

# An Efficient Route to Thieno[2,3-*d*]pyrimidine Derivatives by Tandem [2,3] and [3,3] Sigmatropic Rearrangement

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**Abstract:** Synthesis of biologically important thieno[2,3-*d*]pyrimidine derivatives **6a-f** in 65-78% yields have been reported. The conditions applied here are based on the less studied tandem rearrangement protocol. The precursor sulfides in 73-85% were prepared from *N,N*-dimethyl-6-chlorouracil and 1-aryloxy-4-chlorobut-2-yne by phase transfer catalyzed reaction condition.

**Keywords:** [2,3] and [3,3] sigmatropic rearrangement, *m*-chloroperoxybenzoic acid, thieno[2,3-*d*]pyrimidine.

## INTRODUCTION

Compounds containing pyrimidine moiety continue to attract considerable interest due to their diverse biological and pharmacological activities. Numerous pyrimidine-based molecules are found to be active against cancer [1] and AIDS viruses [2]. A 6-substituted uracil derivative, 1-(2-hydroxymethyl)-6-phenylthiothymine [3] has attained considerable significance as a specific inhibitor for HIV-1, a causative agent for AIDS [4]. Recently there has been a flurry of activity in the synthesis of thieno[2,3-*d*]pyrimidine derivatives due to their remarkable biological and medicinal properties. Thienopyrimidine derivative containing biaryl moiety eg, 5-(*N*-benzyl-*N*-methylaminomethyl)-1-(2,6-difluorobenzyl)-6-[4-(3-methoxyureido)phenyl]-3-phenylthieno[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione [5] is found to be highly potent and an orally active non peptide LH-releasing hormone antagonist. Another thienopyrimidine derivative where N(3) is substituted with [(2-methoxyphenyl) piperazinyl]ethyl moiety and hydrogen at N(1) is a potent oral antihypertensive agent in spontaneously hypertensive rats [6]. Some 2-alkoxy and 2-alkyl substituted thienopyrimidine show significant antifungal and antibacterial activities [7,8]. Several methodologies are available for the synthesis of thieno[2,3-*d*]pyrimidine derivatives [9-11]. But no such convenient high yielding one-pot methodology for the synthesis of thienopyrimidine moiety is available in literature.

For the last few years, we embarked on the synthesis of novel heterocyclic compounds having potential biological activity by the application of sigmatropic rearrangement [12] and free radical cyclization approach [13]. For the construction of five-membered nitrogen and sulfur heterocycles the application of tandem sigmatropic rearrangement protocol is quite useful and most interesting [14]. The uniqueness of this methodology lies in its inherent approach which describes a tandem [2,3] and [3,3] sigmatropic rearrangements where the second [3,3] sigmatropic rearrangement step takes place through two hetero atoms. Hence we decided to apply this excellent high yielding

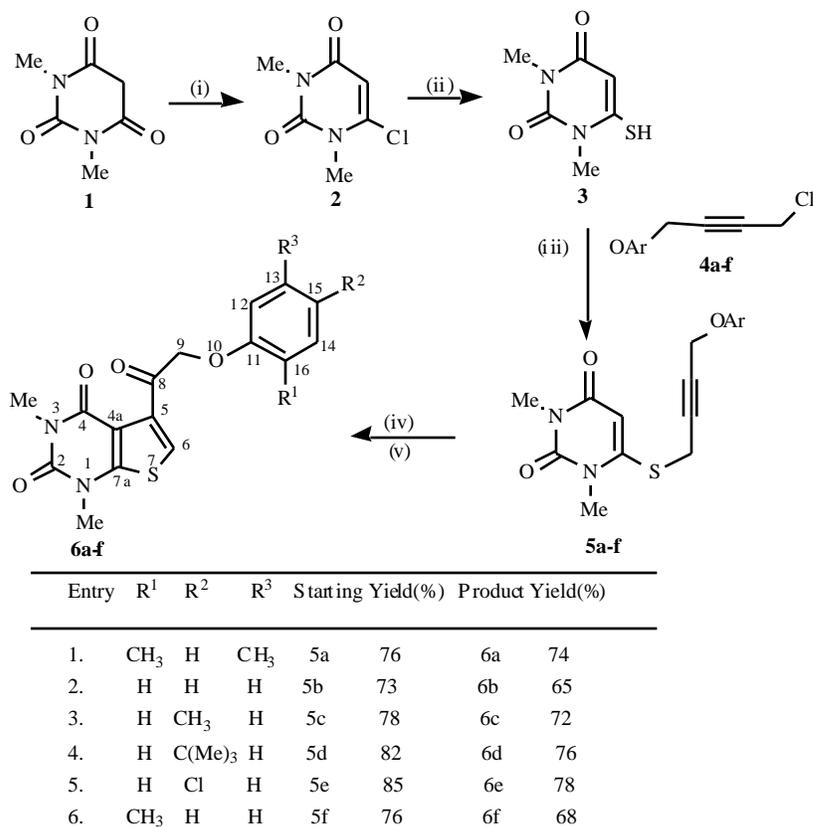
methodology for the construction of thieno[2,3-*d*]pyrimidine moiety. In this paper we wish to report the successful application of this general approach towards the synthesis of potentially bioactive thieno[2,3-*d*]pyrimidine derivatives.

