



## One-Pot Synthesis of 3,4-Dihydropyrimidine-2(1H)-thione Derivatives Using DBU as Green and Recyclable Catalyst

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A short and simple one-pot synthesis of 3,4-dihydropyrimidine-2(1H)-thione derivatives was accomplished in excellent yields by reaction of aryl ketone, aryl aldehydes and thiourea in aqueous ethanol (50 %) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a reusable catalyst.

**Keywords:** Green synthesis, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), Pyrimidine-2(1H)-thione, Multicomponent synthesis.

### INTRODUCTION

Pyrimidine compounds till now been synthesized mainly because of their wide range of pharmacological and biological properties. These compounds have reported important applications in medicinal chemistry. Pyrimidine derivatives have found applications such as antimicrobial [1], antitumor [2] and antifungal [3]. In addition, pyrimidine compounds have been considered to be significant for drugs and agricultural intermediates [4]. This kind of important application of pyrimidines encouraged the present synthesis of some pyrimidine derivatives.

Various methods have been reported for the synthesis of dihydropyrimidine-2(1H)-thione derivatives by cyclization of chalcones with thiourea in the presence of ionic liquid [5], potassium hydroxide in ethanol [6-10], potassium *tert*-butoxide or sodium ethoxide in absolute ethanol [12]. It is also reported by reaction of 1,3-diphenyl-3-(phenylsulfonyl)propan-1-one with thiourea in presence of potassium hydroxide [13]. Pyrimidine derivatives can also be prepared by the reaction of certain aryl ketone, aryl aldehyde with thiourea in the presence of sodium *tert*-butoxide in ethanol [14], 1-methylimidazolium hydrogen sulfate [15], triphenyl phosphine [16] and neutral alumina [17]. The main disadvantages of all these methods are longer reaction times, tedious work up procedures. Some of the catalysts are highly expensive and after workup cannot be recovered and reused. These inadequacies surely show the need for a safe, ecofriendly and efficient method to synthesize these compounds. Recently the path of science and technology has been shifting more towards environmental, natural product

resources and reusable catalysts. Herein, we report a novel one-pot synthesis of dihydropyrimidine-2(1H)-thiones from the three component condensation of aldehyde, ketone, thiourea in aqueous ethanol (50 %) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a green and recyclable catalyst.

### EXPERIMENTAL

All the chemicals were purchased from Merck and Sigma Aldrich. All the reactions were performed and monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F<sub>254</sub> pre-coated plates (0.25 mm) and visualized by UV fluorescence lamp. IR spectra were recorded on PerkinElmer 683(FT)-IR spectrometer with KBr pellets. <sup>1</sup>H and <sup>13</sup>C NMR spectra in dimethyl sulfoxide (DMSO-*d*<sub>6</sub>) as solvent were recorded on Bruker 400 MHz and 100 MHz with tetramethylsilane (TMS) as internal standard.

**Synthesis of 3,4-dihydropyrimidine-2(1H)-thione derivatives:** Aryl ketone (**1**) (8 mmol), aryl aldehyde (**2**) (8 mmol) and thiourea (**3**) (8 mmol) in 15ml of aqueous ethanol (50 %) were mixed in 50 mL round bottom flask and DBU (20 mol %) was added to the reaction mixture at room temperature. Then, the resulting mixture was heated to 80 °C and stirred for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to 0 °C and compound was filtered and recrystallized from toluene to afford desired product 3,4-dihydropyrimidine-2(1H)-thione derivatives (**4a-4n**) (Table-1). The filtrate aqueous ethanol (50 %) containing DBU was used as such for investigating the recyclability of the catalyst. The product was identified by spectral data.

## Characterization data of synthesized compounds

**3,4-Dihydro-4,6-diphenylpyrimidine-2(1H)-thione (4a):** m.p. 182-184 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3172 (NH), 1643 (C=N), 1558, 1479 (C=C), 1183 (C=S).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 4.87 (1H, d,  $J$  = 5.0 Hz, 4-CH), 5.17 (1H, d,  $J$  = 5.0 Hz, 5-CH), 6.78-7.19 (10H, m, Ar-H), 8.87 (1H, bs, NH), 9.59 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 55.1, 101.6, 126.4, 126.8, 127.2, 128.86, 129.4, 129.4, 133.8, 134.8, 144.7, 175.9. MS  $m/z$ : 267 [M+1] $^+$ .

