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A RAPID AND FACILE DOMINO SYNTHESIS OF STRUCTURALLY DIVERSE 3, 4-DIHYDROPYRIMIDIN-2(1*H*)-THIONES DERIVATIVES

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ABSTRACT
An efficient one-pot synthesis of structurally diverse 3,4-dihydropyrimidin-2(1*H*)-thiones derivatives by *p*-TSA promoted three component reaction of ethyl acetoacetate with thiourea/phenylthiourea and aryl aldehydes is described. The present protocol provides excellent yields of structurally complex, biologically relevant dihydropyrimidin-2(1*H*)-thiones in a single operation.
Keywords: Multicomponent Domino reactions (MDRs), DHPMs, Thiourea, Thiones.

INTRODUCTION

Multicomponent Domino reactions (MDRs) have emerged as a versatile protocol for the efficient construction of highly functionalized complex molecule in single transformation avoiding the complicated purification procedures, saving both solvents and reagents.[1] Due to the inherent characteristics of MDRs like atom efficiency, flexibility, ease of execution, diversity orientation and high convergent nature, they are the essential tool for the generation of heterocyclic libraries with high molecular complexity and diversity.[2] In the recent years, the designing of MCRs for drug discovery has emerged as new endeavor of research.[3]

Nitrogen and sulphur-containing heterocycles are widespread in nature and play a significant role in chemical biology. Among these, 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) and their sulphur analogues are associated with unique biological activities such as antitumor, antihypertensive, anti-HIV, antimicrobials, anti-inflammatory, antifungal, and anthelmintic activities, kinase inhibitors, anticancer, anti-malarial, antihypertensive, potassium channel antagonists, anti-HIV, anti-epileptics, anti-tubercular, anti-bacterial etc.[4-14] The sulphur derivatives of Dihydropyrimidines are the core structural skeleton in variety of drugs and pharmaceutical potentials compounds[15](Figure-1).

The *Biginelli*-product DHPMs have always been the elegant target of synthesis. Recently, the DHPMs derivatives were reported to be synthesized by solvent-free ball milling technique using ZnO NPs as catalyst.[16] The 5-phosphonato- and 4-methyl heteroaryl- derivative of DHPMs have been reported respectively as anti-inflammatory[17] and hepatitis B Virus (HBV) capsid inhibitors.[18] Encouraged by their recent synthetic protocol and diverse biological and pharmacological importance for drug discovery, we have been interested in developing efficient methodology for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-thiones derivatives.

EXPERIMENITAL

Material and Methods

Melting points were measured on the electro thermal melting point apparatus using open capillary tube and were uncorrected. All reagents were commercial grade. The purity of all the synthesized compounds was checked by TLC. IR spectra were measured with a Shimadzu 8400S FTIR spectrometer.

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^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-300 Advance Spectrometer as DMSO-d*6*. Chemical shifts (δ) are expressed in ppm downfield from the internal standard tetramethylsilane.

General procedure

A round bottom flask containing 6 mL of ethanol was charged with ethyl acetoacetate (1mmol), aryl aldehyde (1 mmol) and substituted thiourea (1 mmol) and *p*-TSA (10 mol %). The reaction mixture was stirred for appropriate time at 80 °C. The progress of the reaction was monitored by TLC. After completion of the reaction (TLC), the solid was filtered off. The solid obtained was washed with distilled water and cold ethanol and purified further by recrystallization from ethanol to yield the pure products.