## RESULTS AND DISCUSSION

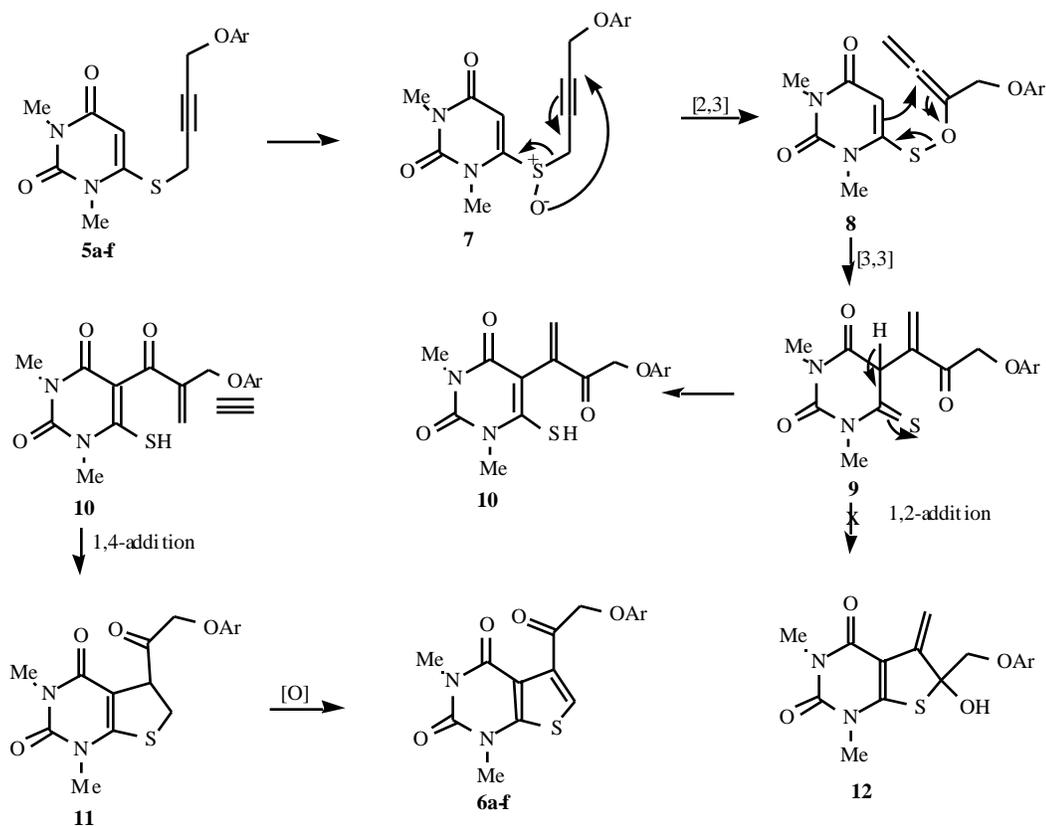
Accordingly, the synthetic precursors 6-[4'-(aryloxy)but-2'-ynyl]thio-1,3-dimethylpyrimidine-2,4-dione (**5a-f**) for this investigation were prepared starting from very simple *N,N*-dimethylbarbituric acid (Scheme 1). Treatment of barbituric acid with POCl<sub>3</sub> under refluxing condition for 2h furnished 6-chlorouracil which was then treated with NaSH in dry EtOH at 0°C followed by room temperature stirring for 4h to afford 6-mercaptopuracil derivative. Phase transfer catalyzed alkylation of this compound with different 1-aryloxy-4-chlorobut-2-yne [15] using benzyl triethyl ammonium chloride BTEAC as phase transfer catalyst led to the formation of compounds **5a-f** in 73-85% yield. The compounds **5a-f** were characterized from their elemental analyses and spectral data.

