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INNOVATIVE STRATEGIES FOR THE SYNTHESIS OF FIVE MEMBERED HETEROCYCLIC RINGS IN THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

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ABSTRACT
Many fields, including chemistry for medicinal use, agricultural chemicals, and materials science, are interested in the synthesis of novel five-membered heterocycles. In this study, we detail a flexible method for constructing such heterocyclic compounds, with -oxoketene dithioacetals serving as the central building blocks. Because of their adaptability as building blocks, a number of different synthetic routes can be facilitated by -oxoketene dithioacetals. The relevance of this synthetic method is demonstrated by its use in a wide range of fields. The availability of novel scaffolds for the creation of drugs aids medicinal chemistry, and the discovery of newly functionalized molecules aids agrochemical studies. The heterocyclic structures that have been synthesized are useful in the development of new electrical and optoelectronic materials. Dithioacetals provide a flexible and powerful method for synthesizing five-membered heterocycles from -oxoketene. The successful use of this strategy has the potential to transform industries by contributing to pharmaceuticals, agriculture, and innovative materials, in addition to enriching chemical variety.
Keywords: Five-membered heterocycles, beta-oxoketene dithioacetals, pharmaceuticals, agricultural compounds, and structural materials.

1. INTRODUCTION
Heterocycles, whether they be natural or synthetic, have been extensively researched as potential medicinal agents and have shown substantial biological activity. Half of the 20 millennium compounds discovered in the new millennium are heterocyclic. [1] The heterocyclic scaffold can be found in the structure of the therapeutic drugs now used to treat fatal diseases. Antibiotics, antivirals, and chemotherapeutic medicines have been demonstrated to be effective in treating life-threatening disorders such infectious infections. Heterocyclic moieties are present in the most cutting-edge antibiotics used against both gram-positive and gram-negative bacteria. The study of heterocyclic compounds is an integral part of organic chemistry. The medical and agricultural industries make extensive use of heterocycles because of their great variety of bioactive qualities. [2] Around 60% of all pharmacological ingredients are heterocyclic compounds, the most significant group of molecules in the pharma and agrochemical industries. As a result of their prevalence in many pharmaceuticals, both natural and synthetic, heterocycles containing nitrogen have gained considerable attention as a class of

organic compounds. Heterocycles with nitrogen are significant not just due to their abundance, but also because of the wide range of useful biological and chemical features they exhibit. Many vitamins, hormones, antibiotics, and alkaloids contain nitrogen heterocycles, and these compounds have also cemented their place in the pharmaceutical sector. [3]

Heterocycles with nitrogen (N), oxygen (O), or sulfur (S) heteroatoms are the most frequent type of heterocyclic compound. The simple heterocyclic compounds pyridine, pyrrole, furan, and thiophene are the most well-known. Each molecule of pyrrole, furan, and thiophene is made up of a ring with five carbon atoms and one each of nitrogen, oxygen, and sulphur. [4]

Heterocyclic compounds are extremely diverse and likely make up the biggest family of organic molecules. One of the most vital and numerous classes of naturally occurring substances is derived from the simple fused ring heterocycle purine. About 65 percent of organic chemistry literature is devoted to heterocyclic molecules, the focus of heterocyclic chemistry. Two of the complementary bases that make up DNA are the amino molecules adenine and guanine. Pollutant heterocyclic aromatic compounds are found everywhere from the soil to the air to the sediments to the water to the tissues of animals and plants. While some of these chemicals (like alkaloids) may have a natural history, their widespread occurrence in the environment is mostly attributable to human activities. [5]

One alternative approach to direct C-H functionalization is electrophilic substitution. In this technique, a C-H bond is attacked by an electrophilic reagent, leading to the creation of a new link. Aromatic C-H bonds are frequently functionalized using this strategy. The Friedel-Crafts reaction, for instance, is a common technique for the electrophilic functionalization of aromatic C-H bonds. [6]

Direct C-H functionalization can also be accomplished with the use of radical chemistry. Here, a radical species is utilized to directly attack the C-H bond, forming a new bond in the process. The functionalization of non-aromatic C-H bonds is an area where this approach shines. In the presence of a radical initiator, the Birch reduction is a common technique for functionalizing non-aromatic C-H bonds. [7]

Multi-step procedures are common for indirect C-H functionalization, in which a functional group is first installed onto an adjacent carbon atom and then the C-H bond is functionalized. This can be accomplished in a number of ways, such as by oxidation, reduction, or the exchange of functional groups. For indirect functionalization of C-H bonds in the presence of an alcohol functional group, the Swern oxidation is a typical approach.