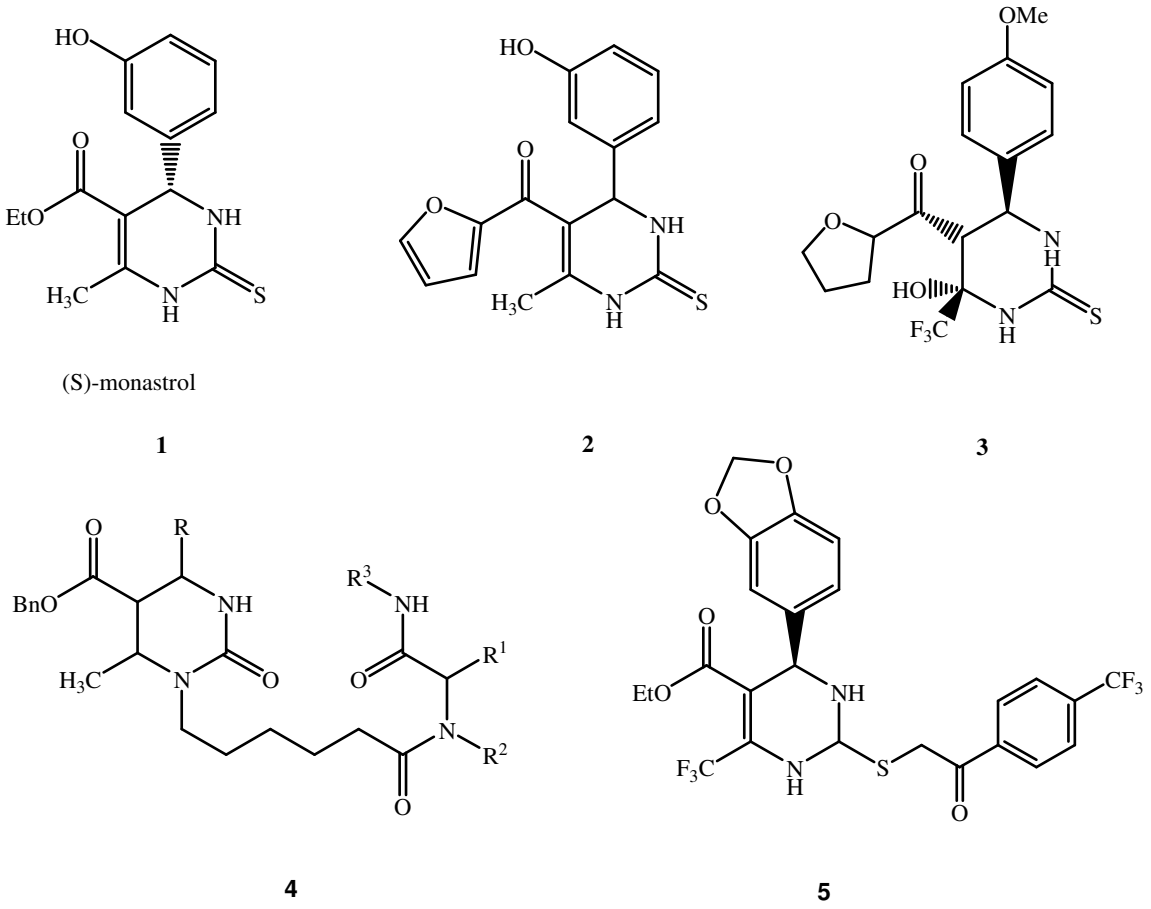


Fig.-1: Biologically active DHPMs Derivatives

RESULTS AND DISCUSSION

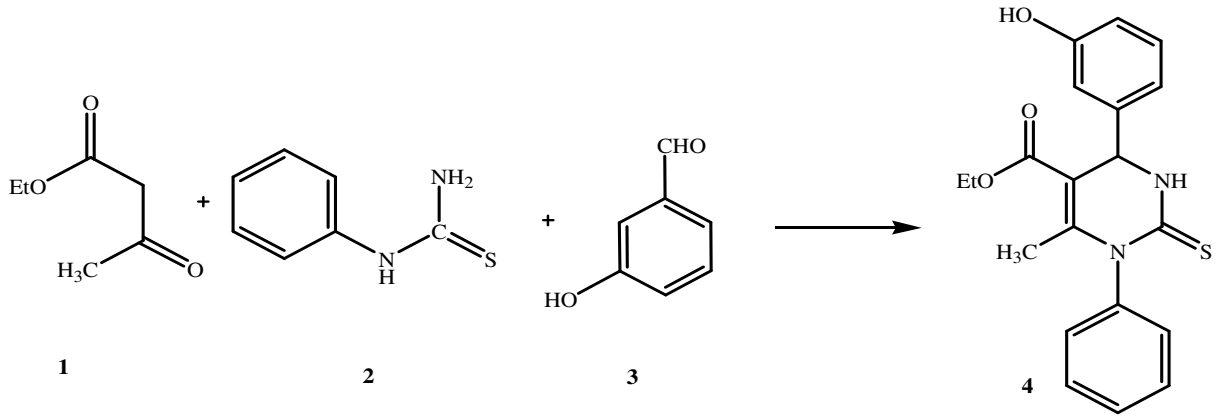
Initially, to achieve suitable conditions, for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-thione a representative *Biginelli*-type reaction of ethyl acetoacetate **1** (1 mmol) with phenylthiourea **1** (1 mmol) and 3-hydroxybenzaldehyde **3** (1mmol) was performed as a simple model substrate in various solvents in the presence of $FeCl_3$, *p*-TSA and CuI as an inexpensive and readily available catalyst (Scheme-1).