Having synthesized the desired precursors with vinyl-propargyl segment the stage was set for evaluating the construction of C-C bond at the C-5 position of the uracil moiety *via* tandem rearrangement protocol [14]. We considered the exceedingly simple and mild sulfoxide rearrangement [14a] reaction for the construction of fused thiophene ring. Consequently the sulfide **5a** was oxidized to the sulfoxide by the slow addition of *m*-chloroperoxybenzoic acid in chloroform at 0-5°C over one hour. The sulfoxide is not very stable and partially rearranges during the work up of the reaction mixture. Therefore, no attempt was made to isolate the sulfoxide. The crude product was refluxed for 2h in chloroform to afford 5-(3,5-dimethylphenoxyacetyl)-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4-dione (**6a**) in 74% yield (Scheme 1). This was characterized from its elemental analysis and spectral data. The <sup>1</sup>H NMR spectra of the compound **6a** displayed as one-proton singlet at 5.20 indicating the presence of the aryloxymethylene protons adjacent to the ketonic carbonyl group. The C<sub>6</sub> proton of the thiophene ring appeared as one proton singlet at 7.26. Two *N*-methyl groups appeared at 3.39 and 3.58 as three-proton singlet each. Two aromatic methyl groups appeared as three

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**Scheme 1.** Reagent and Conditions: (i) POCl<sub>3</sub>, Reflux, 2h. (ii) NaSH, EtOH, 0°C, rt. (iii) BTEAC, CH<sub>2</sub>Cl<sub>2</sub>, NaOH, H<sub>2</sub>O; (iv) *m*-CPBA, CHCl<sub>3</sub>, 0-5°C (v) CHCl<sub>3</sub>, Reflux, 2h.



**Scheme 2.**

proton singlet each at 2.20 and 2.27. Mass spectrum of the compound **6a** showed a molecular ion peak at  $m/z = 358$  ( $M^+$ ). Encouraged by the result, the remaining substrates were similarly treated to furnish compounds **6b-f** in 65-78% yield (Scheme 1).

The formation of thieno[2,3-*d*]pyrimidines **6a-f** can be rationalized by assuming a tandem rearrangement protocol as described in Scheme 2. The sulfoxides **7a-f** formed by the initial addition of *m*-chloroperoxybenzoic acid to the sulfide solution in chloroform undergo a [2,3] sigmatropic rearrangement to produce allene intermediates **8** which then undergo [3,3] sigmatropic rearrangement through the S-O bond followed by tautomerization to produce intermediates **10**. The intermediates **10** contain nucleophilic SH functionality suitably juxtaposed to an  $\alpha,\beta$ -unsaturated enone moiety so as to allow intramolecular Michael type addition to give compounds **11a-f**. Alternatively there could be a possibility of 1,2-addition of SH group to the carbonyl group to produce cyclic tertiary alcohol **12**. But at the present instance no such product was isolated. The aromatization of **11a-f** to the final **6a-f** was observed *via* an unknown mechanism. It may be assumed that the greater stability of the aromatized products as compared to their dihydro-precursors might be responsible for the instantaneous dehydrogenation.

Here we have demonstrated a facile route to the synthesis of thieno[2,3-*d*]pyrimidine derivatives which may have biological activity. The methodology adopted here to synthesize these compounds is found to be mild and general for the regioselective synthesis of fused thiophene ring. Additionally an unusual instantaneous dehydrogenation reaction is observed along with tandem rearrangement. This is an extremely facile route to thieno[2,3-*d*]pyrimidine derivatives.

