# Microwave Assisted One Pot, One Step Synthesis of Substituted-2-Aminothiophenes through the Gewald Reaction & Study of its Antibacterial, Antifungal Activities

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***Abstract:*** **A Series of 5 novel substituted 2-aminothiophenes (3C, NR2, NR3, NR4, NR6) were synthesized under microwave accelerated synthetic method by a 3-component one pot Gewald reaction. Which gives the products in short time and the synthesized compounds were characterized by the spectroscopic method, physicochemical and analytical data. By using Agar diffusion method Antibacterial and Antifungal activities were tested.**

***Key words: Substituted 2-aminothiophenes, Microwave accelerated organic synthesis, Gewald reaction.***

## I. INTRODUCTION

Derivatives of Thiophenes having different uses in the field of Industrial and Medicinal Chemistry. Substituted thiophenes exhibit important applications in the Medicinal Chemistry, acts as building blocks in the Dye and other Industries. Amongst the various methods of synthesis reported for thiophenes, the Gewald reaction is an interesting one. It is an organic reaction involving the condensation of a ketone or an aldehyde with a α-cyano ester in the presence of elemental sulphur & base to give a polysubstituted 2 aminothiophenes[1-3].

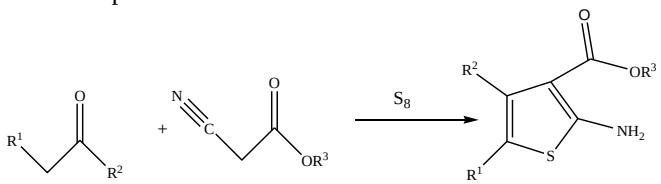



Figure 1: General example for Gewald reaction.

One of our research goal is focused on developing one pot, one step method using microwave oven by Gewald reaction method. This method has application in organic synthesis to improve yield and reduce time of reaction.

**Draw backs of Conventional method in Gewald reaction.**

i. Loss of catalyst during workup.
ii. Duration of reaction was more.
iii. Lengthy procedure for isolation of product.
iv. Use of organic solvents having high boiling points and toxic. Ex: 1,4-dioxane, DMF.
v. Low yield and use of dangerous bases. Ex: Morphine.

Since this method is simple, quick and environmental friendly for the synthesis of substituted-2-aminothiophene derivatives.

In the present study we report the synthesis & antimicrobial, antifungal activities of 5 novel substituted 2-aminothiophenes using microwave accelerated synthesis carried out in good yield, short reaction time or mild conditions

## II. EXPERIMENTAL SECTION

The IR spectra of synthesized compounds were characterized by FTIR & $^1$HNMR spectroscopy. The IR spectra of synthesized compounds were characterized by FTIR obtained on a Brucker infrared spectrometer and $^1$HNMR spectra from Jeol 400MHz spectrometer with Internal standard TMS.

**Procedure for the synthesis of (3C) Ethyl-5-amino-4-cyano-3-methyl thiophene-2-carboxylate under microwave oven irradiation method.**

A mixture of Ethyl Acetoacetate (0.1mole), Malononitrile (0.1mole), Elemental Sulphur (0.05mole) in Ethanol (15ml) were charged to a 250ml round bottom flask, kept in microwave oven maintain temperature 70$^0$C for 8 minutes. The reaction completion was monitored by TLC, filter the reaction mixture, wash with ethanol, to the filtrate check pH by using litmus paper then keep the filtrate in oven 5 minutes to remove excess ethanol, after attaining room temperature add ice cubes we get black coloured precipitate, workup using cold water, black amorphous precipitate was formed filter and washed with cold water, dried to afford corresponding substituted 2-aminothiophene, product weight 0.62 g.

**Procedure for synthesis of (NR2) Ethyl-2-amino-4-(3-formylpropyl)thiophene-3-carboxylate under microwave oven irradiation method.**

A mixture of Ethylcyanoacetate (0.1mole), Glutaraldehyde (0.1mole), elemental sulphur (0.05mole), DMF (0.1mole) in ethanol (15ml) were charged to a 250ml round bottom flask, kept in microwave oven maintain temperature 70$^0$C, Triethylamine (0.01mole) add two times with stirring for 1 hour, workup with methanol and water mixture,

dark brown colour shiny scalp like amorphous precipitate formed after dried, product weight 1.46g.

