A Novel Synthesis of Thieno-pyrimidines Using Inorganic Solid Support

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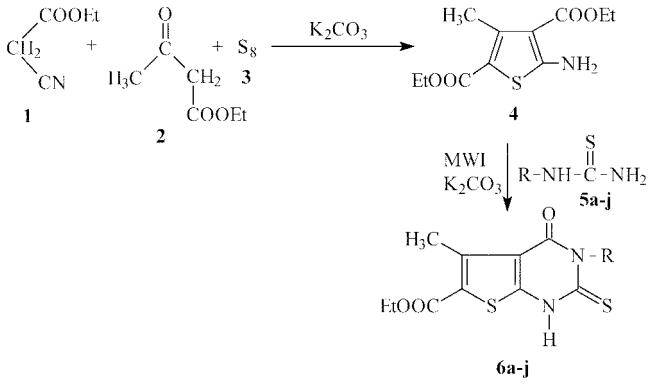
The chemistry of pyrimidines and it's derivatives has been studied for over a century due to their diverse biological activities.[1-4] They possess antibacterial,[5] antiviral,[6] antitumor,[7-9] antihypertensive[10] and antiinflammatory[11,12] activities. Thieno-pyrimidines, formed by the fusion of thiophene moiety with pyrimidine ring, have been reported to be chemotherapeutically more active.[13]

Though many synthetic strategies[14-16] have been reported for the preparation of thieno-pyrimidine derivatives, most of them include use of expensive, commercially non-available or hazardous reagents, drastic reaction conditions, longer reaction time and difficult work-up. Application of microwaves in solid supported organic synthesis has added a new dimension to chemists.[17,18] The use of solid support in organic synthesis,[19-21] especially when coupled with microwave irradiations, not only reduce the reaction time and enhance the yield considerably, but also eliminates the requirement of solvents from reaction step. An appreciable amount of solvents though is still required for adsorption of reagents in the solid supports and elution of the products.

In this paper, some novel 5-methyl-6-ethylcarboxylate-2-thioxo-thieno [3,2-d]pyrimidine-4(1H)-ones, are synthesized from 2-amino-3,5-diethyl carboxylate-4-methyl-thiophene and monosubstituted thioureas using microwave technology under the solid support of K_2CO_3.



6a, R = C_6H_5
6b, R = p-MeC_6H_4
6c, R = p-$MeOC_6H_4$
6d, R = p-HOC_6H_4
6e, R = p-$O_2NC_6H_4$
6f, R = p-ClC_6H_4
6g, R = p-BrC_6H_4
6h, R = 2-furyl
6i, R = 2-thionyl
6j, R = 2-pyridinyl

Scheme 1

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Experimental Section

Microwave reactions were carried out in Kenstar Microwave Oven, Model No. OM9925E (2450 MHz, 800 W) and IR spectra were recorded on Perkin Elmer FTIR-1710 spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on FT NMR Hitachi R-600 (60 MHz) instrument. Elemental analyses were performed using Heraeus CHN-Rapid Analyser. Temperature of reaction mixture was measured through AZ, Mini Gun Type, Non-Contact IR thermometer, Model No. 8868. The melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Chemical shifts, δ, for ^{1}H NMR, are given in ppm, relative to internal reference, tetramethylsilane (TMS) and IR frequency, ν, in cm^{-1}. The purity of the compounds were checked on Aluminium plates coated with silica gel (Merck).

General Procedure for the Synthesis of Monosubstituted Aryl Thioureas (5a-j). To a solution of 0.01 mol of appropriate amine, R-NH_2, R = a-j (Scheme), in 10 mL of aqueous HCl (15% aqueous solution of HCl), was added 15 mL of conc. aqueous solution of ammonium thiocyanate (0.01 mol). The resulting solution was then refluxed for about 1 hour until viscous layer or turbidity was appeared followed by neutralization with ammonia solution after cooling. The neutral reaction mixture was then poured into 250 g of crushed ice with stirring to obtain the precipitate of monosubstituted arylthiourea **5a-j**. The product was filtered, washed with cold water, and recrystallized from MeOH.

General Procedure for the Synthesis of 2-Amino-3,5-diethylcarboxylate-4-methyl-thiophene (4). 0.01 mol of ethylcyanoacetate was dissolved in 5 mL of EtOH and 0.01 mol each of ethylacetoacetate and powdered sulphur were added to the same solution. 1 g of K_2CO_3 was also added to the resulting solution as inorganic basic support. The heterogeneous mixture was stirred at room temperature in r.b. flask for 14 hrs.

After the completion of the reaction as monitored by TLC, the reaction mixture was filtered off to separate K_2CO_3 as residue and the filtrate was poured into 50 mL of ice-cold water. The product got precipitated out, which was filtered and recrystallized from MeOH.