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#### REFERENCES

- [1] (a) Heidegger, C. *Pyrimidine and Pyrimidine Antimetabolites in Cancer Medicine*; Holland, J. F.; Frei, E., Eds.; Lea and Febiger: Philadelphia **1984**; 801; (b) Taylor, E. C.; Liu, B. *J. Org. Chem.*, **2003**, *68*, 9938.
- [2] Macilwain, C. *Nature*, **1993**, *365*, 378.
- [3] (a) Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R. T.; Balzarini, J.; Declercq, E. *J. Med. Chem.*, **1989**, *32*, 2507; (b) Baba, M.; Tanaka, H.; Declercq, E.; Pauwels, R.; Balzarini, J.; Schols, D.; Nakashima, H.; Perno, C. F.; Walker, R. T.; Miyasaka, T. *Biochem. Biophys. Res. Commun.*, **1989**, *165*, 1375; (c) Declercq, E. *Med. Res. Rev.*, **1993**, *13*, 229.
- [4] (a) Gallo, R. C. *Sci. Am.*, **1986**, *255*, 78; (b) Gallo, R. C. *Sci. Am.*, **1987**, *256*, 38.
- [5] Saski, S.; Cho, N.; Nara, Y.; Harada, M.; Endo, S.; Suzuki, N.; Furuya, S.; Fujino, M. *J. Med. Chem.*, **2003**, *46*, 113.
- [6] Russell, R. K.; Press, J. B.; Rampulla, R. A.; McMally, J. J.; Falcotico, R.; Keisre, J. A.; Bright, D. A.; Tobia, A. *J. Med. Chem.*, **1988**, *31*, 1786.
- [7] Aboulwafa, O. M.; Ismail, K. A.; Koreishi, E. A. *Farmaco*, **1992**, *47*, 631.
- [8] Hozien, J. A.; Atta, F. M.; Hassan, K. M.; Abdel-Wahab, A. A.; Ahmed, S. A. *Synth. Commun.*, **1996**, *26*, 3733.
- [9] Ding, M-W.; Yang, S-J.; Zhu, J. *Synthesis*, **2004**, 75.
- [10] Hirota, K.; Shirahashi, M.; Senda, S.; Yogo, M. *J. Heterocycl. Chem.*, **1990**, *27*, 717.
- [11] Senga, K.; Ichiba, M.; Nishigaki, S. *J. Org. Chem.*, **1978**, *43*, 1677.
- [12] (a) Majumdar, K. C.; Das, U. *J. Org. Chem.*, **1998**, *63*, 9997; (b) Majumdar, K. C.; Kundu, U. K.; Ghosh, S. K. *Org. Lett.*, **2002**, *4*, 2629; (c) Majumdar, K. C.; Kundu, U. K.; Ghosh, S. *J. Chem. Soc. Perkin Trans. I*, **2002**, 2139; (d) Majumdar K. C.; Ghosh, S. K. *Tetrahedron Lett.*, **2002**, *43*, 2115.
- [13] (a) Majumdar, K. C.; Mukhopadhyay, P. P. *Synthesis*, **2004**, 1864; (b) Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P. K. *Synth. Commun.*, **2004**, *35*, 1291; (c) Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P. K. *Synth. Commun.*, **2004**, *35*, 1291; (d) Majumdar, K. C.; Chattopadhyay S. K. *Tetrahedron Lett.*, **2004**, *45*, 6871.
- [14] (a) Majumdar, K. C.; Thyagarajan, B. S.; *J. Chem. Soc. Chem. Commun.*, **1972**, 83; (b) Thyagarajan, B. S.; Hillard, J. B.; Reddy, K. V.; Majumdar, K. C. *Tetrahedron Lett.*, **1974**, *23*, 1999.
- [15] Hillard, J. B.; Reddy, K. V.; Majumdar, K. C.; Thyagarajan, B. S. *J. Heterocycl. Chem.*, **1974**, *11*, 369.