**Procedure for the synthesis of (NR3) Ethyl-2-amino-4-(2-Bromophenyl)thiophene-3-carboxylate.**

A mixture of Ethylcyanoacetate (0.1mole), 2-Bromoacetophenone (0.1mole), elemental sulphur (0.05mole) in ethanol (15ml) were charged to a 250ml round bottom flask, kept in microwave oven maintain temperature $120^0$C for 21 minutes, workup by dissolving reaction mixture in DCM and water then shake well separate organic layer by using separating funnel, to the organic layer add brine solution to remove water, kept the organic layer for dry in beaker, get dark brown colour amorphous precipitate, product weight 0.35 g.

**Procedure for the synthesis of (NR4) Ethyl-2-amino-4-(4-nitrophenyl) thiophene-3-carboxylate under microwave oven irradiation method.**

A mixture of Ethylcyanoacetate (0.1mole), 4-Nitroacetophenone (0.1mole), elemental sulphur (0.05mole) in ethanol (15ml) were charged to a 250ml round bottom flask, kept in microwave oven maintain temperature $120^0$C for 46 minutes. The reaction completion was monitored by TLC, after the completion of reaction workup by using ethanol : methanol = 2 : 1 ration, dark brown coloured amorphous precipitate settled at the bottom of beaker, filtered and kept it for dry. Product weight 0.72g.

**Procedure for the synthesis of (NR6) Ethyl-2-amino-4-(3,5-dichlorophenyl) thiophene-3- carboxylate under microwave oven irradiation method.**

A mixture of Ethylcyanoacetate (0.01mole), 3-Hydroxyacetophenone (0.01mole), elemental sulphur (0.05mole) in ethanol (15ml) were charged to a 250ml round bottom flask, kept in microwave oven maintain temperature $120^0$C for 48 minutes. The reaction completion was monitored by TLC, after the completion of reaction workup by using ethanol : methanol = 2 : 1 ration, dark brown coloured amorphous precipitate settled at the bottom of beaker, filtered and kept it for dry. Product weight 0.45g.

## III. RESULT AND DISCUSSION

This work consists of demonstrating the synthesis of substituted-2-aminothiophenes by using microwave oven. The reaction of different acetophenones with elemental sulphur either ethylcyanoacetate or malononitrile gave the substituted 2-aminothiophenes. The products were characterized by the spectral data of $^1$H NMR., FTIR, physicochemical & analytical data.

**IR and $^1$H NMR Spectral data for selected synthesized compounds**

**Compound 3C: Ethyl-5-amino-4-cyano-3-methylthiophene-2carboxylate**

Black precipitate, IR (KBr) ($cm^{-1}$) : 3300 (N-H), 2222 (C≡N), 1650 (C-H), 1310 (C=O), 1030 (C-S) ; $^1$H NMR (400MHz; $CDCl_3$), δ (ppm) : δ 8.34 (m, J=13.206Hz, 2H), δ 2.00 (d, J=5.008Hz, 3H), δ 3.35 (t, J=12.618Hz, 2H), δ 1.13 (s, J=5.126Hz, 3H).

**Compound NR3 : Ethyl-2-amino-4-(2-bromophenyl)thiophene-3-carboxylate**

Brown precipitate, , IR (KBr) ($cm^{-1}$) : 2900 (C-H), 1506 (C-C), 1650 (C-H), 1342 (N-H), 1250 (C-O), 1030 (C-S), 690 (C-Br) ; $^1$H NMR (400MHz; $CDCl_3$), δ (ppm) : δ 5.92 (t, J=4.029Hz, 2H), δ 3.84 (q, J=17.124Hz, 2H), δ 3.00 (s, J=3.452Hz, 1H).

**Compound NR4 : Ethyl-2-amino-4-(4-nitrophenyl)thiophene-3-carboxylate**

Brown precipitate, , IR (KBr) ($cm^{-1}$) : 2900 (C-H), 1674 (C=O), 1500 (N-O), 1342 (N-H), 1030 (C-S), 840 (C=C) ; $^1$H NMR (400MHz; $CDCl_3$), δ (ppm) : δ 3.00 (t, J=3.993Hz, 2H), δ 1.07 (s, J=2.687Hz, 1H), δ 2.12 (q, J=17.124Hz, 2H).\

**Compound NR6 : Ethyl-2-amino-4-(3,5-dichlorophenyl)thiophene-3-carboxylate**

Brown precipitate, IR (KBr) ($cm^{-1}$) : 3500 (N-H), 2222 (C≡N), 1650 (C-H), 1250 (C-N), 1030 (C-S), 790 (C-Cl), 665 (C=C) ; $^1$H NMR (400MHz; $CDCl_3$), δ (ppm) : δ 2.09 (t, J=3.99Hz, 2H), δ 3.00 (s, J=2.646Hz, 3H), δ 1.28 (q, J=17.12Hz, 2H), δ 1.25 (s, J=3.452Hz, 1H).