General Procedure for the Synthesis of 5-Methyl-6-ethylcarboxylate-2-thioxo-thieno[3,2-d]pyrimidine-4(1H)-ones (6a-j). Conventional Method (Solution Phase): To a solution of 0.01 mol of thioureas **5a-j** in 10 mL of DMF was

Table 1. Comparison of reaction time and yield of the compounds (**6a-j**)

Compd. No.	Reaction Time		Yield, %	
	Solid Supported Microwave (min.)	Solution phase conventional (hrs.)	Solid supported microwave	Solution phase conventional
6a	7.0	2.5	82	61
6b	6.5	2.0	90	65
6c	6.5	2.0	92	70
6d	6.0	2.0	82	67
6e	6.5	2.5	93	62
6f	6.5	3.0	95	64
6g	6.0	2.5	85	57
6h	7.0	3.0	86	63
6i	6.5	2.5	83	56
6j	7.0	3.0	91	65

Table 2. Physical and analytical data of the compounds (**6a-j**)

Compd. No.	Molecular formula	m.p. (°C)	% CHN, Found (Calcd.)		
			C	H	N
6a	$C_{16}H_{14}N_2O_3S_2$	145	55.53 (55.49)	4.08 (4.04)	8.11 (8.09)
6b	$C_{17}H_{16}N_2O_3S_2$	115	56.68 (56.66)	4.46 (4.44)	7.79 (7.77)
6c	$C_{17}H_{16}N_2O_4S_2$	131	54.30 (54.26)	4.21 (4.25)	7.41 (7.44)
6d	$C_{16}H_{14}N_2O_4S_2$	190	53.06 (53.03)	3.87 (3.86)	7.76 (7.73)
6e	$C_{16}H_{13}N_3O_5S_2$	117	49.14 (49.10)	3.29 (3.32)	10.70 (10.74)
6f	$C_{16}H_{13}N_2O_3S_2Cl$	181	50.47 (50.45)	3.45 (3.41)	7.32 (7.35)
6g	$C_{16}H_{13}N_2O_3S_2Br$	172	45.15 (45.17)	3.01 (3.05)	6.60 (6.58)
6h	$C_{14}H_{12}H_2O_4S_2$	125	50.03 (50.00)	3.61 (3.57)	8.29 (8.33)
6i	$C_{14}H_{12}N_2O_3S_3$	141	47.70 (47.72)	3.42 (3.40)	7.98 (7.95)
6j	$C_{15}H_{13}N_3O_3S_2$	120	51.91 (51.87)	3.77 (3.74)	12.13 (12.10)

added 0.01 mol of thiophene derivative **4** and the solution was refluxed for 2-3 hours. After the completion of the reaction as monitored by TLC, the reaction mixture was poured into 50 mL of ice-cold water. The product **6a-j** got precipitated out, which was filtered, washed, dried and recrystallized from MeOH.

Microwave Method (Solid Support): Equimolar amounts (0.01 mol) of thiophene derivative **4** and thioureas **5a-j**, were dissolved in 10 mL of EtOH and the solution was adsorbed in K_2CO_3 (10 g) in a small beaker. The mixture was dried in air and kept in alumina bath in the microwave oven followed by irradiations for 6-7 minutes intermittently. After the completion of the reaction as monitored by TLC, whole of the reaction mixture was treated with ice-cold water to get the precipitate of the product **6a-j**, leaving behind K_2CO_3 dissolved in water. The product was filtered, washed with water and recrystallized from MeOH.

Table 3. Spectral data of the compounds (**6a-j**)