## SUPPORTING DATA

## Experimental

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer L 120-000A spectrometer ( $\nu_{\max}$  in  $\text{cm}^{-1}$ ) on KBr disks. UV absorption spectra were recorded in  $\text{CHCl}_3$  on a Shimadzu UV-2401PC spectrophotometer ( $\lambda_{\max}$  in nm).  $^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (125.7 MHz) spectra were recorded on a Varian-400 FT-NMR and Bruker DPX-500 spectrometers in  $\text{CDCl}_3$  (chemical shifts in  $\delta$ ) with TMS as internal standard. Elemental analyses were recorded on a Leco 932 CHNS analyzer. Mass spectra were recorded on a JEOL JMS-600 instrument. Silica gel [(60-120 mesh), Spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether refers to the fraction boiling between  $60^\circ\text{C}$  -  $80^\circ\text{C}$ .

The 1-aryloxy-4-chlorobut-2-yne were prepared according to the published procedure [15].

## General Procedure for the Preparation of 6-Mercapto Uracil

A mixture of *N,N*-dimethylbarbituric acid (2g, 12.8mmol) in phosphorous oxychloride (10ml) was refluxed for 2h. The excess phosphorous oxychloride was then removed by distillation. To the crude mixture, crushed ice was added. The mixture was neutralized by adding solid sodium carbonate and extracted with dichloromethane. The organic layer was washed with water. After removal of the solvent the crude mass, was dissolved in ethanol and added drop wise to the stirring solution of sodium hydrogen sulfide in ethanol at  $0^\circ\text{C}$  for 1h. The stirring was continued at room temperature for another 4h till complete consumption of 6-chlorouracil. Ethanol was removed under reduced pressure and the crude mass was acidified with 6N HCl. The reaction mixture was then extracted with dichloromethane (4x10ml) and washed with water (1x10ml). Due to the unstable nature of 6-mercaptouracil, this was immediately used in the next step.

## General Procedure for the Preparation of Compounds 5a-f

To a stirred solution of 6-mercapto uracil (obtained from 2g, 12.8mmol of barbituric acid) in dichloromethane (40ml) were added a solution of 1-aryloxy-4-chlorobut-2-yne (1g, 5.7mmol) in dichloromethane (10ml), 50ml 1% NaOH solution, benzyl triethyl ammonium chloride (0.5g, 1.8 mmol) at room temperature. The stirring was continued for 12h at the same temperature, the reaction mixture was diluted with water (20ml) and was extracted with dichloromethane (2 x 25ml). The organic layer was washed with dilute HCL (10ml), with water (10ml) and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of the solvent (dichloromethane) gave the crude product, which was purified by column chromatography (ethyl acetate/petroleum ether = 1:3.5) to give compounds **5a-f**.

**6-[4'-(2,5-dimethylphenoxy)but-2'-ynyl]thio-1,3-dimethylpyrimidine-2,4-dione (5a)**

Yield: 76%; Brownish solid; mp:  $108^\circ\text{C}$ .

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 220, 280 nm.

IR (KBr):  $\nu_{\max}$  = 1428, 1652, 1700, 2950  $\text{cm}^{-1}$ .

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 2.16 (s, 3H, Ar-**CH<sub>3</sub>**), 2.29 (s, 3H, Ar-**CH<sub>3</sub>**), 3.32 (s, 3H, *N*-**CH<sub>3</sub>**), 3.44 (s, 3H, *N*-**CH<sub>3</sub>**), 3.70 (s, 2H, -**SCH<sub>2</sub>**), 4.68 (s, 2H, -**OCH<sub>2</sub>**), 5.64 (s, 1H, C=CH), 6.67 (s, 1H, Ar-**H**), 6.70 (d,  $J$  = 7.8 Hz, 1 H, Ar-**H**), 6.98 (d,  $J$  = 7.8 Hz, 1 H, Ar-**H**).

MS:  $m/z$  = 344 ( $\text{M}^{+\cdot}$ )

Anal. Cald. for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ : C, 62.79; H, 5.81; N, 8.13. Found: C, 62.95; H, 6.02; N, 8.28 %.

**6-[4'-(phenoxy)but-2'-ynyl]thio-1,3-dimethylpyrimidine-2,4-dione (5b)**

Yield: 73%; Viscous liquid.

