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SYNTHESIS OF SOME NEW THIOPHENES AS ANTI-INFLAMMATORY AND ANTIMICROBIAL AGENT

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ABSTRACT

A new series of 2-[(substituted benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophenes were synthesized by the reaction of cyclic ketone with cyanoacetamide in strong basic medium followed by Schiff base formation. Then newly synthesized compounds were characterized by IR spectroscopy, ^{1}H NMR and mass spectral data. The newly synthesized compounds were screened for antifungal and antibacterial and anti-inflammatory activities. Among them ss8e and ss8m exhibited good antifungal and antibacterial activities and ss8f & ss8e showed promising anti-inflammatory activity.

Key words: Cyanoacetamide, Cyclic ketone, Gewald reaction, Anti-inflammatory activity.

INTRODUCTION

It is proved from the literature that, apart from possessing several biological activities[1-38], thiophenes are also useful intermediates[39-52] for the synthesis of several chemical and pharmacological classes of therapeutic agents having heterocyclic structures in them. Also a number of thiophenes with novel substituents were earlier prepared in our laboratories. These thiophenes were endowed with significant biological activities. Based on these observations, it was considered worthwhile to synthesize some new substituted thiophenes by Gewald reaction in the present study. To synthesize and characterize series of some novel 2-[(substituted benzylidene)imino]-3-(N-methylcarboxamido) -4,5-trimethylene thiophenes.

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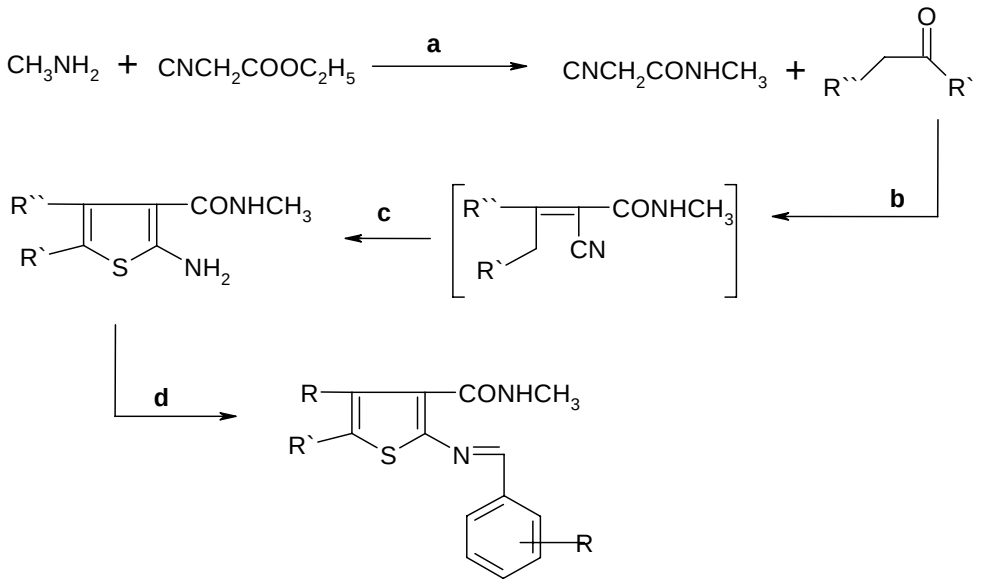
EXPERIMENTAL

Materials and methods

The melting point of synthesized compounds was determined in open capillary tubes using melting point apparatus, expressed in ^{0}C and is uncorrected. Reactions were monitored by thin layer chromatography on pre-coated plates (SD fine Chem. Ltd) using different solvent systems. The purity of the compound was ascertained by TLC, using iodine vapours as visualizing agents. The structures of the compound were confirmed by I.R., NMR and Mass spectra.



(a) = cold cond.; (b) = NH_4OOCH_3, CH_3COOH, C_6H_6, reflux; (c) = S, C_2H_5OH, DEA; (d) = isopropanol, CH_3COOH, aromatic aldehyde

Scheme

Synthesis of methyl cyanoacetamide (ss7)

A mixture of methyl amine (0.4 mole) and ethyl cyanoacetate (0.4 mole) was taken in a conical flask and placed on an ice bath for 1.5 h (hours) for cold condensation. After 1.5 h. the solid obtained was filtered to get the methyl cyanoacetamide. This product was dried and recrystallized with ethanol. **ss 7-** IR (KBr) 3282 cm^{-1} (NH); 1684 cm^{-1} (C=O); 1709 cm^{-1} (C≡N); 2951 cm^{-1} (Ali-CH).

