# AN EFFICIENT SYNTHESIS OFTHIAZOLOPYRIMIDINE DERIVATIVES EMPLOYING SILICA SODIUM CATALYST

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*Abstract :* A new convenient strategy fort he synthesis of a series of thiazolopyrimidine derivatives by using recyclable Silica Sodium Catalyst (SSC).The reaction is clean with admirable yield and shorter reaction time.

**Keywords:** Thiazolopyrimidine, Silica Sodium Catalyst (SSC).

## I. INTRODUCTION

Heterocyclic compound containing thiazole ring is a fascinating building block in a range of natural products such as vitamin $B_1$ (thiamine) and the penicillin thiazoles as well as bioactive compounds applicable in variety of pharmaceuticals or agrochemical agents [1–3]. Thiazolopyrimidines have turn out to be of curiosity due to their ability to inhibit 2-methylerythritol-2, 4-cyclodiphosphate synthase [4]. They have been also relevant as analgesic, antiparkinsonian [5], anticancer [6–8], acetyl cholinesterase inhibitors [9] and phosphate inhibitors [10]. A sort of condensed thiazolopyrimidines have been reported as antimicrobial [11-13], inhibitors of HIV-1 reverse transcriptase [14] and anti-inflammatory [15].

In the conventional methods for the synthesis of thiazolopyrimidine and its derivatives most commonly used catalyst is anhydrous $K_2CO_3$ [16] and Triethyl amine [17] further than this, there has been no any catalyst used in their synthesis until now. In contrast, the easy separation by simple filtration and reusability after completion of the reaction is acknowledging much more concentration in design and synthesis of reusable heterogeneous catalyst. The entire process is eco-friendly due to reusability of catalyst, and thus plays an excellent role in organic chemistry due to environmental and economic considerations. Correspondingly heterogeneous and reusable catalysts are predominant over homogeneous catalysts. Although supported catalysts are available on different supports, including charcoal, alumina, silica, and polymer.

Amongst them silica supported catalyst could be placed in the vanguard because of its idiosyncratic features such as no swelling, good mechanical and thermal stability, high efficiency due to large surface area, high mechanical and thermal stabilities, greater selectivity, low toxicity, reusability, and simplicity of handling. Encouraged by these features and it is evident from the previous literature that silica-supported catalyst has invoked vast attention as a potential green, heterogeneous, and eco-friendly catalyst to construct carbon–carbon and carbon-heteroatom bonds in various organic transformations, we wish to report silica supported sodium carbonate catalyst [18, 19] in the synthesis of a series of substituted thiazolopyrimidiine derivatives.

