

CHAPTER 3

**Metal-free C-C Bond Formation via C-H
Activation of Methylarenes Using
Lemon Juice as a Biodegradable
Catalyst: A Sustainable Pathway
Towards the Synthesis of
Chromenopyrimidine Derivatives**

Metal-free C-C Bond Formation via C-H Activation of Methylarenes Using Lemon Juice as a Biodegradable Catalyst: A Sustainable Pathway Towards the Synthesis of Chromenopyrimidine Derivatives

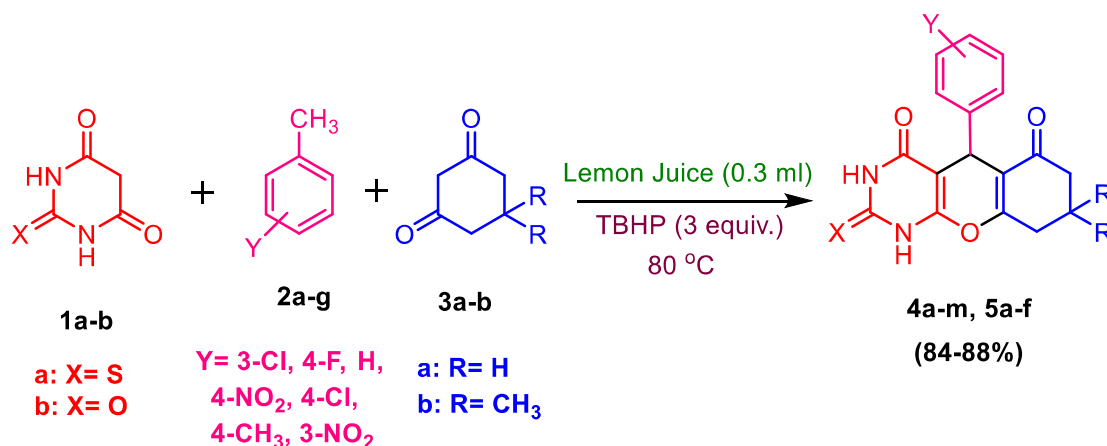
3.1 Introduction

Recently, the direct C-H bond functionalization/ C-C bond formation of hydrocarbons via C-H bond activation has attracted much attention in organic synthesis [1-6]. Especially, in view of the green perspective, selective and controlled functionalization without using metal catalyst has become a challenging area for organic chemists. As a characteristic C-H bond functionalization route, the direct benzylic oxidation of alkylarenes is a vital procedure to afford the parallel carbonyl compounds [7-10] which is used as a constituent in the construction of well-designed fine chemicals and pharmaceuticals [11-13]. Methylarenes are the most abundant and inexpensive naturally available surrogates for carbonyl compounds, which are obtained from crude oil as a by-product in the production of gasoline and coke. A number of methods have been reported for the direct benzylic oxidation of alkylarenes using heavy metal catalysts such as stoichiometric amount of KMnO_4 [14], Cr(VI) [15], excess amount of Fe [16], Ru [17], Mn [18], Bi [19], Co [20], Au [21], Rh [22], with an oxidant. These methods are non-selective, tiresome, environmentally unfavorable and operationally difficult. In view of the above, the direct selective oxidation of methylarenes to benzaldehydes is of crucial importance. Thus, there is a demand of operationally simple, high yielding, green, eco-friendly protocol using metal free oxidants and high-atom economical pathway. The

controlled oxidation of methylarenes to benzaldehyde in good yield [23-25] provoked us to design a new process that utilizes methylarenes as a green, low-cost and readily accessible starting material for the *in-situ* generation of benzaldehydes.

Recent developments in the utilization of benzylic C-H bonds inspired us to look into the C-H bond activation of easily available and inexpensive methylarenes to achieve the synthesis of biologically active chromenopyrimidines. In past decades, the use of natural catalysts in organic synthesis has also attracted considerable attention due to their eco-friendly and environmentally acceptable nature. Lemon juice is a biodegradable and natural catalyst. The existence of citric and ascorbic acid introduces the lemon juice as an acidic catalyst in organic synthesis [26-29].

In spite of previous efforts, a metal-free and mild approach for the synthesis of chromenopyrimidine derivatives using accessible, inexpensive, naturally available and sustainable surrogates are still in high demand. By considering all the above facts and as a part of our contemporary research on the design and construction of biologically active compounds [30], we herein report a lemon juice catalyzed, metal-free, one-pot synthesis of chromenopyrimidine derivatives via C-H activation of methylarenes by using *tert*-butyl hydroperoxide (TBHP, 70% in H₂O) as an oxidant (**Scheme 3.1**).



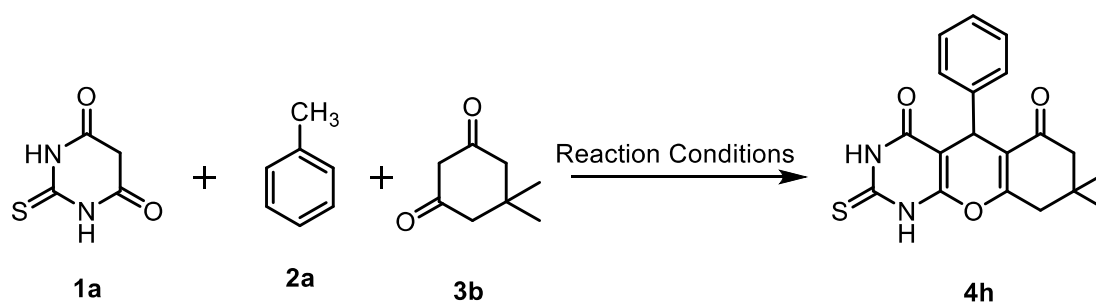
Scheme 3.1 Lemon juice catalyzed one-pot synthesis of chromenopyrimidine derivatives.

3.2 Results and Discussion

The work initiated by taking thiobarbituric acid (1.0 mmol), toluene (2.0 mmol) and dimedone (1.0 mmol) as a model reaction. The desired product (**4h**) could not be obtained in sufficient yield when 10 mol% of sulfamic acid, benzoic acid, formic acid and acetic acid were used with 10 equiv. of TBHP (70% in H₂O) (**Table 3.1, entry 1-4**). When lemon juice was used with TBHP, 40% yield of the product was obtained (**Table 3.1, entry 5**). Subsequently, screening of various solvents like benzene, CCl₄, hexane, CH₂Cl₂, CHCl₃, H₂O (**Table 3.1, entries 6-11**) was done. Pleasingly, 67% yield was afforded with lemon juice (0.2 ml) and TBHP (4 equiv.) under solvent-free condition (**Table 3.1, entry 14**). Now the amount of lemon juice and TBHP were optimized and it was found that 0.3 ml of lemon juice with 3 equivalents of TBHP worked best, giving 85% yield of the product (**Table 3.1, entry 17**). Since lemon juice contains citric acid and ascorbic acid, their different amounts were tested under optimized condition (**Table 3.1, entry 19-24**) and it was found that lemon juice has better catalytic properties than citric

acid followed by ascorbic acid. Better catalytic activity of citric acid than ascorbic acid can be attributed to the higher K_a (acid dissociation constant) value of citric acid. Encouraged by this, numerous oxidants like H_2O_2 , oxone, $K_2S_2O_8$, meta-chloroperoxybenzoic acid (*m*-CPBA), peracetic acid (PAA), benzyl peroxide, benzoyl peroxide, *tert*-butyl peroxybenzoate (TBPB) and di-*tert*-butyl peroxide (DTBP) were tested with lemon juice, under solvent-free condition but unfavourable results were obtained (Table 3.1, entry 25-33). In the further optimization, lemon juice without TBHP (Table 3.1, entry 34), TBHP without lemon juice (Table 3.1, entry 35) and reaction without lemon juice and TBHP (Table 3.1, entry 36) under solvent-free condition have been done but they did not lead to the desired product. Combinations of citric and ascorbic acid have been tested under optimized condition to investigate their effect in lemon juice catalyzed reactions and results are summarized in Table 3.1 (entry 37-40). Combinations have been made on the basis of amount of citric and ascorbic acid present in lemon juice [31, 32].