Table 1. Chemical data of substituted 2-aminothiophenes.

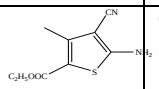
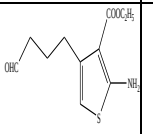
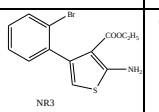
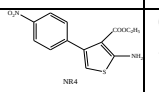
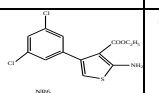
| S. N | Name of Compound | Molecular formula & Molecular mass | Structural formula | Yield | Colour |
|---|---|---|---|---|---|
| 1 | Ethyl-5-amino-4-cyano-3-methylthiophene-2-carboxylate. | $C_9H_{10}O_2N_2S$, 210.25g/mole |  | 0.62g | Black colour |
| 2 | Ethyl-2-amino-4-(3-formylpropyl)thiophene-3-carboxylate. | $C_{11}H_{15}SO_3N$, 241.31g/mole |  | 1.46g | Dark shiny brown colour |
| 3 | Ethyl-2-amino-4-(2-bromophenyl)thiophene-3-carboxylate. | $C_{13}H_{12}O_2NSBr$, 326.21g/mole |  | 0.35g | Brown colour |
| 4 | Ethyl-2-amino-4-(4-nitrophenyl)thiophene-3-carboxylate. | $C_{13}H_{12}N_2SO_4$, 292.31g/mole |  | 0.72g | Brown colour |
| 5 | Ethyl-2-amino-4-(3,5-dichlorophenyl)thiophene-3-carboxylate. | $C_{13}H_{11}Cl_2NSO_2$, 316.2g/mole |  | 0.45g | Brown colour |

Table 2. Analytical and Physicochemical data of the synthesized compounds.

| S. N | Compound | Molecular formula | Melting point ($^0$C) | Yield (%) | Analysis (calculated/found) (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | S |
| 1 | 3C | $C_9H_{10}N_2O_2S$ | 294-295 | 25 | 51.41/51.48 | 4.79/5.11 | 13.32/13.00 | 15.25/15.43 |
| 2 | NR2 | $C_{11}H_{15}NO_3S$ | 245-246 | 58 | 54.75/54.45 | 6.27/6.32 | 5.80/6.12 | 13.29/13.34 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3 | NR3 | $C_{13}H_{12}BrNO_2S$ | >300 | 45 | 47.86/47.59 | 3.71/4.10 | 4.29/4.33 | 9.83/9.78 |
| 4 | NR4 | $C_{13}H_{12}N_2O_4S$ | >300 | 12 | 53.42/53.40 | 4.14/4.21 | 9.58/9.31 | 10.97/10.34 |
| 5 | NR6 | $C_{13}H_{11}Cl_2NO_2S$ | >300 | 11 | 49.38/49.40 | 3.51/3.49 | 4.43/4.58 | 10.14/10.20 |

Table 3. Antibacterial activity of substituted 2-aminothiophenes.

| S.N | Organism: Bacillus cereus (Gram +ve), Control : 11mm (Ciprofoxacin) | | | |
|---|---|---|---|---|
| | Compound | Conc.1 (50µl) | Conc.2 (150µl) | Conc.3 (200µl) |
| 1 | 3C | 6mm | 9mm | 10mm |
| 2 | NR2 | 4mm | 6mm | 9mm |
| 3 | NR3 | 3mm | 5mm | 10mm |
| 4 | NR4 | 6mm | 10mm | 12mm |
| 5 | NR6 | 3mm | 8mm | 11mm |

Table 4. Antifungal activity of substituted 2-aminothiophenes.

| S.N | Organism: Candida albicans, Control : 20mm (Itraconazole) | | | |
|---|---|---|---|---|
| | Compound | Conc.1 (50µl) | Conc.2 (150µl) | Conc.3 (200µl) |
| 1 | 3C | 12mm | 14mm | 17mm |
| 2 | NR2 | 6mm | 10mm | 15mm |
| 3 | NR3 | - | 5mm | 7mm |
| 4 | NR4 | 8mm | 10mm | 17mm |
| 5 | NR6 | 6mm | 10mm | 20mm |

## IV. CONCLUSION

In this work we described an efficient and suitable modification to the Gewald reaction carried in microwave oven gives moderate to excellent yields and 3C and NR6 compounds shows significant Antifungal activity.

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