Research Article

Microwave Assisted Synthesis of Some 2-[(Substituted Benzylidene) Imino]-3-(N-Benzyl Carboxamido) -4, 5-Di Substituted Thiophenes

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ABSTRACT

In this present work, a series of new 2-[(substituted benzylidene) imino]-3-(N-Benzyl carboxamido)-4,5-di substituted thiophenes were synthesized in a multi step method. In the first step Benzyl cyano acetamide [1] was synthesized by the condensation of benzylmine with ethylcyanoacetate. Reaction of compound [1] with methylenic ketone using ammonium acetate and glacial acetic acid as an acidic catalyst was carried out by refluxation in benzene for 8hrs by employing Dean Stark apparatus afforded 2-Cyano –2- (alkylidene)-N- benzyl carboxamides [2] Compound [2] represents the important key intermediate from which all the new target polysubstituted thiophenes were synthesized thus compound [2] was introduced in reaction with elemental sulfur in the presence of basic catalyst, diethyl amine in ethanol to form 2-amino-3-(benzyl carboxamido)-4,5-di substituted thiophenes [MSR8,9 &10]. In the final step the prepared thiophenes were irradiated in microwave with various aromatic di substituted aldehydes [a-k] in isopropyl alcohol with glacial acetic acid as a catalyst producing the target thiophenes [MSR8a-k, 9a-k & 10a-k].

Keywords: Benzyl cyano acetamide, 2-cyano-2-(alkylidene)N-benzyl carboxamides.

INTRODUCTION

Heterocycles often seemed to be perfect bioisosteres according to they can delivery equal or even better biological efficacy through their similarity in structural shape and electronic distribution[1].

The appreciation of thiophene derived heterocyclic compounds diverse biological applications and the continuous application of thiophene derivatives as synthons in organic synthesis, has led to the synthesis of thiophene analogues and their subsequent heterocyclics.

The recent improvement in the knowledge of the mechanism of action of the available drug in the biochemical mechanism of resistance to them may be used as a basis for designing new and better action against diseases[2]. Research and Development of new medicinal compounds comprises of the following major steps, the synthesis of the new chemical entities, characterization using different analytical and spectral analyses; Screening of the molecule for pharmacological and biological activity. Published literature and articles are considered the evidence for feasibility of such synthetic procedures and their reported pharmacological activity.

Microwave irradiation was recognized in the mid-1980s to be an efficient heating source for chemical reactions, where reactions that require several hours under conventional conditions can often be completed in a few minutes with very high yields and reaction selectivities. Many reports have been published on the beneficial effect of microwave irradiation in organic synthesis, e.g., for the preparation of heterocycles and for organometallic and rearrangement reactions. A number of review articles have appeared that cover the underlying theory of microwave dielectric heating, the relevant dielectric parameters, and microwave-assisted organic reactions[3].

Generally many drugs are obtained from plants and animals, but most drugs used in modern medicine are products of advances in synthetic organic chemistry and biotechnology. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry.

Various thiophenes have been reported for their biological and pharmacological activities such as antimicrobial[4, 10], antifungal[5], anti tubercular[6], anti tumor[7], antimycobacterial[8],anti proliferative[9], antibacterial[11, 12], antiviral, anti protozoal, herbicidal, anti ulcer, CNS depressant & anticonvulsant[13], analgesic, anti inflammatory activites[14] and so on

In view of these observations and their increasing importance in pharmaceutical and biological field, it was considered of interest to synthesize some new chemical entities incorporating the molecular frame work and to evaluate their biological activities.

EXPERIMENTAL

SYNTHESIS

Synthetic procedure for the preparation of Benzyl cyano acetamide compound [1]

A mixture of Benzylamine (0.5 M) and ethyl cyano acetate (56.5 ml; 0.5 M) was taken in a conical flask and heated on mantle for 3-4 hrs at 160- 170°C. Then the reaction mixture was transferred into a beaker and kept at room temperature for over night. The solid obtained was washed with ethanol, dried & recrystallized by ethanol.

