International Journal of Advance and Applied Research
www.ijaar.co.in
ISSN – 2347-7075 Impact Factor – 8.141
Peer Reviewed Bi-Monthly
Vol. 12 No.2 Nov-Dec 2024

An efficient and green one-Pot Synthesis of 8-(3-Bromo-4,5-Dimethoxyphenyl)-6-(Nitrophenyl)-4-Imino-2-(Methylsulfanyl)-4H-Pyrido [1,2-a] Pyrimidine-3,9-Dicarbonitrile

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DOI- 10.5281/zenodo.14407876

Abstract:
A mixture of 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-6-(4-nitrophenyl)pyridine-3-carbonitrile and bis(methylthio)methylene malononitrile (BMMM) was combined with banana peel powder (1gm) in DMF as the solvent and refluxed for approximately 4-6 hours to obtain the pyrido-pyrimidine nucleus (yield: 77%). The structures of the synthesized compounds were confirmed through IR, ^{1}H NMR, and mass spectral analyses.

Keywords: Bis methyl thio methylene malononitrile, banana peel powder, DMF.

Introduction:

Heterocyclic compounds containing nitrogen, oxygen, and sulfur exhibit significant pharmacological activity. Compounds such as pyridine, pyrimidine, and triazine demonstrate noteworthy pharmacological properties, with some fused heterocyclic compounds containing pyridine showing remarkable antitubercular activity[1]. Additionally, fused heterocyclic compounds featuring pyrido-pyrimidine and its derivatives display enhanced antibacterial activity against both Gram-positive and Gram-negative bacteria[2]. Researchers have long been interested in the chemistry of these heterocyclic compounds and their derivatives due to their promising biological activities[3].

A.B.A. El-Gazzar et al.[4] reported a one-step synthesis of pyrido[2,3-d]pyrimidine-2-thiones through the reaction of an appropriate aldehyde, malononitrile, and 6-amino thiouracil. They also described an alternative method using arylidine malononitrile with 6-amino thiouracil to obtain the same compound. Sangeeta Bhargava et al. [5]synthesized novel pyrido-pyrimidine derivatives and investigated their microbial properties. They prepared a series of these derivatives via the condensation of 2-amino-3-cyano-4,6-disubstituted pyridine with various reagents, such as formamide, urea, and thiourea. All synthesized compounds were reported to exhibit antibacterial and antifungal activity. Additionally, heterocyclic compounds containing cyanopyridine and cyanopyrane derivatives demonstrate versatile biological activities, including antimicrobial,[6] antitubercular, [7] anti-inflammatory, [8] antitumor, [9]antiviral, [10] D.H. Vyas et al. [1] reported the synthesis and antimicrobial activity of several novel cyanopyridine and cyanopyrane compounds. They prepared cyanopyridines by reacting substituted chalcones with malononitrile in the presence of ammonium acetate, yielding 2-amino-3-cyanopyridine. Based on this literature review, we believe it is worthwhile to synthesize bicyclic heterocyclic compounds containing a pyrido-pyrimidine nucleus and its 2-substituted derivatives.

Recently, there has been an increasing demand for heterogeneous catalysts in chemical transformations due to their ease of handling, operational simplicity, high selectivity, and reusability. To address the drawbacks of homogeneous catalysts, such as difficulties in separation and regeneration, it is essential to focus on the use of inexpensive and readily available heterogeneous catalysts.[11] Natural waste, such as Musa sapientum (banana) peel, is an easily accessible heterogeneous catalyst that can be utilized for the synthesis of benzofuran-2-yl phenyl methanone derivatives. The peel, which constitutes a significant portion of fruit and vegetable waste, accounts for approximately 40% of banana production. Composition analysis of banana peel reveals a high concentration of various minerals.[12] On average, a banana contains about 460 mg of potassium, with the peel containing around 40% of that amount, or approximately 180 mg of potassium per peel. This potassium is present in the form of potassium ions, which can be quantified by the weight of potassium carbonate.[13] We present an eco-friendly protocol for synthesizing 8-(3-Bromo-4,5-Dimethoxyphenyl)-6-(Nitrophenyl)-4-Imino-2-(Methylsulfanyl)-4H-Pyrido[1,2-a]Pyrimidine-3,9-dicarbonitrile using 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-6-(4-nitro -phenyl) pyridine -3-carbonitrile and bis(methylthio)methylene

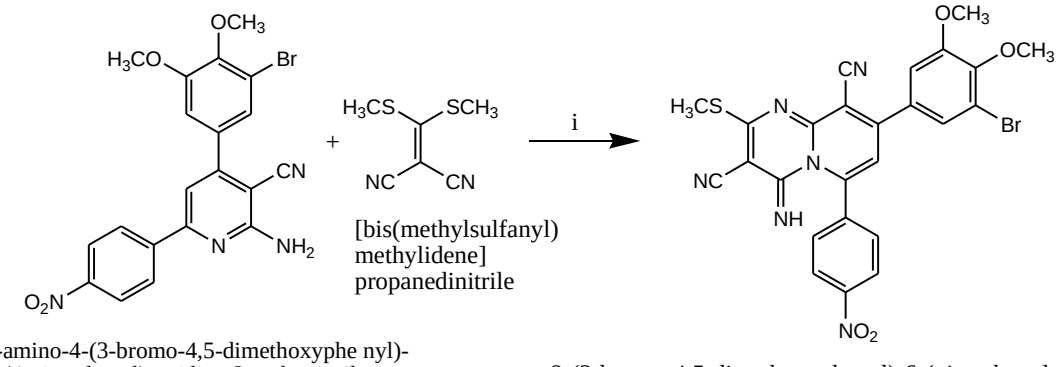
malononitrile (BMMM). This reaction is conducted in the presence of banana peel powder, a natural and biodegradable catalyst, in acetone at room temperature **(Scheme 1)**.