To search the suitable solvent, the reaction was examined in various solvents such as methanol, ethanol, DMF and dichloromethane under refluxing condition (Table-1).

As is shown in Table-1, in refluxing organic solvents, ethanol has provided higher yield (Table-1, entry 4). It was observed that the excellent yield of products have obtained when the reaction was performed in the presence of *p*-TSA in ethanol (Table-2, entry 4), while without catalyst trace product was formed after 4 hrs.(Table-2, entry 4). The 10 mol % of *p*-TSA as catalyst is sufficient to complete the reaction in 24

min with 93% yield. The optimal reaction temperature was also explored by performing reaction in ethanol with *p*-TSA at different temperatures range from 60 °C to 90 °C. The excellent results were obtained at 80 °C.

With the optimized reaction conditions, to explore its scope and generality, the present methodology was extended for library construction (Table-2). The results summarized in Table-2 showed that substituted thiourea and aryl aldehydes react efficiently with ethyl acetoacetate to give the desired product in excellent yields.



1 **2** **3** **4**

Scheme-1: Model Reaction

Table-1: Model reaction, conditions and yield

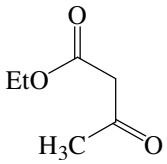
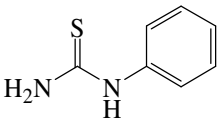
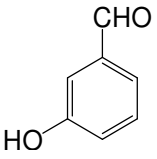
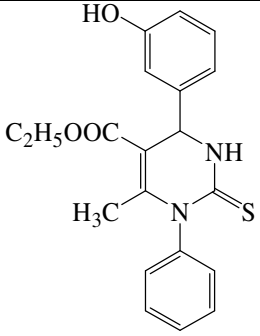
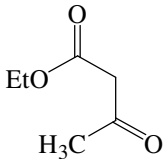
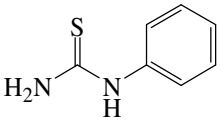
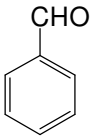
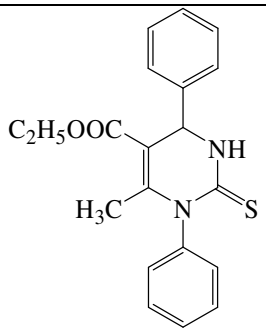
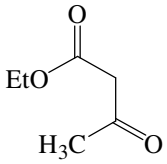
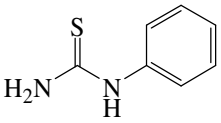
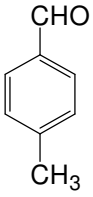
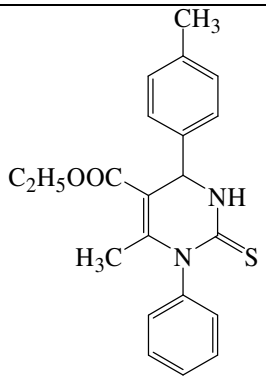
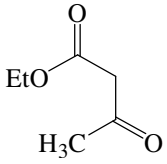
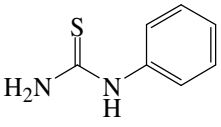
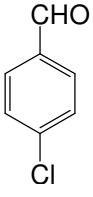
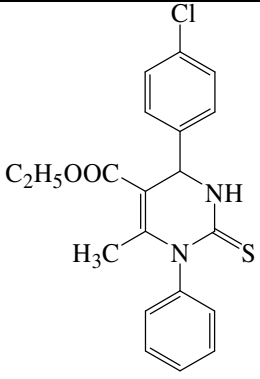
Entry	Solvent	Catalyst	Time	Yield (%)
1.	Methanol	$FeCl_3$	50 min	92
2.	Methanol	*p*-TSA	46 min	89
3.	Methanol	CuI	1 hrs 10 min	85
4.	Ethanol	*p*-TSA	24 min	93
5.	Ethanol	CuI	55 min	90
6.	Ethanol	$FeCl_3$	60 min	85
7.	Ethanol	No catalyst	more than 4 hrs	traces
8.	DMF	*p*-TSA	1 hrs 25 min	80
9.	DMF	$FeCl_3$	60	82
10.	Dichloromethane	*p*-TSA	1 hrs 40 min	76