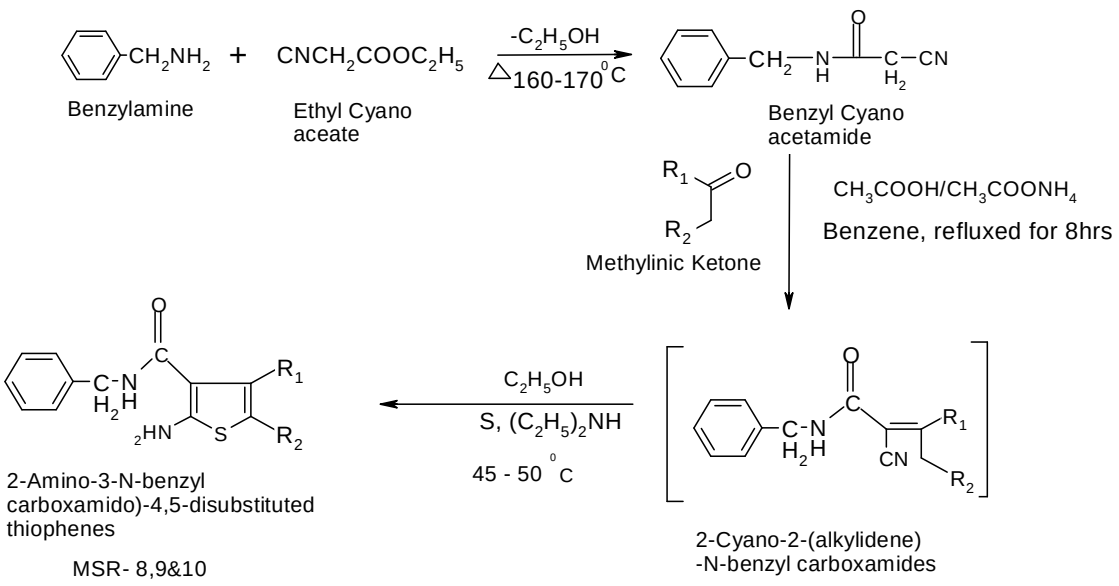
Synthetic procedure for the preparation of 2-Cyano –2- (alkylidene)-N- benzyl carboxamides **compound [2]**

A mixture of benzyl cyano acetamide [1] (0.04 M), appropriate methylenic ketones (0.04 M), ammonium acetate (2 g) and glacial acetic acid (2 ml) in benzene (100 ml) was refluxed with an arrangement for continuous separation of water involving dean stark apparatus. After 8 hrs the reaction mixture was cooled, diluted with 10 ml benzene and washed succesively with sodium carbonate solution (10% w/v in water) and water; Dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the intermediate crude product obtained was immediately processed for next step.

Synthetic procedure for the preparation of 2-amino-3-(benzyl carboxamido)-4, 5-di substituted thiophenes [MSR-8, 9 & 10]

The intermediate obtained from the previous step is dissolved in alcohol (30 ml) sulphur (1.28g; 0.04M) was added with stirring by maintaining the temperature between 45-50ºC during addition. To the reaction mixture, diethyl amine (6.0 ml) was added drop wise the stirring was continued for 1hr at 45-50ºC and chilled over night. The solid obtained was filtered, washed with ethanol and crystallized from ethanol.

Reaction

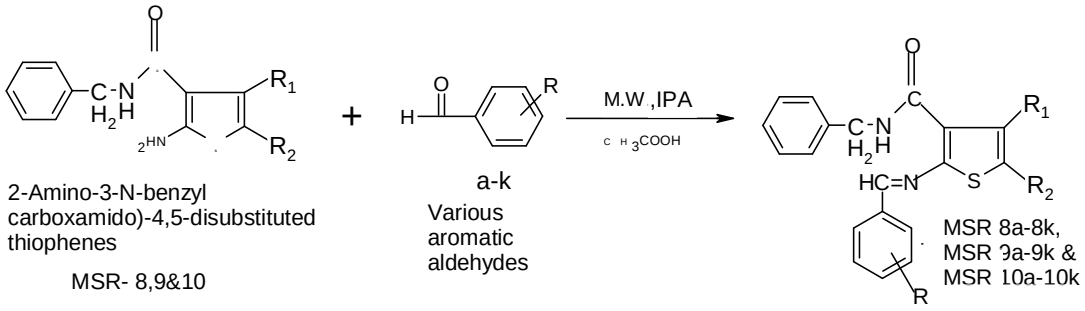


Where: R_1, R_2 = - $(CH_2)_3$-, - $(CH_2)_4$-, - $(CH_2)_5$-.