Synthesis of 2-amino-3-(N-methyl carboxamido)-4,5-trimethylene thiophene (ss8)[1-3]

A mixture of methyl cyanoacetamide (0.04 mole), cyclo pentanone (0.04 mole), ammonium acetate (2 g) and glacial acetic acid (2 mL) in benzene (80 mL) was refluxed for 10 hrs. in Dean and Stark apparatus with continuous separation of water.

After 10 h. the reaction mixture was cooled and washed with sodium carbonate solution (10% w/v solution in water) and water successively and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the intermediate crude product obtained was immediately processed for next step.

To a mixture of intermediate (2-cyano-2-cyclopentylidene-N-methyl acetamide) and sulphur (0.04 mole) in alcohol (30 mL) at 45^0-50^0C, diethyl amine (6.0 mL) was added drop wise with stirring till the sulphur goes in the solution. The reaction was stirred for further 1 h. at same temperature. The reaction mixture was chilled over night. The solid obtained was filtered, washed with ethanol and recrystallized with isopropanol. **ss8-** ^{1}HNMR δ = 8.0 (1H, s, CO-NH); 4.0 (2H, s, -NH_2); 2.74 (3H, s, NH-CH_3); 2.55 (4H, m, CH_2, Cyclopentane); 1.95 (2H, d, CH_2, Cyclopentane); IR (KBr) 3283 cm $^{-1}$ (NH); 1680 cm $^{-1}$ (C=O); 2953 cm^{-1}; 2940 cm^{-1}; (Ali-CH); 1559 cm^{-1} (Ar. C=C); 1223 cm^{-1} (thiophene); m/ z (M+1) 197.

Synthesis of 2-substituted benzylidene imino-3-(N-methyl carboxamido)-4,5-trimethylene thiophenes (Schiff bases) (ss8a to ss8m)

A mixture of 2-amino-3-(N-methyl carboxamido)- 4,5-trimethylene thiophene (**ss8**) (0.005 mole) and the required substituted aryl aldehydes (0.005 mole) in 30 mL of isopropanol along with catalytic amount of glacial acetic acid (2-3 drops) was refluxed for 2 h. The reaction mixture was allowed to cool. The solid obtained was filtered, washed with ethanol, dried and recrystallized using isopropanol. All the compounds of the series were prepared in the same manner.

(a) 2-[(4'-N,N-dimethylamino benzylidene)imino]-3-(N methyl carboxamido)-4,5-trimethylene thiophene (ss8a): δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH_2); 7.5 (2H, d, CH, Aro. protons); 7.1 (2H, m, CH, Aro. protons); 2.7 (3H, s, NH-CH_3); 2.55 (4H, m, CH_2 of cyclo pentane ring); 3.65 (6H, s, N $(CH_3)_2$); 1.95 (2H, m, CH_2 of cyclopentane); 3279 cm^{-1} (NH); 1682 cm^{-1} (C=O); 1709cm^{-1} (C≡N); 2951, 2940 cm^{-1} (Ali-CH).

(b) 2-[(4'-hydroxy benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8b): δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH); 7.5 (1H, d, CH, Aro.

protons); 7.25 (1H, d, CH, Aro. protons); 6.8 (2H, m, CH Aro. protons); 5.1 (1H, s, =C-OH); 2.76 (3H, s, CH_3); 2.55 (4H, m, CH_2 of cyclopentane); 1.95 (2H, m, CH_2 of cyclopentane); 3268 cm^{-1} (NH); 1662 cm^{-1} (C=O); 2944 cm^{-1}; 2930 cm^{-1}; (Ali-CH); 1559 cm^{-1} (Ar. C=C); 1204 cm^{-1} (thiophene).

c) 2-[(2'-nitro benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8c) - δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH_2); 7.5 (2H, d, CH, Aro. protons); 7.2 (2H, m, CH, Aro. protons); 2.7 (3H, s, NH-CH_3); 2.55 (4H, m, CH_2 of cyclo pentane ring); 1.95 (2H, m, CH_2 of cyclopentane); 3288 cm^{-1} (NH); 1684 cm^{-1} (C=O); 1709 cm^{-1} (C≡N); 2951, 2940 cm^{-1} (Ali-CH).

