



## Research Article

### SYNTHESIS AND ANTIOXIDANT ACTIVITY OF 6-IMINO-4-(METHYLTHIO)-2-(PYRIDINE-3-YL)-6H-1,3-THIAZINE-5-CARBONITRILE

Datta S. Kawale, Sambhaji P. Vartale \* and Balasaheb D. Kalyankar

PG Research Centre, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded, Maharashtra, India

\*Corresponding Author Email: spvartale@gmail.com

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#### ABSTRACT

Synthesis of novel heterocyclic 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6H-1,3-thiazine-5-carbonitrile (3) was prepared by condensing thionicotinamide (1) with bis(methylthio)methylene malononitrile (2) in DMF and potassium carbonate as catalyst. Compound (3) has methylthio group at fourth position, which is replaced by different nucleophiles such as substituted anilines, phenols, heteryl amines and compounds containing active methylene group to afford 4-substituted derivatives of compound (3). The newly synthesized compounds were characterized by IR, <sup>1</sup>H-NMR, Mass spectral analysis. Furthermore, these synthesized compounds were tested for antioxidant activity. The result of antioxidant activity reveals that most of the compounds shows potent activity. The major advantage of this protocol is operational simplicity and high yield.

**Keywords:** Bis(methylthio)methylene malononitrile, DMF, potassium carbonate and thionicotinamide.

#### INTRODUCTION

Heterocyclic chemistry is recently experiencing broad area of interest because of their potent biological activity<sup>1-3</sup>. Incorporation of hetero atoms within the carbon framework often leads to new type of molecules, which are primarily biological important. The heterocyclic compound containing nitrogen and sulphur serve as the versatile moiety for drug designing which has potential pharmacological properties<sup>4-8</sup>.

Thiazine is the six membered aromatic ring system which contains two hetero atoms such as nitrogen and sulphur placed at 1,3-positions. Thiazines are very useful units in the field of medicinal chemistry and have been reported to exhibit a variety of biological activities such as antimicrobial<sup>9-11</sup>, antiviral<sup>12</sup>, antifungal<sup>13</sup>, blood platelet aggregation inhibitors<sup>14</sup>, antihistaminic<sup>15</sup>, antioxidant<sup>16</sup>. Moreover, thiazine derivatives act as effective corrosion inhibitor<sup>17-18</sup> for carbon steel in acidic media due to the presence of heteroatoms (N and S) which has lone pairs and ring has planar pi-electrons are two important structural features that determines the absorption of molecules on the surface of metal. Thiazine derivatives are also used in the preparation of peptide resin inhibitors and good colour photographic materials<sup>19-20</sup>. Literature survey reveals that number of synthetic methods are available for the synthesis of thiazine compounds and screening of their biological studies<sup>21-23</sup>. Recently Sambhaji P. Vartale *et al* 2013 has reported the synthesis of substituted pyrimido [2,1-*b*] [1,3] thiazines<sup>24</sup>.

In the view of above bioapplications, we embarked on the development of novel system having different pharmacophores on the same ring. Hence part of our ongoing programme to develop efficient method for the synthesis of 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6H-1,3-thiazine-5-carbonitrile (3) and its 4-substituted derivatives (4a-7d).

#### MATERIAL AND METHODS

Electrothermal IA 9000 SERIES digital melting point apparatus was used to determine the melting points of synthesized compounds and were uncorrected. Homogeneity of all the compounds were routinely checked on 0.2 mm silica gel-C plates using ethyl acetate:hexane (3:7) as irrigant, the spots were examined under UV light chamber. Infrared spectra were recorded in Nujol or as potassium bromide pellets on infrared spectrophotometer, nuclear magnetic resonance spectra were obtained on Bruker advance spectrophotometer 400 MHz in DMSO-d<sub>6</sub> using tetramethylsilane (TMS) as internal reference, Mass spectra were recorded on FT-VC-7070 H Mass spectrometer using the EI technique at 70 eV. All the reactions were carried out under ambient atmosphere.