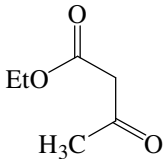
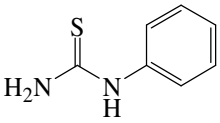
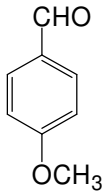
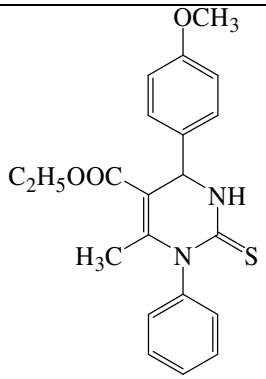
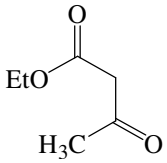
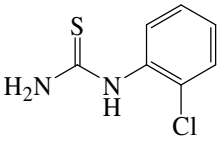
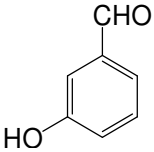
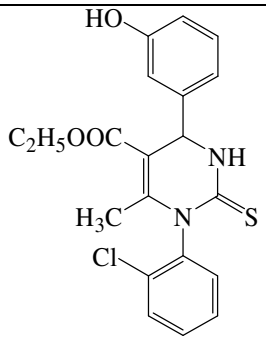
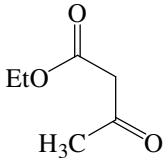
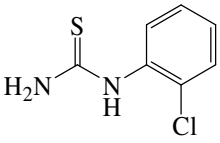
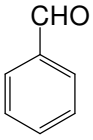
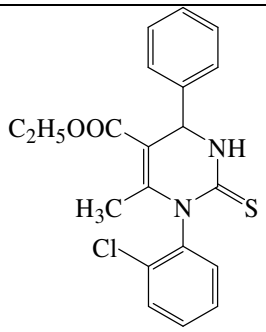
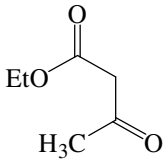
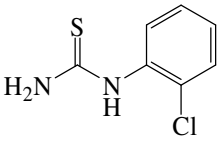
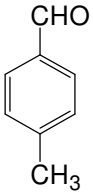
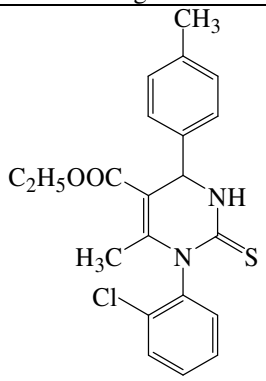
3-hydroxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), phenylthiourea (1 mmol) and catalyst (10 mol%)

