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Research Article

Synthesis of Novel 4-Imino-6,8-Dimethyl-2-(Methylthio)-4H-Pyrimido [1, 2-A] Pyrimidine-3-Carbonitrile and its 2-Substituted Derivatives

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Abstract

In this study, we report a novel and efficient synthetic strategy for the construction of a fused bicyclic heterocyclic system with promising potential in medicinal chemistry. The synthesis begins with the reaction of ethyl bis(methylthio)methylene malononitrile with guanidine nitrate in the presence of potassium carbonate as a base, using dimethylformamide (DMF) as the solvent under reflux conditions. This reaction furnishes 2-amino-1,6-dihydro-6-imino-4-(methylthio)pyrimidine-5-carbonitrile as a key intermediate. Subsequent treatment of this intermediate with acetylacetone under acidic conditions initiates a Michael addition followed by a Robinson annulation, leading to intramolecular cyclization. This tandem sequence proceeds smoothly to afford the target compound, 4-imino-6,8-dimethyl-2-(methylthio)-4H-pyrimido[1,2-a]pyrimidine-3-carbonitrile in excellent yield. The synthesized compound was characterized by various spectroscopic techniques including IR, NMR, and mass spectrometry confirming its proposed structure. Notably, the target molecule contains a replaceable methylthio (-SCH_3) group at the 2-position making it a versatile precursor for further functionalization. The reactivity of this compound was explored through its reactions with different nucleophiles, such as substituted aromatic amines, aromatic phenols, heterocyclic amines, and active methylene compounds to afford a series of novel derivatives in good to excellent yields. Overall, this synthetic approach offers a convenient, efficient, and versatile route to access pyrimido[1,2-a]pyrimidine scaffolds which are of significant interest for the development of bioactive and pharmacologically relevant molecules.

Keywords

Guanidine Nitrate, Acetyl Acetone, Aromatic Amines, Phenols, MICHAEL Addition and Robinson Annulations

1. Introduction

Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in chemotherapy of AIDS. Pyrimidine nucleus occurs in biologically important products such as nucleic acids, vitamins, coenzymes and pharmacologically useful natural products of plant origin. Pyrimidines are an important class of heterocyclic compounds, which possess a wide range of biologi-

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cal activities such as anticancer, [1, 2] antibacterial, [3] anti-inflammatory, [4] antiviral, [5] antitubercular, [6] antihypertensive [7] and anticonvulsant [8] activities. The pyrimidopyrimidine moiety represents a core structure that is a useful template for the design of a variety of tyrosine kinase inhibitors [9] From high throughput screening, a pyrimidopyrimidine analogue was identified as a dual inhibitor of the growth factor receptors. This analogue was a significantly less potent inhibitor of the other tested kinases. In a programme to design and develop mechanismbased compounds active as substrates and inhibitors of dihydrofolate reductase (DHFR), Gebauer et al. [10] have reported the synthesis and physical properties of the 6-methyl, 8-methyl and 8-ethyl derivatives of the parent 2-aminopyrimido [4, 5-d] pyrimidin-4-(3H)- one. These compounds are the first members of a class of heterocycles related to 8-alkylpterins (N8-alkyl-2-aminopteridin-4(8H)-ones), which have been shown to be novel substrates for DHFR. Although various procedures for synthesis of pyrimidine derivatives have been developed, it is convenient to synthesize substituted pyrimidines by the reaction of amidine or guanidine derivatives with a variety of 1, 3-dielectrophilic three-carbon units such as α, β- unsaturated carbonyl compounds. [11] Multi_component reactions (MCRs) [12] are masterpieces of synthetic efficiency and reaction design. Therefore, mastering unusual combinations and sequences of elementary organic reactions under similar conditions is the major conceptual challenge in engineering novel types of MCR. Most advantageously and practically, MCR can often be extended into combinatorial [13] and solid phase syntheses promising manifold opportunities for developing novel lead structures of active agents, catalysts and even novel molecule based materials. Inevitably, many classical heterocyclic syntheses are MCR that are based upon carbonyl group condensations. Hence, medicinal chemistry is largely found on these easily accessible heterocyclic frameworks. The use of multicomponent reactions (MCRs) to generate interesting and novel, drug_like scaffolds is replete in the recent chemical literature [14]. For novel Biginelli_like scaffold synthesis, the use of the common open chain в_dicarbonyl compounds in Biginelli reactions has been extended to the use of cyclic β_diketones [15], β_ketolactones [16], cyclic β_diesters or β_diamides, benzocyclic ketones and α_keto acids. All of these reactions were performed using conventional heating and reaction times were long. Microwave promoted solvent_free reactions [17] are well known as environmentally benign methods that also usually provide improved selectivity, enhanced reaction rates, cleaner products and manipulative simplicity.