## II. EXPIRMENTAL

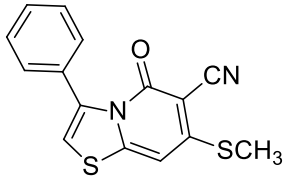
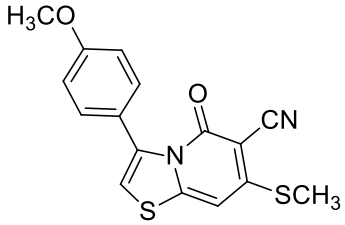
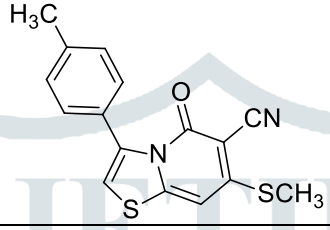
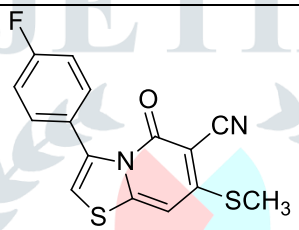
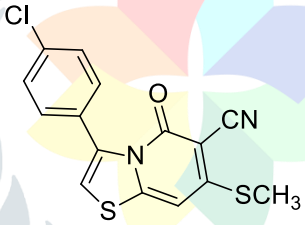
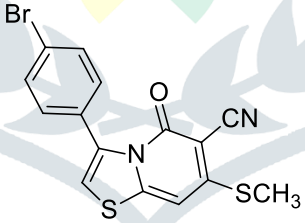
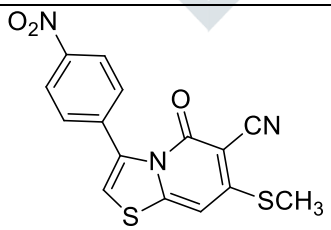
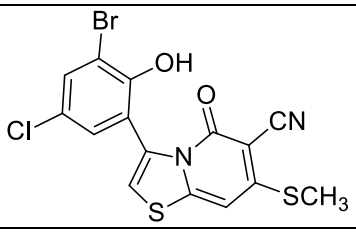
All reagents were obtained from commercial suppliers and used without further purification. Reaction progress was monitored through thin layer chromatography (TLC) on pre-coated Merk alu-foil plate (silica gel 60F-254, 0.25 mm thickness) visualized by iodine vapors. Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded (in KBr pallets) on SCHIMADZU spectrophotometer. $^1$H NMR spectra were recorded on Avance/ Bruker 400 MHz spectrophotometer using TMS as an internal standard. All NMR spectra were obtained in DMSO d6/ duterated chloroform ($CDCl_3$); chemical shifts are reported in parts per million, and coupling constant in hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), m (multiplet). The mass spectra were recorded on GC-MS SHIMADZU (Q2010PLUS) in EI mode spectrometer and mass values are reported I m/z.

**General procedure for the synthesis of3-(substitutedphenyl)-7-(methylthio)-5-oxo-5H-thiazolo[3,2-a]pyridine-6-carbonitrile(3a-h):**

In a clean, dry 100 ml round bottom flask, take (1 mmol) of 4-(substitutedphenyl)thiazol-2-amine **(1a-h)** and (1 mmol) of ethyl 2-cyano-3,3-bis(methylthio)acrylate **(2)** in DMF (5 ml) as a solvent and SSC as a basic catalyst in a catalytic amount. Reflux this reaction mixture for 3-4. After completion of reaction as monitored by TLC, the solid catalyst was separated by simple filtration. The mother liquor was poured on crushed ice and neutralized it. The solid separated was filtered, dried and recrystalized by ethanol solvent, to get the final products **(3a-h).**

**7-(methylthio)-5-oxo-3-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile(3a):** Yellow solid; FT-IR: 3100, 2912, 2235, 1664, 1632, $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 2.51(s, 3H, -$SCH_3$), δ 7.10-7.77 (m, 6H, ArH + CH of thiazole); . $^{13}$C NMR (DMSO-d6) $^{\delta}$C: 15.5, 86.9, 110.5, 115, 127.9,128.3, 128.6, 134.2, 148.9, 158.3, 160, 170.6; Mass (m/z): 299($M^+$).

**Table 3:**

| Sr. No. | Comp. Code | Product | Yield (%) | M.P. °C. |
|---|---|---|---|---|
| 1 | 3a |  | 88 | 150-152 |
| 2 | 3b |  | 87 | 152-154 |
| 3 | 3c |  | 86 | 156-158 |
| 4 | 3d |  | 89 | 154-156 |
| 5 | 3e |  | 90 | 158-160 |
| 6 | 3f |  | 92 | 164-166 |
| 7 | 3g |  | 87 | 181-183 |
| 8 | 3h |  | 85 | 174-176 |

**Reaction conditions:** 4-(substitutedphenyl)thiazol-2-amine **(1a-h)** (1 mmol), ethyl 2-cyano-3,3-bis(methylthio)acrylate **(2)** and SSC in a catalytic amount, Isolated yield.