#### General procedure

##### Synthesis of 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6H-1,3-thiazine-5-carbonitrile (3)

A mixture thionicotinamide (1) (0.01mol) and bis(methylthio)methylene malononitrile (2) (0.01mol) in 10 ml of DMF and anhydrous potassium carbonate (10mg) was refluxed for 6 hours. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystallized from acetone-ethanol (2:8) mixture to give pure compound (3).

##### Synthesis of 4-substituted derivatives of 6-imino-2-(pyridin-3-yl)-6H-1,3-thiazine-5-carbonitrile (4a-7d)

A mixture of compound (3) (0.001mol) refluxed independently with substituted anilines/ phenols/ heteryl amines/ compound containing active methylene groups (0.001mol) in 10 ml of DMF and anhydrous potassium carbonate (10mg) for 4-5 hours.

The reaction progress was checked by TLC. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystallized from acetone-ethanol (2:8) mixture to give pure compounds (4a-4d,5a-5d,6a-6d,7a-7d).

**Physicochemical data:** The Physicochemical data of all synthesized compounds are given in table no. 2.

**Spectral Analysis**

**6-imino-4-(methylthio)-2-(pyridin-3-yl)-6H-1,3-thiazine-5-carbonitrile (3).**

IR (KBr/cm<sup>-1</sup>) 1642 (C=N), 2235 (CN), 3358 (=NH): <sup>1</sup>H-NMR (400 MHz,DMSO-d<sub>6</sub>): δ 2.56 (s, 3H, SCH<sub>3</sub>), 7.22-8.64 (m, 4H, Ar-H), 9.38 (s, 1H, =NH): EI-MS(m/z: RA% ): 260 (M<sup>+</sup>).

**6-imino-2-(pyridin-3-yl)-4-(4-methoxyphenylamino)-6H-1,3-thiazine-5-carbonitrile (4b).**

IR (KBr/cm<sup>-1</sup>) 1660 (C=N), 2254 (CN), 3418 (=NH): <sup>1</sup>HNMR (400 MHz,DMSO-d<sub>6</sub>): δ 3.82 (s, 3H, Ar-OCH<sub>3</sub>), 6.86 (s, 1H, Ar-

NH ), 6.99-8.80 (m, 8H, Ar-H), 9.32 (s, 1H, =NH): EI-MS(m/z: RA% ): 335 (M<sup>+</sup>).

**4-(p-tolyloxy)-6-imino-2-(pyridin-3-yl)-6H-1,3-thiazine-5-carbonitrile (5a).**

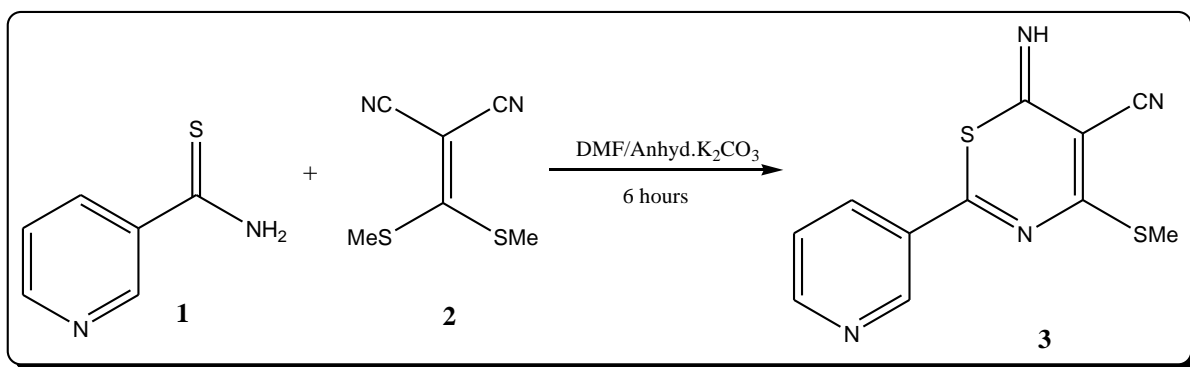
IR (KBr/cm<sup>-1</sup>) 1654 (C=N), 2230 (CN), 3345 (=NH): <sup>1</sup>HNMR (400 MHz,DMSO-d<sub>6</sub>): δ 2.52 (s, 3H, Ar-CH<sub>3</sub>), 7.5-8.9 (m, 8H, Ar-H), 9.54 (s, 1H, =NH): EI-MS (m/z: RA% ): 320 (M<sup>+</sup>).