2. Methods

Melting points were measured using open capillary tubes and are reported without correction. Thin layer chromatography (TLC) was carried out on silica gel plates containing F254 indicator; spots were visualized under ultraviolet (UV) light followed by exposure to iodine vapor. Column chromatography was conducted employing silica gel (BDH, particle size 100–200 mesh). All solvents were purified following established standard methodologies. Spectroscopic analyses were performed as follows: infrared (IR) spectra were obtained using KBr pellets on a Perkin-Elmer RX1 FT-IR spectrometer; proton nuclear magnetic resonance (^1H NMR) spectra were recorded in $CDCl_3$ at 200 MHz on a Varian Gemini 200 spectrometer. Elemental compositions were determined using a Heraeus CHN-O rapid elemental analyzer.

2.1. 4-imino-6,8-dimethyl-2-(methylthio)-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile

Step 1: Synthesis of Intermediate

In the first step, ethyl bis(methylthio) methylene malononitrile is reacted with guanidine nitrate in the presence of potassium carbonate as a base, using dimethylformamide (DMF) as the solvent. The reaction is carried out under reflux conditions, which facilitates the cyclization and condensation process. This leads to the formation of a key intermediate. 2-amino-1, 6-dihydro-6-imino-4-(methylthio) pyrimidine-5-carbonitrile. This compound contains a pyrimidine core and is an essential precursor for further cyclization into the fused heterocyclic system.

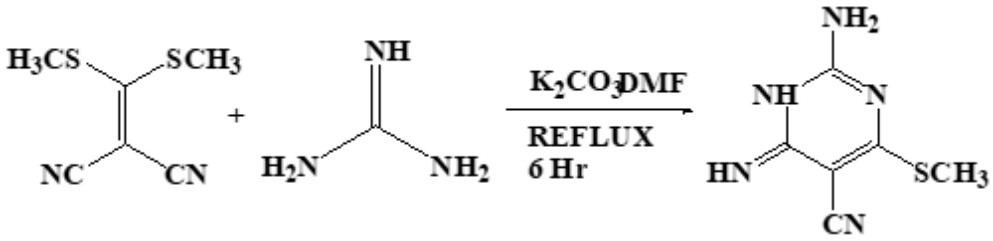

Figure 1. *First compoud.*

Step 2: Cyclization to Fused Bicyclic Compound.

In the second step, the synthesized intermediate is treated with acetylacetone under acidic conditions. The reaction undergoes a Michael addition at the activated double bond, followed by Robinson annulation, which involves intramolecular cyclization to form a fused bicyclic structure. This tandem reaction results in the formation of the final target compound. 4-imino-6, 8-dimethyl-2-(methylthio)-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile. This fused pyrimido [1, 2-a] pyrimidine framework is obtained in good yields and represents a novel heterocyclic system with potential pharmacological relevance. The target molecule confirmed by IR, ^{1}H and C^{13} NMR and MS analytical data.

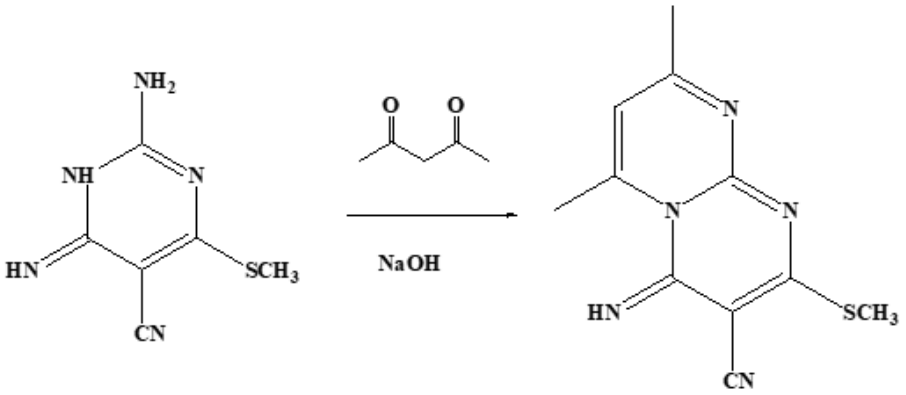

Figure 2. *Targetmolecule.*

Mechanism Pathway:- Proposed pathway for formation of 4-imino-6, 8-dimethyl-2-(methylthio)-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile.