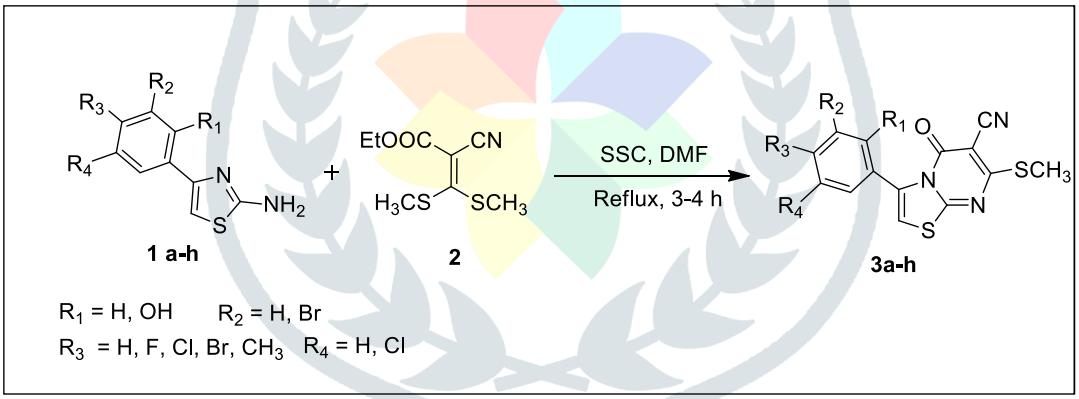
**3-(4-methoxyphenyl)-7-(methylthio)-5-oxo-5H-thiazolo[3,2-a]pyridine-6-carbonitrile(3b):**
Yellow solid; FT-IR: 3163, 2906,2218, 1674, 1626, 1577, 1477, 1284, 1087, 908, 833 $cm^{-1}$.$^1$H-NMR (400 MHz, DMSO-$d_6$) δ 2.51(s, 3H, -$SCH_3$), δ 3.88 (s, 3H, $OCH_3$), δ 7.0-8.15 (m, 5H, -ArH+ CH of thiazole) ppm.$^{13}$C NMR (DMSO-d6) $^{\delta}$C: 15.8, 56, 86, 110, 117, 121, 127, 130, 149.1, 157.3, 160, 161, 171.1; Mass (m/z): 330 ($M^+$).
**3-(4-chlorophenyl)-7-(methylthio)-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile(3e):** Yellow solid, FT-IR: 2212, 1644, 1592 $cm^{-1}$; $^1$H NMR (DMSO-d6): δ 2.58 (s, 3H, $SCH_3$ ), δ 7.16 (s, 1H, 5H-thiazole), δ 7.31–7.67 (m, 4 H, Ar-H) ppm;$^{13}$C NMR (DMSO-d6) $^{\delta}$C:15.7, 87.2, 110.8, 115, 120.7, 128, 132.5, 134.2, 149, 158.9, 161.3, 170.8; Mass (m/z): 334 (M+1).
**3-(4-bromophenyl)-7-(methylthio)-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (3f):** Yellow solid, FT-IR: 2232, 1652, 1598 $cm^{-1}$. $^1$H NMR (DMSO-d6): δ 2.64 (s, 3H, $SCH_3$ ), δ 7.21 (s, 1H, 5H-thiazole), δ 7.41–7.74 (m, 4 H, Ar-H) ppm;$^{13}$C NMR (DMSO-d6) $^{\delta}$C:15.7, 87.2, 111. 3, 115.9, 123.7, 128, 132.5, 134.2, 149, 158.9, 161.3, 170.8; Mass (m/z): 378 (M+1).
**3-(3-bromo-5-chloro-2-hydroxyphenyl)-7-(methylthio)-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (3h):** Yellow solid, FT-IR (KBr): 3444, 3335, 3203, 2922, 2231, 1670, 1629, 1308, 1262, 1045, 856 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 2.51 (s, 3H, $SCH_3$), δ 7.52-7.94 (m, 3H, -Ar H+ 5-H of thiazol), δ 13.5 (s, 1H, -OH) ppm. $^{13}$C NMR (DMSO-d6) $^{\delta}$C: 15.9, 87.7, 110.8, 112.9, 115.4, 116.1, 126.1, 130.4, 135, 150, 157.2, 158.9, 161.3, 172: Mass (m/z): 428 ($M^+$).