**4-(dicyanomethyl)-6-imino-2-(pyridine-3-yl)-6H-1,3-thiazine-5-carbonitrile (6a).**

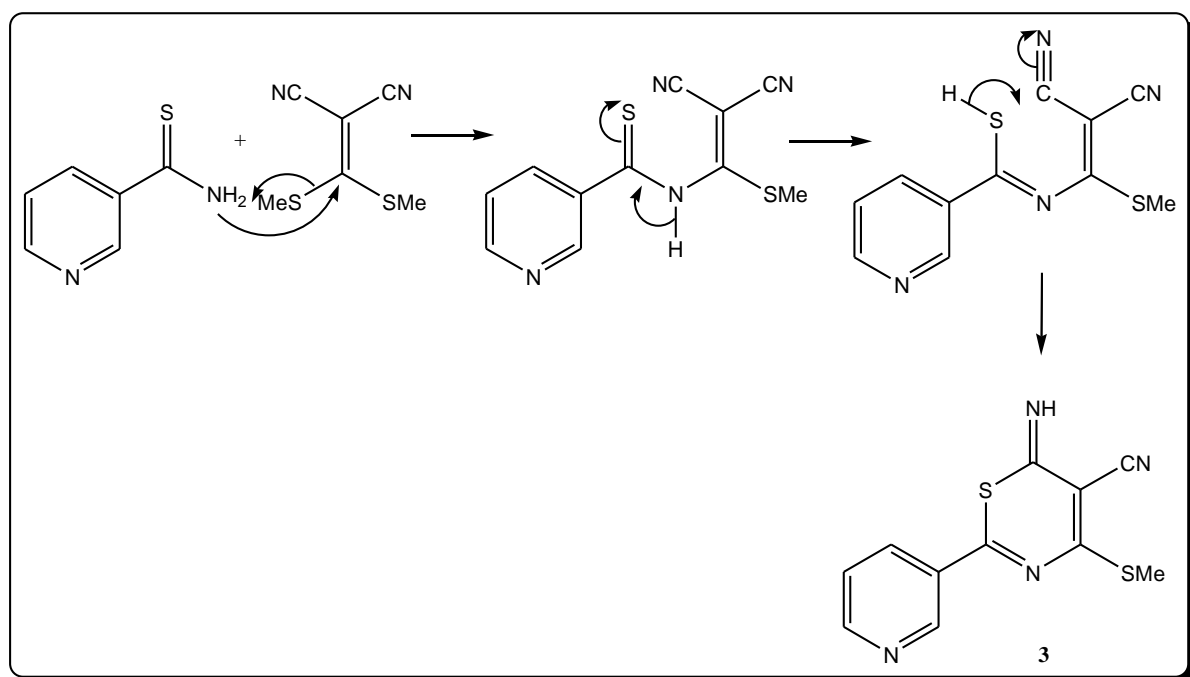
IR (KBr/cm<sup>-1</sup>) 1640 (C=N), 2216 (CN), 3402 (=NH): <sup>1</sup>HNMR (400 MHz,DMSO-d<sub>6</sub>): δ 4.23 (s, 1H, -CH), 7.61-8.80 (m, 4H, Ar-H), 9.33 (s, 1H, =NH): EI-MS (m/z: RA% ): 278 (M<sup>+</sup>).

