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Synthesis of Different Derivatives of Pyrido[1,2-*a*] Pyrimidine and Evaluation of their Antioxidant Activities

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Abstract: ***The reaction of 2-amino-5-bromopyridine (1) with ethyl 2-cyano-3,3-bis(methylthio)acrylate (2) in N, N-dimethylformamide (DMF) in the presence of anhydrous potassium carbonate afforded 7-bromo-3-cyano-4-oxo-2-(methylthio)-4H-pyrido[1,2-a] pyrimidine (3). The synthesized pyrido[1,2-a] pyrimidine derivative was subsequently subjected to nucleophilic substitution reactions with various substituted aromatic amines and phenols to obtain a series of 7-bromo-3-cyano-4-oxo-2-(substituted)-4H-pyrido[1,2-a]pyrimidine derivatives.***

Keywords: Pyrido[1,2-a] pyrimidine, ethyl 2-cyano-3,3-bis(methylthio)acrylate, N, N-dimethylformamide, nucleophilic substitution

1. Introduction

Pyrido [1, 2-a] pyrimidine derivatives constitute an important class of fused heterocyclic compounds and have been reported to possess a broad spectrum of pharmacological activities. These compounds exhibit antibacterial, antitumor, and anti-HIV properties and have also attracted considerable attention for their potential applications in the treatment of neurodegenerative disorders, including Parkinson's disease, as well as for antidepressant and antiasthmatic activities[7]

The significant biological properties associated with pyrido[1,2-a] pyrimidines have stimulated considerable interest in the design and synthesis of novel heterocyclic systems incorporating an pyrimidine moiety fused with another biologically relevant nucleus, such as pyridine, through a nitrogen atom. Such fused heterocyclic frameworks may serve as important pharmacophores and could potentially exhibit enhanced pharmacological properties.

Shakir M. Alwan et al.[8] reported the synthesis of 2H-pyrido[1,2-a] pyrimidine-2,4(3H)-dione by treating 2-aminopyridine with diethyl malonate. A survey of the literature indicates that pyrido[1,2-a] pyrimidine derivatives possess a wide range of biological activities. These findings prompted us to design and synthesize novel derivatives based on this biologically significant heterocyclic scaffold.

2. Materials and Methods

Melting points were determined using open-capillary tubes and were uncorrected. The progress of all reactions was monitored by thin-layer chromatography (TLC) using 0.2 mm silica gel-C plates, with iodine vapors employed for visualization. Infrared (IR) spectra were recorded in Nujol or as potassium bromide (KBr) pellets using an infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance spectrophotometer operating at 400 MHz. Mass spectra were obtained using an FT-VC-7070 H mass spectrometer by the electron ionization (EI) technique at 70 eV. All reactions were carried out under ambient atmospheric conditions.

3. Experimental Section

(1) Synthesis of 7-bromo -3-cyano -4-oxo -2-(methylthio) -4*H*-pyrido [1,2-*a*] pyrimidine (3).
A solution of 2-amino-5-bromopyridine (1) (1.73 g, 0.01 mol) in DMF (20 mL) was treated with ethyl 2-cyano-3,3-bis(methylthio)acrylate (2) (1.7 g, 0.01 mol) and anhydrous K_2CO_3 (10 mg). The reaction mixture was refluxed for 5 h, and the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was treated with ice-cold water to facilitate separation of the product. The resulting solid was filtered, washed thoroughly with water, and recrystallized from an ethanol–DMF mixture to afford compound (3) as a brown solid.

