Triton-B/CS_2 Mediated Synthesis of Substituted Thiophene Derivatives and their Antimicrobial Screening

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Abstract
Synthesis and the antimicrobial activities of novel substituted thiophene derivatives (1-15) are reported in this communication. The synthesized compounds were identified by ^1H NMR, elemental analysis and mass spectra. On screening the synthesized compounds for their antimicrobial activity against Escherichia coli, Staphylococcus aureus and Candida albicans, promising results have been obtained. Here antibiotic oxytetracycline and antifungal fluconazole were used as positive control for bacteria and fungus respectively.

Keywords: Antimicrobial activity, thiophene derivatives, CS_2, alkyl halide, Triton-B, m-CPBA.

Introduction
Sulfur containing substituted thiophenes are significant aromatic heterocyclic derivatives which have diverse applications as pharmaceutical and agrochemical, antimicrobial[15], anti-HIV[10], antifungal[2], antibacterial[11] and anti-psoriatic[13]. Thiophene derivatives are also known for their antidiabetic[12], antihypertensive[14], therapeutic[3], analgesic and anti-inflammatory[4], cholesterol inhibition[7], antiviral[8] and antitumor[19], insecticidal and acaricidal[9] activities. Also, such compounds have extensive applications in coordination chemistry[1,16] and have been used as intermediates in organic synthesis[17,18].

Due to numerous and diverse applications of substituted thiophene derivatives, we have worked upon developing new efficient and object-oriented synthetic method for thiophene derivatives by intramolecular cyclization of easily available *S*-containing alkyl substrates under mild conditions employing green synthesis.

Our group has been involved from past several years for the development of new methodologies for the preparation of carbamates, dithiocarbamates and related compounds using cheap, abundantly available and safe reagents like carbon dioxide and carbon disulphide respectively.[5] In recent years, we found that Triton-B has emerged as a best catalyst for the synthesis of carbamates, dithiocarbamates, carbazates, dithiocarbazates, dithiocarbonates employing a variety of reagents and catalytic systems.[6]

In the present study, we report here an efficient and novel, one-pot, solvent-free synthesis of thiophene derivatives starting from their corresponding 2,4-pentanedione or 4-chlorophenyl acetonitrile, methyl iodide, chloro acetonitrile or methyl chloroacetate employing Triton B/CS_2 system.