Heterocyclic compounds with five atoms:

One C=C bond in benzene is thought to have been replaced by a hetero atom with a lone pair of electrons to create these heterocyclic molecules. [8] To further categorize this group of heterocyclic compounds, we can look at the number of hetero atoms contained in the cyclic ring.

Single-heteroatom heterocyclic compounds:

Furan, thiophene, and pyrrole are all members of this class of chemicals.

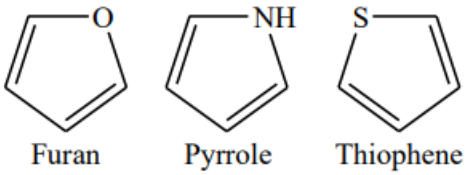

Fig. 1 Heterocyclic compounds with five members and one hetero atom.

Multiple hetero-atom heterocyclic compounds:
These hetero atoms could be identical or dissimilar. Heterocyclic compounds like pyrazole, imidazole, thiazole, oxazole, triazole, and tetrazole are all examples of this class of chemicals.

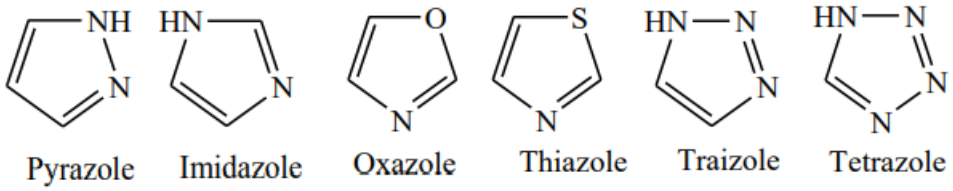

Fig 2 Heterocyclic compounds with two hetero atoms and five members.

Heterocyclic compounds with a ring of five atoms, where at least one of the atoms is a heteroatom like nitrogen, oxygen, or sulfur, are referred to as five-membered heterocyclic compounds.

Applications:

The five-membered heterocycles that were synthesized exhibit a wide variety of biological functions and practical uses. [9]

In the field of medicinal chemistry, many heterocyclic compounds are of interest as potential new drugs because of their pharmacological properties. These heterocycles can be used as foundations upon which novel therapeutic medicines can be built.

Crop protection and yield enhancement solutions can be found in the innovative agrochemicals that have been developed thanks to the synthesized heterocycles' varied reactivity and functionalization potential.

The field of materials science makes use of functionalized heterocycles in the creation of electrical and optoelectronic materials, polymers, and sensors.

2. MATERIALS AND METHODS

Heterocycle Synthesis Using a-Oxoketene Dithioacetals with Five Rings

Using -oxoketene dithioacetals as three-carbon 1,3-electrophilic synthons and reacting them with symmetrical and unsymmetrical bifunctional heteronucleophiles like hydrazine and hydroxyl amine, we have developed new general routes for the synthesis of biologically important five- and six-membered heterocycles. [10] By reacting -oxoketene dithioacetals with hydrazine hydrate or phenyl hydrazine, 5-(3-methylthio)pyrazoles were produced. Under various reaction conditions, the regioselective synthesis of 3- or 5- (methylthio)isoxazoles from

hydroxylamine and -oxoketene dithioacetals was studied. These -oxoketene dithioacetals were used in an O, S-acetal synthesis to produce 5-alkoxyisoxazoles. These reactive intermediates were also used in the regioselective synthesis of 1-aryl-3,4-disubstituted/annulated-5-(methylthio)pyrazoles, which was extremely effective. Similarly, 1,3-diaryl (1-aryl-3-alkyl) and 1,5-diaryl (1-aryl-5-alkyl)-5-(or 3)(N-cycloamino)pyrazoles were synthesized from -oxoketene dithioacetals and 1-aryl-3-alkyl pyrazoles, respectively, via N,S-acetals in a highly regiocontrolled manner.

