

Synthesis and Antioxidant activities of pyrido[1,2-*a*] pyrimidine derivatives

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Dates Summation: 15/08/2026 Revised: 23/08/2026 Accepted: 27/08/2026 Published: 30/08/2026	Abstract The bis (methylthio) methylene malononitrile (1) on treatment with 2-amino-5-bromo pyridine (2) in <i>N,N</i>-dimethyl formamide (DMF) and anhydrous potassium carbonate, gives 7-bromo 3-cyano-4-imino-2-(methylthio)-4<i>H</i>-pyrido[1,2-<i>a</i>]pyrimidine (3). This pyrimidine derivative then further reacted with nucleophiles different substituted aromatic amines and Phenols. Keywords: DMF, Pyrido pyrimidine, Bis (methylthio) methylene malononitrile
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1. INTRODUCTION:

Pyrido [1,2-*a*] pyrimidine derivatives exhibit wide range of pharmacological activities¹. They exhibit antibacterial², antitumor³, anti-HIV⁴ activities and are extensively valuable in the treatment of neurodegenerative disorders with Parkinson's disease⁵, antidepressant⁶, antiasthmatic⁷. These observations have sparked great interest to explore synthesis of new potent

heterocycles containing imino pyrimidine ring fused with another active nucleus such as pyridine through nitrogen atom, which is an important pharmacophore and would give remarkable pharmacological activities.

Shakir M. Alwan et al⁸ described synthesis of 2*H*-pyrido[1,2-*a*] pyrimidine -2,4-(3*H*) dione by treating 2-amino pyridine and diethyl malonate. Thus, literature survey indicates that pyrido pyrimidines derivatives exhibit a wide spectrum of biological activities, which has motivated us to design and synthesizenovel derivatives of this important heterocycles.

2. MATERIALS AND METHODS

The melting points of the newly synthesized compounds were determined using open capillary tubes. FTIR spectroscopy was employed to record the infrared spectra of the synthesized compounds. Bruker Avance 300 MHz spectrometer was used for¹H-NMR. Mass spectra of the compounds were obtained using an FT-VG-7070 mass spectrometer equipped with an ESI technique.

Experimental Section:

(1) Synthesis of 7-bromo -3-cyano -4-imino -2-(methylthio) -4*H*-pyrido [1,2-*a*] pyrimidine (3).

To a solution of 2-amino-5-bromo pyridine (**1**) (1.73 g, 0.01 mol) in 20 ml of DMF, bis (methylthio)methylene malanonitrile (**2**) (1.7 g, 0.01 mol) and anhydrous K₂CO₃ (10mg) was added and allowed to reflux for 5 hours. The process of reaction was monitored by TLC. After completion of reaction, Ice cold water is used for separation of product. The separated solid product was filtered washed with water and recrystallized using ethanol- DMF mixture to give (**3**) as brown solid.

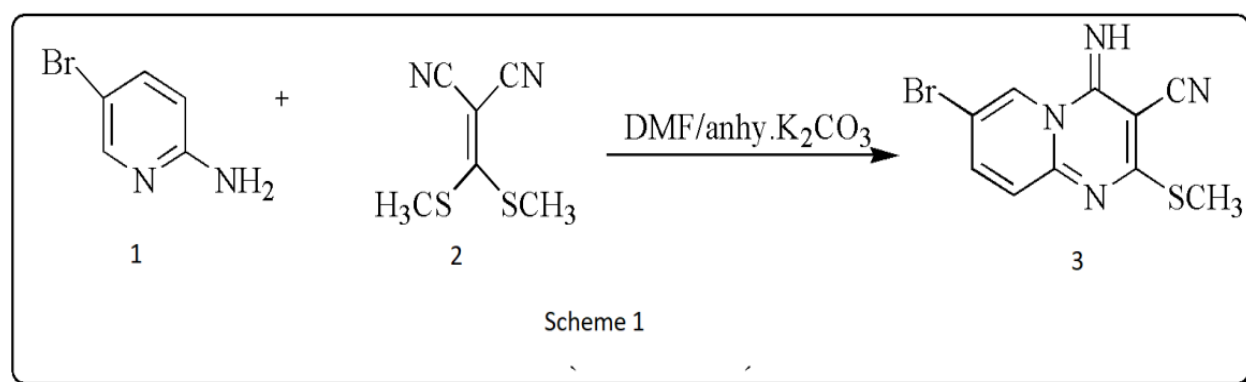
(2) Synthesis of 7-bromo -3-cyano -4-imino -2-(substituted) -4*H*-pyrido [1,2-*a*] pyrimidine derivatives (4 a-e), (5 a-e).