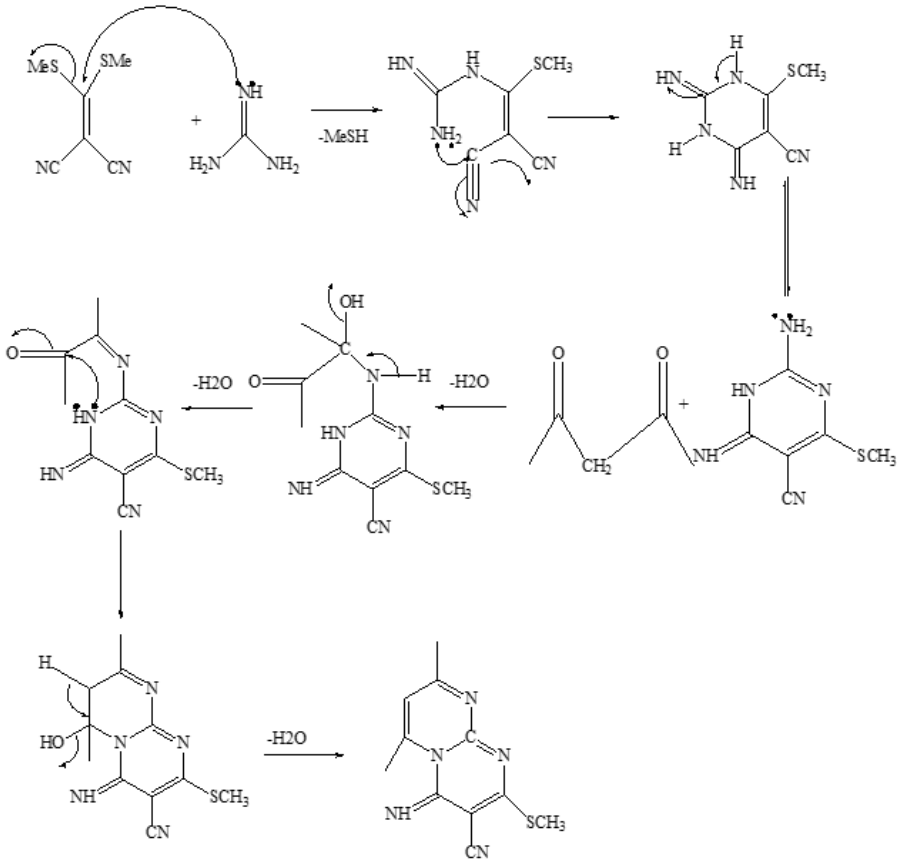

Figure 3. *Mechanism.*

2.2. Synthesis of Derivatives

The target molecule (1mmol) and independently, various substituted aromatic amines, aromatic phenols, heteryl amines and active methylene compounds (1mmol) in DMF (10 ml) and anhydrous potassium carbonate (10 mg) was reflux for 4 to 6 hrs. The reaction mixture cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallised using ethyl alcohol.