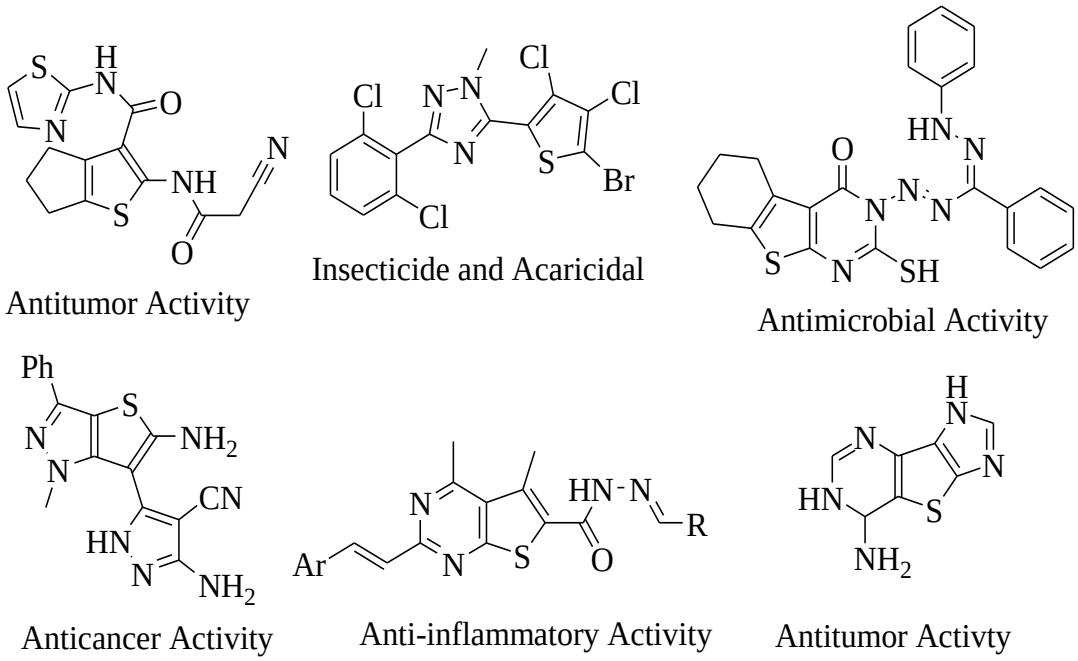


Figure 1: Structurally diverse and biologically potent thiophene derivatives

Material and Methods

The chemicals employed in the synthesis were of GLR, AVRA, Alfa-Aesar and Lobachem, Finar, Lab chem. The ^{1}H NMR spectra of the synthesized compounds were done on AC-400F-nuclear magnetic resonance spectrometer at 400 MHz ($CDCl_3$ or DMSO-d_6), with Me_4Si as internal standard. The elemental assessment of synthesized compounds was performed on 1110-CHNO-S (Carlo-ErbaEA) analyser and it was found that the calculated and observed values coincided approximately. Melting and boiling points were determined on a Gallen Kamp apparatus in open capillaries. The column chromatography having column packed with silica gel G was used for purification of the synthesized compounds.

General protocol: 1 millimol solution of 2,4-pantanedione or 4-Chlorophenylacetonitrile was taken in DMSO along with 10 millimoles of CS_2. The reaction mixture was stirred thoroughly for 15 min and then add 3 millimoles of Triton-B which is phase transfer catalyst. The reaction mass was again stirred for 10 minutes.1.0 milli mole of methyl iodide was added drop-wise and again stirred for 1.0 hrs after which 1.0 millimoles of chloroacetonitrile or methyl chloroacetate was added drop-wise under argon atmosphere and the reaction mass was stirred at room temperature for 1-2 hours.

The reaction mass was checked on TLC plate from time to time to ascertain the stage of reaction. When reaction completed, the reaction mass was quenched with 50 cm^3 distilled H_2O and synthesized compound was extracted with ethyl acetate thrice. The organic layer was separated, dried in presence of anhydrous Na_2SO_4. It was then concentrated to yield the crude compound. Crude compound was purified by silica-gel (100-200 mesh) on elution with 20% ethyl acetate in hexane to get the substituted thiophene derivatives (Scheme I).

The methylthio group in the substituted thiophene derivatives at position 4 was further oxidized with the help of *meta*-chloroperoxybenzoic acid (m-CPBA) to yield methylsulfonyl and methylsulfinyl derivatives. Here the substituted thiophene derivative was taken in DCM and add m-chloroperbenzoic acid at 0^{o}C and stir for 30 min at same temperature under argon atmosphere. After completion, the reaction mass was quenched with 1N NaOH solution and extracted with DCM. Combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. It was filtered and the filterate on reduced pressure concentration gave crude form of methylsulfinyl and methylsulfonyl derivatives of thiophene (Scheme II). The products were further purified by column chromatography.

Data analysis of the synthesized compounds

4-Acetyl-3-methyl-5-(methylthio)-thiophene-2-carbo nitrile (1): Yellow solid, M. P. 174^{o}C; Elemental analysis for $C_9H_9NS_2O$, Calculated (%): C = 51.16, H = 4.29, N = 6.63, S = 30.35. Found (%): C = 51.26, H = 4.59, N = 6.93, S = 30.65. ^{1}H NMR 400 MHz ($CDCl_3$): δ 2.608 (s, 3H), 2.591 (s, 3H), 2.562 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 211.01, Found $(M+1)^+$= 211.30.