Table 3.1 Optimized reaction condition for the model reaction **4h**.^[a]



Entry	Catalyst	Oxidant(eq.)	Solvent	Temperature (°C)	Time(h)	Yield ^[b] (%)
1	Sulfamic acid (10 mol%)	TBHP(10)	-	80	10	15
2	Benzoic Acid (10 mol%)	TBHP(10)	-	80	10	18
3	Formic acid (10 mol%)	TBHP(10)	-	80	10	10
4	Acetic acid (10 mol%)	TBHP(10)	-	80	10	12
5	Lemon Juice (0.2 ml)	TBHP(10)	-	80	10	40
6	Lemon Juice (0.2 ml)	TBHP(10)	Benzene	80	7	Trace
7	Lemon Juice (0.2 ml)	TBHP(10)	CCl ₄	80	7	Trace
8	Lemon Juice (0.2 ml)	TBHP(10)	Hexane	80	7	28
9	Lemon Juice (0.2 ml)	TBHP(10)	CH ₂ Cl ₂	80	7	30
10	Lemon Juice (0.2 ml)	TBHP(10)	CHCl ₃	80	7	32
11	Lemon Juice (0.2 ml)	TBHP(10)	H ₂ O	80	7	50
12	Lemon Juice (0.2 ml)	TBHP(5)	H ₂ O	80	7	50
13	Lemon Juice (0.2 ml)	TBHP(4)	H ₂ O	80	7	50
14	Lemon Juice (0.2 ml)	TBHP(4)	-	80	3	67
15	Lemon Juice (0.2 ml)	TBHP(3)	-	80	3	76
16	Lemon Juice (0.2 ml)	TBHP(2)	-	80	3	65
17	Lemon Juice (0.3 ml)	TBHP(3)	-	80	3	85
18	Lemon Juice (0.4 ml)	TBHP(3)	-	80	3	75

19	Citric acid (1 mol%)	TBHP(3)	-	80	5	34
20	Citric acid (2 mol%)	TBHP(3)	-	80	5	40
21	Citric acid (3 mol%)	TBHP(3)	-	80	5	46
22	Citric acid (5 mol%)	TBHP(3)	-	80	5	58
23	Citric acid (10 mol%)	TBHP(3)	-	80	5	60
24	Ascorbic acid (10 mol%)	TBHP(3)	-	80	5	8
25	Lemon Juice (0.3 ml)	H ₂ O ₂ (3)	-	80	3	N.R.
26	Lemon Juice (0.3ml)	Oxone(3)	-	80	3	N.R.
27	Lemon Juice (0.3 ml)	K ₂ S ₂ O ₈ (3)	-	80	3	trace
28	Lemon Juice (0.3 ml)	<i>m</i> -CPBA(3)	-	80	3	N.R.
29	Lemon Juice (0.3 ml)	PAA(3)	-	80	3	trace
30	Lemon Juice (0.3 ml)	Benzyl Peroxide(3)	-	80	3	N.R.
31	Lemon Juice (0.3 ml)	Benzoyl Peroxide(3)	-	80	3	N.R.
32	Lemon Juice (0.3 ml)	TBPB(3)	-	80	3	20
33	Lemon Juice (0.3 ml)	DTBP(3)	-	80	3	30
34	Lemon Juice (0.3 ml)	-	-	80	3	N.R.
35	-	TBHP(3)	-	80	3	N.R.
36	-	-	-	80	12	N.R.
37	Citric acid: Ascorbic Acid (10:1)	TBHP(3)	-	80	3	45
38	Citric acid: Ascorbic Acid (100:1)	TBHP(3)	-	80	3	50

39	Citric acid: Ascorbic Acid (1000:1)	TBHP(3)	-	80	3	57
40	Citric acid: Ascorbic Acid (10000:1)	TBHP(3)	-	80	3	67

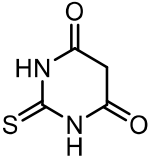
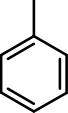
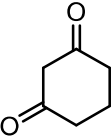
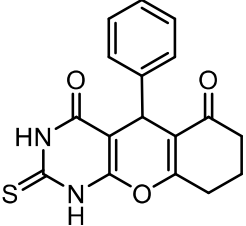
^[a]Reaction condition: thiobarbituric acid (1.0 mmol), toluene (2.0 mmol), dimedone (1.0 mmol).

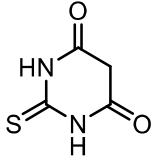
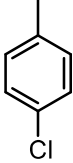
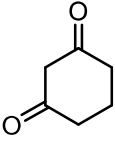
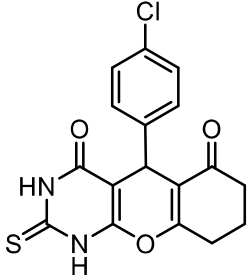
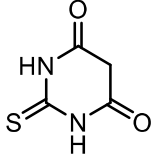
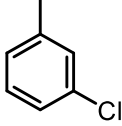
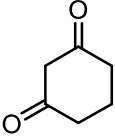
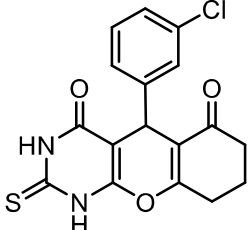
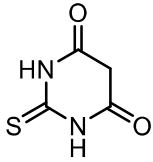
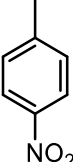
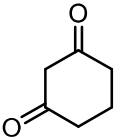
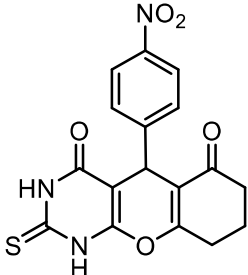
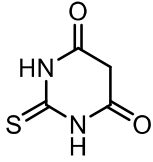
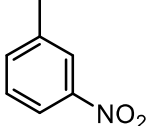
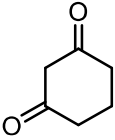
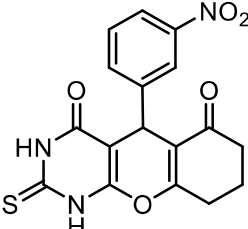
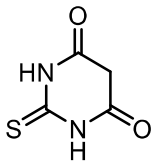
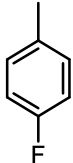
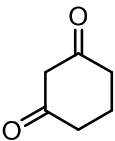
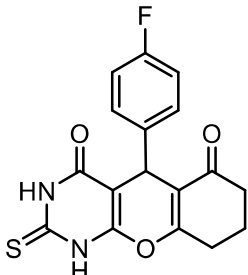
^[b]Isolated yield after column chromatography.

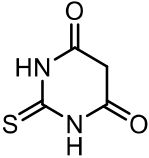
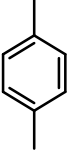
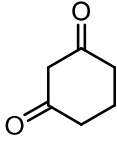
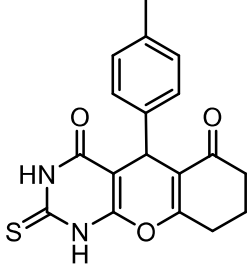
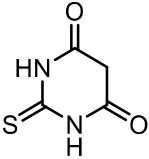
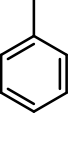
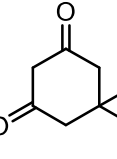
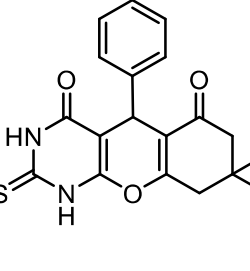
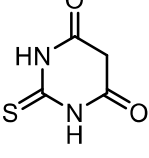
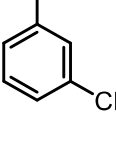
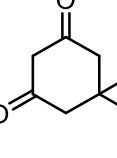
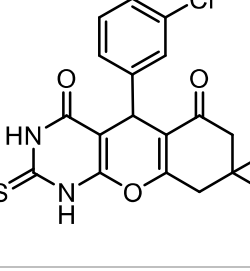
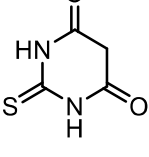
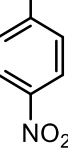
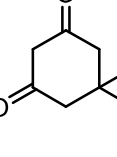
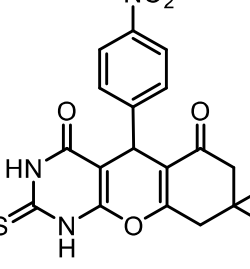
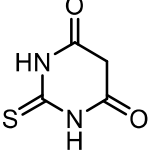
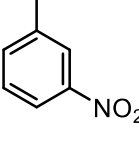
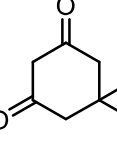
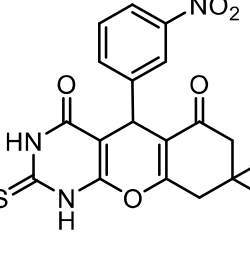
N.R.=no reaction

