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Simple efficient and one pot synthesis of novel fused tricyclic heterocyclestetraaza-phenanthrene and their derivatives.

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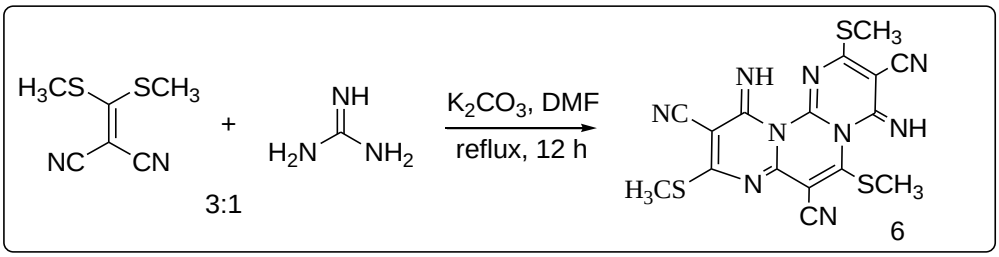
ABSTRACT:
In the present study, the reaction of bis (methylthio) methylene malanonitrile and guanidine nitrate with potassium carbonate in DMF at reflux condition is reported. The molar ratios of these substrates are 3:1 for the preparation of 4,8-dimino-2,6,9-tris-methylsulfanyl-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7,10-tricarbonitrilewith good yields and the parent compound was used for further derivatization. This synthetic strategy is based on suitably substituted tetraaza phenanthrene act as a tris-electrophilic species reacting with various nucleophiles and construct 4,8-dimino-2,6,9- tris-substituted-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7,10-tricarbonitrile in good yields (70-76%).4,8-dimino-2,6,9-tris-methylsulfanyl-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7,10-tricarbonitriletrile



Keywords : Michel type reaction, tris-electrophilic species, tetraaza-phenanthrene, bis (methylthio) methylene malanonitrile.

I. INTRODUCTION

The synthesis of fused tricyclic heterocyclic compounds possessing a tetraaza-phenanthrene central core is described herein. Several synthetic routes to this class of compounds have been reported previously [1-6]. This type of compounds shows a wide range of biological properties such as antibacterial, antiallergic, anti-inflammatory and antitumor activity; some of them are phosphodiesterase inhibitors and drugs against parkinsonism [1-6]. In literature there are many reports on synthesis of tetraaza-phenanthrene [7,8]. The pyrimidine derivatives exhibit a variety of biological activities [9,10]. The physiologically active pyrimidinederivatives can be prepared starting with anα, β- unsaturated nitrile system [11,12]. The reaction of guanidine nitrate withα,β-unsaturated system (Michael acceptor) yieldstetraaza-phenanthrenecompounds [13,14].

The present report is related toother work described in the litearature [15-21]. In the present study, the reaction of bis (methylthio) methylene malanonitrile(**1**) and guanidine nitrate (**2**) was carried out in the presence of potassium carbonate in DMF under reflux conditions with molar ratio 3:1 to obtain 4,8-dimino-2,6,9-tris-methylsulfanyl-4H,8H-1,4a,5,8a-tetraaza-phenanthrene-3,7,10-tricarbo- nitriletrile (**3**) in excellent yield. Compound **3** was used as a substrate for the preparation of its derivatives in a manner previously described for its analogs [22-27].

II. RESULTS AND DISCUSSION

The fused heterocyclic compound **3**was prepared by the reaction ofbis (methylthio) methylene malanonitrile(**1**) and guanidine nitrate (**2**)in the presence of a catalytic amount of potassium bicarbonate in DMF under reflux conditions. The optimized molar ratio of these substrates is3:1.The proposed mechanistic pathway is depicted in Scheme 1.