Ethyl 4-acetyl-2-methyl-5-(methylthio)-thiophene-3-carboxylate (2): Yellow solid, M. P. 85^{o}C; Elemental analysis for $C_{11}H_{14}S_2O_3$, Calculated (%): C = 51.14, H = 5.46, S = 24.82. Found (%): C = 51.54, H = 5.86, S = 24.92. ^{1}H NMR 400 MHz ($CDCl_3$): δ 4.329 (q, *J* = 7.2 Hz, 2H), 2.736 (s, 3H), 2.577 (s, 3H), 2.558 (s, 3H), 1.372 (t, *J* = 7.2 Hz, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 258.04, Found $(M+1)^+$= 258.36.

4-Acetyl-3-methyl-5-(methylsulfinyl)-thiophene-2-carbo nitrile (3): Yellow solid, M. P. 97^{o}C; Elemental analysis for $C_9H_9NS_2O_2$, Calculated (%): C = 47.56, H = 3.99, N = 6.16, S = 28.21. Found (%): C = 47.86, H = 4.86, N = 6.45, S = 28.36. ^{1}H NMR 400 MHz ($CDCl_3$): δ 3.021 (s, 3H), 2.709 (s, 3H), 2.601 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 227.01, Found $(M+1)^+$= 227.30.

Methyl 4-(4-chlorophenyl)-4-cyano-5-(methylthio)-thio phene-2-carboxylate (4): Yellow solid, M. P. 87^{o}C; Elemental analysis for $C_{14}H_{10}NS_2O_2Cl$, Calculated (%): C = 51.93, H = 3.11, N = 4.33, Cl = 10.95, S = 19.80. Found C = 52.91, H = 3.81, N = 4.38, Cl = 11.85, S = 20.81. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.435 (d, *J* = 8.0 Hz, 2H), 7.349 (d, *J* = 8.0 Hz, 2H), 3.759 (s, 3H), 2.735 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 322.98, Found $(M+1)^+$= 323.82.

Methyl 4-(4-chlorophenyl)-3-cyano-5-(methylsulfinyl)-thiophene-2-carboxylate (5): Yellow solid, M. P. 162^{o}C; Elemental analysis for $C_{14}H_{10}NS_2O_3Cl$, Calculated (%): C = 49.48, H = 2.97, N = 4.12, Cl = 10.43, S = 18.87. Found C = 49.48, H = 3.97, N = 4.82, Cl = 10.52, S = 19.87. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.473 (d, *J* = 8.0 Hz, 2H), 7.363 (d, *J* = 8.0 Hz, 2H), 3.828 (s, 3H), 3.120 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 338.98, Found $(M+1)^+$= 339.82.

Methyl 4-(4-chlorophenyl)-3-cyano-5-(methylsulfonyl)-thiophene-2-carboxylate (6): Yellow solid, M. P. 121^{o}C; Elemental analysis for $C_{14}H_{10}NS_2O_4Cl$, Calculated (%): C = 47.26, H = 2.83, N = 3.94, Cl = 9.96, S = 18.02. Found C = 47.81, H = 2.63, N = 4.63, Cl = 10.96, S = 18.82. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.488 (d, *J* = 8.0 Hz, 2H), 7.358 (d, *J* = 8.0 Hz, 2H), 3.842 (s, 3H), 3.407 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 354.97, Found $(M+1)^+$= 355.82.

4-(4-chlorophenyl)-4-cyano-N-methyl-5-(methylthio)-thiophene-2-carboxamide(7): Yellow solid, M. P. 121^{o}C; Elemental analysis for $C_{14}H_{11}N_2S_2OCl$, Calculated (%): C = 52.09, H = 3.43, N = 8.68, Cl = 10.98, S = 19.86. Found C = 52.19, H = 3.83, N = 8.98, Cl = 11.98, S = 20.86. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.435 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 3.759 (s, 3H), 2.736 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 322, Found $(M+1)^+$= 322.83.

4-(4-chlorophenyl)-4-cyano-N-methyl-5-(methylsulfinyl) -thiophene-2-carboxamide (8): Yellow solid, M. P. 131^{o}C;

Elemental analysis for $C_{14}H_{11}N_2S_2O_2Cl$, Calculated (%): C = 49.63, H = 3.27, N = 8.27, Cl = 10.46, S = 18.93. Found C = 49.83, H = 3.67, N = 8.87, Cl = 12.46, S = 20.93. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.435 (d, *J* = 8.4 Hz, 2H), 7.358 (d, *J* = 8.0 Hz, 2H), 3.759 (s, 3H), 3.736 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 338, Found $(M+1)^+$= 338.83.