**4-(4-Chlorophenyl)-6-phenyl-3,4-dihydropyrimidine-2(1H)-thione (4b):** m.p. 180-182 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3153 (NH), 1648 (C=N), 1549, 1473 (C=C), 1185 (C=S).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 4.87 (1H, d,  $J$  = 5.0 Hz, 4-CH), 5.28 (1H, d,  $J$  = 5.0 Hz, 5-CH), 7.03-7.56 (9H, m, Ar-H), 8.77 (1H, bs, NH), 9.70 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 50.1, 56.3, 100.6, 111.3, 121.4, 126.2, 126.7, 128.5, 129.1, 129.4, 132.1, 133.6, 134.8, 155.7, 172.2. MS  $m/z$ : 301 [M+1] $^+$ .

**3,4-Dihydro-6-(naphthalen-2-yl)-4-phenylpyrimidine-2(1H)-thione (4c):** m.p. 212-214 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3190 (NH), 1675 (C=N), 1559, (C=C), 1184 (C=S).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 5.14 (1H, d,  $J$  = 5.0 Hz, 4-CH), 5.55-5.60 (1H, d,  $J$  = 5.0 Hz, 5-CH), 7.30-8.10 (12H, m, Ar-H), 9.07 (1H, bs, NH), 9.59 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 56.0, 102.8, 124.29, 125.2, 126.9, 127.5, 127.9, 127.9, 128.9, 130.4, 130.7, 134.9, 138.4, 142.2, 175.9. MS  $m/z$ : 317 [M+1] $^+$ .

**4-(4-Chlorophenyl)-3,4-dihydro-6-(naphthalen-2-yl)pyrimidine-2(1H)-thione (4d):** m.p. 214-216 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3190 (NH), 1673 (C=N), 1561, (C=C), 1182 (C=S).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 5.21 (1H, d,  $J$  = 5.0 Hz, 4-CH), 5.57 (1H, d,  $J$  = 5.0 Hz, 5-CH), 7.1-8.15 (11H, m, Ar-H), 9.22 (1H, bs, NH), 10.07 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 54.4, 101.9, 124.2, 125.3, 125.7, 127, 127.1, 127.9, 128.3, 128.6, 128.7, 129.1, 129.3, 130.7, 132.6, 132.9, 133.3, 134.8, 143.4, 175.7. MS  $m/z$ : 351 [M+1] $^+$ .

**4-(2-Chlorophenyl)-3,4-dihydro-6-(naphthalen-2-yl)pyrimidine-2(1H)-thione (4e):** m.p. 210-212 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3181 (NH), 1675 (C=N), 1562 (C=C), 1186 (C=S).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 5.04 (1H, d,  $J$  = 5.0 Hz, 4-CH), 5.54-5.62 (1H, d,  $J$  = 5.0 Hz, 5-CH), 7.31-

8.11 (11H, m, Ar-H), 9.02 (1H, bs, NH), 9.92 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 56.1, 102.8, 124.29, 125.2, 126.9, 127.5, 127.8, 127.9, 128.9, 130.4, 130.7, 134.9, 138.4, 142.2, 176.8. MS  $m/z$ : 351 [M+1] $^+$ .

**3,4-Dihydro-6-(naphthalen-2-yl)-4-*p*-tolylpyrimidine-2(1H)-thione (4f):** m.p. 226-228 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3181 (NH), 1672 (C=N), 1562, (C=C), 1188 (C=S).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 2.3 (3H, s, CH<sub>3</sub>), 5.1 (1H, d,  $J$  = 5.0 Hz, 4-CH), 5.5 (1H, d,  $J$  = 5.0 Hz, 5-CH), 7.2-8.15 (11H, m, Ar-H), 9.15 (1H, bs, NH), 9.97 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 21.9, 54.9, 102.5, 124.2, 125.1, 126.8, 127, 127.05, 127.9, 128.3, 128.7, 129.6, 130.8, 133, 133.3, 134.4, 137.2, 141.6, 175.5. MS  $m/z$ : 331 [M+1] $^+$ .

**4-(3-Bromophenyl)-3,4-dihydro-6-(naphthalen-2-yl)pyrimidine-2(1H)-thione (4g):** m.p. 232-234 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3174 (NH), 1679 (C=N), 1562, (C=C), 1182 (C=S).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 5.12 (1H, d,  $J$  = 5.0 Hz, 4-CH), 5.53-5.58 (1H, d,  $J$  = 5.0 Hz, 5-CH), 7.39-8.10 (11H, m, Ar-H), 9.17 (1H, bs, NH), 9.99 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 56.1, 102.8, 124.2, 125.2, 126.8, 127.5, 127.8, 127.9, 128.9, 130.4, 130.7, 134.9, 138.4, 142.2, 177.7. MS  $m/z$ : 396 [M+1] $^+$ .