A mixture of **3** (0.295 g, 0.001 mol) and independently various aromatic amines, substituted phenols, (0.001 mol) in 15 ml of DMF and anhydrous K₂CO₃ (10 mg) was reflux for 4-5 hours, the process of reaction was monitored by TLC. Ice cold water is used for separation of product. The separated solid product was filtered, washed with water and recrystallized usingethanol- DMF mixture to afford (**4 a-e**), (**5a-e**), derivatives respectively.

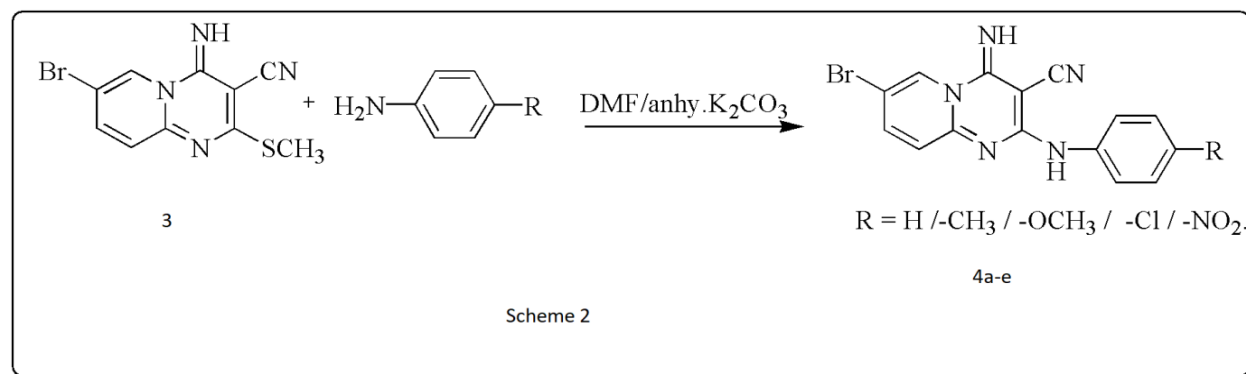
3. RESULT AND DISCUSSION:

A literature survey reveals that not a single reference is available on 7-bromo-3-cyano-4-imino-2-(methylthio)-4*H*-pyrido [1,2-*a*] pyrimidine (**3**) and its 2-substituted derivatives. Therefore, in this present investigation, we report synthesis of 7-bromo-3-cyano-4-imino-2-(methylthio)-4*H*-pyrido [1,2-*a*] pyrimidine (**3**) and preparation of its 2- substituted derivatives. The compound (**3**) was prepared by condensation of 2-amino-5-bromo-pyridine (**1**) with bis (methylthio) methylene malanonitrile (**2**) in presence of DMF and anhydrous K_2CO_3 as catalyst.

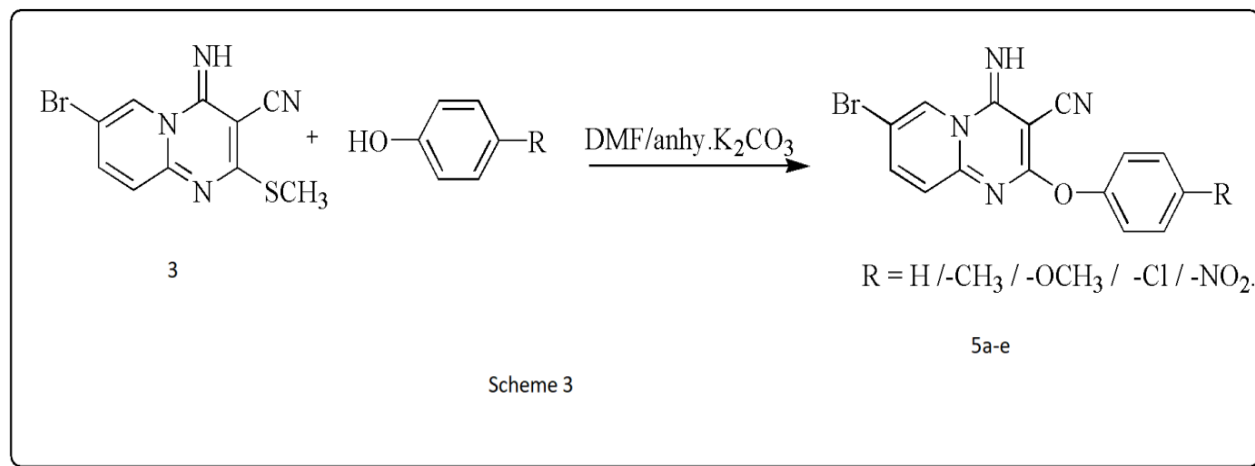
As, the parent compound (**3**) contains active methylthio group at 2-position which is easily replaceable, hence its susceptibility towards substitution with different reagents like aryl amines, substituted phenols.