## III. RESULT AND DISCUSSION

To optimize the reaction condition, we initiate our examination of the reaction of 4-(substitutedphenyl)thiazol-2-amine **(1a-h)** and ethyl 2-cyano-3,3-bis(methylthio)acrylate **(2)** in the presence of different catalysts and solvent DMF (Table 1). To create the factual effectiveness of the solvent for the synthesis of 3-(4-substitutedphenyl)-7-(methylthio)-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile **(3a-h)**derivatives, the test reaction was performed without catalyst. It was found that only a 25 % amount of product was obtained in the absence of catalyst in DMF as a solvent even after 12h (**Table 1, entry 1**). Then we performed the test reaction by using different catalysts such as triethylamine, $K_2CO_3$, $Na_2CO_3$and SSC, at that time we obtained 60% (refluxing for 8h), 75% (refluxing for 6h), 78% (refluxing for 6h) and 92% (for refluxing 4h) yields of product respectively (**Table 1, entries 2-5**). From these results we come to know that, SSC was shown tobe more effective in terms of yield and time for completion of the reaction (**Table 1, entry 5**).The use of the SSC catalyst has several advantages over a conventional catalyst, such as its ease of handling (as a bench top catalyst), stable, inexpensive, recyclability and reusability. Therefore, we disclosed a novel methodology in the synthesis of thiazolopyrimidine derivatives.

For best of our knowledge, nobody reported synthesis of thiazolopyrimidine derivatives using silica sodium carbonate as a heterogeneous catalyst.