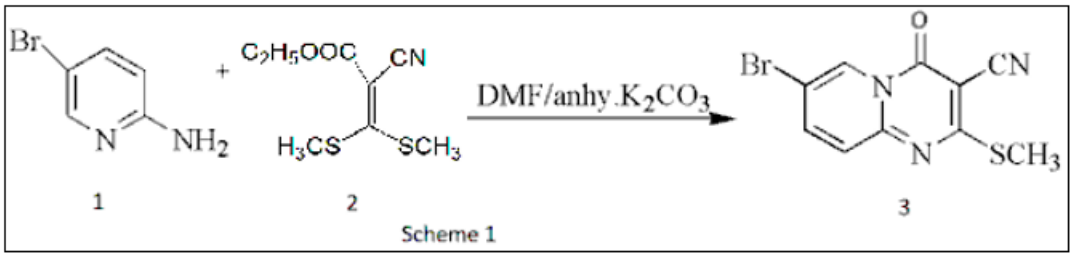
(2) Synthesis of 7-bromo -3-cyano -4-oxo -2-(substituted) -4*H*-pyrido [1,2-*a*] pyrimidine derivatives (4 a-e), (5 a-e).
A mixture of compound **(3)** (0.001 mol) and the corresponding aromatic amine or substituted phenol (0.001 mol) was dissolved in DMF (15 mL). Anhydrous K_2CO_3 (10 mg) was then added, and the reaction mixture was refluxed for 4–5 h. The progress of each reaction was monitored by TLC. After completion, the reaction mixture was treated with ice-cold water to precipitate the product. The separated solid was filtered, washed with water, and recrystallized from an ethanol–DMF mixture to afford the corresponding derivatives **(4a–e)** and **(5a–e)**, respectively.

4. Result and Discussion

The present investigation was undertaken to synthesize compound (3) and subsequently prepare a series of its 2-substituted derivatives.

Compound (3) was synthesized through the condensation of 2-amino-5-bromopyridine (1) with ethyl 2-cyano-3,3-bis(methylthio)acrylate (2) in DMF in the presence of anhydrous K_2CO_3. The reaction afforded 7-bromo-3-cyano-4-oxo-2-(methylthio)-4H-pyrido[1,2-a] pyrimidine (3).

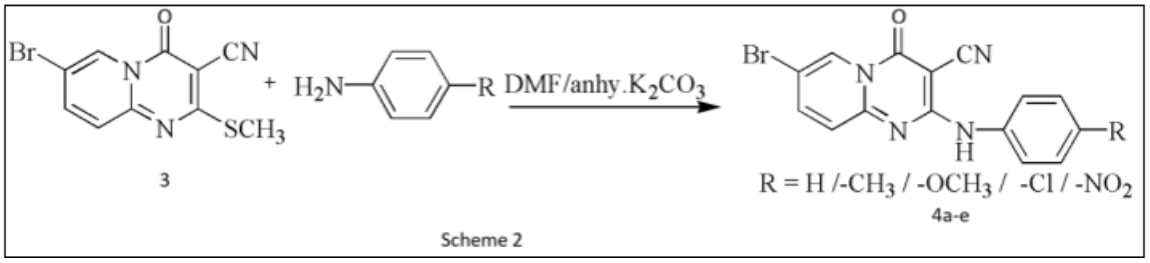
The presence of a methylthio group at the 2-position of compound (3) makes this position susceptible to nucleophilic displacement. Accordingly, compound (3) was further reacted with different nucleophiles, including aromatic amines and substituted phenols, to obtain the corresponding 2-substituted pyrido[1,2-a] pyrimidine derivatives. This approach enabled the synthesis of a series of novel derivatives based on the pyrido[1,2-a] pyrimidine scaffold.



1 2 3

Scheme 1

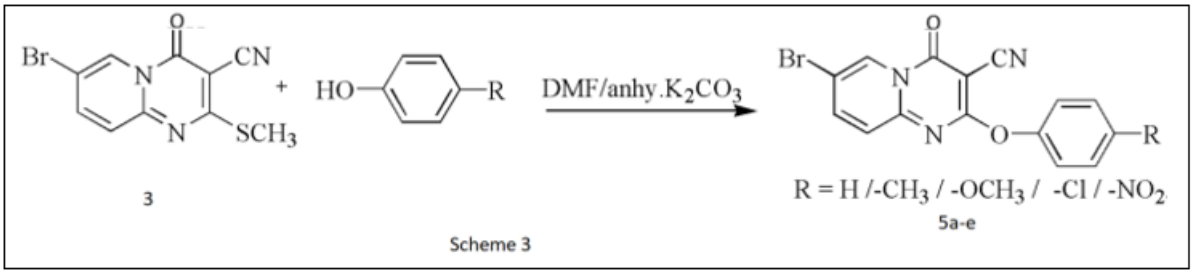
The amino derivatives of compound (3) were synthesized by independently treating compound (3) with aniline, p-toluidine, p-anisidine, p-chloroaniline, and p-nitroaniline in DMF in the presence of anhydrous K_2CO_3 as a catalyst, affording the corresponding compounds **(4a–e)** as shown in **Scheme 2**. The IR spectra of all the synthesized compounds exhibited strong absorption bands in the range of **2204–2205 cm⁻¹**, attributable to the –C≡N stretching vibration. The absorption bands observed in the range of **3217–3346 cm⁻¹** were assigned to the –NH stretching vibration, while bands in the range of **1620–1650 cm⁻¹** corresponded to the C=O stretching vibration. The mass spectra of the synthesized compounds exhibited molecular ion peaks consistent with their respective molecular weights. Furthermore, the ^1H NMR spectra showed the disappearance of the singlet at **δ 2.63** ppm, confirming the replacement of the active methylthio group by the corresponding amino substituents.