4-(4-chlorophenyl)-4-cyano-N-methyl-5-(methyl sulfonyl)-thiophene-2-carboxamide (9): Yellow solid, M. P. 137ºC; Elemental analysis for $C_{14}H_{11}N_2S_2O_3Cl$, Calculated (%): C = 47.39, H = 3.12, N = 7.89, Cl = 9.99, S = 18.07. Found C = 47.56, H = 3.96, N = 8.79, Cl = 14.99, S = 16.07.^{1}H NMR 400 MHz ($CDCl_3$): δ 7.486 (d, *J* = 8.0 Hz, 2H), 7.356 (d, *J* = 8.4 Hz, 2H), 3.839 (s, 3H), 3.404 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 353.99, Found $(M+1)^+$= 354.83.

Methyl 3-cyano-5-(methylthio)-4-phenylthiophene-2-carboxylate (10): Yellow solid, M. P. 82ºC; Elemental analysis for $C_{14}H_{11}NS_2O_2$, Calculated (%): C = 58.11, H = 3.83, N = 4.84, S = 22.16. Found C = 58.25, H = 4.83, N = 6.84, S = 23.16.^{1}H NMR 400 MHz ($CDCl_3$): δ 7.447-7.399 (m, 5H), 3.743 (s, 3H), 2.734 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 289.02, Found $(M+1)^+$= 289.37.

Methyl 3-cyano-5-(methylsulfinyl)-4-phenylthiophene-2-carboxylate (11): Yellow solid, M. P. 120ºC; Elemental analysis for $C_{14}H_{11}NS_2O_3$, Calculated (%): C = 55.06, H = 3.63, N = 4.59, S = 21.00. Found C = 55.86, H = 3.82, N = 4.69, S = 21.56.^{1}H NMR 400 MHz ($CDCl_3$): δ 7.514 (m, 5H), 3.821 (s, 3H), 3.407 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 305.02, Found $(M+1)^+$= 305.37.

Methyl 3-cyano-5-(methylsulfonyl)-4-phenylthiophene-2-carboxylate (12): Yellow solid, M. P. 98ºC; Elemental analysis for $C_{14}H_{11}NS_2O_4$, Calculated (%): C = 52.32, H = 3.45, N = 4.36, S = 19.96. Found C = 52.56, H = 3.86, N = 5.16, S = 20.91. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.514 (m, 5H), 3.750 (s, 3H), 3.611 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 321.01, Found $(M+1)^+$= 321.37.

4-(4-chlorophenyl)-3-cyano-5-(methylthio)-thiophene- 2-carboxylic acid (13): Yellow solid, M. P. 171ºC; Elemental analysis for $C_{13}H_8NS_2O_2Cl$, Calculated (%): C = 50.40, H = 2.60, Cl = 11.44, N = 4.52, S = 20.70. Found C = 50.56, H = 2.92, Cl = 11.82, N = 4.43, S = 21.31. ^{1}H NMR 400 MHz ($CDCl_3$): δ 11.29 (s, 1H), 7.513 (d, *J* = 8.4 Hz, 2H), 7.465 (d, *J* = 8.4 Hz, 2H), 2.790 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 308.97, Found $(M+1)^+$= 309.79.

3-Cyano-N-methyl-5-(methylthio)-4-phenylthiophene-2-carboxamide (14): Yellow solid, M. P. 81ºC; Elemental analysis for $C_{14}H_{11}NS_2O$, Calculated (%): C = 58.31, H = 4.19, N = 9.71, S = 22.24. Found C = 58.62, H = 4.42, N = 13.02, S = 22.31. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.554-7.419 (m, 5H), 3.687 (bs, 1H), 3.082 (s, 3H), 2.710 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 273.03, Found $(M+1)^+$= 273.37.