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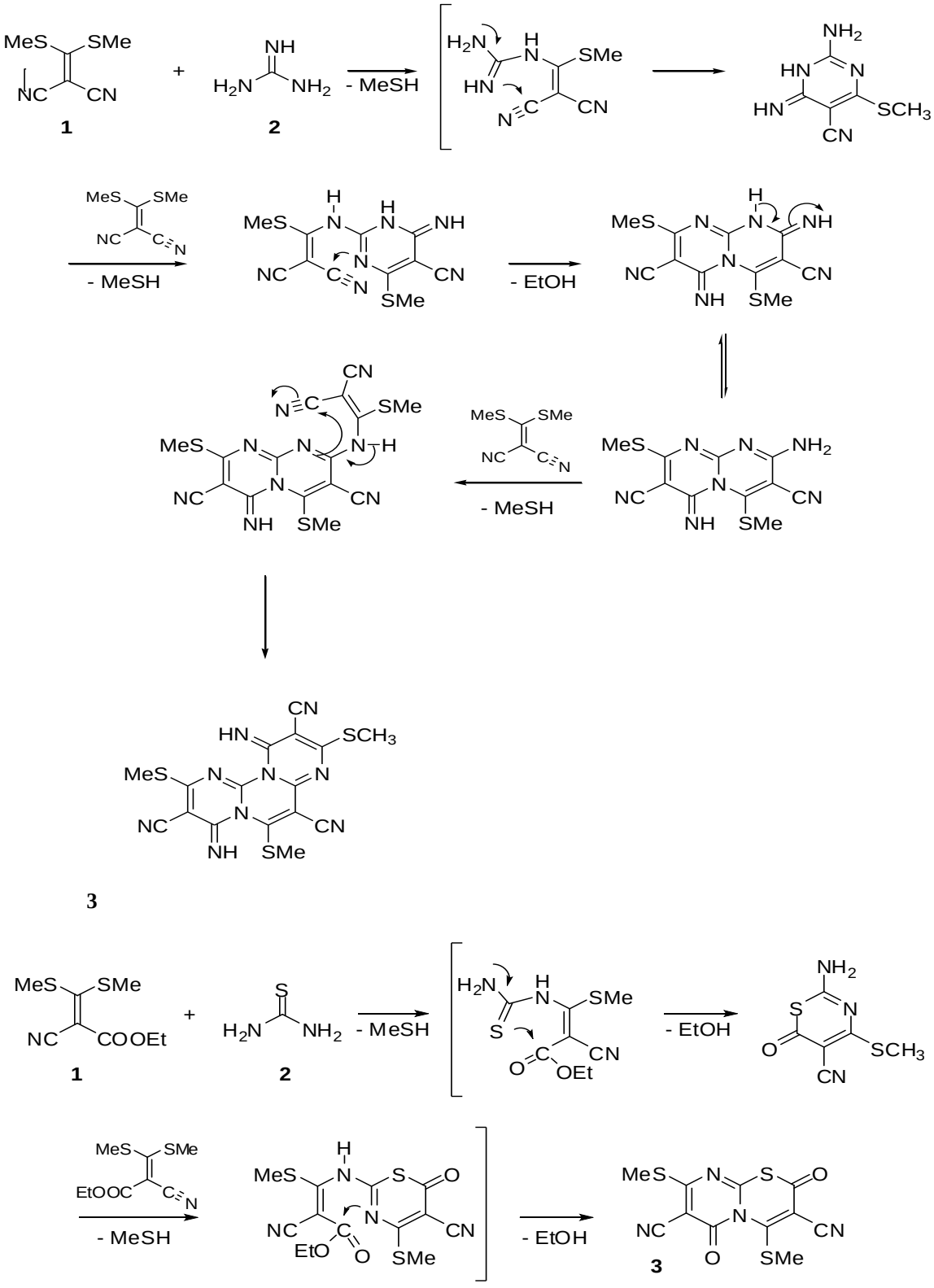