d) 2-[(3'-nitro benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8d)- δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH_2); 7.7 (2H, d,CH, Aro. protons); 7.3 (2H, m, CH, Aro. protons); 2.7 (3H, s, NH-CH_3); 2.55 (4H, m, CH_2 of cyclo pentane ring); 1.95 (2H, m, CH_2 of cyclopentane); 3263 cm^{-1} (NH); 1678 cm^{-1} (C=O); 2953 cm^{-1}; 2940 cm^{-1}; (Ali-CH); 1559 cm^{-1} (Ar. C=C); 1223 cm^{-1} (thiophene).

e) 2-[(3',4',5'-trimethoxy benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8e)- δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH); 6.4 (2H, s, Aro. protons); 3.80 (9H, s, OCH_3); 2.74 (3H, s, NH-CH_3,); 2.55 (4H, m, CH_2, cyclopentane); 1.95 (2H, m, CH_2 cyclopentane); 3226 cm^{-1} (NH); 3026 cm^{-1} (Ar. CH); 2929 cm^{-1} (Ali-CH); 1669 cm^{-1} (C=O); 1532 (N= CH); 1510 cm^{-1} (Ar-C=C); 1223 cm^{-1} (thiophene); 1305 cm^{-1} (CN); 1099 cm^{-1} (-C-O-C); m/z (M+1) 375.

f) 2-[(2'-hydroxy benzylidene)imino]-3-(N-methylcarboxamido)-4,5- trimethylene thiophene (ss8f): δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH); 7.6 (1H, d, CH, Aro. protons); 7.3 (1H, d, CH, Aro. protons); 6.8 (2H, m, CH Aro. protons); 5.0 (1H, s, =C-OH,); 2.7 (3H, s, CH_3); 2.55 (4H, m, CH_2 of cyclopentane); 1.95 (2H, m, CH_2 of cyclopentane); 3432 cm^{-1} (OH); 3316 cm^{-1} (NH); 3024 cm^{-1} (Ar. CH); 2888 cm^{-1} (Ali-CH); 1669 cm^{-1} (C=O); 1536 cm^{-1} (N=CH); 1533 cm^{-1} (Ar-C=C); 1321 cm^{-1} (C-N); 1228 cm^{-1} (thiophene).

g) 2-[(benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8g): δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH_2); 7.5 (2H, d, CH, Aro. protons); 7.2 (3H, m, CH, Aro. protons); 2.7 (3H, s, NH-CH_3); 2.55 (4H, m, CH_2 of cyclo pentane ring); 1.95 (2H, m, CH_2 of cyclopentane); 3224 cm^{-1} (NH); 3026 cm^{-1} (Ar. CH); 2929 cm^{-1} (Ali-CH); 1669 cm^{-1} (C=O); 1532 (N= CH); 1510 cm^{-1} (Ar-C=C); 1223 cm^{-1} (thiophene); 1305 cm^{-1} (CN); 1099 cm^{-1} (-C-O-C).

h) 2-[(4'-hydroxy-3'-methoxy benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8h): δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH); 7.4 (1H, d, CH, Aro. protons); 7.1 (1H, d, CH, Aro. protons); 6.8 (2H, m, CH Aro. protons); 5.4 (1H, s, =C-OH,); 3.8 (3H, s, OCH_3), 2.7 (3H, s, CH_3); 2.55 (4H, m, CH_2 of cyclopentane); 1.95 (2H, m, CH_2 of cyclopentane); 3401 cm^{-1} (OH); 3236 cm^{-1} (NH); 3084 cm^{-1} (Ar. CH); 2928 cm^{-1} (Ali-CH); 1669 cm^{-1} (C=O); 1536 cm^{-1} (N=CH); 1523 cm^{-1} (Ar-C=C); 1321 cm^{-1} (C-N); 1223 cm^{-1} (thiophene).

i) 2-[(2'-chloro benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8i): δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH_2); 7.5 (2H, d,CH, Aro. protons); 7.1 (2H, m, CH, Aro. protons); 2.6 (3H, s, NH-CH_3); 2.55 (4H, m, CH_2 of cyclo pentane ring); 1.95 (2H, m, CH_2 of cyclopentane); 3324 cm^{-1} (NH); 3102 cm^{-1} (Ar. CH); 2904 cm^{-1} (Ali-CH); 1658 cm^{-1} (C=O); 1532 (N=CH); 1516 cm^{-1} (Ar-C=C); 1233 cm^{-1} (thiophene); 1305 cm^{-1} (CN); 1099 cm^{-1} (-C-O-C).