Substituted or annulated 2-(methylthio)furans were obtained via the treatment of sulfonium ylide with -oxoketene dithioacetals, followed by an acidic treatment. In addition, the same team of scientists has described the intramolecular Aldol condensation of in situ produced sulfonium ylide intermediates in the Simmon's Smith reaction, leading to the synthesis of 3,4-substituted and annulated thiophenes. Darzen's glycidic ester condensation on -oxoketene dithioacetals has been shown to produce substituted and annulated furan-2-carboxylates in high yields. Additional research employed 1,4-addition to -oxoketene dithioacetals, followed by intramolecular cyclocondensation using ethyl glycinate, to produce pyrroles. In addition, 2,3,4-substituted pyrroles were obtained using 1,3-dipolar cycloaddition with carbanions generated from activated methylene isocyanides.

ONE-POT ROUTE TO SUBSTITUTED BENZO[B]THIOPHENES AND THEIR HETERO-FUSED ANALOGS VIA IODINE MEDIATED INTRAMOLECULAR ARYLTHIOLATION OF IN SITU GENERATED B-(HET)ARYL-B-CYANOENETHIOLATES

General Information.

All reagents were obtained from commercial sources and utilized as received. The solvents were dried in the conventional manner. [11] Thin layer chromatography on conventional TLC silica gel plates, visible under UV light, was used to track all reactions. Silica gel (mesh range of 100-200) was used in a column chromatograph. Using an FT-NMR spectrometer with $CDCl_3$ or DMSO-d6 as the solvent, nuclear magnetic resonance spectra were acquired. Using residual solvent protons as an internal standard, the chemical shifts for ^{1}H-NMR (7.26 for $CDCl_3$ and 2.50 for DMSO-d6) and 13C-NMR (77.16 for $CDCl_3$ and 39.52 for DMSO-d6) were reported in ppm. The values of the coupling constants, J, were given in Hertz (Hz). The various possible divisions are denoted by the letters s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), dd (double doublet), dt (doublet of triplet), td (triplet of doublet), ddd (doublet of doublet of doublet), m (multiplet), or br (broad). The FT-IR instrument and the HRMS on the Q-TOF spectrometer were used to record the infrared spectra of the pure samples in ATR (attenuated total reflectance) mode. The electrothermal capillary melting point equipment was used to record the melting points without any corrections.

General Synthesis of (E)-3-mercapto-2-(3-methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile:

With the addition of arylacetonitriles (0.09 ml, 1.0 mmol) and (het)aryl dithioester (198 mg,

1.0 mmol) at 0 °C and while stirring at room temperature for 1 h (monitored by TLC), a suspension of KOtBu (224 mg, 2.0 mmol) in 1,4-dioxane (5 ml) was prepared under N_2 atmosphere. The reaction mixture was diluted with acidified 5% aq. HCl and added to ice-cold water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 after being washed with EtOAc (3 x 25 mL), water (2 x 25 mL), and brine (1 x 25 mL). Under reduced pressure, the solvent was evaporated, leaving crude enethiol, which was then refined using column chromatography with a hexane/EtOAc mixture. [12]

Hetero-fused thiophenes and substituted 2-aryl/alkyl benzo[b]thiophenes synthesized in a single pot:

The equivalent (het)arylacetonitrile (1.0 mmol) in 1,4-dioxane (2mL) was slowly added to a KOtBu (2.0 mmol) in 1,4-dioxane (5 mL) suspension at 0 °C while stirring. The reaction mixture was stirred at 0 °C for 10 minutes before a solution of corresponding dithioester (1.0 mmol) in 1,4-dioxane (2 mL) was added. The mixture was then stirred for 1 hour at room temperature (under TLC monitoring). After adding iodine (506 mg, 2.0 mmol), the reaction mixture was heated to 90 °C while being continuously stirred (under TLC supervision). It was then extracted with EtOAc three times for a total of fifty milliliters, diluted with a 10% aq. $Na_2S_2O_3$ solution, washed with water three times for a total of twenty-five milliliters, rinsed with brine once for twenty-five milliliters, dried with anhydrous sodium sulfite, and concentrated under vacuum. Silica gel column chromatography with EtOAc/hexane as the eluent was used to refine the raw materials. [13]

3. RESULTS

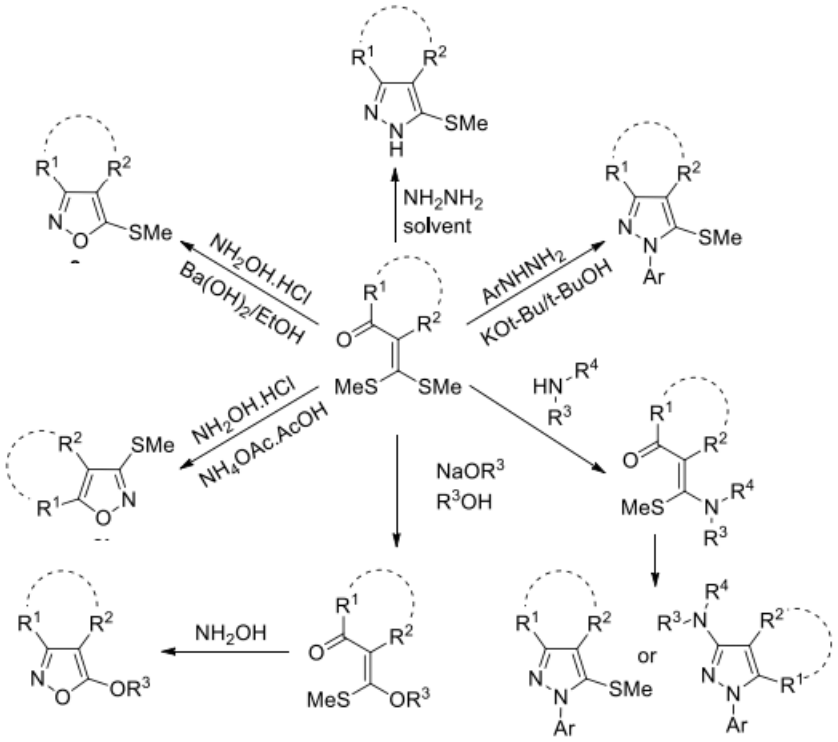

Fig 3 Five-membered heterocycles synthesized from beta-oxoketene dithioacetals

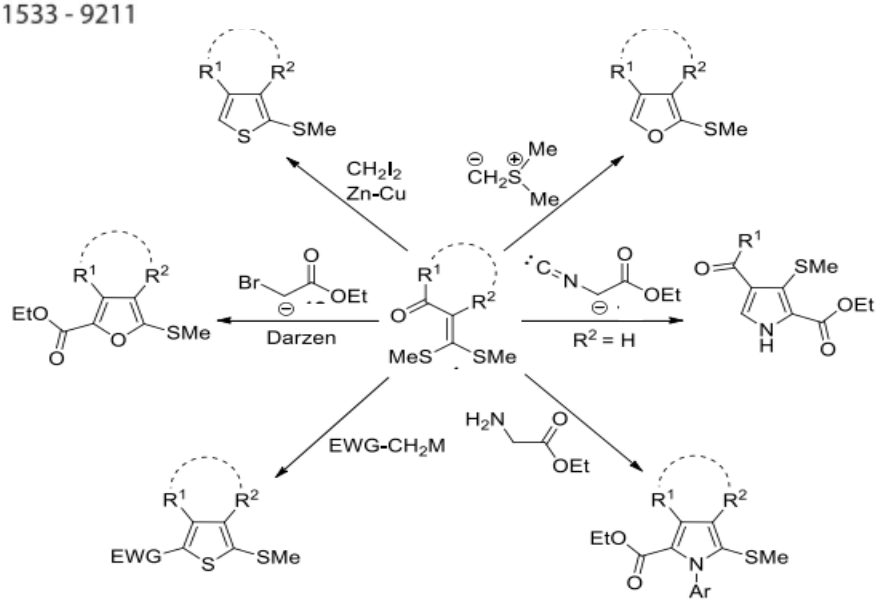

Fig 4 The synthesis of five-membered heterocycles from beta-oxoketene dithioacetals.