**6-imino-2-(pyridin-3-yl)-4-(pyrrolidin-1-yl)-6H-1,3-thiazine-5-carbonitrile (7a).**

IR (KBr/cm<sup>-1</sup>) 1622 (C=N), 2271 (CN), 3346 (=NH): <sup>1</sup>HNMR (400 MHz,DMSO-d<sub>6</sub>): δ 1.27 (m, 4H, 2-CH<sub>2</sub>), 2.73 (t, 4H, 2-NCH<sub>2</sub>), 7.6-8.88 (m, 4H, Ar-H), 9.52 (s, 1H, =NH): EI-MS (m/z: RA% ): 283 (M<sup>+</sup>).



Scheme-1. Formation of 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6H-1,3-thiazine-5-carbonitrile

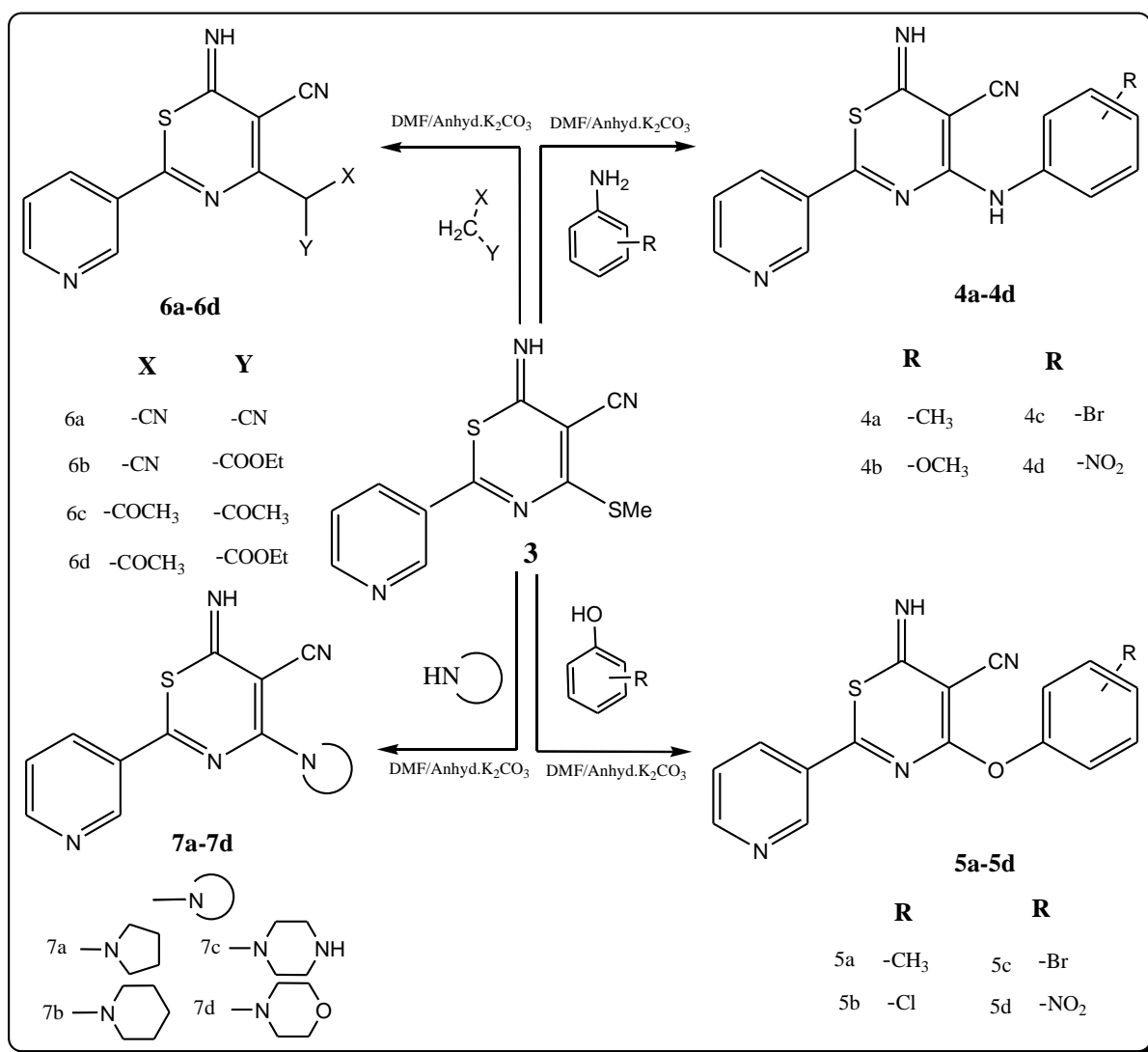


Scheme-1. Plausible mechanism of formation for compound (3).

## RESULT AND DISCUSSION

The therapeutic importance of these rings promoted us to develop new molecules in which substituents should be arranged by such pattern which displays higher pharmacological activities. Thus in present view we have synthesized a 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6H-1,3-thiazine-5-carbonitriles and its 4-substituted derivatives (4a-7d). The synthetic route leading to title compound is summarized in scheme-1 and scheme-2. In our first scheme we condensed thionicotinamide (1) and bis(methylthio)methylene malononitrile (2) in DMF and catalytic amount of anhydrous  $K_2CO_3$  to afford (3) **Scheme-1**.

The compound (3) possesses replaceable active thiomethyl group at 4<sup>th</sup>-position and electron withdrawing nature of cyano group at 5<sup>th</sup>-position. Due to presence of electron withdrawing group such as thiomethyl and cyano on compound (3) which has susceptibility for nucleophilic substitution. When compound (3) was condensed independently with substituted anilines/phenols/heteryl amines/ compound containing active methylene groups under similar experimental condition to afford 4-substituted derivatives of 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6H-1,3-thiazine-5-carbonitriles (4a-7d) **Scheme-2**.



Scheme-2. Formation of 4-substituted derivatives of parent compound (3).