j) 2-[(4'-methoxy benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8j): δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH); 7.4 (1H, d, CH, Aro. protons); 7.1 (1H, d, CH, Aro. protons); 6.8 (2H, m, CH Aro. protons); 3.93 (3H, s, OCH_3), 2.7 (3H, s,CH_3); 2.55 (4H, m, CH_2 of cyclopentane); 1.95 (2H, m, CH_2 of cyclopentane); 3451 cm^{-1} (OH); 3236 cm^{-1} (NH); 3038 cm^{-1} (Ar. CH); 2910 cm^{-1} (Ali-CH); 1669 cm^{-1} (C=O); 1536 cm^{-1} (N=CH); 1540 cm^{-1} (Ar-C=C); 1321 cm^{-1} (C-N); 1223 cm^{-1} (thiophene).

k) 2-[(3',4'-dimethoxy benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8k): δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH); 7.4 (1H, d, CH, Aro. protons); 7.1 (1H, d, CH, Aro. protons); 6.8 (2H, m, CH Aro. protons); 3.76 (6H, m, 2X OCH_3), 2.7 (3H, s,CH_3); 2.55 (4H, m, CH_2 of cyclopentane); 1.95 (2H, m, CH_2 of cyclopentane); 3230 cm^{-1} (NH); 3026 cm^{-1} (Ar CH); 2930 cm^{-1}, 2904 cm^{-1} (Ali-CH); 1668 cm^{-1} (C=O); 1536 cm^{-1} (N=CH); 1302 cm^{-1} (C-N); 1229 cm^{-1} (thiophene); 1124 cm^{-1} (-C-0-C).

l) 2-[(4'-chloro benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8l): δ = 8.1 (1H, s, -N=CH); 8.0 (1H, s, -CO-NH_2); 7.5 (2H, d, CH, Aro. protons); 7.1 (2H, m, CH, Aro. protons); 2.7 (3H, s, NH-CH_3); 2.55 (4H, m, CH_2 of cyclo pentane ring); 1.95 (2H, m, CH_2 of cyclopentane); 3236 cm^{-1} (NH); 1669 cm^{-1} (C=O); 1539 cm^{-1} (N=CH); 3018 cm^{-1} (Ar-CH); 2929 cm^{-1} (Ali-CH); 1669 cm^{-1} (C=O); 1238 cm^{-1} (thiophene); 1093 cm^{-1} (-C-O-C).

m) 2-[(4'-methyl benzylidene)imino]-3-(N-methylcarboxamido)-4,5-trimethylene thiophene (ss8m): δ = 8.0 (1H, s, -N=CH); 7.9 (1H, s, -CO-NH_2); 7.4 (2H, d, CH, Aro.

protons); 7.0 (2H, m, CH, Aro. protons); 2.7 (3H, s, NH-CH_3); 2.55 (4H, m, CH_2 of cyclo pentane ring); 2.35 (3H, s, =C-CH_3); 1.95 (2H, m, CH_2 of cyclopentane); 3246 cm^{-1} (NH); 1660 cm^{-1} (C=O); 1534 cm^{-1} (N=CH); 3024 cm^{-1} (Ar-CH); 2920 cm^{-1} (Ali-CH); 1669 cm^{-1} (C=O); 1233 cm^{-1} (thiophene); 1093 cm^{-1} (-C-O-C).

Antibacterial activity

The test compounds were tested for their *in vitro* antibacterial activity by cup-plate method[53-55] against strains of microbes, which are *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and *Klebsiella pneumoniae.*

Table 1: Physical data

Compd.	R	Molecular formula	Relative molecular mass (RMM)	Melting point (^oC)	Yield %
ss8	-	$C_9H_{12}N_2OS$	196	134	57.62
ss8a	4'-N,N-dimethyl amino	$C_{18}H_{21}N_3SO$	327	226	54.64
ss8b	4'-hydroxy	$C_{16}H_{16}N_2SO_2$	300	237	57.47
ss8c	2'-nitro	$C_{16}H_{15}N_3SO_3$	329	221	60.72
ss8d	3'-nitro	$C_{16}H_{15}N_3SO_3$	329	212	61.45
ss8e	3',4',5'-tri methoxy	$C_{19}H_{22}N_2SO_4$	374	227	50.86
ss8f	2'-hydroxy	$C_{16}H_{16}N_2SO_2$	300	209	56.46
ss8g	Hydrogen	$C_{16}H_{16}N_2SO$	284	224	63.46
ss8h	4'-hydroxy-3'-methoxy	$C_{17}H_{18}N_2SO_3$	330	218	61.48
ss8i	2'-chloro	$C_{16}H_{15}N_2SOCl$	318	215	57.28
ss8j	4'-methoxy	$C_{17}H_{18}N_2SO_2$	314	218	65.35
ss8k	3',4'-dimethoxy	$C_{18}H_{20}N_2SO_3$	344	233	62.75
ss8l	4'-chloro	$C_{16}H_{15}N_2SOCl$	318	224	58.38
ss8m	4'-methyl	$C_{17}H_{18}N_2SO$	298	227	63.46