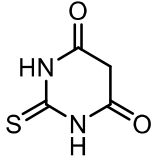
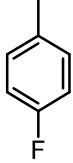
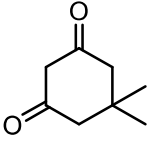
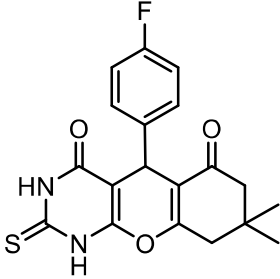
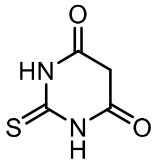
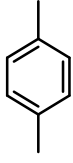
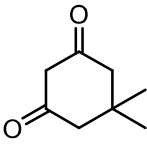
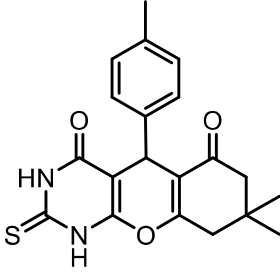
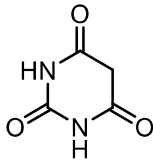
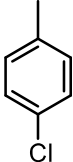
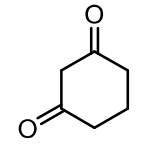
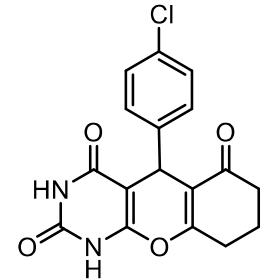
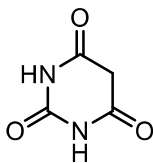
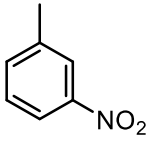
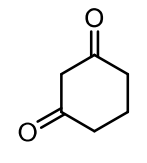
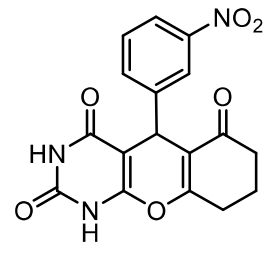
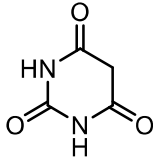
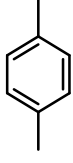
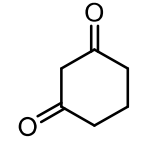
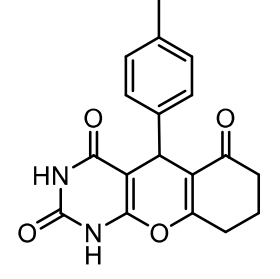
In order to extend the scope of this methodology, a wide range of methylarenes i.e. both electron-donating as well as electron-withdrawing groups containing methylarenes such as toluene (**2a**), 1-chloro-4-methylbenzene (**2b**), 1-chloro-3-methylbenzene (**2c**), 1-methyl-4-nitrobenzene (**2d**), 1-methyl-3-nitrobenzene (**2e**), 1-fluoro-4-methylbenzene (**2f**), *p*-xylene (**2g**) were investigated under optimal conditions. All the methylarenes worked efficiently with thiobarbituric acid (**1a**) / barbituric acid (**1b**) and 1,3-cyclohexanedione (**3a**) / dimedone (**3b**) to afford the desired products in good yields (84-88%) (Table 3.2).

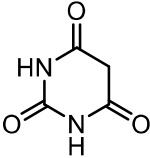
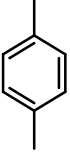
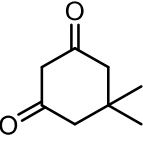
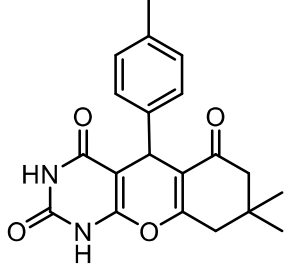
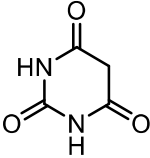
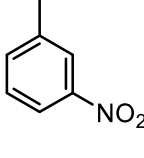
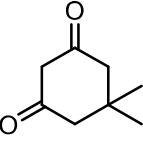
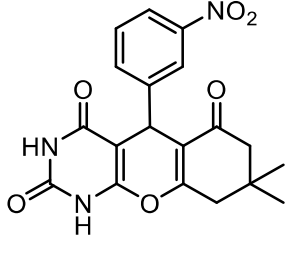
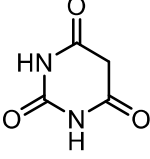
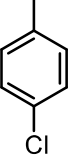
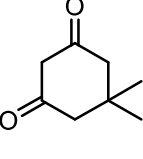
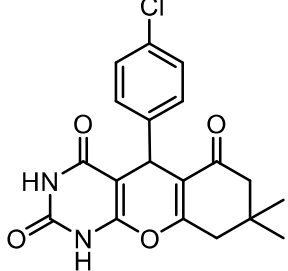
Table 3.2 Screening of substrates for the synthesis of chromenopyrimidines.^[a]

Entry	1	2	3	4 ^[a]	Yield ^[b] (%)
4a	 1a	 2a	 3a		85

4b	 1a	 2b	 3a	 86
4c	 1a	 2c	 3a	 88
4d	 1a	 2d	 3a	 87
4e	 1a	 2e	 3a	 86
4f	 1a	 2f	 3a	 84

4g	 1a	 2g	 3a	 85
4h	 1a	 2a	 3b	 87
4i	 1a	 2c	 3b	 88
4j	 1a	 2d	 3b	 86
4k	 1a	 2e	 3b	 84

4l	 1a	 2f	 3b	 85
4m	 1a	 2g	 3b	 88
5a	 1b	 2b	 3a	 87
5b	 1b	 2e	 3a	 85
5c	 1b	 2g	 3a	 88

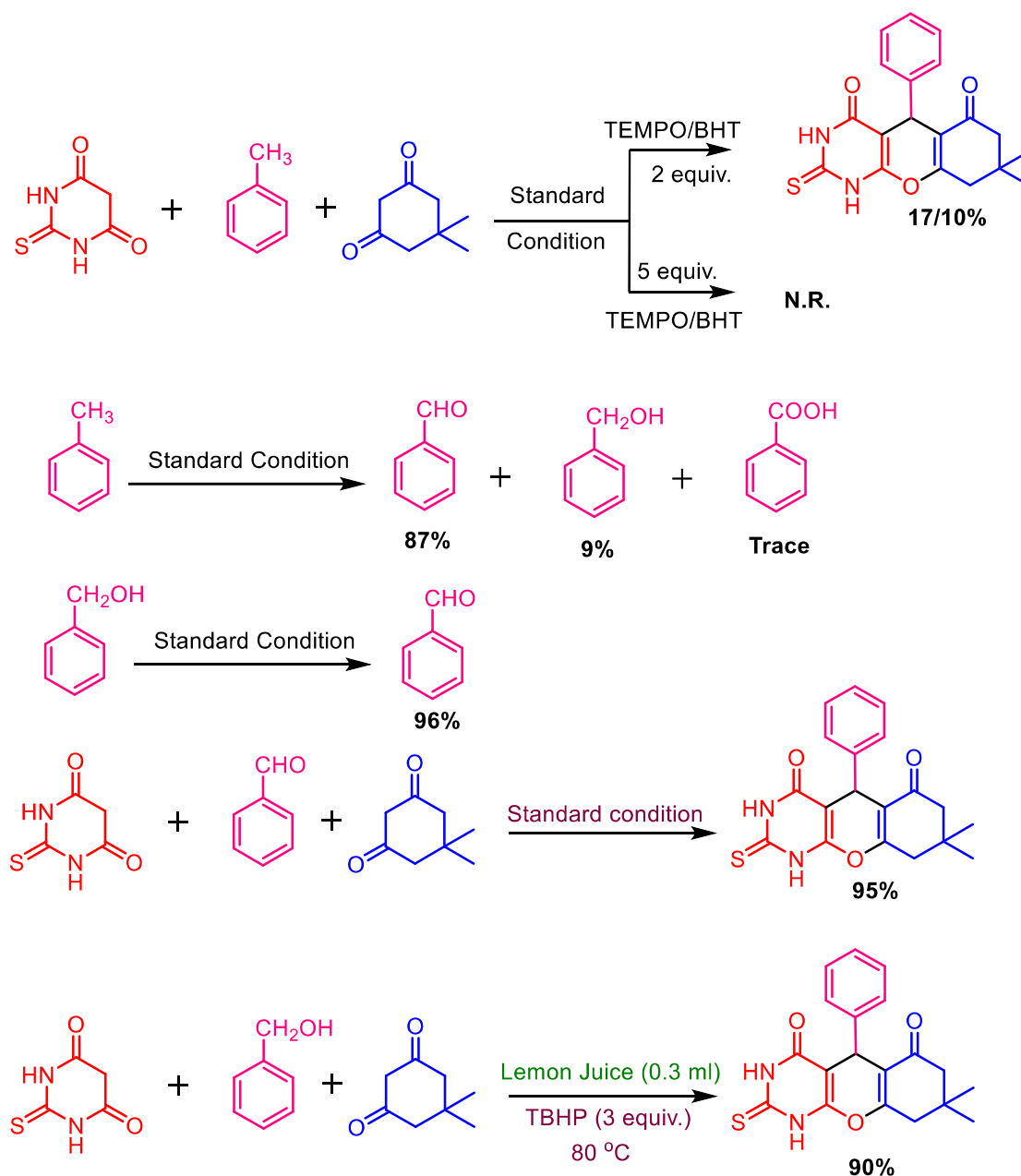
5d	 1b	 2g	 3b	 86
5e	 1b	 2e	 3b	 84
5f	 1b	 2b	 3b	 85