Amino derivatives of (**3**) are prepared by reacting it independently with aniline, p-toulidine, p- anisidine, p-chloro aniline and p- nitro aniline in DMF and anhydrous K_2CO_3 as a catalyst to yield compounds (**4a-e**) (Scheme 2). All the compounds show strong absorption bands in the range of $2204-2205\text{ cm}^{-1}$ which can be assigned to $-CN$ stretch and in the range $3217-3346\text{ cm}^{-1}$ are due to $-NH$, $=NH$ stretch. Mass spectra showed the molecular ion peak which corresponds to their respective molecular weight. ^1H NMR spectra showed absence of singlet at $\delta 2.63$ which indicates that substitution of active methylthio group takes place.



Phenoxy derivatives of compound (**3**) are prepared by reacting it independently with phenol, p-methyl phenol, p-methoxy phenol, p-chloro phenol, and p-nitro phenol in DMF and anhydrous K_2CO_3 to yield compound (**5 a-e**) (**Scheme 3**). All these compounds show $-CN$ and $=NH$ strong absorption bands at inbetween $2203-2206\text{ cm}^{-1}$ and $3230-3360\text{ cm}^{-1}$ respectively



Antioxidant Activity:

Antioxidants are substances that can inhibit or delay the oxidation of other molecules. Oxidation involves the transfer of electrons from one substance to an oxidizing agent and may lead to the formation of free radicals. These free radicals can initiate chain reactions that cause cellular damage. Antioxidants help prevent such damage by scavenging free-radical intermediates and undergoing oxidation themselves, thereby interrupting the chain reactions.

Reactive oxygen species (ROS) and free radicals can cause oxidative damage to cellular components, including lipids, proteins, cell membranes, and DNA. Such oxidative stress has been associated with aging and the development of various degenerative disorders, including cancer, atherosclerosis, and cataracts. Therefore, the inhibition of oxidative damage through antioxidant or free-radical-scavenging agents may help reduce the risk of these diseases. In the present study, the antioxidant potential of selected synthesized compounds was evaluated using established free-radical-scavenging assays.

DPPH Radical Scavenging Assay:

The DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity of the synthesized compounds was evaluated according to the reported method of Kato et al. (1998), with slight modifications. Briefly, 1 mL of the test compound solution was mixed with an equal volume of 0.1 mM DPPH solution prepared in ethanol. The reaction mixture was incubated at room temperature for 20 min. The reduction in DPPH radicals was determined by measuring the

absorbance at 517 nm using a spectrophotometer. Ascorbic acid was used as the reference standard.

Hydroxyl Radical Scavenging Assay:

The hydroxyl radical scavenging activity of the synthesized compounds was determined using the previously reported method of Yu et al. (2004), with minor modifications. The reaction mixture consisted of 60 μ L of 1 mM FeCl₃, 90 μ L of 1 mM 1,10-phenanthroline, 2.4 mL of 0.2 M phosphate buffer (pH 7.8), 150 μ L of 0.17 M H₂O₂, and 1.5 mL of the test compound at different concentrations. The reaction mixture was incubated at room temperature for 5 min, after which the absorbance was measured at 560 nm using a spectrophotometer. α -Tocopherol was employed as the reference standard.

Antioxidant activity of newly synthesized compounds:

Table: Antioxidant potential of 7-Bromo-3-cyano-4-imino-2-methylthio-4H pyrido [1,2-a] pyrimidine and its 2-substituted derivatives.

Sr. No	Compound	DPPH radical scavenging activity (%)	OH, radical scavenging activity (%)
1	3	55 $\pm$ 0.34	37 $\pm$ 0.72
2	4a	41 $\pm$ 0.29	11 $\pm$ 0.82
3	4c	35 $\pm$ 0.25	51 $\pm$ 0.38
4	4e	21 $\pm$ 0.89	23 $\pm$ 0.72
5	5d	41 $\pm$ 0.12	66$\pm$0.52
6	5e	23 $\pm$ 0.17	46 $\pm$ 0.65
7	5b	61 $\pm$ 0.28	51 $\pm$ 0.42
8	Ascorbic Acid	86 $\pm$ 0.88	NA
9	α- Tocopherol	NA	81$\pm$0.19

5. CONCLUSION

Synthesis of 7-bromo -3-cyano -4-imino -2-(substituted) -4H-pyrido [1,2-a] pyrimidine (4 a-e), (5 a-e). has been presented. Among these synthesized compounds (5d) showed remarkable antioxidant activity. The result of the present work demonstrate that pyrido pyrimidines are potent

antioxidant and it will attract researchers to design new potent pharmacological pyrido pyrimidines.

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