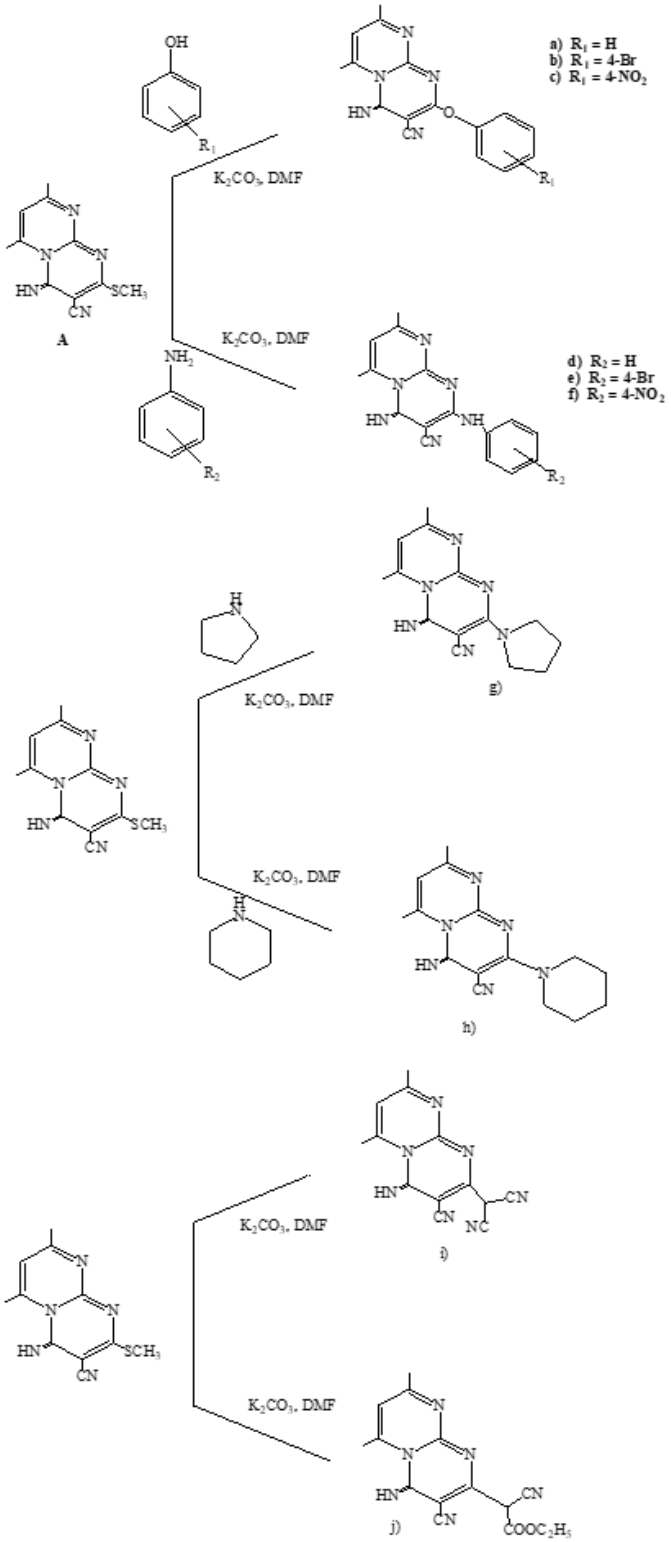

Figure 4. *Derivatives of target molecules.*

3. Result and Discussion

The title compound, 4-imino-6, 8-dimethyl-2-(methylthio)-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile, was successfully synthesized via a multi-step synthetic pathway involving the condensation of appropriate precursors under controlled conditions. The product was obtained as a crystalline solid with a yield of [60%] and a melting point of [147-149 ℃], consistent with related pyrimido [1, 2-a] pyrimidine derivatives reported in the literature.

Structural Elucidation:

Infrared spectroscopy confirmed key functional groups, with a sharp band near 2200cm⁻¹ for nitrile (–C≡N) stretching and a distinct imino (–C=NH) signal around 1650cm⁻¹. Additional C–N and C=S absorptions appeared in expected regions. The ^{1}H NMR spectrum showed singlets for two methyl groups (δ 2.3–2.6ppm), a methylthio signal (~2.5ppm), aromatic/heteroaromatic protons (δ 6.5–8.0ppm), and a broad imino proton (~10–12ppm). ^{13}C NMR supported the structure, showing nitrile (δ ~115–120ppm) and thiocarbonyl (δ 160–180ppm) signals. Mass spectrometry confirmed the molecular ion, supporting the assigned formula. The scaffold's substituents may enhance lipophilicity and bioactivity via electronic and hydrogen-bonding interactions.

4. Conclusion

The data obtained for 4-imino-6, 8-dimethyl-2-(methylthio)-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile confirm the successful synthesis and characterization of the compound. The product was isolated as a crystalline solid with a 60% yield and a melting point of 147–149 ℃, which is consistent with values reported for similar pyrimido [1, 2-a] pyrimidine derivatives. These results support the formation of the desired heterocyclic structure and validate the effectiveness of the synthetic method employed.