^[a] Products were characterized by ¹H, ¹³C NMR and IR analysis.

^[b] Isolated yield.

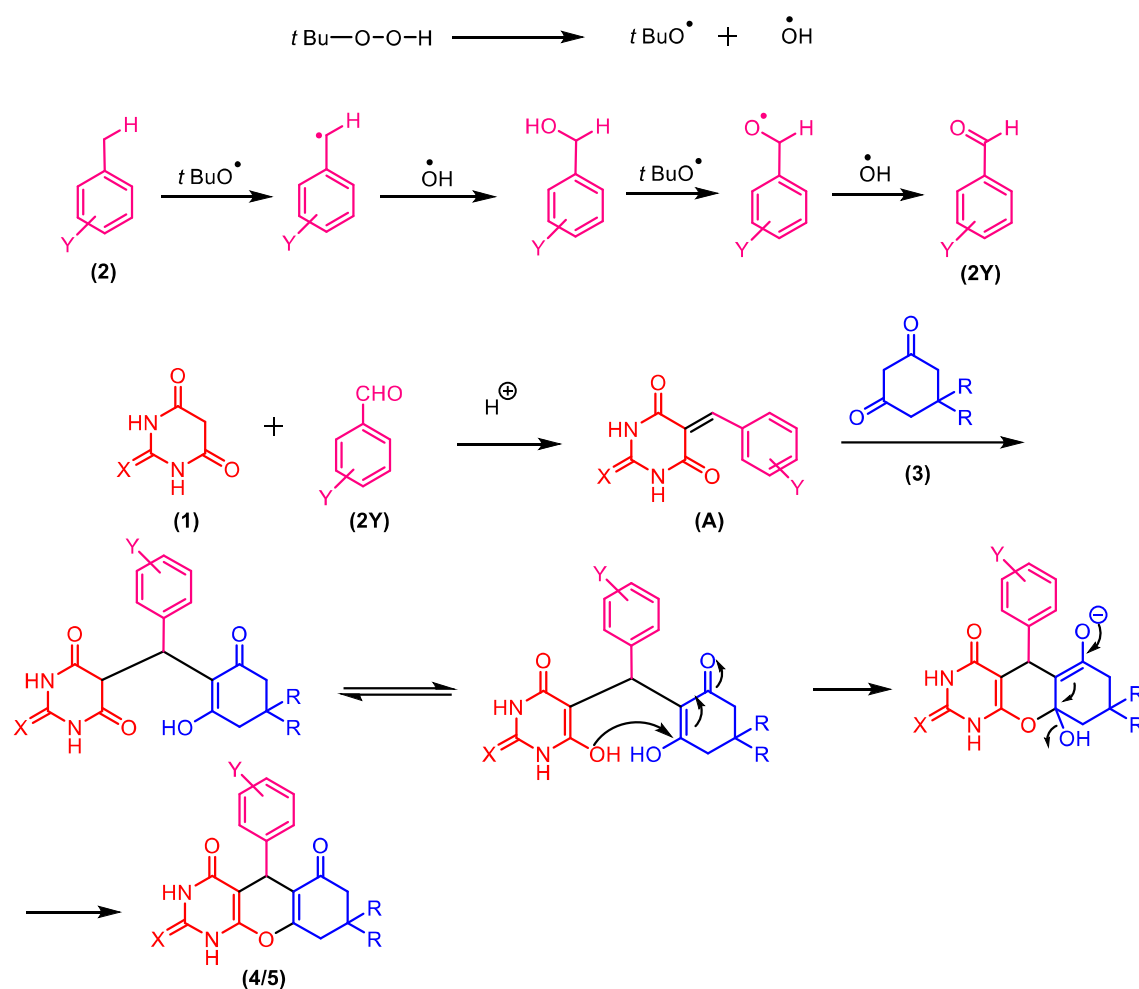
Some control experiments were carried out to establish the reaction mechanism. By performing quenching experiments with radical scavengers like (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) and butylatedhydroxytoluene (BHT), the participation of free-radical species in the reaction was established. The model reaction gave the corresponding product **4h** in 17% and 10% yields in the presence of 2 equiv. of TEMPO and BHT respectively, under standard conditions whereas the product formation quenched completely with 5 equivalents. Thus, the involvement of radical intermediate

was established by the inhibitory action of TEMPO and BHT. A blank experiment was performed by taking toluene with TBHP which resulted in 87% of benzaldehyde, 9% of benzyl alcohol and trace amount of benzoic acid.



Scheme 3.2 Control experiments to establish mechanism of the reaction.

The intermediacy of benzyl alcohol was confirmed by subjecting benzyl alcohol to standard conditions to deliver benzaldehyde in 96% yield. Further, the intermediacy of benzyl alcohol was confirmed by using it in the synthesis of **4h** under standard reaction conditions (**Scheme 3.2**).



Scheme 3.3 Plausible reaction mechanism.

The plausible reaction mechanism based on reported literature, isolated product and controlled experiment is given in **Scheme 3.3**. Oxidation of methylarenes (**2**) by

TBHP leads to corresponding aromatic aldehyde (**2Y**) through radical pathway. Now Knoevenagel condensation takes place between (**1**) and (**2Y**) to produce (**A**). Ultimately Michael addition between (**A**) and (**3**) followed by removal of H₂O produced the final products (**4/5**).

3.3 Conclusion

In conclusion, a practical and efficient protocol for the metal-free C-C bond formation via C-H activation of inexpensive methylarenes has been developed. Lemon juice has been exploited as a natural and biodegradable catalyst for the green and environmentally benign synthesis of chromenopyrimidine derivatives by multi-component reaction of barbituric/ thiobarbituric acid, 1, 3-diketones and methylarenes.

3.4 Experimental Section

3.4.1 General Procedure for Extraction of Lemon Juice (Preparation of catalyst) [33]

Fresh fruits of *Citrus limon* (lemon) were bought from the local shop and washed with water thoroughly. The juice was extracted by a fruit juicer and then filtered with cotton to remove the solid substance and to obtain a clear portion of juice. Now clear juice was used as an acid catalyst after measuring its pH (between 2- 3).