3-Cyano-N,N-dimethyl-5-(methylthio)-4-phenylthio phene-2-carboxamide(15): Yellow solid, M. P. 132ºC; Elemental analysis for $C_{15}H_{14}N_2S_2O$, Calculated (%): C = 59.57, H = 4.67, N = 9.26, S = 21.21. Found C = 59.91, H = 4.87, N = 9.63, S = 21.69. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.411 (m, 5H), 2.896 (s, 3H), 2.690 (s, 3H), 2.419 (s, 3H). MS (ESI): *m/z* $(M)^+$Calculated = 302.05, Found $(M+1)^+$= 302.41.

Antimicrobial activity: The antimicrobial screening of thiophene derivatives against the selected microbial species i.e. *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* was performed by agar well diffusion method. Muller Hinton Agar media for bacteria and Sabouraud Dextrose Agar media for fungus were prepared and autoclaved, then pour 25 ml in each sterile Petri plate and allow to solidify. From the microbial and fungal broth, 100µl was spread over the solidified plate via sterile glass rod spreader and was allowed to set for ten minutes. Then wells were punctured on the plate using micropipette tips and then 20µl of compounds solutions in ethyl acetate were loaded in different wells. The control for bacteria was 1000 ppm oxy-tetracycline antibiotic and for fungi it was 10000 ppm of fluconazole antifungal and ethyl acetate was loaded in one well as reference to check whether the inhibition is due to its effect or by compound itself.

Each plate had five wells one of control (antibiotic), one of reference (ethyl acetate) and three of the compounds. The plates were left for 15-20 minutes in LAF and then sealed and incubated at 37ºC for 12-14 hours. After incubation, the plates were observed and their clear zones around wells called as zones of inhibition were measured in mm (Table 2).

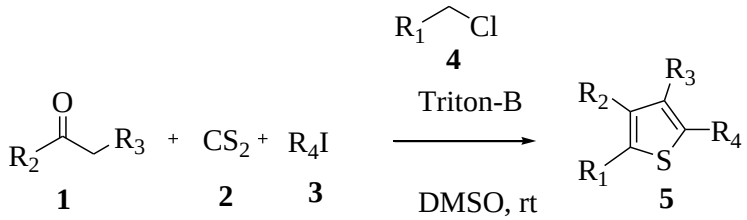
Results and Discussion

In the present work, nucleophilic addition reaction of 2,4-pantanedione or 4-Chlorophenylacetonitrile, CS_2, CH_3I and Triton-B (Trimethyl benzyl ammonium Hydroxide) catalyst is performed, then add chloroacetonitrile or methyl chloroacetate. This method used normal conditions at room temperature, involved easy work-up and gave higher yield.

The reaction of 2,4-pantanedione or 4-Chlorophenylacetonitrile, 1 in DMSO (dimethylsulfoxide) and CS_2 2, CH_3I 3, ($ClCH_2CN$ or methyl chloroacetate) 4 in the presence of Triton-B to form substituted thiophene derivatives 5 is shown by (scheme I).

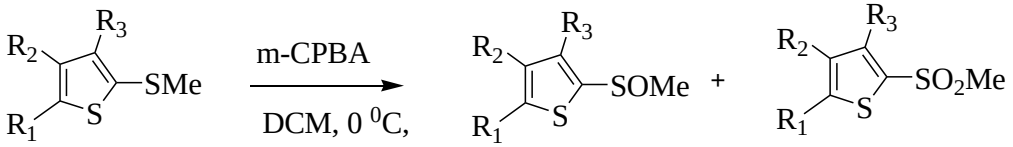
The methylthio group in the substituted thiophene derivatives at position 4 was further oxidized with the help of *meta*-chloroperbenzoic acid (m-CPBA) to yield methylsulfinyl and methylsulfonyl derivatives.

The five membered rings in a compound (1-15) exhibits an intramolecular cyclisation with C-S bond formation. ^{1}H NMR and MS spectra of the synthesized compounds support the structures and expected reactions..