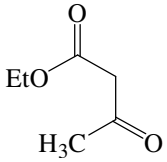
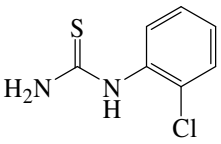
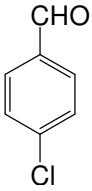
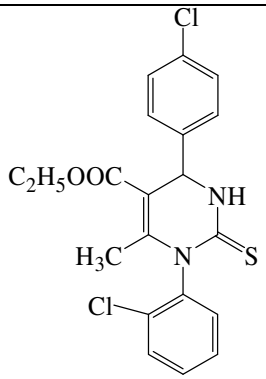
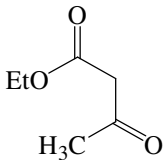
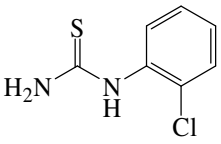
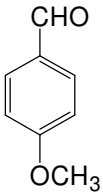
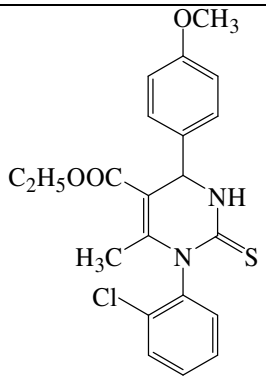
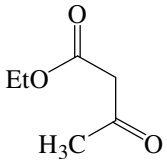
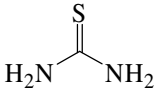
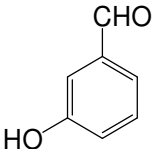
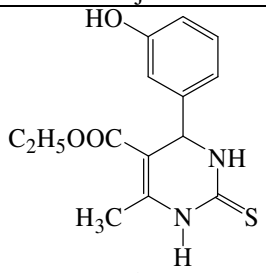
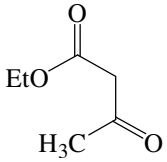
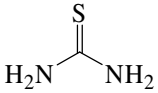
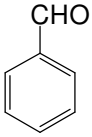
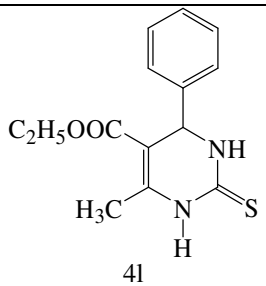
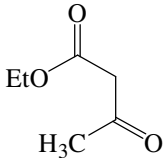
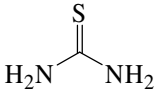
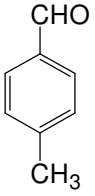
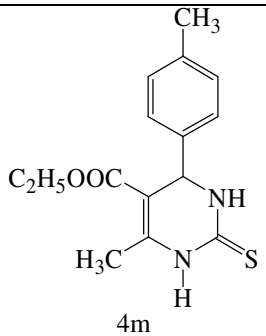
5-Ethoxycarbonyl-1-phenyl-4-(3-hydroxyphenyl-)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione*(4a)*
M.p.139-141°C, IR (KBr, *v max, cm*$^{-1}$); 3395, 3281, 1733, 1613, 1210, 1014. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.30 (3H, *s*, CH_3), 1.73(3H, *t*, CH_3), 2.04 (1H, *s*, NH), 4.17 (2H, *q*, CH_2), 4.62(1H, *s*, CH), 5.1(1H,*s*, OH),6.42-7.06(9H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 171.1, 165.3, 147.1, 142.6, 139.1, 128.2, 128.5, 127.3, 126.7, 125.5, 124.2, 102.1, 59.5, 54.6, 15.3, 13.9. Anal. Calcd (%) for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60; found C, 65.14; H, 5.44; N, 7.53.