3 4a-e

Scheme 2

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 C=O strong absorption bands at in between **2203-2206** cm^{-1} and **1620-1650** cm^{-1} respectively



3 5a-e

Scheme 3

Antioxidant Activity:

Antioxidants are compounds capable of inhibiting or delaying the oxidation of other molecules. Oxidation involves the transfer of electrons from a substrate to an oxidizing agent and can result in the generation of free radicals. These highly reactive species may initiate chain reactions that cause oxidative damage to cellular components. Antioxidants counteract this process primarily by scavenging free-radical intermediates and undergoing oxidation themselves, thereby terminating or inhibiting oxidative chain reactions. Reactive oxygen species (ROS) and free radicals can induce oxidative damage to various cellular constituents, including lipids, proteins, cell membranes, and DNA. Excessive oxidative stress has been implicated in the aging process and in the pathogenesis of several degenerative diseases, including cancer, atherosclerosis, and cataracts. Consequently, compounds possessing antioxidant and free-radical-scavenging properties may help protect biological systems against oxidative damage and may contribute to the prevention of oxidative stress-associated disorders. In the present investigation, the antioxidant potential of selected synthesized compounds was assessed 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 µL of 1 mM $FeCl_3$, 90 µL of 1 mM 1,10-phenanthroline, 2.4 mL of 0.2 M phosphate buffer (pH 7.8), 150 µL of 0.17 M H_2O_2, 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-oxo-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	53+0.31	32±0.72
2	4b	42±0.39	12±0.82
3	4c	63±0.21	68±0.42
4	4d	20±0.88	33±0.71
5	5a	44±0.12	42±0.38
6	5c	25±0.17	39±0.66
7	5d	60±0.27	52±0.42
8	Ascorbic Acid	86 ± 0.88	NA
9	α- Tocopherol	NA	81±0.19

5. Conclusion

A series of 7-bromo-3-cyano-4-oxo-2-(substituted)-4H-pyrido[1,2-a] pyrimidine derivatives **(4a–e and 5a–e)** was successfully synthesized and characterized. Among the synthesized compounds, compound **(4c)** exhibited remarkable antioxidant activity. The findings of the present study indicate that pyrido[1,2-a] pyrimidine derivatives possess promising antioxidant potential. These results may encourage further research toward the design and development of novel pyrido[1,2-a] pyrimidine derivatives with enhanced pharmacological properties.

References

[1] Katritzky A.R., Rogers J.W., Witek R.M., Nair S.K., *ARKIVOC,* 2011, 2: 297-309.
[2] Ferrarini P.L., Mori C, Armani G, Rossi L., *Farmaco*, 1995, 50: 69-72.
[3] Yao P, Zhai X, Liu D, Qi BH, Tan H.L, *Arch Pharm (Weinheim),* 2010, 343: 17-23.
[4] Joseph S., Burke J.M., *J Biol Chem.,* 1993, 268: 24515-24518.
[5] Jasinski J.P., Butcher R.J., Hakim Al-Arique Q.N., Yathirajan H.S., Narayana B., *Acta Crystallogr Sect E Struct Rep Online,* 2009, 65: 2201-2202.
[6] Bishnoi A., Akstk S.S., *J Chem Sci*, 2013, 125: 305-312.
[7] Yanagihara, Y.; Kasai, H.; Kawashima, T.; Shida, T. *Jpn. J. Pharmacol*. 1988, 48, 91−101.
[8] Shakir M. Alwan, Jaafar abdul- sahib al- kaabi and rafid MM Hashim., *Med. Chem*., 2014, 4:9