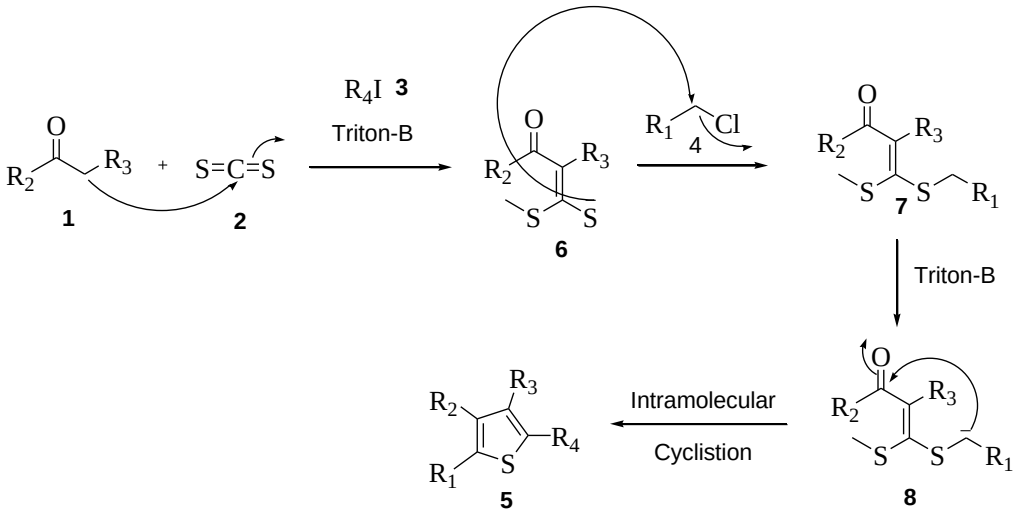


R_1 = CO_2Me, CO_2Et
R_2 = CO_2Me, CN, Me
R_3 = COMe, 4-Cl-Ph, Ph,
R_4 = SMe, SOMe, SO_2Me

Scheme I: Synthesis of substituted thiophene derivative's catalysed by Triton-B.



Scheme II: Synthesis of methylsulfinyl and methylsulfonyl derivatives from methylthio thiophenes



Scheme III: Proposed mechanism of the reaction

Table 1
Substituted-thiophene derivatives synthesized

Comp. No.	R_1	R_2	R_3	R_4	Mol. Formula	M. Wt.	Melt. Point	Yield %
1	CN	Me	$COCH_3$	SCH_3	$C_9H_9NS_2O$	211.01	174ºC	70%
2	CH_3	CO_2Et	$COCH_3$	SCH_3	$C_{11}H_{14}S_2O_3$	258.04	85ºC	75%
3	CN	Me	$COCH_3$	$SOCH_3$	$C_9H_9NS_2O_2$	227.01	97ºC	80%
4	CO_2CH_3	CN	4-Cl-C_6H_4	SCH_3	$C_{14}H_{10}NS_2O_2Cl$	322.98	87ºC	75%
5	CO_2CH_3	CN	4-Cl-C_6H_4	$SOCH_3$	$C_{14}H_{10}NS_2O_3Cl$	338.98	162ºC	70%
6	CO_2CH_3	CN	4-Cl-C_6H_4	SO_2CH_3	$C_{14}H_{10}NS_2O_4Cl$	354.97	121ºC	75%
7	$CONHCH_3$	CN	4-Cl-C_6H_4	SCH_3	$C_{14}H_{11}N_2S_2OCl$	322	121ºC	72%
8	$CONHCH_3$	CN	4-Cl-C_6H_4	$SOCH_3$	$C_{14}H_{11}N_2S_2O_2Cl$	338	131ºC	80%
9	$CONHCH_3$	CN	4-Cl-C_6H_4	SO_2CH_3	$C_{14}H_{11}N_2S_2O_3Cl$	353.99	137ºC	75%
10	CO_2CH_3	CN	C_6H_5	SCH_3	$C_{14}H_{11}NS_2O_2$	289.02	82ºC	75%
11	CO_2CH_3	CN	C_6H_5	$SOCH_3$	$C_{14}H_{11}NS_2O_3$	305.02	120ºC	78%
12	CO_2CH_3	CN	C_6H_5	SO_2CH_3	$C_{14}H_{11}NS_2O_4$	321.01	98ºC	70%
13	CO_2H	CN	4-Cl-C_6H_4	SCH_3	$C_{13}H_8NS_2O_2Cl$	308.97	171ºC	70%
14	$CONHCH_3$	CN	C_6H_5	SCH_3	$C_{14}H_{11}NS_2O$	273.03	81ºC	75%
15	$CON(CH_3)_2$	CN	C_6H_5	SCH_3	$C_{15}H_{14}N_2S_2O$	302.05	132ºC	80%