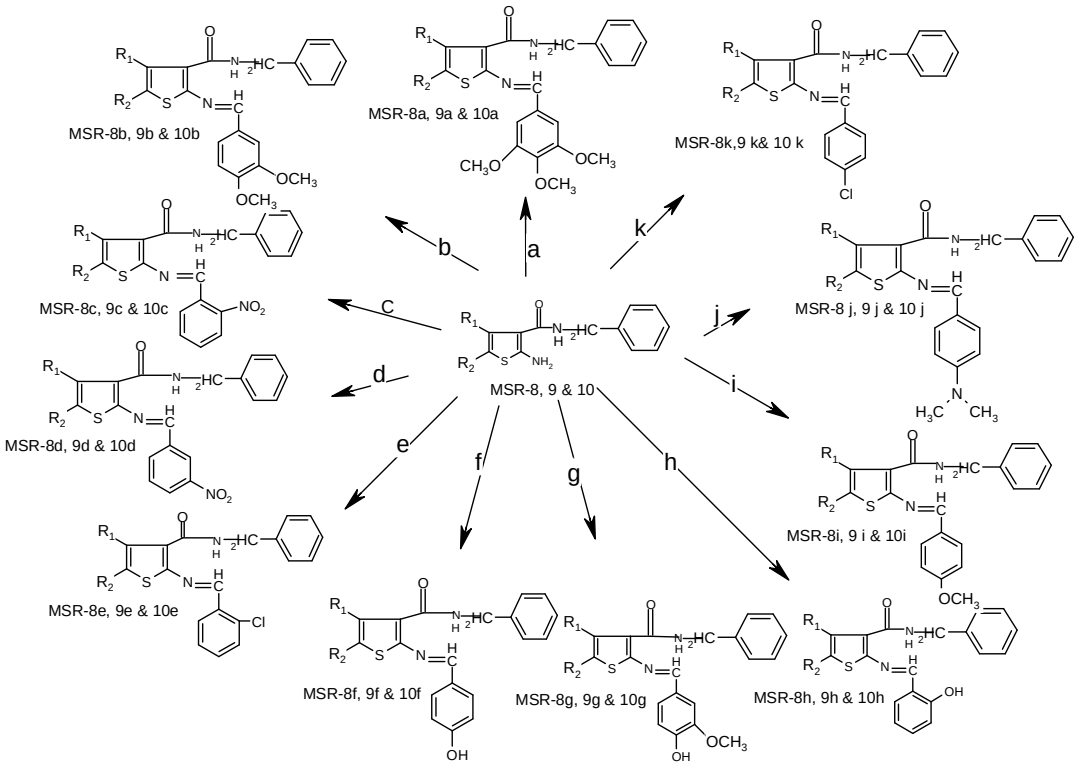
Microwave assisted synthetic procedure for the preparation of 2-[(substituted benzylidene) imino]-3-(N-Benzyl carboxamido)-4, 5-di substituted thiophenes [8a-8k, 9a-9k & 10a-10k]:

A mixture of the starting compounds (8, 9 & 10) (0.005 M) and the required aryl aldehydes (0.005 M) in isopropyl alcohol (30 ml) and catalytic amount of glacial acetic acid (2 ml) was taken into a conical flask and subjected to microwave irradiation for 30 seconds. The mixture was cooled to room temperature, the solid separated was filtered, washed with isopropyl alcohol and recrystallised with DMF: Water mixture (5:1).

Reaction

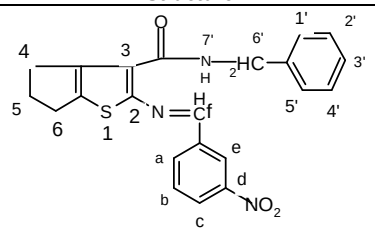
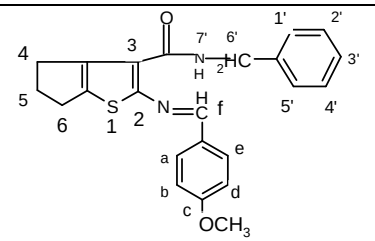
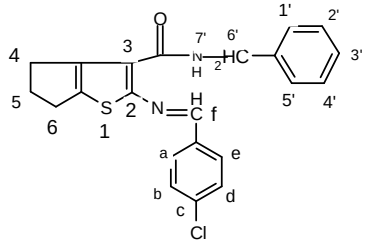
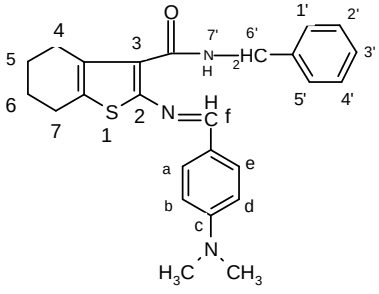