Scheme 1

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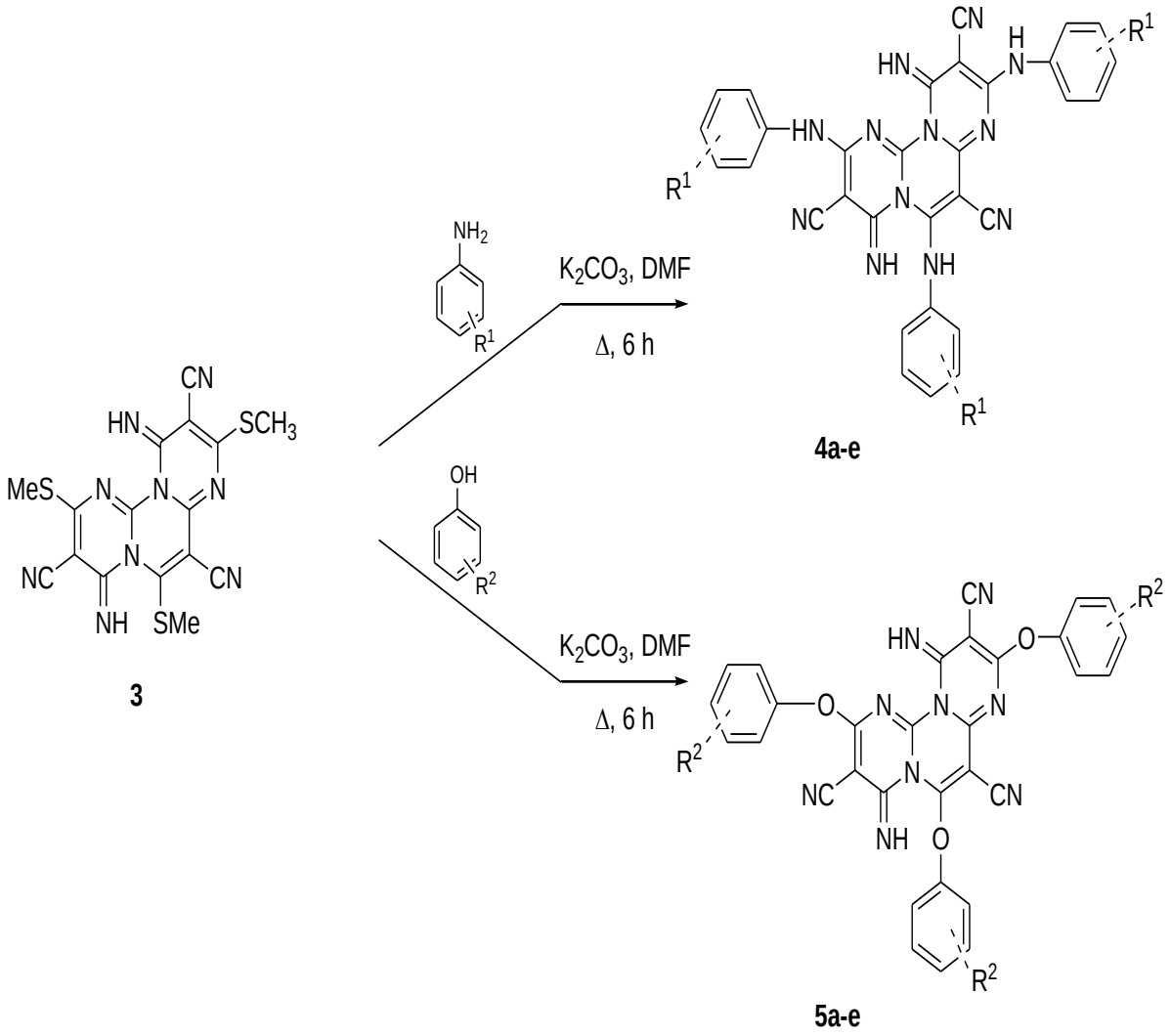
Compound **3**contains methylthio groups (-SMe) at positions 2,6 and 9 thatare activated by adjacent ring nitrogen atoms and electron-withdrawing cynide groups towards a nucleophilic displacement. Compound **3**was allowed to react with various selected nucleophiles includingarylamines and phenols. The successful synthesis of products **4a-e** and **5a-e** is shown in Scheme 2.