3.4.2 General Procedure for the Synthesis of Chromenopyrimidine Derivatives (4/5)

Methylarene (2.0 mmol) and TBHP (70% in H₂O, 3.0 equiv.) were stirred at room temperature for 10 min then thiobarbituric acid/ barbituric acid (1.0 mmol), cyclic 1, 3-

diketone (1.0 mmol) and extracted lemon juice (0.3 ml) were added to it. The reaction mixture was heated at 80 °C for 3 h. After the completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature and mixed with water. The mixture was extracted with ethyl acetate, dried over sodium sulfate and organic solvent was evaporated under reduced pressure to obtain the product. Pure compounds were obtained by column chromatography.

3.4.3 Analytical Data

5-Phenyl-2-thioxo-2,3,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-4,6(5H,7H)-dione (4a) Yellow powder (85% yield); mp >300°C; IR (KBr) ν cm⁻¹: 3189, 2935, 2830, 1676; ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)= 13.54 (s, 1H,NH), 12.43 (s, 1H,NH), 7.24 - 7.21 (m, 4H, Ar-H), 7.15 - 7.11(m, 1H, Ar-H), 4.55 (s, 1H,CH), 2.72 -2.68 (m, 2H,CH₂), 2.32 - 2.28 (m, 2H,CH₂), 1.97 - 1.87 (m, 2H,CH₂);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.31, 173.99, 164.65, 160.94, 152.41, 143.66, 128.52, 128.37, 126.88, 115.81, 95.70, 36.68, 32.06, 26.70, 20.09; Anal. Calc. for C₁₇H₁₄N₂O₃S: C, 62.56; H, 4.32; N, 8.58; Found: C, 62.68; H, 4.21; N, 8.45.

5-(4-Chlorophenyl)-2-thioxo-2,3,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-4,6(5H,7H)-dione (4b) Yellow powder (86% yield); mp: 290°C; IR (KBr) ν cm⁻¹: 3205, 3076, 2950, 1713, 1663; ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)= 13.54 (s, 1H,NH), 12.45 (s, 1H,NH), 7.27 (s, 4H, Ar-H), 4.53(s, 1H,CH), 2.67 -2.65 (m, 2H,CH₂), 2.31-2.28 (m, 2H,CH₂), 1.96 -1.87 (m, 2H,CH₂);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.36, 174.08, 164.81, 160.95, 152.49, 142.64, 131.46, 130.52, 128.25, 115.36, 95.15,

36.64, 31.78, 26.72, 20.05; **Anal. Calc. for C₁₇H₁₃ClN₂O₃S**: C, 56.59; H, 3.63; N, 7.76 ; Found: C, 56.47; H, 3.77; N, 7.89.

5-(3-Chlorophenyl)-2-thioxo-2,3,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-4,6(5H,7H)-dione (4c) White powder (88% yield); mp: 270°C; **IR (KBr) ν cm⁻¹**: 3171, 3045, 2830, 1703, 1672; **¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)**= 13.59 (s, 1H,NH), 12.46 (s, 1H,NH), 7.30 (s, 1H, Ar-H), 7.27 - 7.24 (m, 1H, Ar-H), 7.22 - 7.20 (m, 2H, Ar-H), 4.53 (s, 1H,CH), 2.71 - 2.69 (m, 2H,CH₂), 2.31-2.28 (m, 2H,CH₂), 1.97-1.89 (m, 2H,CH₂); **¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)**= 196.41, 174.11, 165.03 160.98, 152.55, 146.00, 132.90, 130.26, 128.64, 127.28, 126.96, 115.11, 94.94, 36.64, 32.20, 26.75, 20.05; **Anal. Calc. for C₁₇H₁₃ClN₂O₃S**: C, 56.59; H, 3.63; N, 7.76 ; Found: C, 56.46; H, 3.52; N, 7.65.

5-(4-Nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-4,6(5H,7H)-dione (4d) Yellow powder (87% yield); mp: 273°C; **IR (KBr) ν cm⁻¹**: 3109, 2856, 1708, 1678, 1623; **¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)**= 13.63 (s, 1H,NH), 12.48 (s, 1H,NH), 8.10 -8.05 (m,2H, Ar-H), 7.56 (d, *J* = 8.6 Hz, 2H,Ar-H), 4.65 (s, 1H,CH), 2.68 -2.70 (m, 2H,CH₂), 2.31 -2.28 (m, 2H,CH₂), 1.98 -1.89 (m, 2H,CH₂); **¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)**= 196.46, 174.24, 165.29, 152.66, 151.21, 149.48, 146.55, 130.20, 123.50, 114.77, 94.53, 36.61, 32.69, 26.82, 20.04; **Anal. Calc. for C₁₇H₁₃N₃O₅S**: C, 54.98; H, 3.53; N, 11.32 ; Found: C, 55.09; H, 3.65; N, 11.20.

5-(3-Nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-4,6(5H,7H)-dione (4e) Yellow powder (86% yield); mp >300°C; **IR (KBr) ν cm⁻¹**: 3098,

2853, 1713, 1674; ^1H NMR (500 MHz, DMSO- d_6) δ (ppm)= 13.63 (s, 1H,NH), 12.48 (s, 1H,NH), 8.09 -8.08 (m,1H, Ar-H), 8.03 -8.01 (m,1H, Ar-H), 7.75 -7.73 (m,1H, Ar-H), 7.55 -7.52 (m,1H, Ar-H), 4.67 (s, 1H,CH), 2.72 -2.70(m, 2H,CH₂), 2.31 -2.28 (m, 2H,CH₂), 1.98 -1.96 (m, 2H,CH₂); ^{13}C NMR (126 MHz, DMSO- d_6) δ (ppm)= 196.50, 174.23, 165.35, 161.03, 152.65, 147.81, 145.70, 135.42, 129.92, 123.47, 122.06, 114.75, 94.55, 36.60, 32.54, 26.80, 20.05; **Anal. Calc. for C₁₇H₁₃N₃O₅S:** C, 54.98; H, 3.53; N, 11.32 ; Found: C, 54.87; H, 3.42; N, 11.45.

5-(4-Fluorophenyl)-2-thioxo-2,3,8,9-tetrahydro-1H-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (4f) Yellow powder (84% yield); mp:230°C; **IR (KBr)** ν cm⁻¹: 3183, 3067, 2875, 1747, 1676; ^1H NMR (500 MHz, DMSO- d_6) δ (ppm)= 13.54 (s, 1H,NH), 12.44 (s, 1H,NH), 7.29 -7.26 (m, 2H, Ar-H), 7.05 -7.02 (m, 2H, Ar-H), 4.54 (s, 1H,CH), 2.68 - 2.65 (m, 2H,CH₂), 2.30-2.27 (m, 2H,CH₂), 1.97 - 1.88 (m, 2H,CH₂); ^{13}C NMR (126 MHz, DMSO- d_6) δ (ppm)= 196.43, 174.07, 164.75, 162.22, 161.00, 160.29, 152.44, 139.87, 139.85, 130.52, 130.45, 115.64, 115.12, 114.95, 95.49, 36.69, 31.55, 26.74, 20.10; **Anal. Calc. for C₁₇H₁₃FN₂O₃S:** C, 59.29; H, 3.81; N, 8.14; Found: C, 59.43; H, 3.92; N, 8.28.

5-(*p*-Tolyl)-2-thioxo-2,3,8,9-tetrahydro-1H-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (4g) White powder (85% yield); mp:260°C; **IR (KBr)** ν cm⁻¹: 3201, 3096, 2884, 1750, 1642; ^1H NMR (500 MHz, DMSO- d_6) δ (ppm)= 13.53 (s, 1H,NH), 12.41 (s, 1H,NH), 7.11 (d, J = 7.7 Hz, 2H, Ar-H), 7.03 (d, J = 7.9 Hz, 2H, Ar-H), 4.50 (s, 1H,CH), 2.68-2.63 (m, 2H,CH₂), 2.29-2.27 (m, 2H,CH₂), 2.20 (s, 3H, CH₃), 1.96 - 1.86

(m, 2H,CH₂);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.28, 173.95, 164.45, 160.92, 152.33, 140.76, 135.96, 128.93, 128.38, 115.94, 95.81, 36.69, 31.60, 26.68, 20.95, 20.11; **Anal. Calc. for C₁₈H₁₆N₂O₃S**: C, 63.51; H, 4.74; N, 8.23; Found: C, 63.67; H, 4.89; N, 8.39.