4-imino-6, 8-dimethyl-2-(methylthio)-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile

IR: 3312(-NH), 2235 (-C≡N), 1680 (>C=N) cm^{-1}. ^{1}H-NMR: δ3.25 (s, 3H, SMe), 8.35 (s, 1H, =NH), 2.35-2.50 (s,6HCH$_3$) ^{13}C-NMR ($CDCl_3$): δ62.9, 70.0,125.9,134.6, 155,175.2. ESI-MS: m/z 246 [M$^{+\cdot}$] Anal. Calcd for: C, 53.86; H, 4.52; N, 28.55; S, 13.07 $C_{11}H_{11}N_5S$ Found: C, 53.84; H, 4.55; N, 28.50; S, 13.12 Mol. Formula: $C_{11}H_{11}N_5S$ Mol. Wt.: 246.

a) 4-imino-6, 8-dimethyl-2-phenoxy-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile.

IR: 3313(-NH), 2234 (-C≡N), 1682 (>C=N) cm-1. ^{1}H NMR: 1H-NMR: δ8.35 (s, 1H, =NH), 2.35-2.50 (s,6HCH$_3$) 5.52 (s, 1HCH), 7.24 (s, 5H Ar-H), ESI-MS: m/z 291 [M+.] Anal. Calcd for: C, 65.97; H, 4.50; N, 24.04; O, 5.49 $C_{16}H_{13}N_5$ Found: C, 65.97; H, 4.50; N,24.04; O, 5.49 Mol. Formula: $C_{16}H_{13}N_5$ Mol. Wt.: 291.

b) 2-(4-bromophenoxy)-4-imino-6, 8-dimethyl-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile. IR: 3332(-NH), 2236 (-C≡N), 1688 (>C=N) cm-1. ^{1}H NMR: 1H-NMR: δ8.32 (s,1H,=NH), 2.32-2.51 (s,6HCH$_3$) 5.53 (s, 1HCH), 6.91 (dd, 2H Ar- H), 7.20 (dd, 2H Ar-H), ESI-MS: m/z 369 [M+.] Anal. Calcd for: C, 51.91; H, 3.27; Br, 21.58; N, 18.92; O, 4.32 $C_{16}H_{12}BrN_5O$ Found: C, 51.91; H, 3.27; Br, 21.58; N, 18.92; O, 4.32 Mol. Formula: $C_{16}H_{12}BrN_5O$ Mol. Wt.: 369.

c) 2-(4-nitrophenoxy)-4-imino-6, 8-dimethyl-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile.

IR: 3330(-NH), 2237 (-C≡N), 1681 (>C=N) cm-1. ^{1}H NMR: 1H-NMR: δ8.35 (s,1H,=NH), 2.35-2.50 (s,6HCH$_3$) 5.52 (s, 1HCH), 6.90 (dd, 2H Ar- H), 7.21 (dd, 2H Ar-H), ESI-MS: m/z 336 [M+.] Anal. Calcd for: C, 57.14; H, 3.60; N, 24.99; O, 14.27 $C_{16}H_{12}BrN_5O$ Found: C, 57.14; H, 3.60; N, 24.99; O, 14.27 Mol. Formula: $C_{16}H_{12}BrN_6O_3$Mol. Wt.: 336.

d) 4-imino-6, 8-dimethyl-2-(phenylamino)-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile.

IR: 3310(-NH), 2230 (-C≡N), 1683 (>C=N) cm-1. ^{1}H NMR: 1H-NMR: δ8.31 (s, 1H,=NH), 2.31-2.52 (s,6HCH$_3$) 5.50 (s,1HCH), 7.23 (s, 5H Ar-H), ESI-MS: m/z 290 [M+.] Anal. Calcd for: C, 66.19; H, 4.86; N, 28.95, $C_{16}H_{13}N_5$ Found: C, 66.19; H, 4.86; N, 28.95 Mol. Formula: $C_{16}H_{14}N_6$ Mol. Wt.: 290.

e) 2-(4-bromophenylamino)-4-imino-6, 8-dimethyl-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile. IR: 3328(-NH), 2237 (-C≡N), 1689 (>C=N) cm-1. ^{1}H NMR: 1H-NMR: δ8.32 (s,1H,=NH), 2.28-2.48 (s,6HCH$_3$) 5.49 (s, 1HCH), 6.89 (dd, 2H Ar- H), 7.22 (dd,2H Ar-H), ESI-MS: m/z 369 [M+.] Anal. Calcd for: C, 52.05; H, 3.55; Br, 21.64; N, 22.76 $C_{16}H_{12}BrN_5O$ Found: C, 52.05; H, 3.55; Br, 21.64; N, 22.76. Mol. Formula: $C_{16}H_{13}BrN_6$ Mol. Wt.: 369.