Experimental:

General details: Melting points were determined in open capillary tube and were uncorrected. TLC was carried out with Merck silica gel 60-F-254 aluminum plates. IR spectra were obtained using the potassium bromide pellet technique. ^{1}H NMR spectra were recorded on an AVANCE 300 MHz spectrometer in DMSO, with TMS as the internal standard. Mass spectra were acquired using an FT VG-7070 H mass spectrometer employing the EI technique at 70 eV.

General procedure for the synthesis of Synthesis of 8-(3-bromo-4,5dimethoxy phenyl)-6-(nitrophenyl-4-Imino -2 (methylsulfanyl)-4H-pyrido[1,2-a] pyrimidine-3,9dicarbonitrile:

In this study, we report the synthesis of 8-(3-bromo-4,5-dimethoxyphenyl)-6-(nitrophenyl)-4-imino-2-(methylsulfanyl)-4H-pyrido[1,2-a]pyrimidine-3,9-dicarbonitrile. This was achieved by refluxing a mixture of 1 g (0.0017 mmol) of 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-6-(4-nitrophenyl)pyridine-3-carbonitrile with 0.29 g (0.0017 mmol) of [bis(methylsulfanyl)methylidene]propane dinitrile in the presence of banana peel powder (1gm) and DMF as the solvent for approximately 4-6 hours. The purity of the compound was assessed using TLC, where it appeared as a single spot in benzene. The structure of the compound was confirmed through elemental analysis and spectral data.



2-amino-4-(3-bromo-4,5-dimethoxyphe nyl)-6-(4-nitrophenyl)pyridine-3-carboni trile

8-(3-bromo-4,5-dimethoxyphenyl)-6-(nitrophenyl-4imino-2-(methylsulfanyl)-4 H -pyrido[1,2a] pyrimidine3,9-dicarbonitrile

Scheme 1: (i) -*Reaction conditions:* DMF, Banana peel powder, Reflux 4-6 hrs

Spectral data:

8-(3-bromo-4,5-dimethoxyphenyl)-6-(nitrophenyl-4imino-2-(methylsulfanyl)-4 H -pyrido[1,2a] pyrimidine3,9-dicarbonitrile: Yield: 77 %, **M.P** : 261^{0}C, **IR**:(KBr/cm-1) : 3444 (=NH), 3382 (-NH), 1622 (C=N), 1518 & 1340 (-NO2, asymmetric and symmetric stretching), **EI-MS**: (m/z:RA%) : 577 (M+1), **Elemental analysis** : $C_{25}H_{17}BrN_6O_4S$ Calculated: (%) C 52.00, H 2.97, N 14.55, O 11.08, S 5.55 Found (%) : C 51.90, H 2.95, N 14.50, O 11.03, S 5.50.

Result and discussion: A literature survey reveals that significant work has been published on pyrimido-pyrimidine heterocycles. Compounds containing pyrimido-pyridine derivatives have demonstrated notable anti-inflammatory, antiallergic, antitumor, and antihypertensive activities. In the present study, we report the synthesis of pyrido-pyrimidine and its 2-anilino derivatives.

The pyrido-pyrimidine nucleus, specifically 8-(3-bromo-4,5-dimethoxyphenyl)-6-nitrophenyl-4-imino-2-(methylsulfanyl)-4H-pyrido[1,2-a]pyrimidine-3,9-dicarbonitrile, was synthesized through the reaction of 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-6-(4-nitrophenyl)pyridine-3-carbonitrile with bis(methylthio)methylene malononitrile in the presence of banana peel powder in DMF. The compound features a methylthio group at the 2-position, which serves as an excellent leaving group. This group can be replaced by selected nucleophiles, such as substituted aniline groups. Thus, the reaction of pyrido-pyrimidine with these selected nucleophiles in the presence of banana peel powder in DMF yields the corresponding 2-anilino derivatives of the pyrido-pyrimidine nucleus.

Conclusion:

In conclusion, we have developed a straightforward one-pot synthesis for the target compounds using readily available starting materials. This method involves a series of reaction equilibria that ultimately lead to an irreversible step, resulting in the desired product. Compared to multi-step syntheses, one-pot reactions require minimal effort and often achieve quantitative yields.

Acknowledgement:

The authors are grateful to the Principal, Lal Bahadur Shastri Mahavidyalaya, Dharmabad for providing the laboratory facilities.

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