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 220, 277 nm.

IR (Neat):  $\nu_{\max}$  = 1493, 1651, 1698, 2923  $\text{cm}^{-1}$ .

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 3.32 (s, 3H, *N*-**CH<sub>3</sub>**), 3.43 (s, 3H, *N*-**CH<sub>3</sub>**), 3.69 (s, 2H, -**SCH<sub>2</sub>**), 4.69 (s, 2H, -**OCH<sub>2</sub>**), 5.65 (s, 1H, C=CH), 6.90-6.99 (m, 3H, Ar-**H**), 7.29-7.25 (m, 2H, Ar-**H**).

MS:  $m/z$  = 316 ( $\text{M}^{+\cdot}$ )

Anal. Cald. For  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ : C, 60.75; H, 5.06; N, 8.86. Found: C, 60.55; H, 5.28; N, 8.69 %.

**6-[4'-(4-methylphenoxy)but-2'-ynyl]thio-1,3-dimethylpyrimidine-2,4-dione (5c)**

Yield: 78%; Brownish solid; mp:  $84^\circ\text{C}$ .

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 222, 278 nm.

IR (KBr):  $\nu_{\max}$  = 1427, 1649, 1693, 2937  $\text{cm}^{-1}$

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 2.27 (s, 3H, Ar-**CH<sub>3</sub>**), 3.33 (s, 3H, *N*-**CH<sub>3</sub>**), 3.43 (s, 3H, *N*-**CH<sub>3</sub>**), 3.69 (s, 2H, -**SCH<sub>2</sub>**), 4.65 (s, 2H, -**OCH<sub>2</sub>**), 5.65 (s, 1H, C=CH), 6.80 (d,  $J$  = 8.4 Hz, 2H, Ar-**H**), 7.06 (d,  $J$  = 8.4 Hz, 2H, Ar-**H**).

MS:  $m/z$  = 330 ( $\text{M}^{+\cdot}$ )

Anal. Cald. For  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ : C, 61.81; H, 5.45; N, 8.48. Found: C, 61.96; H, 5.67; N, 8.62 %.

**6-[4'-(4-tertiarybutylphenoxy)but-2'-ynyl]thio-1,3-dimethylpyrimidine-2,4-dione (5d)**

Yield: 82%; Viscous Liquid

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 222, 282 nm.

IR (Neat):  $\nu_{\max}$  = 1428, 1652, 1701, 2960  $\text{cm}^{-1}$ .

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 1.28 (s, 9H, -**CM<sub>3</sub>**), 3.33 (s, 3H, *N*-**CH<sub>3</sub>**), 3.44 (s, 3H, *N*-**CH<sub>3</sub>**), 3.70 (s, 2H, -**SCH<sub>2</sub>**), 4.66 (s, 2H, -**OCH<sub>2</sub>**), 5.68 (s, 1H, C=CH), 6.84 (d,  $J$  = 8.7 Hz, 2H, Ar-**H**), 7.28 (d,  $J$  = 8.7Hz, 2H, Ar-**H**).

MS:  $m/z$  = 372 ( $\text{M}^{+\cdot}$ )

Anal. Cald. For  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ : C, 64.51; H, 6.45; N, 7.52; Found: C, 64.32; H, 6.61; N, 7.38.

**6-[4'-(4-chlorophenoxy)but-2'-ynyl]thio-1,3-dimethylpyrimidine-2,4-dione (5e)**

Yield: 85%; Brownish solid; mp:  $98^\circ\text{C}$ .

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 224, 280 nm.

IR (KBr):  $\nu_{\max}$  = 1490, 1651, 1699, 2944  $\text{cm}^{-1}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 3.33 (s, 3H, *N-CH*<sub>3</sub>), 3.44 (s, 3H, *N-CH*<sub>3</sub>), 3.69 (s, 2H, *-SCH*<sub>2</sub>), 4.66 (s, 2H, *-OCH*<sub>2</sub>), 5.64 (s, 1H, C=CH), 6.84 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.21 (d, *J* = 8.8 Hz, 2H, Ar-H).