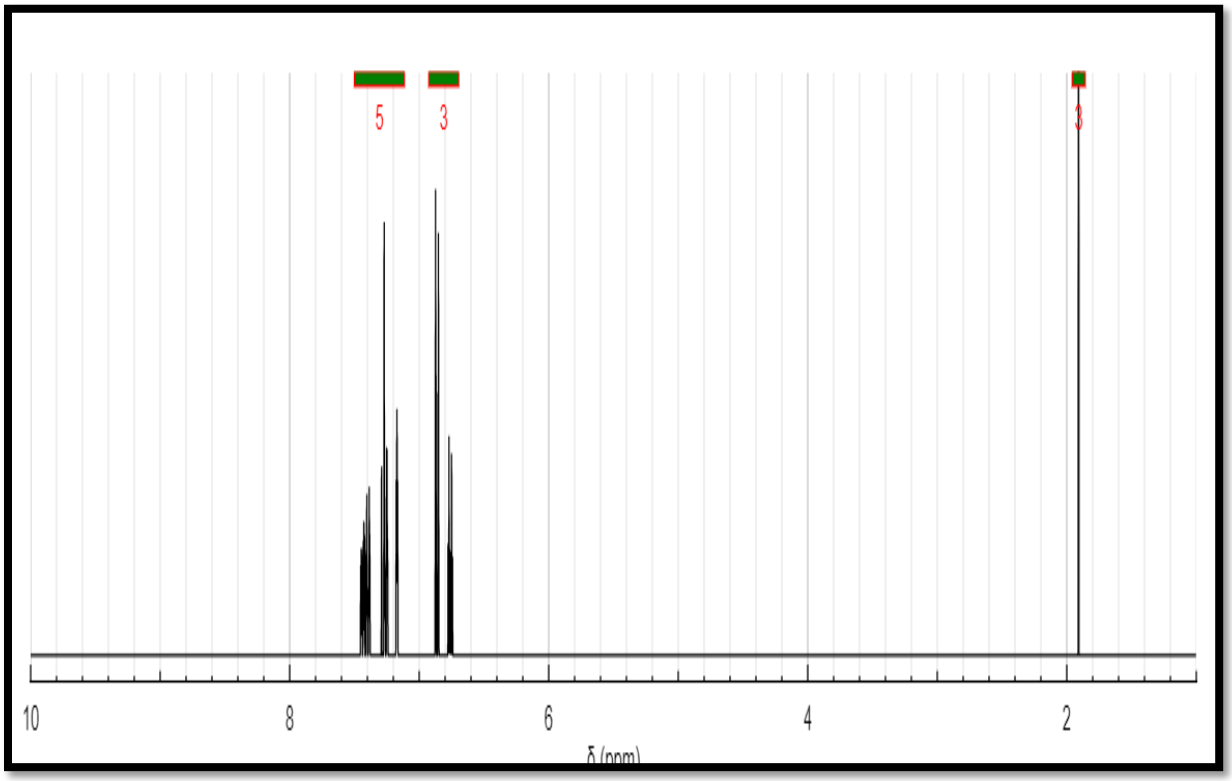

Fig 5 ^{1}H spectra of (E)-3-mercapto-2-(3-methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile

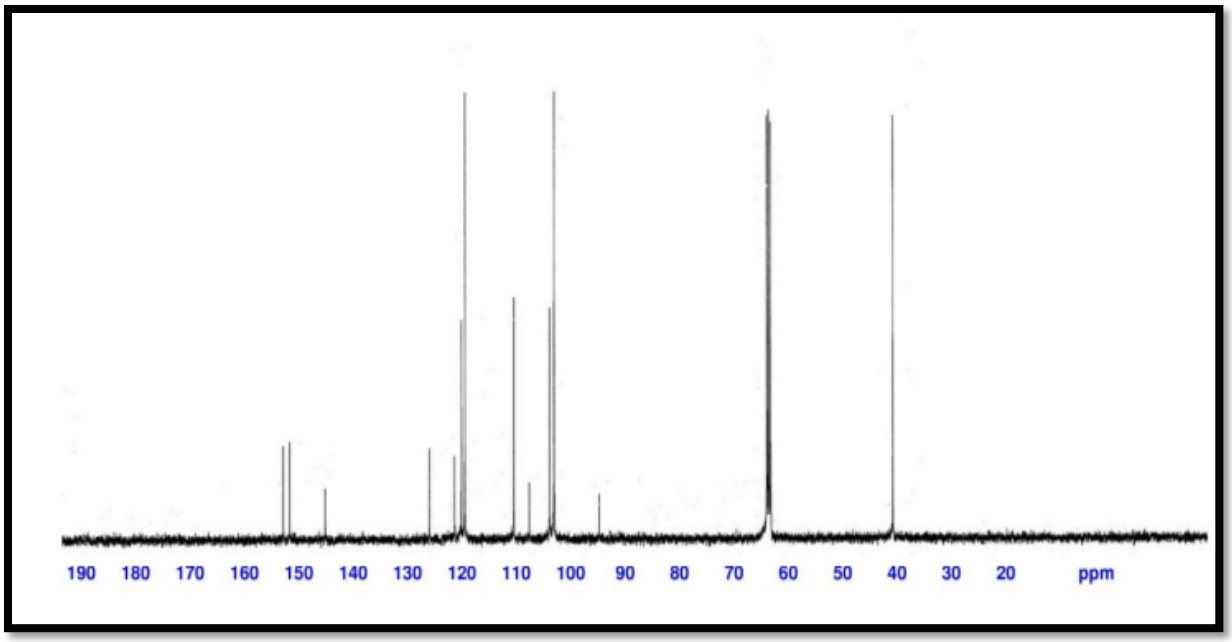

Fig 6 ^{13}C NMR spectra of (E)-3-mercapto-2-(3-methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile

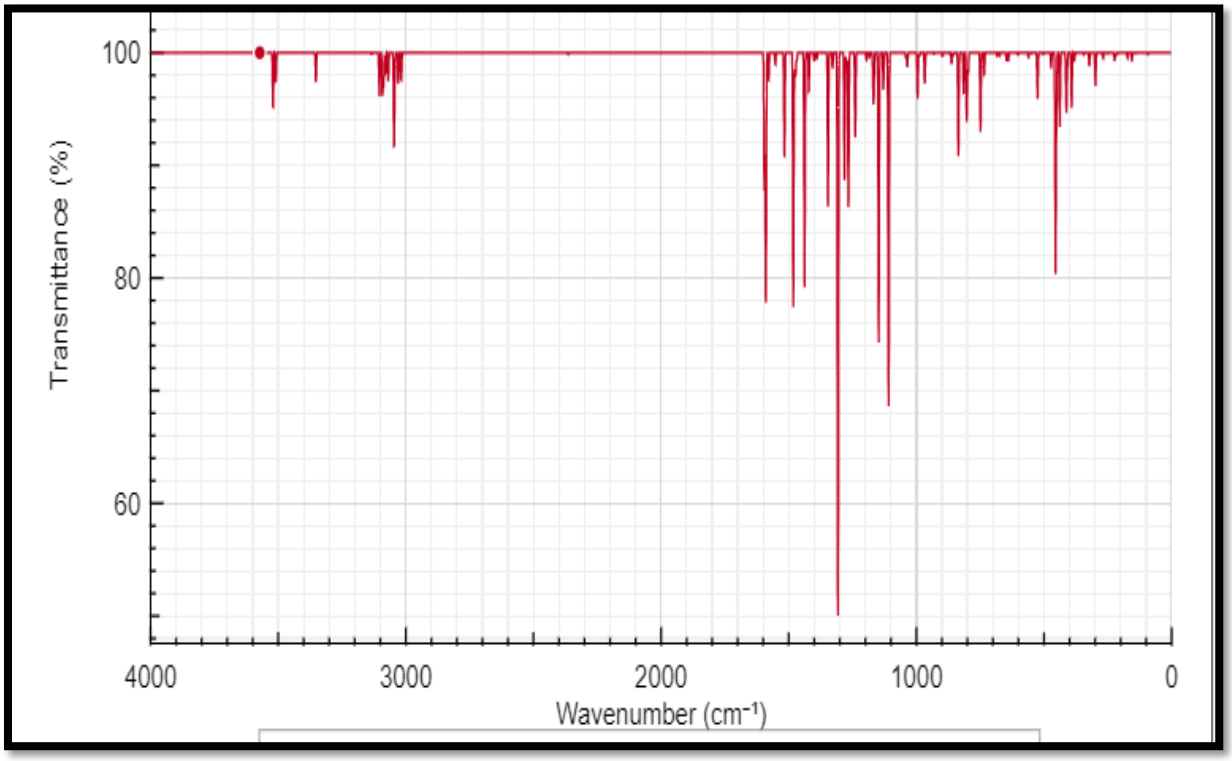

Fig 7 IR Spectra of (E)-3-mercapto-2-(3-methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile

4. DISCUSSIONS

With the two-step synthesis of benzo[b]thiophene from enethiols now improved, we set out to create a one-pot synthesis of the compound using iodine-mediated oxidative cyclization of the thioenolate anion, which was produced on-site from arylacetonitrile and dithioester in the presence of base. [14] Thus, to our delight, the reaction proceeded smoothly under these conditions, affording in comparable yield of 91% when was reacted with dithioester in the presence of potassium t-butoxide at room temperature in dioxane, followed by in situ addition of iodine (2 equiv.), and heating at 90 °C (monitored by TLC) for 8 hours. As a result, we synthesized a wide range of substituted benzo- and heterofused thiophenes using only these refined one-pot conditions. After perfecting the two-step, one-pot reaction for iodine-mediated intramolecular arylthiolation to produce benzo[b]thiophene, we investigated the method's generality and substituent scope and presented our findings graphically. To obtain the desired methoxy-substituted benzo[b]thiophenes, the electron-rich 3-methoxy- and 3,4-dimethoxyphenylacetonitrile experienced a simple condensation-intramolecular arylthiolation with different dithioesters in identical one-pot reaction conditions. [15] Good yields of the matching 6-fluoro-substituted benzo[b]thiophene were likewise produced from 4-fluorophenylacetonitrile. 5-Fluoro- and 5-Cyano-benzo[b]thiophenes were not produced in any appreciable amount from 3-fluoro- or 3-cyano-phenylacetonitriles with electron-withdrawing groups para to the site of cyclization. Using the same 2-naphthylacetonitrile and (hetero)aryl dithioesters, the corresponding 2,3-substituted naphtho[b]thiophenes were produced in high yields.

5. CONCLUSIONS

An adaptable and novel approach to get access to a wide range of structurally complex chemicals is the synthesis of five-membered heterocycles from -oxoketene dithioacetals. These approaches give fast access to heterocyclic frameworks of important relevance in medicinal chemistry, agrochemicals, and materials science via a variety of synthetic paths, including Pictet-Spengler events, annulation reactions, and cycloaddition processes. A potent strategy for the synthesis of structurally varied and physiologically relevant chemicals is the use of -oxoketene dithioacetals as precursors for the synthesis of five-membered heterocycles. This approach not only helps to increase our understanding of chemistry, but also has the potential to revolutionize the disciplines of medicine, agriculture, and materials science. The impact of these heterocyclic compounds on numerous industries is set to be revolutionary as we continue to investigate their many potential uses.

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