The absorption peak for characteristic thiophene ring for (1-15) appears as singlet in the region of O-CH_3(δ 3.92-3.78 ppm) and S-CH_3 (δ 3.91-2.51 ppm). The probable mechanism of the reaction is given in scheme III.

The synthesized compounds (1-15) are given in the table 1. The synthesized compounds have shown good antibacterial and antifungal activity in comparison to the standard drugs available in the market. The antibacterial and antifungal characteristics of the synthesized compounds are given in the table 2.

This method involves intramolecular cyclisation which is significantly one step direct and atom-economical approach to synthesize this very important class of heterocycles.

As a matter of fact, substituted thiophene rings are regiospecific and formed in one step with high yields through intramolecular cyclisation reaction, starting from readily available starting materials. The alkyl*S*-containing precursors can be simply prepared in one step from commercially available starting compounds through simple synthetic steps.

In present work, herein, we have developed the novel method of synthesis of new thiophene derivatives. The new derivatives were screened for their *in vitro* antimicrobial activity against bacterial stains *Staphylococcus aureus*, *Escherichia coli* and fungal stain *Candida albicans*. They were found to possess significant antimicrobial activity against the bacterial and fungal strain.

Conclusion

We have developed highly proficient, solvent-free, one pot approach of four-components coupling reaction of different 2,4-pantanedione or 4-Chlorophenylacetonitrile via Triton-B/CS_2 system. A dramatic decrease in reaction time and increase in yield is observed for this procedure as compared to traditional methods to develop C-S bonds which are important in organic syntheses.

These compounds show variable activity against the tested microbes and none of the compound shows resistance to tested compounds. So they can be further explored in pharmaceutical industries as *in vivo* antimicrobial agent after further study.

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Table 2
Zone of inhibition of the synthesized compounds for their anti-microbial activity

S. N.	Compounds	Zone of Inhabitation (mm)								
		Against S. aureus			Against E coli			Against C. Albicans		
		Compds.	(+Ve) Control	(–Ve) Control	Compds.	(+Ve) Control	(–Ve) Control	Compds.	(+Ve) Control	(–Ve) Control
1	$C_9H_9NS_2O$	18	23	Nil	17	22	Nil	13	25	Nil
2	$C_{11}H_{14}S_2O_3$	16			16			12		
3	$C_9H_9NS_2O_2$	15			17			13		
4	$C_{14}H_{10}NS_2O_2Cl$	17	23	Nil	18	22	Nil	12	25	Nil
5	$C_{14}H_{10}NS_2O_3Cl$	17			16			13		
6	$C_{14}H_{10}NS_2O_4Cl$	17			20			11		
7	$C_{14}H_{11}N_2S_2OCl$	17	23	Nil	16	22	Nil	14	25	Nil
8	$C_{14}H_{11}N_2S_2O_2Cl$	18			18			11		
9	$C_{14}H_{11}N_2S_2O_3Cl$	16			16			14		
10	$C_{14}H_{11}NS_2O_2$	16	23	Nil	19	22	Nil	10	25	Nil
11	$C_{14}H_{11}NS_2O_3$	16			19			12		
12	$C_{14}H_{11}NS_2O_4$	17			18			12		
13	$C_{13}H_8NS_2O_2Cl$	15	23	Nil	15	22	Nil	12	25	Nil
14	$C_{14}H_{11}NS_2O$	16			13			13		
15	$C_{15}H_{14}N_2S_2O$	18			15			10		

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