multistandard synthesis [36]', as part of the identification of new target molecules in natural extracts or as part of the preparation of a series of standard compounds. It can be used also as a convenient tool in total synthesis.

4. Experimental

Microwave irradiation was carried out in a Kenstar microwave open model no. OM 9925E, operating at 800 W (2450 MHz). The IR spectra (ν_{max} in cm^{-1}, KBr or Nujol) were recorded on a 1710 Perkin Elmer FTIR spectrometer. ^{1}H-NMR spectra were recorded at 60 MHz and 300 MHz using TMS as internal standard. (Chemical shift in δ ppm). Elemental analyses were determined by mean of Heraeus C H N rapid analyzer and EI mass spectra were taken on a Jeol JMS-DX 303. The temperature of reaction was monitored using gun type IR thermometer. The purity of compound and completion of reaction was checked on aluminum plates coated with silica gel (merk) using ethyl acetoacetate and benzene (2:8) as eluant and compound was purified using column chromatography using silica.

4.1 *Synthesis of 5-amino-4-cyano-3-methyl thiophene-2-ethyl carboxylate (3)-ACMT*

A mixture of equimolar neat reactant, that is (0.01 mol, 1.30 g) ethyl acetoacetate, (0.01 mol, 0.66 g) malononitrile, (0.1–0.11 g) sulphur and 1 g of K_2CO_3 were taken in an Erlenmeyer flask and subjected to microwave irradiation for 6-min. Reaction was monitored at interval of 30 sec by TLC. On completion, the reaction mixture was stirred with ice cold water. The product precipitated out and was filtered and recrystallised using methanol. The melting point and spectral data is accordance with literature [32].

4.2 *Microwave-assisted synthesis: General procedure for the synthesis of thieno[2,3-d]pyrimidine 5a–e and 7a–b*

To an equimolar solution of ACMT (**3**) (0.01 mol) and (0.01 mol) **4a–e**/**6a–b** in ethanol-acetone (4:6) was added Montmorillonite K-10 clay (Aldrich 11, 6168, Surface area 220–270 m^2/ g, Bulk density 300–370 g/L)/Aluminium Oxide Basic (Brockmann-I, Standard grade ~150 mesh, 58 Å CAMAG-50-16-A-I, Surface area 55 m^2/ g, pH of aqueous Suspension 9.5 + 0.5 (15 g) with constant stirring. The mixture was air dried at room temperature in a beaker. The beaker was then placed in bath of bulk alumina and was subjected to MWI for 1–2 minutes. TLC monitored completion of the reaction at an intervals of 30-sec. After completion of the reaction product was eluted with (2 × 10 ml) of acetone and obtained in solid state, after removing the solvent by distillation under reduce pressure. The product **5a–e**/**7a–b** were purified using silica gel (Aldrich 24, 217–9, 70 35–70 mesh 40 Å Surface

area 675 m^2/ g) column chromatography and isolated compounds were recrystallised from rectified spirit.

4.3 *Conventional Procedure for the synthesis of thieno[2,3-d]pyrimidine 5a–e and 7a–b*

The reaction mixture was prepared as in method **4.2** and heated in oil bath maintained at 100–120°C for 5–6 hours. The product was worked up as in method **4.2**.

4.4 *Data for compounds 5a–e and 7a–b*

4.4.1 2,5-Dimethyl-4-oxo-3, 4-dihydro-thieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester(5a). ^{1}H-NMR 60 MHz ($CDCl_3$+DMSO d_6): δ 1.01 (s, 3H, CH_3,), 1.25 (t, J =6.7 Hz, 3H, $-OCH_2$–CH_3), 2.43 (S, 3H, CH_3), 4.42 (q, J =7.3 Hz, 2H, $-OCH_2$), 7.65 (brs, 1H, ex NH). IR (ν_{max} cm^{-1}, KBr): 3268 (N–H str.), 1700 (C=O str.), 1570 (C=N str.). Anal. calcd. for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10. Found: C, 51.98; H, 4.65; N, 10.99. EI^+ m/z: 252.0 (M).

4.4.2 5-Methyl-4-oxo-2-propyl-3,4-dihydro-thieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester(5b). ^{1}H-NMR 60 MHz ($CDCl_3$+DMSO d_6): δ 0.94 (t, J = 6.5 Hz, 3H, CH_3,), 1.23 (m, 2H, CH_2), 1.35 (t, J = 6.7 Hz, 3H, $-OCH_2$–CH_3), 1.41 (t, J = 6.6 Hz, 2H, CH_2), 2.39 (S, 3H, CH_3), 4.44 (q, J = 7.2 Hz, 2H, $-OCH_2$), 7.56 (brs, 1H, ex NH). IR (ν_{max} cm^{-1}, Nujol): 3274 (N–H str.), 1708 (C=O str.), 1563 (C=N str.). Anal. calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.32; H, 5.21; N, 9.57. Found: C, 55.70; H, 5.75; N, 9.99. EI^+ m/z: 280.1 (M).