MS: *m/z* = 350, 352 ( $\text{M}^+$ )

Anal. Cald. For  $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_3\text{S}$ : C, 54.70; H, 4.27; N, 7.97. Found: C 54.96; H, 4.45; N, 8.09 %.

**6-[4'-(2-methylphenoxy)but-2'-ynyl]thio-1,3-dimethylpyrimidine-2,4-dione (5f)**

Yield: 76%; Brownish solid; mp: 118°C.

IR (KBr):  $\nu_{\max}$  = 1427, 1650, 1693, 2939  $\text{cm}^{-1}$ .

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 219, 277 nm.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 2.21 (s, 3H, Ar-*CH*<sub>3</sub>), 3.32 (s, 3H, *N-CH*<sub>3</sub>), 3.43 (s, 3H, *N-CH*<sub>3</sub>), 3.69 (s, 2H, *-SCH*<sub>2</sub>), 4.70 (s, 2H, *-OCH*<sub>2</sub>), 5.64 (s, 1H, C=CH), 6.85 (m, 2H, Ar-H), 7.11 (m, 2H, Ar-H).

MS: *m/z* = 330 ( $\text{M}^+$ )

Anal. Cald. For  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ : C, 61.81; H, 5.45; N, 8.48. Found: C, 61.58; H, 5.61; N, 8.26 %.

**General Procedure for the Preparation of Compounds 6a-f**

To a stirred solution of compounds **5a-f** (0.28m.mol) in chloroform (10ml) at 0°C, a solution of *m*-chloroperoxybenzoic acid (77%, 125 mg, 0.72 mmol) in chloroform (10ml) was added drop wise for 1h. The stirring was continued for another one hour. Then the reaction mixture was washed with saturated solution of sodium carbonate (3x5ml) to remove the organic acid followed by water (2x10ml) and brine (10ml) and dried ( $\text{Na}_2\text{SO}_4$ ). The chloroform solution was then refluxed for 4h. After removal of chloroform a viscous liquid obtained which was column chromatographed (ethyl acetate/petroleum ether = 1:3) to give compounds **6a-f**.

**5-(2,5-dimethylphenoxyacetyl)-1,3-dimethylthieno[2,3-d]pyrimidine-2,4-dione (6a)**

Yield: 74%; Yellowish solid; mp: 108°C.

IR (KBr):  $\nu_{\max}$  = 1496, 1662, 1697, 2923  $\text{cm}^{-1}$ .

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 221, 278 nm.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 2.20 (s, 3H, Ar-*CH*<sub>3</sub>), 2.27 (s, 3H, Ar-*CH*<sub>3</sub>), 3.39 (s, 3H, *N-CH*<sub>3</sub>), 3.58 (s, 3H, *N-CH*<sub>3</sub>), 5.20 (s, 2H, *-OCH*<sub>2</sub>), 6.61 (s, 1H, Ar-H), 6.64 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.94 (d, *J* = 7.8 Hz, 1 H, Ar-H), 7.26 (s, 1H, C=CH-S).

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 125.7MHz): 204.9, 161.2, 152.0, 154.7, 155.9, 138.7, 136.8, 131.0, 130.9, 122.2, 124.5, 120.3, 113.1, 56.4, 32.4, 22.0, 21.7, 16.1.

MS: *m/z* = 358 ( $\text{M}^+$ ).

Anal. Cald. For  $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4\text{S}$ : C, 60.33; H, 5.02; N, 7.82. Found: C, 60.48; H, 4.79; N, 8.06 %.

**5-(phenoxyacetyl)-1,3-dimethylthieno[2,3-d]pyrimidine-2,4-dione (6b)**

Yield: 65%; Viscous liquid.

IR (Neat):  $\nu_{\max}$  = 1493, 1652, 1701, 2953  $\text{cm}^{-1}$ .

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 223, 277 nm.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 3.40 (s, 3H, *N-CH*<sub>3</sub>), 3.59 (s, 3H, *N-CH*<sub>3</sub>), 5.29 (s, 2H, *-OCH*<sub>2</sub>), 6.88-6.96 (m, 3H, Ar-H), 7.23-7.25 (m, 2H, Ar-H), 7.31 (s, 1H, C=CH-S).