The structure of newly synthesized compounds were assigned on the basis of IR, <sup>1</sup>H NMR, Mass spectral data.

**IR Spectrums :** In IR spectrum of compounds absorption bands appear in the region 2275-2215 and 3420-3340  $cm^{-1}$  for -CN, =NH respectively.

**<sup>1</sup>H NMR spectrum :** <sup>1</sup>H NMR spectra of compounds shows singlet and multiplet peaks in the region of 9.2-9.8, 7.0-8.5 ppm due to, =NH and Ar-H protons respectively .

**MASS spectrum :** MASS spectra shows molecular ion peak which is an agreement with the molecular weight of respective compounds.

All spectral analysis shows that compounds were stable and does not show any tautomerism. The result of DPPH radical scavenging activity of newly synthesized 4-substituted derivatives of 6-imino-4-(methylthio)-2-(pyridine-3-yl)-6H-1,3-thiazine-5-carbonitrile (4a-7d) are summarized in table-2. DPPH is relatively stable nitrogen centred free radical that easily accept

an electron or hydrogen radical to become a stable diamagnetic molecule. DPPH antioxidant assay is based on the ability of 1,1-diphenyl-2-picryl hydrazyl, a stable free radical to decolourise in the presence of antioxidants. When DPPH accepts an electron from antioxidant compound, the DPPH is decolourise which can be quantitatively measured from change in absorbance. Such reactivity has been widely used to test the ability of compounds to act as free radical scavengers. The overall DPPH radical scavenging activity of tested 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6*H*-1,3-thiazine-5-carbonitrile and its 4-substituted derivatives were in a range of 9.00-38.57 % where as standard ascorbic acid shows (90.15%). The highest DPPH radical scavenging activity was exhibited by **5b**, whereas **4c** demonstrate lowest activity. From the result of present work, it can be concluded that tested 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6*H*-1,3-thiazine-5-carbonitrile and its 4-substituted derivatives are essential to boost the antioxidant activity.