Compd. No.	IR ν, cm^{-1}, KBr pellets	^1H NMR δ, ppm, $CDCl_3$ & DMSO-d_6
6a	1210 (C=S)	1.3 (t, 3H, OCH_2CH_3)
	1715 (C=O)	2.2 (s, 3H, CH_3)
	3505 (N-H)	4.0 (q, 2H, OCH_2CH_3)
		7.2-7.3 (m, 5H, Ar-H)
		11.7 (brs, 1H, NH)
6b	1200 (C=S)	1.3 (t, 3H, OCH_2CH_3)
	1705 (C=O)	2.2-2.4 (s, 6H, 2 x CH_3)
	3495 (N-H)	4.0 (q, 2H, OCH_2CH_3)
		7.2-7.3 (m, 4H, Ar-H)
		11.7 (brs, 1H, NH)
6c	1220 (C=S)	1.3 (t, 3H, OCH_2CH_3)
	1725 (C=O)	2.2 (s, 3H, CH_3)
	3510 (N-H)	4.0 (s, 3H, OCH_3)
		4.1 (q, 2H, OCH_2CH_3)
		7.0-7.3 (m, 4H, Ar-H)
		11.7 (brs, 1H, NH)
6d	1190 (C=S)	1.3 (t, 3H, OCH_2CH_3)
	1715 (C=O)	2.2 (s, 3H, CH_3)
	3495 (N-H)	4.1 (q, 2H, OCH_2CH_3)
	3650 (O-H)	4.3 (brs, 1H, OH)
		6.9-7.1 (m, 4H, Ar-H)
		11.7 (brs, 1H, NH)
6e	1240 (C=S)	1.3 (t, 3H, OCH_2CH_3)
	1530 (-NO_2)	2.2 (s, 3H, CH_3)
	1740 (C=O)	4.1 (q, 2H, OCH_2CH_3)
	3525 (N-H)	7.3-8.0 (m, 4H, Ar-H)
		11.7 (brs, 1H, NH)
6g	1210 (C=S)	1.3 (t, 3H, OCH_2CH_3)
	1725 (C=O)	2.2 (s, 3H, CH_3)
	3505 (NH)	4.0 (q, 2H, OCH_2CH_3)
		7.2-7.3 (m, 4H, Ar-H)
		11.7 (brs, 1H, NH)
6h	1242 (C=S)	1.3 (t, 3H, OCH_2CH_3)
	1740 (C=O)	2.2 (s, 3H, CH_3)
	3525 (N-H)	4.0 (q, 2H, OCH_2CH_3)
		6.3-7.0 (m, 3H, furan)
		11.7 (brs, 1H, NH)
6i	1242 (C=S)	1.3 (t, 3H, OCH_2CH_3)
	1735 (C=O)	2.2 (s, 3H, CH_3)
	3510 (N-H)	4.0 (q, 2H, OCH_2CH_3)
		7.1-7.3 (m, 3H, thiophene)
		11.7 (brs, 1H, NH)
6j	1240 (C=S)	1.3 (t, 3H, OCH_2CH_3)
	1740 (C=O)	2.2 (s, 3H, CH_3)
	3520 (N-H)	4.1 (q, 2H, OCH_2CH_3)
		6.9-8.5 (m, 4H, pyridine)
		11.7 (brs, 1H, NH)
6f	1230 (C=S)	1.3 (t, 3H, OCH_2CH_3)
	1735 (C=O)	2.2 (s, 3H, CH_3)
	3520 (N-H)	4.1 (q, 2H, OCH_2CH_3)
		7.2-7.3 (m, 4H, Ar-H)
		11.7 (brs, 1H, NH)

Results and Discussion

2-amino-3,5-dicarboxylate-thiophene **4** derivative was prepared by the cyclization of ethylacetoacetate and ethylcyanoaetate with elemental sulphur in the presence of K_2CO_3 that makes the medium basic. The same synthesis has been reported earlier by using morpholine as a base.[23,24] But the use of K_2CO_3 instead of morpholine avoids expensive and hazardous solvents and enables the work-up simply in cold water. K_2CO_3 dissolves in water leaving behind the product as precipitate. Moreover the reaction proceeded conveniently with excellent yield. An attempt to synthesize thiophene derivative **4** under microwave irradiations proved to be unsuccessful since elemental sulphur causes chemical hazards during the irradiations.

The condensation of equimolar amounts of thiophene **4** and thioureas **5a-j**, using K_2CO_3 as solid support under microwave irradiations, gave thieno-pyrimidines **6a-j**. The reaction took 6-7 minutes for completion affording 82-95% yield. The use of K_2CO_3 as an inorganic solid support not only eliminates the use of external bases for catalysing the reactions but also avoids the use of organic solvents for elution. The product got precipitated out upon the treatment of reaction mixture with cold water leaving behind K_2CO_3 in the solution. Only a limited amount of EtOH was used for adsorbing the reactants on the solid support. K_2CO_3 mediated organic synthesis is proved efficient in terms of reaction time, yield and elimination of organic solvents and external bases.

The same reaction took 2-3 hours accompanied by 50-65% yield in conventional methods. Replacement of K_2CO_3 with basic alumina, silica gel and montmorillonite K10 clay needed organic solvents for elution and resulted in no significant change in reaction time and yield.

The structures of the synthesized thieno-pyrimidines **6a-j** were confirmed from spectral and analytical data. IR absorption band at 1190-1242 cm^{-1} gives the indication of the presence of (C=S) group in the compounds. The band at 1715-1740 cm^{-1} is due to (C=O) group and the band at 3495-3525 cm^{-1} confirms the presence of (N-H) linkage in the synthesized thieno-pyrimidines **6a-j**.

In ^1H NMR, δ values at 1.3 and 4.0-4.1 are due to 3H and 2H atoms of ethyl carboxylate group respectively on the thiophene ring. A singlet appears at 2.2 for methyl protons on thiophene ring, whereas a broad singlet at 11.7 is observed due to NH proton on pyrimidine ring. The aromatic and aliphatic protons of aryl substitution on N(3), have shown their characteristic signals in the compounds **6a-j**. All the aromatic protons including that of furan, thiophene and pyridine, appears at the range 6.3-8.5 ppm.

Conclusion

Highly substituted novel, 5-methyl-6-ethylcarboxylate-2-thioxo-thieno [3,2-d]pyrimidine-4(1H)-ones **6a-j**, have been synthesized by the condensation of 2-amino-3,5-diethyl-carboxylate-4-methyl-thiophene **4** and monosubstituted thioureas **5a-j**, under solid supported microwave irradiations. The reaction time has been reduced from 2-3 hours to 6-7 minutes furnishing upto 95% yield. Use of K_2CO_3 as solid support has excluded the need of excess organic solvents and external bases, keeping the environment eco-friendly.

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