4a: R^1 = H
4b: R^1 = 4-Br
4c: R^1 = 4-OMe
4d: R^1 = 4-Me
4e: R^1 = 4-NO_2

5a: R^2 = H
5b: R^2 = 4-Br
5c: R^2 = 4-OMe
5d: R^2 = 4-Cl
5e: R^2 = 4-NO_2

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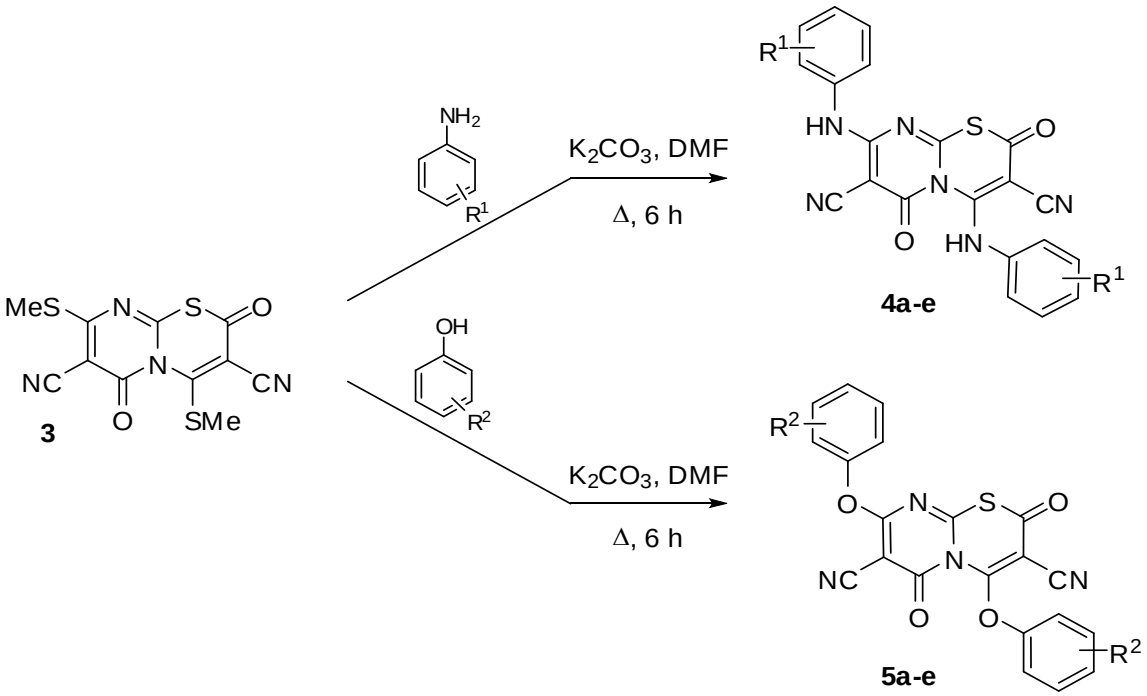

4a: R^1 = H **5a**: R^2 = H
4b: R^1 = 4-Br **5b**: R^2 = 4-Br
4c: R^1 = 4-OMe **5c**: R^2 = 4-OMe
4d: R^1 = 4-Me **5d**: R^2 = 4-Cl
4e: R^1 = 4-NO_2 **5e**: R^2 = 4-NO_2