## ANTIOXIDANT ACTIVITY

### DPPH radical scavenging assay

The DPPH radical scavenging assay has been used for preliminary screening of the sample for antioxidant activity. The proton radical scavenging action is known as an important mechanism of antioxidants. The odd electron in DPPH radical gives a strong absorption maximum at 517 nm and is purple in colour. The colour turns from purple to yellow when the odd electron of DPPH radical becomes paired with hydrogen from free radicals scavenging antioxidants to form reduced DPPH.H. 1ml (1 mM) of test sample was added in to equal quantity of 0.1 mM solution of DPPH in ethanol. After 10 minutes of incubation at room temperature, the DPPH reduction was measured by reading the absorbance at 517 nm. Ascorbic acid was taken as standard reference. The result of DPPH reduction is summarized in Table 1.

Table 1. Antioxidant activity of selected compounds

Sr. No.	Compounds	Antioxidant activity
		DPPH radical scavenging activity (%)
1	3	09.58±0.46
2	4b	11.38±0.72
3	4c	09.00±0.33
4	4d	17.49±0.09
5	5a	09.49±0.51
6	5b	38.57±0.39
7	6b	19.51±0.12
8	6d	18.39±0.73
9	7a	14.30±0.26
10	7b	15.20±0.35
11	Ascorbic acid	90.15±0.53

Table 2. Physicochemical data

ComNo.	Molecular Formula	Mol. Wt.	Colour	Yield %	M.P °C
3	C <sub>11</sub> H <sub>8</sub> N <sub>4</sub> S	260	Gray	72.17	135-36
4a	C <sub>17</sub> H <sub>13</sub> N <sub>5</sub> S	319	Gray	65.08	207-09
4b	C <sub>17</sub> H <sub>13</sub> N <sub>5</sub> OS	335	Brown	71.02	155-57
4c	C <sub>16</sub> H <sub>10</sub> N <sub>5</sub> SBr	382	Yellow	68.94	182-84
4d	C <sub>16</sub> H <sub>10</sub> N <sub>6</sub> O <sub>2</sub> S	350	Yellow	52.11	210-12
5a	C <sub>17</sub> H <sub>12</sub> N <sub>4</sub> OS	320	Yellow	78.53	195-96
5b	C <sub>16</sub> H <sub>9</sub> N <sub>4</sub> OSCl	340	Brown	70.38	175-77
5c	C <sub>16</sub> H <sub>9</sub> N <sub>4</sub> OSBr	385	Yellow	55.64	180-82
5d	C <sub>16</sub> H <sub>9</sub> N <sub>5</sub> O <sub>3</sub> S	351	Yellow	65.41	197-98
6a	C <sub>13</sub> H <sub>6</sub> N <sub>6</sub> S	278	Brown	69.00	164-65
6b	C <sub>15</sub> H <sub>11</sub> N <sub>5</sub> O <sub>2</sub> S	325	Brown	76.88	148-49
6c	C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> S	312	Brown	58.46	168-70
6d	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub> S	342	Brown	72.98	191-93
7a	C <sub>14</sub> H <sub>13</sub> N <sub>5</sub> S	283	Brown	54.66	204-06
7b	C <sub>15</sub> H <sub>15</sub> N <sub>5</sub> S	297	Brown	64.08	188-89
7c	C <sub>14</sub> H <sub>14</sub> N <sub>6</sub> S	298	Yellow	76.42	154-55
7d	C <sub>14</sub> H <sub>13</sub> N <sub>5</sub> OS	299	Brown	62.18	216-18

## CONCLUSION

This work describe proficient and absolute method for the synthesis of novel heterocyclic compounds such as 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6*H*-1,3-thiazine-5-carbonitrile and its 4-substituted derivatives by simple and efficient route with good product yield. The result of antioxidant activity reveals that 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6*H*-1,3-thiazine-5-carbonitrile can act as template for further development through modification to design more effective antioxidant agent.

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