f) 2-(4-nitrophenylamino)-4-imino-6, 8-dimethyl-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile. IR: 3325(-NH), 2225 (-C≡N), 1685 (>C=N) cm-1. ^{1}H NMR: 1H-NMR: δ8.28 (s,1H,=NH), 2.25-2.55 (s,6HCH$_3$) 5.53 (s, 1HCH), 6.85 (dd, 2H Ar- H), 7.11 (dd, 2H Ar-H), ESI-MS: m/z 336 [M+.] Anal. Calcd for: C, 57.31; H, 3.91; N, 29.24; O, 9.54 $C_{16}H_{13}N_7O_2$ Found: C, 57.31; H, 3.91; N, 29.24; O, 9.54Mol. Formula: $C_{16}H_{13}N_7O_2$Mol. Wt.: 335.

g) 4-imino-6, 8-dimethyl-2-(pyrrolidin-1-yl)-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile.

IR: 3320 (-NH), 2215 (-C≡N), 1675 (>C=N) cm^{-1}; ^{1}H NMR: 5.05 (s,1H NH), 6.45 (s,6HCH$_3$) 5.53 (s, 1HCH), 2.60 (t,4H), 1.65 (m, 4H) ESI-MS: 268. Anal. Calcd: $C_{24}H_{22}N_6O_3$, C, 62.67; H, 6.01; N, 31.32 Found: C, 62.67; H, 6.01; N, 31.32 Mol. Formula: $C_{14}H_{16}N_6$Mol. Wt.: 268.

h) 4-imino-6, 8-dimethyl-2-(piperidin-1-yl)-4H-pyrimido [1, 2-a] pyrimidine-3-carbonitrile.

IR: 3322 (-NH), 2217 (-C≡N), 1671 (>C=N) cm^{-1}; ^{1}H NMR: 5.05 (s,1H NH), 6.45 (s,6HCH$_3$) 5.53 (s,1HCH), 3.13 (t, 4H), 1.53 (m, 6H). ESI-MS: 282. Anal. Calcd: $C_{15}H_{18}N_6$, C, 63.81; H, 6.43; N, 29.77 Found: C, 63.81; H, 6.43; N, 29.77 Mol. Formula: $C_{15}H_{18}N_6$ Mol. Wt.: 282.

i) 2-(dicyanomethyl)-4-imino-6, 8-dimethyl-4H-pyrimido

[1, 2-a] pyrimidine-3-carbonitrile.

IR: 3316 (-NH), 2219 (-C≡N), 1672 (>C=N), 1050 (-C≡N), cm^{-1}; ^{1}H NMR: 5.07 (s,1H NH), 6.50 (s,6HCH_3) 5.51 (s, 1HCH), 3.13, 5.51 (s, 1HCH), ESI-MS: 263. Anal. Calcd: $C_{13}H_9N_7$, C, 59.31; H, 3.45; N, 37.24 Found: C, 59.31; H, 3.45; N, 37.24 Mol. Formula: $C_{15}H_{18}N_6$ Mol. Wt.: 263.

j) ethyl 2-cyano-2-(3-cyano-4-imino-6, 8-dimethyl-4H-pyrimido [1, 2-a] pyrimidin-2yl) acetate.

IR: 3316 (-NH), 2219 (-C≡N), 2910, 1710, 1672 (>C=N), 1050 (-C≡N), cm^{-1}; ^{1}H ^{1}H NMR: 5.08 (s,1H NH), 6.44 (s,6HCH_3) 5.51 (s,1HCH), 3.13, 5.51 (s,1HCH), 4.19 (q,2H),1.22 (t,3H). ESI-MS: 310. Anal. Calcd: $C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08; O, 10.31 Found: C, 58.06; H, 4.55; N, 27.08; O, 10.31. Mol. Formula: $C_{15}H_{14}N_6O_2$. Mol. Wt.: 310.

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Conflicts of Interest

The authors declare no conflicts of interest.

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