Scheme 2

III. CONCLUSION

A new pyrimido[2,1-b][1,3]thiazine **3** and its derivatives 4 and 5 were synthesized by using simple and efficient chemistry.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. The silica gel F_{254} plates were used for thin layer chromatography (TLC); the spots were examined under UV light and then developed in an iodine vapor. Column chromatography was performed with silica gel (BDH 100-200 mesh). Solvents were purified according to standard procedures. The spectra were recorded as follows: IR, KBr pellets,a Perkin-Elmer RX1 FT-IR spectrophotometer; ^{1}H NMR, $CDCl_3$, 200 MHz, a Varian Gemini 200 instrument. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

2,6-Dihydro-4,8-bis(methylthio)-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (3)

A mixture of 2-cyano-3,3-bis(methylthio)acrylate **(1**,2 mmol)andthiourea **(2**, 1 mmol), DMF (10 mL) and anhydrous potassium carbonate (10mg) wereheated under reflux for 12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, washed with water (3 x 10 mL) and extracted with ethyl acetate (3 x 10 mL). The extract was concentrated and the residue was subjected to column chromatography (silica gel, hexane-ethyl acetate) to obtain pure solid compound**3**:Yield 86%;mp 135-136°C, IR: 2250, 1690, 1610, 1590 cm^{-1}; ^{1}H NMR: δ3.35 (s, 6H, SMe); ^{13}C NMR (50 MHz,$CDCl_3$): δ190.2, 115.1, 135.9, 132.6, 52.0, 51.9; ESI-MS:m/z 323 $[M+H]^+$. Anal. Calcd for $C_{11}H_6N_4S_3O_2$: C, 41.00%.; H, 1.90%.; N, 17.36%.; S, 29.82. Found: C, 41.01%.; H, 1.93%.; N, 17.40%.; S, 29.79%

4,8-Disubstituted 2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitriles 4a-e and5a-d

A mixture of **3**(1 mmol), a substituted aromatic amine or a substituted aromatic phenol (2

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mmol), DMF (10 mL) and anhydrous potassium carbonate (10mg) was heated under reflux for 6 h, then cooled to room temperature and poured into ice cold water. The separated solid product **4** or **5**was filtered, washed with water and crystallized from ethyl alcohol**.**

2,6-Dihydro-2,6-dioxo-4,8-bis(phenylamino)pyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (4a)

Colorless solid; yield 52%; mp 143-144°C; IR: 2240, 1695, 1615, 1595 cm^{-1}; ^1H NMR:δ4.15 (s, 2H), 6.90-7.70 (m, 10H); ESI-MS:m/z413 $[M+H]^+$. Anal. Calcd for $C_{21}H_{12}N_6O_2S$: C, 61.18; H, 2.94; N, 20.36; S, 7.75. Found: C, 61.20; H, 2.97; N, 20.35; S, 7.80.

4,8-bis(4-Bromophenylamino)-2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicar-bonitrile (4b)

Paleyellowsolid; yield 68%); mp 177-179°C, IR: 2235, 1685, 1622, 1585 cm^{-1}; ^1H NMR: δ4.51 (s, 2H), 7.62 (d, 8H,J=8.0 Hz); ESI-MS:m/z 571, 573 $[M+H]^+$. Anal. Calcd for $C_{21}H_{10}N_6SO_2Br_2$: C, 44.22, H, 1.79, N, 14.75, S, 5.65, Br, 28.05. Found: C, 44.32, H, 1.88, N, 15.00,S, 5.91, Br, 28.01.

4,8-Bis(4-methoxyphenylamino)-2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarboni-trile (4c)

Colorless solid; yield 68%; mp 155-156°C; IR: 2245, 1698, 1627, 1590 cm^{-1}; ^1H NMR:δ3.60 (s, 6H), 4.80 (s, 2H), 7.62 (m, 8H); ESI-MS:m/z 473 $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}N_6SO_4$: C, 58.47, H, 3.41, N, 17.79, S, 6.79. Found: C, 58.50, H, 3.45, N, 17.83,S, 6.84.