**4-(2,6-Dichlorophenyl)-3,4-dihydro-6-(naphthalen-2-yl)pyrimidine-2(1H)-thione (4h):** m.p. 218-220 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3190 (NH), 1676 (C=N), 1559, (C=C), 1184 (C=S).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 5.12 (1H, d,  $J$  = 5.0 Hz, 4-CH), 5.52-5.59 (1H, d,  $J$  = 5.0 Hz, 5-CH), 7.32-8.11 (10H, m, Ar-H), 9.05 (1H, bs, NH), 9.93 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 56.3, 102.8, 124.29, 125.2, 126.9, 127.5, 127.8, 127.9, 128.9, 129.6, 130.4, 130.6, 134.9, 138.4, 142.2, 177.6. MS  $m/z$ : 386 [M+1] $^+$ .

**4-(3,4-Dichlorophenyl)-3,4-dihydro-6-(naphthalen-2-yl)pyrimidine-2(1H)-thione (4i):** m.p. 220-222 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3191 (NH), 1667 (C=N), 1553, (C=C), 1182 (C=S).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 5.12 (1H, d,  $J$  = 5.0 Hz, 4-CH), 5.51-5.59 (1H, d,  $J$  = 5.0 Hz, 5-CH), 7.32-8.12 (10H, m, Ar-H), 9.06 (1H, bs, NH), 9.93 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 56.1, 102.7, 124.29, 125.2, 126.9, 127.6, 127.8, 127.9, 128.9, 129.6, 130.4, 130.6, 134.9, 139.4, 142.2, 177.7. MS  $m/z$ : 386 [M+1] $^+$ .

**4-(4-Fluorophenyl)-3,4-dihydro-6-(naphthalen-2-yl)pyrimidine-2(1H)-thione (4j):** m.p. 216-218 °C, FT-IR (KBr,

TABLE-1  
SYNTHESIS OF 3,4-DIHYDROPYRIMIDINE-2(1H)-THIONE DERIVATIVES

Entry	Ar <sup>1</sup>	Ar <sup>2</sup>	Time (h)	Product	Yield (%)
1	Phenyl	Phenyl	4.0	<b>4a</b>	71
2	Phenyl	4-Chlorophenyl	4.5	<b>4b</b>	76
3	2-Naphthyl	Phenyl	4.0	<b>4c</b>	74
4	2-Naphthyl	4-Chlorophenyl	4.0	<b>4d</b>	76
5	2-Naphthyl	2-Chlorophenyl	4.5	<b>4e</b>	82
6	2-Naphthyl	4-Methylphenyl	4.0	<b>4f</b>	81
7	2-Naphthyl	3-Bromophenyl	5.0	<b>4g</b>	87
8	2-Naphthyl	2,6-Dichlorophenyl	4.0	<b>4h</b>	86
9	2-Naphthyl	3,4-Dichlorophenyl	4.0	<b>4i</b>	81
10	2-Naphthyl	4-Fluorophenyl	4.0	<b>4j</b>	82
11	2-Naphthyl	4-Methoxyphenyl	4.0	<b>4k</b>	79
12	2-Naphthyl	3,4,5-Trimethoxyphenyl	5.0	<b>4l</b>	83
13	2-Naphthyl	3,4-Dimethoxyphenyl	4.0	<b>4m</b>	81
14	2-Naphthyl	1-Naphthyl	4.0	<b>4n</b>	82

$\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3191 (NH), 1674 (C=N), 1551, (C=C), 1181 (C=S).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 5.01 (1H, d,  $J = 5.0$  Hz, 4-CH), 5.59-5.63 (1H, d,  $J = 5.0$  Hz, 5-CH), 7.39-8.16 (11H, m, Ar-H), 9.01 (1H, bs, NH), 9.99 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 56.1, 102.8, 124.29, 125.2, 126.8, 127.5, 127.8, 127.9, 128.5, 130.6, 130.7, 134.7, 138.4, 142.2, 177.9. MS  $m/z$ : 335  $[\text{M}+1]^+$ .

**3,4-Dihydro-4-(4-methoxyphenyl)-6-(naphthalen-2-yl)pyrimidine-2(1H)-thione (4k)**: m.p. 162-164 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3198 (NH), 1669 (C=N), 1565, 1186 (C=S).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 3.77 (3H, s,  $\text{OCH}_3$ ), 4.87 (1H, d,  $J = 5.0$  Hz, 4-CH), 5.17 (1H, d,  $J = 5.0$  Hz, 5-CH), 6.79-7.19 (11H, m, Ar-H), 8.89 (1H, bs, NH), 9.97 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 21.5, 54.6, 55.6, 102.5, 114.4, 124.2, 125.5, 125.7, 127, 127.9, 128.2, 128.6, 128.7, 129, 130.9, 133, 133.3, 134.4, 136.6, 159.2, 175.5. MS  $m/z$ : 347  $[\text{M}+1]^+$ .