**Scheme 1: Synthesis of 3-(substitutedphenyl)-7-(methylthio)-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile**

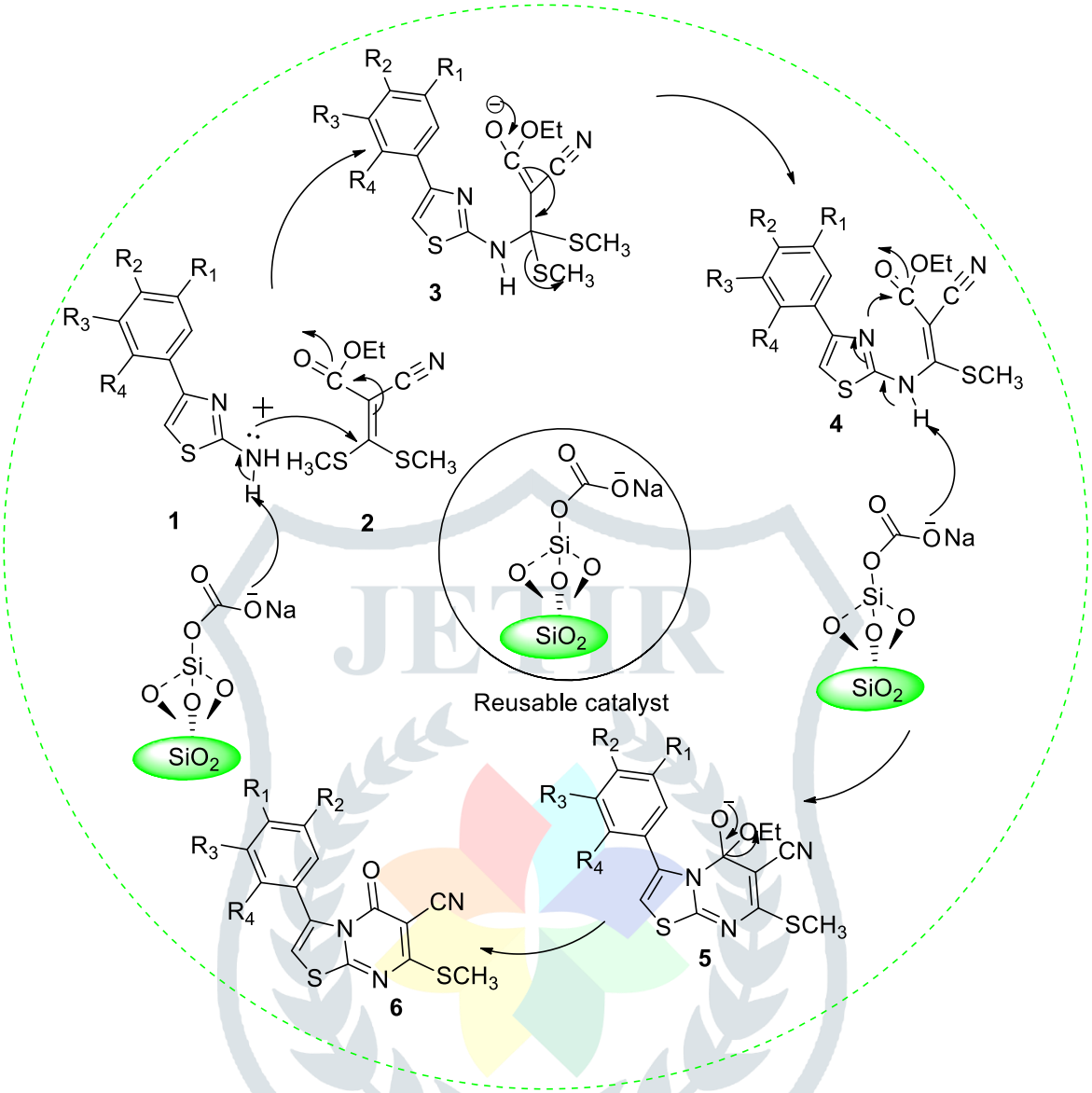



According to previously reported method [20], we have prepared Silica Sodium Carbonate catalyst(SSC).The 3-(substitutedphenyl)-7-(methylthio)-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile **(3a-h)** was obtained by refluxing 4-(substitutedphenyl)thiazol-2-amine**(1a-h)** with ethyl 2-cyano-3,3-bis(methylthio)acrylate **(2)**in the presence of DMF and a catalytic amount of SSC.The structure of **(3a-h)** was confirmed according to its spectral data. A plausible mechanism for the 3-(4-substitutedphenyl)-7-(methylthio)-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (**3a-h)**formation is outlined in scheme 2. The reusability is one of the most imperative advantage of the SSC catalyst and creates it helpful for profitable relevance also. Accordingly, the recovery and reusability of the catalyst were examined. The recyclability of the catalyst was checked with the model reaction (Table 2, entries 1–5). The catalyst was recovered after completion of the first run, the catalyst is separated by simple filtration. The recovered catalyst was dried at 60-70℃ for 10 h and tested in up to four more substrates under the same conditions. The catalyst confirmed excellent recyclability in all these reactions (Table 2), while the reaction times and yield remained almost the same without losing its catalytic activity.

Recyclability and reusability of Catalyst

| Entry | Reaction Cycle | % Yield |
|---|---|---|
| 1 | First | 92 |
| 2 | Second | 92 |
| 3 | Third | 92 |
| 4 | Fourth | 92 |
| 5 | Fifth | 91 |

**Scheme 2: Plausible mechanism for the synthesis of 3-(substitutedphenyl)-7-(methylthio)-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile.**




## IV. CONCLUSION

In conclusion, we have described an eco-friendly approach by means of Silica Sodium Carbonate (SSC) as an efficient catalyst for the synthesis of a new series of thiazolopyrimidine derivatives. The important features of the method are utilization of cheap and easy to handle catalyst, reusability of catalyst, short reaction time with admirable yield.

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