4.4.3 5-Methyl-4-oxo-2-phenyl-3,4-dihydro-thieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester(5c). ^{1}H-NMR 300 MHz ($CDCl_3$+DMSO d_6): δ 1.42 (t, J = 6.8 Hz, 3H, $-OCH_2$-CH_3), 2.37 (S, 3H, CH_3), 4.10 (q, J = 7.2 Hz, 2H, $-OCH_2$), 7.28–7.65(m, 5H, Ph), 8.10 (brs, 1H, ex NH). IR (ν_{max} cm^{-1}, KBr): 3071 (N-H str.), 1687 (C=O str.), 1602 (C=N str.). Anal. calcd. for $C_{16}H_{14}N_2O_3S$: C, 60.87; H, 4.10; N, 8.59. Found: C, 61.13; H, 4.49; N, 8.91. EI^+ m/z: 314.0 (M).

4.4.4 5-Methyl-2-(4-nitro-phenyl)-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester(5d). ^{1}H-NMR 300 MHz ($CDCl_3$ + DMSO d_6): δ 1.33 (t, J = 6.7 Hz, 3H, $-OCH_2$-CH_3), 2.48 (S, 3H, CH_3), 4.25 (q, J = 7.3 Hz, 2H, $-OCH_2$), 7.81–8.10(m, 4H, Ph), 7.21 (brs, 1H, ex NH). IR (ν_{max} cm^{-1}, Nujol): 3315 (N–H str.), 1676 (C=O str.), 1634 (C=N str.). Anal. calcd. for $C_{16}H_{13}N_3O_5S$: C, 52.93; H, 3.53; N, 11.14. Found: C, 53.48; H, 3.65; N, 11.69. EI^+ m/z: 359.0 (M).

4.4.5 2-Furan-2-yl-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester(5e). ^{1}H-NMR 60 MHz ($CDCl_3$+DMSO d_6): δ 1.24 (t, J = 6.7 Hz, 3H, $-OCH_2$–CH_3), 2.36 (S, 3H, CH_3), 4.48 (q, J = 7.2 Hz, 2H, $-OCH_2$), 6.41–7.50 (m, 3H, furanyl), 7.89 (brs, 1H, ex NH). IR (ν_{max} cm^{-1}, Nujol): 3330 (N–H str.), 1640 (C=O str.), 1578 (C=N str.). Anal. calcd. for $C_{14}H_{12}N_2O_4S$: C, 54.86; H, 3.68; N, 9.30. Found: C, 55.25; H, 3.97; N, 9.21. EI^+ m/z: 302.2 (M).

4.4.6 5-Methyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid ethyl ester(7a). ^{1}H-NMR 60 MHz ($CDCl_3$+DMSO d_6): δ 1.28 (t, J = 6.5 Hz, 3H, $-OCH_2-CH_3$), 2.24 (S, 3H, CH_3), 4.41 (q, J = 7.3 Hz, 2H, $-OCH_2$), 6.03 (brs, 1H, ex NH), 7.34 -7.52 (m, 5H, Ph). IR (ν_{max} cm^{-1}, Nujol): 3417 (N–H str.), 1674 (C=O str.), 1628 (C=O str.). Anal. calcd. for $C_{16}H_{14}N_2O_4S$: C, 57.91; H, 3.78; N, 8.17. Found: C, 58.17; H, 4.27; N, 8.48. EI$^+$ m/z: 329.4 (M).

4.4.7 5-Methyl-4-oxo-3-phenyl-2-thioxo-1,2,3,4-tetrahydro-thieno[2,3-d] pyrimidine-6-carboxylic acid ethyl ester(7b). ^{1}H-NMR 60 MHz ($CDCl_3$+DMSO d_6): δ 1.31 (t, J = 6.7 Hz, 3H, $-OCH_2-CH_3$), 2.42 (S, 3H, CH_3), 4.04 (q, J = 7.3 Hz, 2H, $-OCH_2$), 5.63 (brs, 1H, ex NH), 7.60–7.54 (m, 5H, Ph). IR (ν_{max} cm^{-1}, KBr & Nujol): 3506 (N–H str.), 1685 (C=O str.), 1208 (C=S str.). Anal. calcd. for $C_{16}H_{14}N_2O_3S_2$: C, 55.08; H, 4.08; N, 8.17. Found: C, 55.49; H, 4.04; N, 8.09. EI$^+$ m/z: 346.4 (M).

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