**3,4-Dihydro-4-(3,4,5-trimethoxyphenyl)-6-(naphthalen-2-yl)pyrimidine-2(1H)-thione (4l)**: m.p. 198-200 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3183 (NH), 1688 (C=N), 1558, 1186 (C=S).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 3.35-3.78 (9H, s,  $\text{OCH}_3$ ), 5.14 (1H, d,  $J = 5.0$  Hz, 4-CH), 5.15 (1H, d,  $J = 5.0$  Hz, 5-CH), 6.7-8.16 (9H, m, Ar-H), 9.13 (1H, bs, NH), 10.01 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 55.1, 56.3, 60.4, 102.2, 104.0, 124.2, 125.2, 127.4, 127.08, 127.9, 128.4, 128.7, 130.8, 133, 133.3, 134.6, 137.3, 140, 153.5, 175.7. MS  $m/z$ : 407  $[\text{M}+1]^+$ .

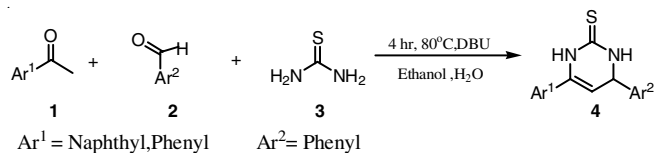
**3,4-Dihydro-4-(3,4-dimethoxyphenyl)-6-(naphthalen-2-yl)pyrimidine-2(1H)-thione (4m)**: m.p. 192-194 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3198 (NH), 1680 (C=N), 1557, 1177 (C=S).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 3.5-7 (6H, s,  $\text{OCH}_3$ ), 5.14 (1H, d,  $J = 5.0$  Hz, 4-CH), 5.5 (1H, d,  $J = 5.0$  Hz, 5-CH), 6.79-7.19 (10H, m, Ar-H), 8.89 (1H, bs, NH), 9.97 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 21.5, 54.65, 55.6, 102.5, 114.4, 124.2, 125.5, 125.7, 127, 127.9, 128.2, 128.3, 128.6, 128.7, 129, 130.9, 133, 133.3, 134.4, 136.6, 159.2, 175.5. MS  $m/z$ : 378  $[\text{M}+1]^+$ .

**3,4-Dihydro-4-(naphthalen-1-yl)-6-(naphthalen-2-yl)pyrimidine-2(1H)-thione (4n)**: m.p. 230-232 °C, FT-IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3173 (NH), 1671 (C=N), 1549, 1465 (C=C), 1173 (C=S).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 5.7 (1H, d,  $J = 5.0$  Hz, 4-CH), 6.01 (1H, d,  $J = 5.0$  Hz, 5-CH), 7.5-8.33 (14H, m, Ar-H), 9.2 (1H, bs, NH), 10.15 (1H, bs, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 52.5, 102.3, 123.7, 124.1, 124.4, 125.1, 126.3, 126.4, 126.9, 127, 127.8, 128.3, 128.7, 129.1, 129.7, 130.8, 132.9, 133.3, 134, 134.4, 139.9, 176.4. MS  $m/z$ : 367  $[\text{M}+1]^+$ .

## RESULTS AND DISCUSSION

Aryl aldehydes (**2**) and thiourea (**3**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is processed rapidly in aqueous ethanol (50 %) at 80 °C to afford dihydropyrimidine-2(1H)-thiones (**4**) in good yield (**Scheme-I**).

Several solvents such as ethanol, methanol, THF, aqueous methanol (50 %), aqueous THF (50 %) and aqueous ethanol (50 %) were investigated. Among them, aqueous ethanol (50 %) gave the best results and the product obtained by simple filtration by cooling of aqueous ethanol to 0 °C after the completion of



**Scheme-I:** One-pot three-component reaction of aryl ketone, aryl aldehyde and thiourea

the reaction. To the filtrate, aryl ketone (**1a**), aryl aldehyde (**2a**) and thiourea (**3a**) were added in the same molar ratio without additional load of DBU. The reaction mixture was stirred for the specified time; marginal loss of the yield was observed.