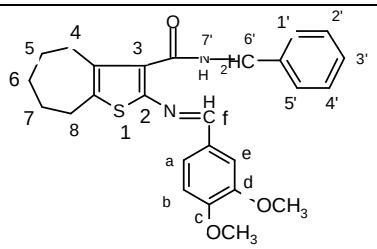
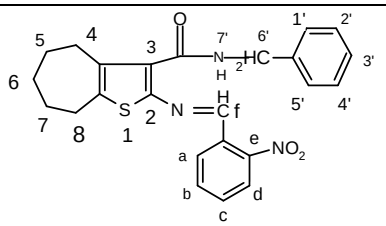
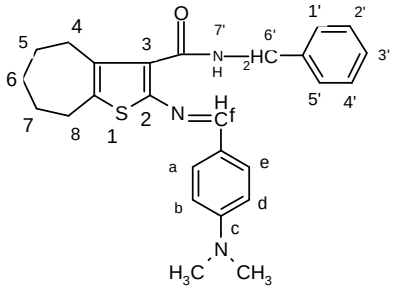
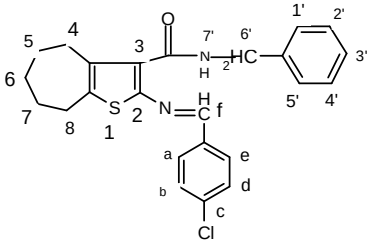
SCHEME



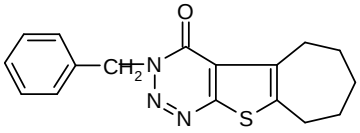
R	M.P °C
a = 3,4,5-Trimethoxy benzaldehyde (MSR-8a, 9a & 10a)	109
b =3,4-Dimethoxy benzaldehyde (MSR-8b, 9b & 10b)	116
c =2-Nitro benzaldehyde (MSR-8c, 9c & 10c)	136
d =3-Nitro benzaldehyde (MSR-8d, 9d & 10d)	105
e= 2-Chloro benzaldehyde (MSR-8e, 9e & 10e)	112
f= 4-Hydroxy benzaldehyde (MSR-8f, 9f & 10f)	113
g=4-Hydroxy-3-methoxy benzaldehyde (MSR-8g, 9g &10g)	118
h = 2-Hydroxy benzaldehyde (MSR-8h, 9h & 10h)	122
i = 4-Methoxy benzaldehyde (MSR-8i, 9i & 10i)	156
j = 4-Dimethyl amino benzaldehyde (MSR-8j, 9j & 10j)	126
k = 4-Chloro benzaldehyde (MSR-8k, 9k & 10k)	105

Table 1: Spectral Data

Comp No	Structure	^{1}H NMR ($CDCl_3$)
8d	 MSR-8d	7.6 (s, 1H, -N=CH-, f); 6.98-7.49 (m, 9H, Ar-H, a,b,c,e,1',2',3',4',5'); 4.85(s, 1H, -NH,7'),3.07 (m, 2H, -CH_2-, 6'); 2.55-2.62(m, 6H, -CH_2-,4,5,6).
8i	 MSR-8i	7.5 (s, 1H, -N=CH-, f); 7.06-7.42 (m, 9H, Ar-H, a,b,d,e,1',2',3',4',5'); 4.87 (s, 1H, -NH,7'); 3.96 (s, 3H, -OCH_3); 3.37 (m, 6H, -CH_2-, 6',5,6); 2.75(t, 2H, -CH_2-,4).
8k	 MSR-8k	7.6(s, 1H, -N=CH-, f); 7.04-7.38 (m, 9H, Ar-H, a,b,d,e,1',2',3',4',5'); 4.82 (s, 1H, -NH,7'); 2.64 (s, 6H, -CH_2-, 4,6,6'); 1.68(s, 2H, -CH_2-,5).
9j	 MSR- 9 j	8.56 (s, 1H, -N=CH-, f); 7.86 (s, 4H, Ar-H, a,b,d,e); 7.0-7.51 (m, 5H, Ar-H,1',2',3',4',5'); 5.6-6.0 (b, 1H, -NH, 7'); 2.98-3.07 (t, 6H,-N{-CH_3}$_2$-, c); 2.88(t, 6H, -CH_2-,6',4,7); 2.65 (t, 4H, -CH_2-, 5,6).

