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ISSN: 2278-1862

Journal of Applicable Chemistry

2022, 11 (3): 351-355

(International Peer Reviewed Journal)

Microwave Assisted Synthesis of Substituted 2-aminothiophenes through the Gewald Reaction and Study of its Antibacterial, Antifungal Activities

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Accepted on 15th May, 2022

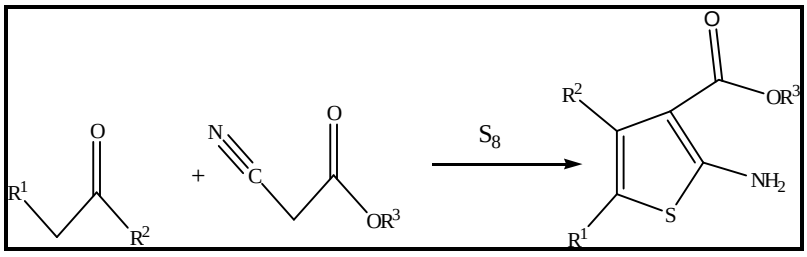
ABSTRACT

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. This provided the products in good yields after short reaction times under mild conditions. All the synthesized compounds were characterized by spectral data and evaluated for in-vitro antibacterial and antifungal activities. Antibacterial and antifungal activities were tested using the agar diffusion method.

Keywords: Gewald reaction, Substituted 2-aminothiophenes, Microwave assisted organic synthesis.

INTRODUCTION

Thiophene derivatives are a very important class of compounds with different uses, including industrial and medicinal chemistry. Further, substituted and fused thiophenes showed interesting applications in the field of medicinal chemistry. 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 and base to give a polysubstituted 2-aminothiophenes [**1-3**].



Polysubstituted 2-aminothiophenes have shown to be versatile synthetic building blocks in the dye and other industries. Many modifications to the Gewald reaction have been developed including the use of solid support, microwave irradiation, ionic liquids and with heterogeneous catalyst [**3**].

One of our research goals is focused on developing a consistent one step, one pot method for the Gewald reaction using microwave oven. Recently, use of microwave energy has become popular in organic synthesis in order to improve yields and reduce the reaction time.

Draw backs of Conventional method in Gewald reaction.

i. Use of hazardous bases such as Piperidine, Morphine.
ii. Use of toxic & high boiling organic solvents such as DMF, 1,4-dioxane.
iii. High reaction temperature.
iv. Long reaction duration.
v. Tedious procedure for product isolation.
vi. Low yields and difficult recovery complete loss of catalysts during workup.

Hence it is relevant to explore a simple, rapid and environmentally friendly method for the synthesis of polysubstituted 2-aminothiophene derivatives [**3**].

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

MATERIALS AND METHODS

The IR spectra of synthesized compounds were characterized by FTIR and ^{1}HNMR spectroscopy. All the synthesized compounds are known and identified from their spectroscopic data. FTIR spectra were obtained on a Brucker infrared spectrometer and ^{1}HNMR spectra were recorded in $CDCl_3$ on a Jeol 400MHz spectrometer with TMS as internal standard.

Typical 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 (0.1 mole), Malononitrile (0.1 mole), Elemental Sulphur (0.05 mole) in Ethanol (15 mL) were charged to a 250 mL round bottom flask, kept in microwave oven maintain temperature 70°C for 8 min. The progress of the reaction was monitered by TLC. After the completion of reaction, 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 (0.1 mole), Glutaraldehyde (0.1 mole), elemental sulphur (0.05 mole), DMF (0.1mole) in ethanol (15 mL) were charged to a 250 mL round bottom flask, kept in microwave oven maintain temperature 70°C, Triethylamine (0.01 mole) add two times with stirring for 1 h, 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 (0.1 mole), 2-Bromoacetophenone (0.1 mole), elemental sulphur (0.05 mole) in ethanol (15 mL) were charged to a 250 mL round bottom flask, kept in microwave oven maintain temperature 120°C for 21 min, 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.

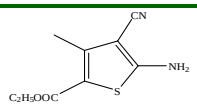
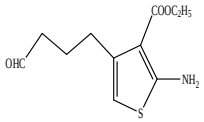
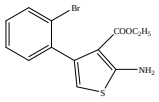
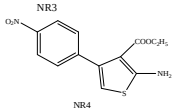
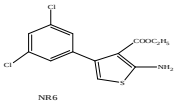
Procedure for the synthesis of (NR4) Ethyl-2-amino-4-(4-nitrophenyl) thiophene-3-carboxylate under microwave oven irradiation method: A mixture of Ethylcyanoacetate (0.1mole), 4-Nitroacetophenone (0.1 mole), elemental sulphur (0.05 mole) in ethanol (15 mL) were charged to a 250 mL round bottom flask, kept in microwave oven maintain temperature 120°C for 46 min. The progress of the reaction was monitered by TLC, after the completion of reaction workup by using ethanol : methanol = 2 : 1 ration, dark brown coloured amorphous precipitate setteled at the bottom of beaker, filtered and kept it for dry. Product weight is 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 (0.01 mole), 3-Hydroxyacetophenone (0.01 mole), elemental sulphur (0.05 mole) in ethanol (15 mL) were charged to a 250 mL round bottom flask, kept in microwave oven maintain temperature 120°C for 48 min. The progress of the reaction was monitered 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 is 0.45g.

RESULTS AND DISCUSSION

In the present work, we are demonstrating the synthesis of thiophene derivatives 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.

Table 1. Chemical data of substituted 2-aminothiophenes

S.No.	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^{-1}	 3C	0.62g	Black colour
2	Ethyl-2-amino-4-(3-formylpropyl)thiophene-3-carboxylate.	$C_{11}H_{15}SO_3N$, 241.31g mole^{-1}	 NR2	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^{-1}	 NR3	0.35g	Brown colour
4	Ethyl-2-amino-4-(4-nitrophenyl)thiophene-3-carboxylate.	$C_{13}H_{12}N_2SO_4$, 292.31g mole^{-1}	 NR4	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^{-1}	 NR6	0.45g	Brown colour

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); ^1H 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); ^1H 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); ^1H 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 2. Antibacterial activity of substituted 2-aminothiophenes

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

Table 3. Antifungal activity of substituted 2-aminothiophenes

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

APPLICATION

In the present study the reactions were carried out in one pot, one step and in short times i.e., in conventional method it takes few days or few hours to complete the reaction but in case of microwave oven within few minutes reaction completion takes place. This work showed that the substituted 2-aminothiophene derivatives nucleus can be used as a template for future development through structure modification and to design more potent and selective antibacterial, antifungal agents [1].

CONCLUSION

In conclusion, we have described in this paper an efficient & convenient modification to the Gewald reaction carried out in microwave oven. The reaction leads to substituted 2-aminothiophene derivatives in moderate to excellent yields and 3C and NR6 compounds shows significant Antifungal activity.

ACKNOWLEDGMENT

Dr. Ravishanakara Shastri P S and Smt.Rathnamma D, thanks for financial support and providing necessary facilities and thankful to Department of Chemistry, UBDT College of Engineering for support to carry out this research work.

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