Different dihydropyrimidine-2(1H)-thione and its derivatives are confirmed by spectral parameters. The  $^1\text{H}$  NMR spectrum of **4a** exhibited two broad singlet's for NH of pyrimidine protons at 8.8 and 9.6 ppm, a multiplet at 6.78-7.19 ppm was assigned to aromatic protons. IR spectrum showed N-H stretching vibration at 3173  $\text{cm}^{-1}$  corresponding to secondary amine in pyrimidine. Weak intensity absorption band at 1643  $\text{cm}^{-1}$  corresponds to C=N stretching vibration. A plausible mechanism is proposed for the formation of product **4** (**Scheme-II**).

DBU-catalyzed condensation between **1** and **2** will give an intermediate **5** which on reaction with **3** gave another intermediate **6**. The intermediate **6** formed *in situ* undergoes cyclization to give the final product **4**.

## Conclusion

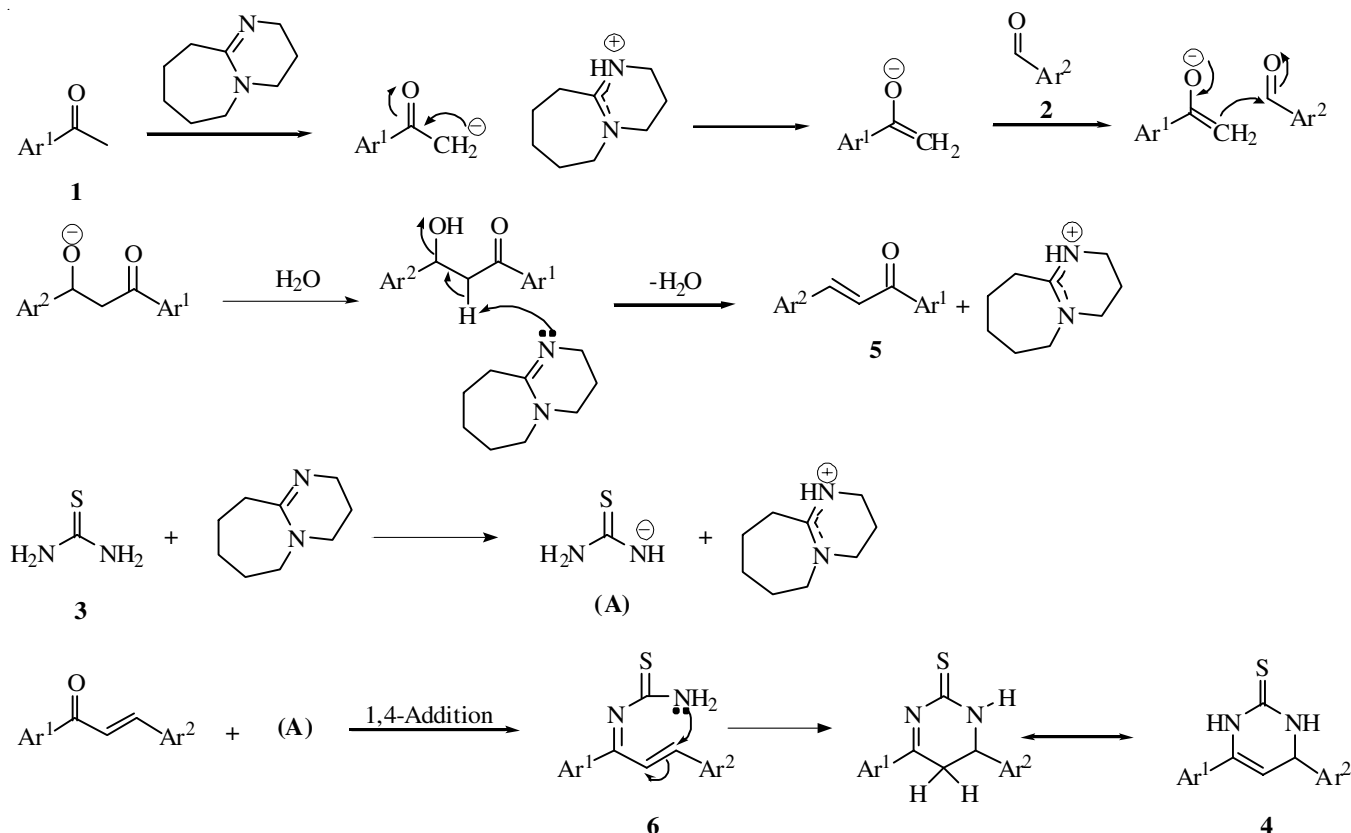
In conclusion, a three-component synthetic method for preparation of some dihydropyrimidine-2(1H)-thione derivatives is carried out. This method has several advantages such as readily available starting materials, easy workup, good yields of the products and DBU as a green and recyclable catalyst.

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Scheme-II: Mechanism of the reaction

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