Table 2: Biological Activity

Compd.	R	Zone of inhibition (mm)				Zone of inhibition (mm)		Anti-inflammatory activity (% Bovine serum inhibition)
		S. aureus	***B. subtilis***	***E. coli***	***K. pneumoniae***	***Aspergillus niger***	***Candida albicans***	
ss8a	4'-N,N-dimethyl amino	13	15	NA	NA	NA	NA	27.28
ss8b	4'-hydroxy	19	15	16	17	15	12	53.22
ss8c	2'-nitro	14	13	13	14	14	11	30.37
ss8d	3'-nitro	17	15	16	14	NA	NA	36.61
ss8e	3',4',5'-tri methoxy	20	16	20	15	16	14	30.26
ss8f	2'-hydroxy	18	15	19	16	14	12	55.18
ss8g	Hydrogen	16	15	NA	NA	13	11	29.64
ss8h	4'-hydroxy-3'-methoxy	15	13	NA	NA	NA	NA	51.35
ss8i	2'-chloro	16	15	18	16	16	13	35.46
ss8j	4'-methoxy	15	13	NA	NA	09	06	32.52
ss8k	3',4'-dimethoxy	13	11	14	17	08	07	38.92
ss8l	4'-chloro	16	15	17	16	13	12	27.64
ss8m	4'-methyl	20	15	18	14	16	17	22.48
Ampicillin	--	**22**	**17**	**24**	**18**	--	--	--
Miconazole nitrate	--	--	--	--	--	**30**	**27**	--
Ibuprofen	--	--	--	--	--	--	--	**68.55**

Antifungal acitvity

The test compounds were tested for their *in vitro* antibacterial activity by cup-plate method[53-55] against *Aspergillus niger* and *Candida albicans*. All the experiments were carried out in triplicate.

Anti-inflammatory activity

The test compounds were tested for *in vitro* anti-inflammatory activity by serum albumin denaturation method[2,56] by dissolving them in minimum amount of DMF and diluted with phosphate buffer (0.2 mole, pH 7.4). Final concentration of DMF in all solution was less than 2.5%. Test solution (1mL) containing different concentrations of drug was mixed with 1 mL of 1 mmole albumin solution in phosphate buffer and incubated at 270 ± 10^{o}C for 15 min. Denaturation was induced by keeping the reaction mixture at 600 ± 10^{o}C in a water bath for 10 min. After cooling the turbidity was measured at 660 nm. (Elico Spectrometer). Percentage inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and the average was taken. The percentage of inhibition is calculated from the following formula.

$$\% \text{ Inhibition} = 100\ (1 - Vt/Vc)$$

RESULTS AND DISCUSSION

The antibacterial activity of Schiff base of thiophenes have been evaluated by using cup-plate method or agar diffusion method against *K. pneumoniae*, *E. coli*, *S. Aureus and B. subtilis*. The results clearly revealed the potential antibacterial activity of all thiophenes, when compared with the standard drug Ampicillin. Of all the compounds tested, compound **ss8e** and **ss8m** having the trimethoxy group and para-methyl on benzene ring, showed maximum activity. The rest of the compounds showed moderate to mild activity and few compounds failed to produce activity against *E. coli* and *K. pneumoniae*.

The antifungal activity of the substituted thiophenes was evaluated against *A. niger* and *C. albicans*, employing miconazole nitrate as the standard drug using the cup-plate method of all the compounds tested, **ss8m** having methyl group substitution at *meta* position of the phenyl ring showed the maximum activity followed by compounds **ss8e** and **ss8i** having trimethoxy group and chlorine substitution at *ortho* position of the phenyl ring, respectively.

The anti-inflammatory activity of all the new thiophenes synthesized have been evaluated by using inhibition of bovine serum albumin denaturation method as compared with standard drug Ibuprofen. Of all the compounds tested, compound **ss8f** and **ss8b** having

hydroxy group substitution at *ortho* and *para* position of the aromatic ring of thiophene showed maximum activity.

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