10b	 MSR-10b	7.62 (s, 1H, -N=CH-, f); 6.92-7.49 (m, 8H, Ar-H, a,b,e,1',2',3',4',5'); 4.60 (s, 1H, -NH,7'); 3.99 (s, 6H, -OCH_3,c,d); 3.04 (t, 4H, -CH_2-,8,6'); 2.99(t, 4H, -CH_2-,4,7); 1.95 (m, 4H, -CH_2-, 5,6).
10c	 MSR-10c	8.4 (s, 1H, -N=CH-, f); 6.91-7.26 (m, 9H, Ar-H, a,b,c,d,1',2',3',4',5); 4.99 (s, 1H, -NH, 7'); 2.78 (s, 2H, -CH_2-, 6'); 2.59(s, 2H, -CH_2-,8); 1.75 (s, 8H, -CH_2-, 4,5,6,7).
10j	 MSR-10 j	8.5 (s, 1H, -N=CH-, f); 8.3 (s, 1H, Ar-H, a); 6.84-7.12 (m, 8H, Ar-H,b,d,e,1',2',3',4',5'); 5.98(b, 1H,-NH, 7'); 3.99 (s, 4H,-CH_2-,4,8); 2.99(s, 3H,-N-CH_3-,c);2.92(s, 3H,-N-CH_3-,c); 2.19-2.45 (s, 6H, -CH_2-,5,6,7).
10k	 MSR-10 k	8.5 (s, 1H, -N=CH-, f); 8.3 (s, 1H, Ar-H, a); 6.84-7.12 (m, 8H, Ar-H,b,d,e,1',2',3',4',5'); 5.98(b, 1H,-NH, 7'); 3.99 (s, 4H,-CH_2-,4,8); 2.99(s, 3H,-N-CH_3-,c);2.92(s, 3H,-N-CH_3-,c); 2.19-2.45 (s, 6H, -CH_2-,5,6,7).

MASS SPECTRUM



MSR-8a

Molecular Weight – 420

RESULTS & DISCUSSION

The formation of the parent compounds were confirmed by Lassingnes test, TLC, UV and IR spectra. The IR spectra exhibit a distinct peak at 3250-3380 cm^{-1} (NH_2 group) confirms the parent compound.

The difference in M.P, TLC, and UV absorption maxima of compound MSR-8, 9 & 10 compared to the starting material and IR distinct amino peaks at 3250-3380cm^{-1}, 3293 cm^{-1}(-NH);1652-1679cm^{-1}(C=O);3150-3050cm^{-1}(Ar-CH);2940-2800cm^{-1}(Ali-CH); 1545-1570cm^{-1}(Ar-C=C);705.56 (S-C); confirms the formation of 2-amino-3-(benzyl carboxamido)-4,5-di substituted thiophenes MSR-8, 9 & 10.

The formation of the title compounds 8a-8k, 9a-9k & 10a-10k were preliminarily confirmed by the difference in MP,Rf value, UV spectra (bathochromic shift), and specific IR peak where there is an absence of the primary aromatic amino peak at 3250-3380 cm^{-1} in 8, 9 & 10 and an appearance of a new peak at 1550-1560 cm^{-1} for -N=CH- (imine) and disappearence of amino peak in the title compounds & specific absorption peaks for other groups like –NO_2, -Cl, -CH_3, -OCH_3

etc…. The NMR spectrum of the compounds no (MSR- 8d, 8i, 8k, 9j, 10b, 10c, 10j &10k) indicated the formation of new compounds due to disappearance of a sharp single peak at δ = 7.29-9.0 of –NH itself is sufficient to explain the formation of the new compounds.

The newly synthesized compound (MSR-8a) was also confirmed by Mass spectra. The spectra show molecular mass peak at 420 for MSR-8a. The possible fragmentation of the same compound was not found due to high stability.

CONCLUSION

Based upon the fact, the present investigation was planned and considerable interest has been shown in the synthesis of 2-amino-3-(benzyl carboxamido)-4,5-di substituted thiophenes (MSR-8, 9 & 10) by Gewald reaction. A new series of title compounds were synthesized from 2-amino-3-(benzyl carboxamido)-4,5-di substituted thiophenes (MSR-8, 9 & 10) by heating in a microwave oven with various substituted aromatic aldehydes in isopropyl alcohol with glacial acetic acid as a catalyst to yield MSR 8a-8k, MSR 9a-9k & MSR 10a-10k .

The new series of title compounds synthesized were confirmed preliminarily by M.P, TLC and spectral analysis (UV, IR) and then by NMR and Mass spectra.

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