8,8-Dimethyl-5-Phenyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-

***d*]pyrimidine-4,6(5*H*,7*H*)-dione (4h)** Brown powder (87% yield); mp: 182°C; **IR (KBr)** ν cm⁻¹: 3486, 3203, 2950, 1719, 1686; **¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)**= 13.57 (s, 1H,NH), 12.43 (s, 1H,NH), 7.22 - 7.14 (m, 5H,Ar-H), 4.52 (s, 1H,CH₂), 2.58 (s, 2H,CH₂), 2.82-2.08 (m, 2H,CH₂), 1.04 (s, 3H,CH₃), 0.93(s, 3H,CH₃);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.24, 174.07, 162.76, 161.00, 152.50, 143.57, 128.60, 128.42, 127.00, 114.84, 95.78, 50.39, 32.35, 32.25, 28.79, 27.05; **Anal. Calc. for C₁₉H₁₈N₂O₃S**: C, 64.39; H, 5.12; N, 7.90; Found: C, 64.56; H, 5.25; N, 8.07.

5-(3-Chlorophenyl)-8,8-dimethyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-

***d*]pyrimidine-4,6(5*H*,7*H*)-dione (4i)** Yellow powder (88% yield); mp: 265°C; **IR (KBr)** ν cm⁻¹: 3212, 2945, 2892, 1716, 1648; **¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)**= 13.59 (s, 1H,NH), 12.46 (s, 1H, NH), 7.28 -7.25 (m, 2H,Ar-H), 7.22 -7.18 (m, 2H,Ar-H), 4.51 (s, 1H,CH), 2.62 -2.54 (m, 2H,CH₂), 2.28 -2.13 (m, 2H,CH₂), 1.04 (s, 3H,CH₃), 0.94 (s, 3H,CH₃);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.22, 174.13, 163.02, 160.97, 152.58, 145.88, 132.87, 130.26, 128.70, 127.26, 126.99, 114.12, 94.96, 50.29, 32.34, 28.64, 27.07; **Anal. Calc. for C₁₉H₁₇ClN₂O₃S**: C, 58.69; H, 4.41; N, 7.20 ; Found: C, 58.87; H, 4.29; N, 7.34.

8,8-Dimethyl-5-(4-nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-4,6(5H,7H)-dione (4j) Orange powder (86% yield); mp: 263°C; IR (KBr) ν cm⁻¹: 3208, 3105, 2967, 1712, 1676; ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)= 12.48 (s, 1H, NH), 8.10 (d, *J* = 8.7 Hz, 2H,Ar-H), 7.55 (d, *J* = 8.6 Hz, 2H,Ar-H), 4.64 (s, 1H,CH), 2.59 (s, 2H,CH₂), 2.29 -2.10 (m, 2H,CH₂), 1.04 (s, 3H,CH₃), 0.94 (s, 3H,CH₃);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.33, 174.29, 163.32, 161.01, 152.75, 151.15, 146.59, 130.23, 123.53, 113.81, 94.59, 50.29, 32.83, 32.36, 28.66, 27.19; **Anal. Calc. for C₁₉H₁₇N₃O₅S**: C, 57.13; H, 4.29; N,10.52 ; Found: C,57.26; H,4.13; N,10.67.

8,8-Dimethyl-5-(3-nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-4,6(5H,7H)-dione (4k) Yellow powder (84% yield); mp:188°C; IR (KBr) ν cm⁻¹: 3116, 2857, 1706, 1675, 1652; ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)= 12.48 (s, 1H,NH), 8.05 -8.01 (m, 2H, Ar-H), 7.74 (d, *J* = 7.7 Hz, 1H,Ar-H), 7.56 -7.53 (m, 2H Ar-H), 4.65 (s, 1H,CH), 2.61 (s, 2H,CH₂), 2.30 (d, *J* = 16.2 Hz, 1H,CH₂), 2.14 (d, *J* = 16.2 Hz, 1H,CH₂), 1.05 (s, 3H,CH₃), 0.94 (s, 3H,CH₃);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.26, 174.26, 163.37, 161.00, 152.71, 147.79, 145.62, 135.44, 129.85, 123.36, 122.05, 113.73, 94.54, 50.21, 32.61, 32.33, 28.66, 27.00; **Anal. Calc. for C₁₉H₁₇N₃O₅S**: C, 57.13; H, 4.29;N,10.52 ; Found: C, 57.29; H, 4.38; N, 10.69.

5-(4-Fluorophenyl)-8,8-dimethyl-2-thioxo-2,3,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-4,6(5H,7H)-dione (4l) White powder (85% yield); mp:215°C; IR (KBr) ν cm⁻¹: 3234, 2967, 2842, 1721, 1684; ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)= 13.55

(s, 1H,NH), 12.42 (s, 1H,NH), 7.27- 7.24 (m, 2H ,Ar-H), 7.06-7.02 (m, 2H, Ar-H), 4.53 (s, 1H,CH), 2.57 (s, 2H,CH₂), 2.28 (d, $J = 16.1$ Hz, 1H,CH₂), 2.14 (d, $J = 16.1$ Hz, 1H,CH₂), 1.04 (s, 3H,CH₃), 0.89 (s, 3H,CH₃);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.23, 174.09, 162.72, 162.20, 160.97, 160.27, 152.48, 139.73, 130.45, 115.14, 114.62, 95.48, 50.34, 32.31, 31.69, 28.74, 27.12; **Anal. Calc. for C₁₉H₁₇FN₂O₃S:** C, 61.28; H, 4.60; N, 7.52 ; Found: C, 61.11; H, 4.78; N, 7.63.

8,8-Dimethyl-5-*p*-tolyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (4m) White powder (88% yield); mp:240°C; **IR (KBr)** ν cm⁻¹: 3203, 2982, 2874, 1760, 1647; **¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)**= 12.55 (s, 1H,NH), 12.42 (s, 1H,NH), 7.10 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.03 -7.03 (m, 2H, Ar-H), 4.48 (s, 1H,CH), 2.57 (s, 2H,CH₂), 2.28 -2.25 (m, 1H,CH₂), 2.21 (s, 3H,CH₃), 2.13 (d, $J = 16.1$ Hz, 1H), 1.04 (s, 3H,CH₃), 0.93 (s, 3H,CH₃);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.09, 173.97, 162.48, 160.89, 152.33, 140.61, 135.98, 128.91, 128.41, 114.88, 95.84, 50.34 ,32.29, 31.74, 28.74, 26.98, 20.94; **Anal. Calc. for C₂₀H₂₀N₂O₃S:** C, 65.20; H, 5.47; N, 7.60; Found: C, 65.05; H, 5.59; N, 7.43.

5-(4-Chlorophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione (5a) Light yellow powder (87% yield); mp:297°C; **IR (KBr)** ν cm⁻¹: 3210, 3083, 2945, 1723, 1672; **¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)**= 12.21 (s, 1H,NH), 11.21 (s, 1H,NH), 7.42 (s, 4H, Ar-H), 4.67 (s, 1H,CH), 2.83 -2.66 (m, 2H,CH₂), 2.47 -2.40 (m, 2H,CH₂), 2.12 -2.03 (m, 2H,CH₂);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.53, 164.95, 163.29, 153.18, 149.82, 143.40, 131.35, 130.48, 129.21, 128.27, 115.75, 90.28,

36.75, 31.79, 26.79, 20.15; **Anal. Calc. for C₁₇H₁₃ClN₂O₄**: C, 59.23; H, 3.80; N, 8.13; Found: C, 59.36; H, 3.96; N, 8.27.

5-(3-Nitrophenyl)-8,9-dihydro-1H-chromeno[2,3-d]pyrimidine-2,4,6(3H,5H,7H)-trione (5b) Yellow powder (85% yield); mp:209°C; **IR (KBr)** ν cm⁻¹: 3235, 3160, 2870, 1739, 1677; **¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)**= 12.14 (s, 1H,NH), 11.10 (s, 1H,NH), 8.08 -8.00 (m,2H, Ar-H), 7.72 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.9 Hz, 1H, Ar-H) 4.65 (s, 1H,CH), 2.72 -2.68 (m, 2H,CH₂), 2.33 -2.29 (m, 2H,CH₂), 1.98 -1.91 (m, 2H,CH₂); **¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)**= 196.65, 165.48, 163.34, 153.37, 149.83, 147.86, 146.49, 135.37, 129.94, 125.97, 123.37, 121.98, 115.09, 89.68, 36.68, 32.55, 26.84, 20.12; **Anal. Calc. for C₁₇H₁₃N₃O₆**: C, 57.47; H, 3.69; N, 11.83; Found: C, 57.64; H, 3.80; N, 11.96.