4,8-Bis(p-tolylamino)-2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (4d)

White solid; yield 68%; mp 155-157°C; IR: 2235, 1701, 1618, 1580 cm^{-1};^1H NMR:δ1.82 (s, 6H,),5.21 (s, 2H), 7.36 (d, 8H,J=8.0 Hz);ESI-MS:m/z 441 $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}N_6SO_2$: C, 62.72, H, 3.66, N, 19.08, S, 7.28. Found: C, 62.74, H, 3.69, N, 19.11,S, 7.32.

4,8-Bis(3-nitrophenylamino)-2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (4e)

Yellow solid; yield 68%;mp 185-187°C; IR: 2248, 1710, 1625, 1590 cm^{-1}; ^1H NMR:δ4.81 (s, 2H), 7.30 (s, 2H), 7.65 (m, 6H);ESI-MS:m/z 503 $[M+H]^+$. Anal. Calcd for $C_{21}H_{10}N_8SO_6$: C, 50.23, H, 2.01, N, 22.30, S, 6.38. Found: C, 50.25, H, 2.06, N, 22.35, S, 6.41.

2,6-Dioxo-4,8-diphenoxy-2H,6H-pyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (5a)

Colorles solid; yield 70%; mp 145-148°C; IR: 2220, 1695, 1615, 1580 cm^{-1};^1H NMR: δ7.20 (s, 10H); ESI-MS:m/z 415 $[M+H]^+$. Anal. Calcd for $C_{21}H_{10}N_4SO_4$: C, 60.89, H, 2.47, N, 13.57, S, 7.82. Found: C,60.92, H, 2.51, N, 13.61,S, 7.84.

4,8-Bis(4-bromophenoxy)-2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (5b)

Yellow solid; yield 73%;mp 165-167°C;IR: 2235, 1690, 1620, 1590 cm^{-1}; ^1H NMR:δ7.55 (d, 8H,J= 8.0 Hz); ESI-MS:m/z573, 575 $[M+H]^+$. Anal. Calcd for $C_{21}H_8N_4SO_4Br_2$: C, 44.09, H, 1.43, N, 9.88, S, 5.64. Found: C, 44.12, H, 1.45, N, 9.81,S, 5.66.

4,8-Bis(4-methoxyphenoxy)-2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (5c)

White solid; yield 60%;mp 144-145°C; IR: 2222, 1695, 1615, 1598 cm^{-1}; ^1H NMR:δ3.80(s 6H),7.70 (d, 8H,J=8.0 Hz), ESI-MS m/z: 475 $[M+H]^+$.Anal. Calcd for $C_{23}H_{14}N_4SO_6$: C, 58.22, H, 2.99, N, 11.82, S, 6.79. Found: C, 58.50, H, 3.00, N, 11.50,S, 6.4.

4,8-Bis(4-chlorophenoxy)-2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (5d)

Whitesolid;yield 65%;mp 155-158°C;IR: 2205, 1705, 1610, 1590 cm^{-1};^1H NMR:δ7.1-7.5 (d, 8H,J=8.0 Hz); ESI-MS:m/z483 $[M+H]^+$. Anal. Calcd for $C_{21}H_8N_4SO_4Cl_2$: C, 52.20, H, 1.72, N, 11.62, S, 6.63. Found: C, 52.22, H, 1.72, N, 11.65, S, 6.67.

4,8-Bis(3-nitrophenoxy)-2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (5e)

Yellow solid; yield 75%;mp 182-183°C; IR: 2215, 1710, 1615, 1595 cm^{-1}; ^1H NMR:δ7.2-7.3 (s, 2H), 7.6-7.8 (m, 6H);ESI-MS:m/z505 $[M+H]^+$. Anal. Calcd for $C_{21}H_8N_6SO_8$: C, 50.07, H, 1.68, N, 16.68, S, 6.34. Found: C, 50.07, H, 1.68, N, 16.72, S, 6.38.

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IV. ACKNOWLEDGEMENTS

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