MS: *m/z* = 330 ( $\text{M}^+$ ).

Anal. Cald. For  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$ : C, 58.18; H, 4.24; N, 8.48. Found: C, 58.32; H, 4.45; N, 8.66 %.

**5-(4-methylphenoxyacetyl)-1,3-dimethylthieno[2,3-d]pyrimidine-2,4-dione (6c)**

Yield: 72%; Yellowish solid; mp: 84°C.

IR (KBr):  $\nu_{\max}$  = 1425, 1650, 1699, 2921  $\text{cm}^{-1}$ .

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 283,222 nm.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 2.27 (s, 3H, Ar-*CH*<sub>3</sub>), 3.40 (s, 3H, *N-CH*<sub>3</sub>), 3.59 (s, 3H, *N-CH*<sub>3</sub>), 5.26 (s, 2H, *-OCH*<sub>2</sub>), 6.80 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.06 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.30 (s, 1H, C=CH-S).

MS: *m/z* = 344 ( $\text{M}^+$ )

Anal. Cald. For  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$ : C, 59.30; H, 4.65; N, 8.13. Found: C, 59.52; H, 4.82, N, 7.78 %.

**5-(4-tertiarybutylphenoxyacetyl)-1,3-dimethylthieno[2,3-d]pyrimidine-2,4-dione (6d)**

Yield: 76%; Viscous Liquid.

IR (Neat):  $\nu_{\max}$  = 1460, 1651, 1701, 2958  $\text{cm}^{-1}$ .

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 222, 282 nm.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 1.28 (s, 9H, *-CMe*<sub>3</sub>), 3.41 (s, 3H, *N-CH*<sub>3</sub>), 3.59 (s, 3H, *N-CH*<sub>3</sub>), 5.26 (s, 2H, *-OCH*<sub>2</sub>), 6.82 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.27 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.31 (s, 1H, C=CH-S).

MS: *m/z* = 386 ( $\text{M}^+$ ).

Anal. Cald. For  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$ : C, 62.17; H, 5.69; N, 7.25. Found: C, 62.40; H, 5.49; N, 7.49 %.

**5-(4-chlorophenoxyacetyl)-1,3-dimethylthieno[2,3-d]pyrimidine-2,4-dione (6e)**

Yield: 78%; Yellowish solid; mp: 98°C.

IR (KBr):  $\nu_{\max}$  = 1493, 1659, 1698, 2931  $\text{cm}^{-1}$ .

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 222, 280 nm.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 3.41 (s, 3H, *N-CH*<sub>3</sub>), 3.60 (s, 3H, *N-CH*<sub>3</sub>), 5.30 (s, 2H, *-OCH*<sub>2</sub>), 6.85 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.20 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.33 (s, 1H, C=CH-S).

MS: *m/z* = 364, 366 ( $\text{M}^+$ )

Anal. Cald. For  $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}_4\text{S}$ : C, 52.60; H, 3.56; N, 7.67. Found: 52.78; H, 3.81; N, 7.52 %.

**5-(2-methylphenoxyacetyl)-1,3-dimethylthieno[2,3-d]pyrimidine-2,4-dione (6f)**

Yield: 68%; White solid; mp: 118°C.

IR (KBr):  $\nu_{\max}$  = 1495, 1661, 1693, 2921  $\text{cm}^{-1}$ .

UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 223, 278 nm.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400MHz):  $\delta$  = 2.08 (s, 3H, Ar-**CH<sub>3</sub>**), 3.40 (s, 3H, *N*-**CH<sub>3</sub>**), 3.59 (s, 3H, *N*-**CH<sub>3</sub>**), 5.26 (s, 2H, -**OCH<sub>2</sub>**), 6.78-6.86 (m, 2H, Ar-**H**), 7.07-7.13 (m, 2H, Ar-**H**), 7.28 (s, 1H, C=**CH-S**).

MS:  $m/z$  = 344 ( $\text{M}^+$ ).

Anal. Cald. For  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$ : C, 59.30; H, 4.65; N, 8.13. Found: C, 59.46; H, 4.42; N, 8.35 %.