5-(*p*-Tolyl)-8,9-dihydro-1H-chromeno[2,3-d]pyrimidine-2,4,6(3H,5H,7H)-trione (5c) Yellow powder (88% yield); mp:198°C; **IR (KBr)** ν cm⁻¹: 3205, 3103, 2879, 1731, 1648; **¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)**= 12.00 (s, 1H,NH), 11.03 (s, 1H,NH), 7.11 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.02 (d, *J* = 7.9 Hz, 2H, Ar-H), 4.50 (s, 1H,CH), 2.71 - 2.64 (m, 2H,CH₂), 2.37 -2.31 (m, 2H,CH₂), 2.21 (s, 3H, CH₃), 1.96 -1.83 (m, 2H,CH₂); **¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)**= 196.52, 164.64, 163.32, 153.08, 149.88, 141.56, 135.87, 129.82, 129.62, 128.99, 128.40, 116.40, 90.95, 36.83, 31.65, 26.79, 21.05, 20.24; **Anal. Calc. for C₁₈H₁₆N₂O₄**: C, 66.66; H, 4.97; N, 8.64; Found: C, 66.79; H, 5.11; N, 8.78.

8,8-Dimethyl-5-*p*-tolyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-

2,4,6(3*H*,5*H*,7*H*)-trione (5d) White powder (86% yield); mp:187°C; IR (KBr) ν cm⁻¹: 3191, 2989, 2861, 1761, 1656; ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)= 11.99 (s, 1H,NH), 10.99 (s, 1H,NH), 7.07 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.01 (d, *J* = 7.7 Hz, 2H, Ar-H), 4.50 (s, 1H,CH),2.58 -2.54 (m, 2H,CH₂), 2.26 (d, *J* = 16.2 Hz, 1H), 2.19 (s, 3H,CH₃), 2.10 (d, *J* = 16.2 Hz, 1H), 1.02 (s, 3H,CH₃), 0.90 (s, 3H,CH₃);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.14, 163.13, 162.53, 152.93, 149.74, 141.26, 135.72, 128.81, 128.29, 115.18, 90.82, 50.34, 32.22, 31.66, 28.81, 26.91, 20.92; Anal. Calc. for C₂₀H₂₀N₂O₄: C, 68.17; H, 5.72; N, 7.95; Found: C, 67.99; H, 5.56; N, 8.11.

8,8-Dimethyl-5-(3-nitrophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-

2,4,6(3*H*, 5*H*,7*H*)-trione (5e) White powder (84% yield); mp:178°C; IR (KBr) ν cm⁻¹: 3180, 2950, 2892, 1739, 1645; ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)= 12.29 (s, 1H,NH), 11.28 (s, 1H,NH), 7.49 -7.46 (m, 2H, Ar-H), 7.42 -7.37 (m, 2H Ar-H), 4.71 (s, 1H,CH), 2.79 -2.71 (m, 2H,CH₂), 2.47 -2.23 (m, 2H,CH₂), 1.25 (s, 3H,CH₃), 1.15 (s, 3H,CH₃);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.46, 163.51, 163.31, 153.37, 149.82, 147.81, 146.36, 135.38, 129.89, 123.23, 121.98, 114.04, 89.68, 50.26, 32.60, 32.34, 28.79, 26.97; Anal. Calc. for C₁₉H₁₇N₃O₆: C, 59.53; H, 4.47; N,10.96; Found: C,59.67; H,4.35; N,10.81.

5-(4-Chlorophenyl)-8,8-dimethyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-

2,4,6(3*H*, 5*H*,7*H*)-trione (5f) Yellow powder (85% yield); mp:171°C; IR (KBr) ν cm⁻¹: 3195, 2962, 2837, 1713, 1694; ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm)= 12.35 (s,

1H,NH), 11.29 (s, 1H,NH), 8.31 (d, $J = 7.3$ Hz, 2H,Ar-H), 7.74 (d, $J = 7.3$ Hz, 2H,Ar-H), 4.83 (s, 1H,CH), 2.83 -2.76 (m, 2H,CH₂), 2.34 -2.28 (m, 2H,CH₂), 1.25 (s, 3H,CH₃), 1.13 (s, 3H,CH₃);¹³C NMR (126 MHz, DMSO- *d*₆) δ (ppm)= 196.42, 163.29, 163.00, 153.25, 149.86, 143.25, 131.35, 130.47, 128.26, 114.69, 90.28, 50.37, 32.32, 31.92, 28.80, 27.06; **Anal. Calc. for C₁₉H₁₇ClN₂O₄**: C, 61.21; H, 4.60; N, 7.51; Found: C, 61.37; H, 4.75; N, 7.68.

3.4.4 Spectral Data of Product 5-(*p*-Tolyl)-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (4g)

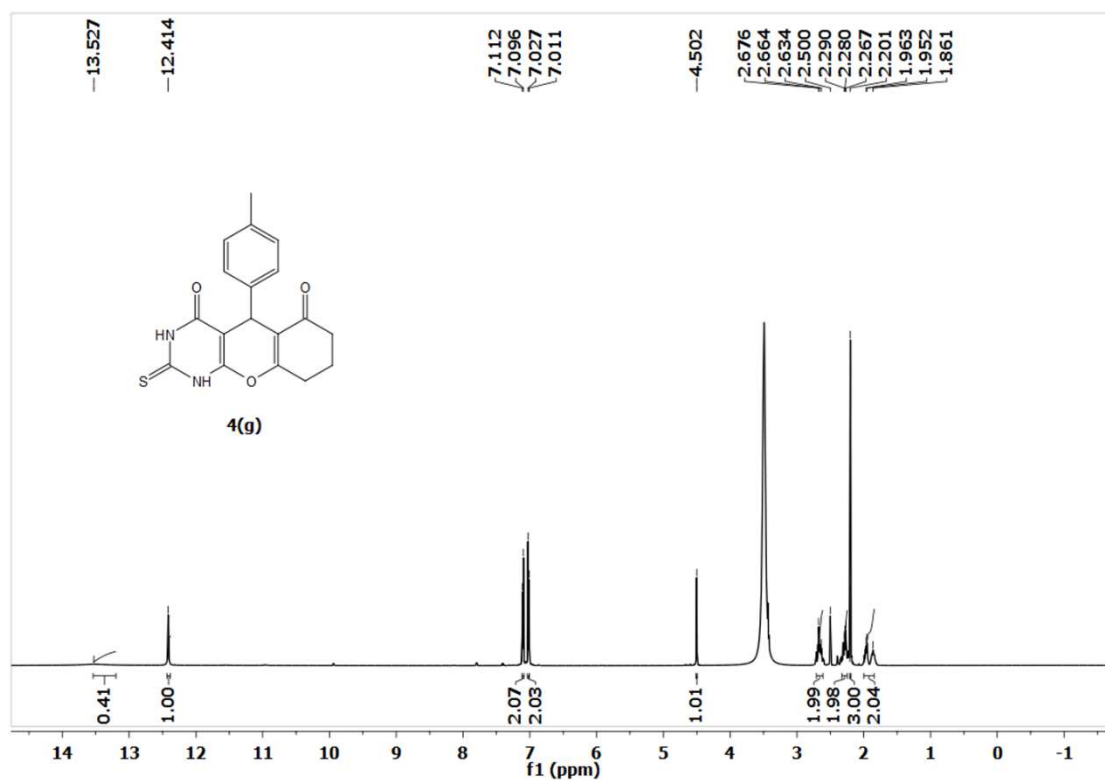


Figure 3.1 ¹H NMR of 5-(*p*-Tolyl)-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (4g)

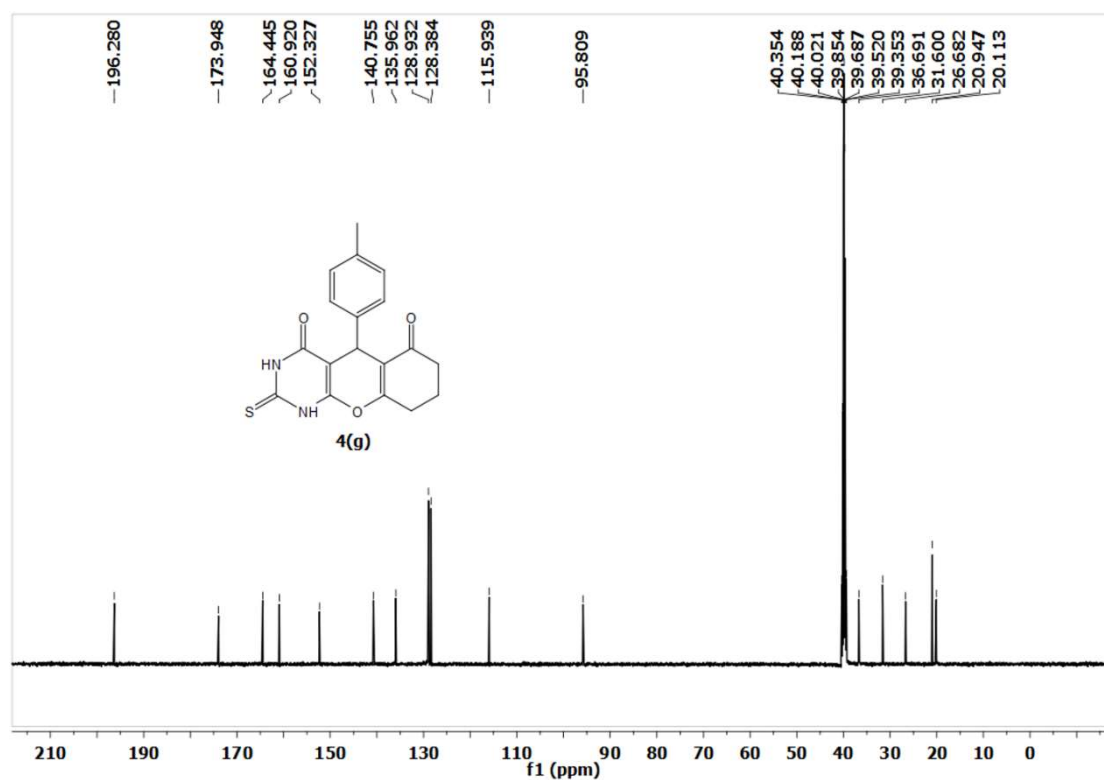


Figure 3.2 ^{13}C NMR of 5-(*p*-Tolyl)-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (4g)

3.4.5 Spectral Data of Product 8,8-Dimethyl-5-Phenyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (4h)

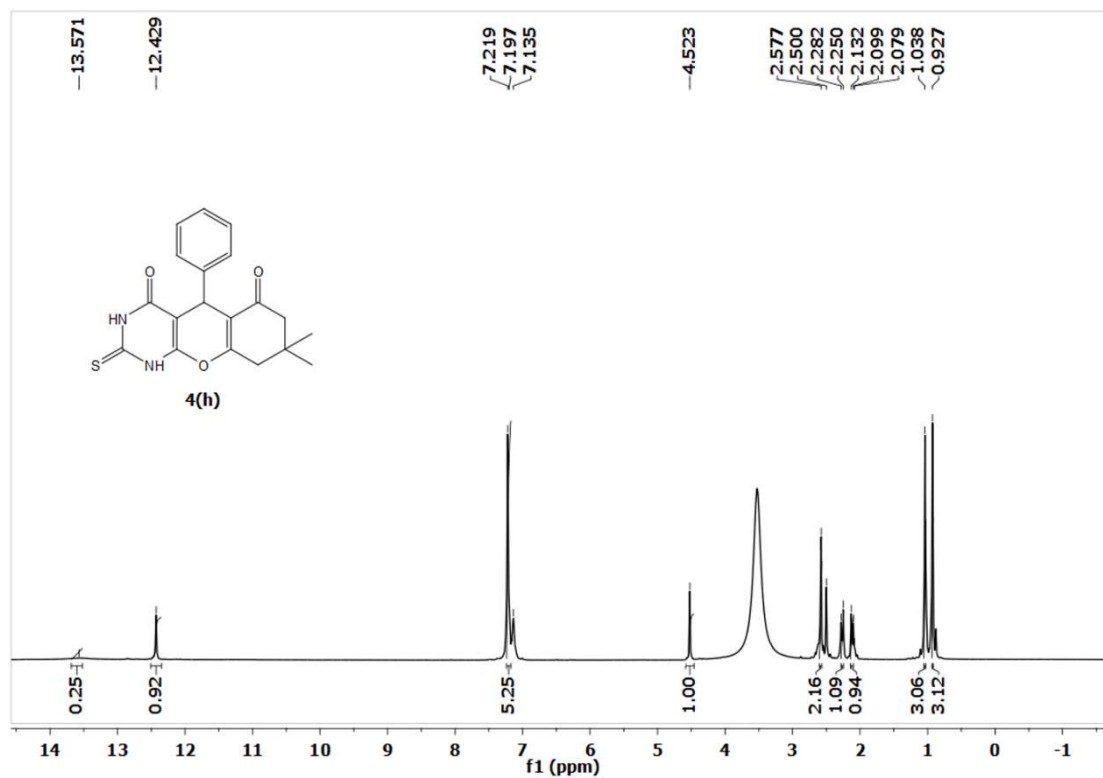


Figure 3.3 ¹H NMR of 8,8-Dimethyl-5-Phenyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (4h)

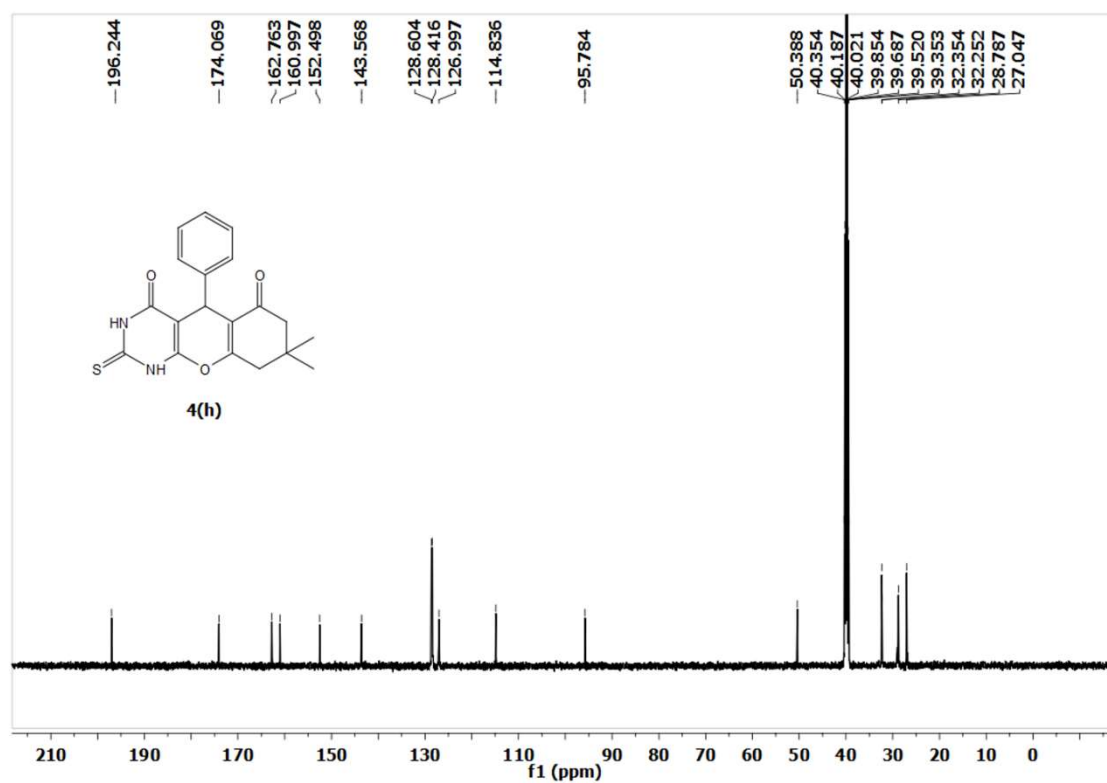


Figure 3.4 ^{13}C NMR of 8,8-Dimethyl-5-Phenyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (4h)

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