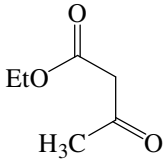
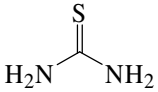
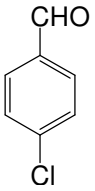
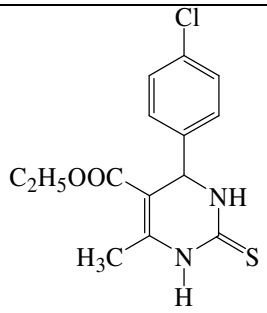
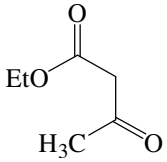
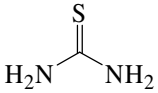
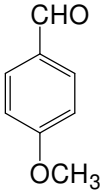
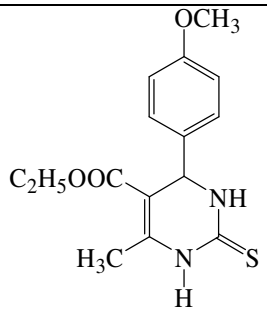
5-Ethoxycarbonyl-1,4-diphenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione*(4b)*
M.p.137-139°C, IR (KBr, *v max, cm*$^{-1}$); 3285, 1742, 1620, 1230, 1020. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.31 (3H, *s*, CH_3), 1.71(3H, *t*, CH_3), 2.0 (1H, *s*, NH), 4.19 (2H, *q*, CH_2), 4.60(1H, *s*, CH), 6.41-7.16(10H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 171.0, 165.1, 147.7, 142.4, 139.5, 128.8, 128.3, 127.1, 126.5, 125.3, 124.4, 102.2, 59.9, 54.9, 15.5, 13.8. Anal.Calcd (%) for $C_{20}H_{20}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95; found C, 68.10; H, 5.69; N, 7.98.

Table-2: Synthesis of 3,4-dihydropyrimidin-2(1H)-thione derivatives

S. No.	Ethyl acetoacetate	Thiourea	Aryl Aldehyde	Product	Time (min)	Yield (%)
1				 4a	24	93
2				 4b	31	95
3				 4c	30	89
4				 4d	35	91

5				 4e	28	88
6				 4f	25	91
7				 4g	30	90
8				 4h	32	88

9				 4i	28	91
10				 4j	25	89
11				 4k	25	90
12				 4l	28	80
13				 4m	25	88

14				 4n	31	89
15				 4o	28	90

5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-1-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione*(4c)*
M.p.151-153°C, IR (KBr, *v max, cm*$^{-1}$); 3270, 1745, 1615,1357, 1227, 1017. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.33 (3H, *s*, CH_3), 1.69(3H, *t*, CH_3), 2.1 (1H, *s*, NH), 2.35(3H, *s*, CH_3), 4.20 (2H, *q*, CH_2), 4.62(1H, *s*, CH), 6.46-7.01(9H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 171.5, 165.4, 147.9, 139.3, 135.7, 129.1, 128.7, 127.1, 125.2, 124.3, 102.0, 59.7, 54.7, 20.9, 15.4, 13.5. Anal. Calcd (%) for $C_{21}H_{22}N_2O_2S$: C, 68.82; H, 6.05; N, 7.64; found C, 68.75; H, 6.00; N, 7.68.

5-Ethoxycarbonyl-4-(4-chloroyphenyl)-6-methyl-1-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione*(4d)*
M.p.159-161°C; IR (KBr, *v max, cm*$^{-1}$); 3284, 1731, 1608, 1235, 1022. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.30 (3H, *s*, CH_3), 1.73(3H, *t*, CH_3), 2.14 (1H, *s*, NH), 4.22 (2H, *q*, CH_2), 4.50(1H, *s*, CH), 6.42-7.15(9H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 171.2, 165.3, 147.5, 140.6, 139.5, 131.8, 129.1, 128.8, 128.7, 128.5, 125.3, 124.7, 102.1, 59.8, 54.8, 15.3, 13.7. Anal. Calcd (%) for $C_{20}H_{19}ClN_2O_2S$: C, 62.09; H, 4.95; N, 7.24; found C, 62.01; H, 4.92; N, 7.26.

5-Ethoxycarbonyl-4-(4-methoxyyphenyl)-6-methyl-1-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione*(4e)*
M.p.197-199 °C; IR (KBr, *v max, cm*$^{-1}$); 3277, 1741, 1625, 1222, 1045, 1017. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.33 (3H, *t*, CH_3), 1.71(3H, *s*, CH_3), 2.11 (1H, *s*, NH), 3.74(3H, *s*, OCH_3), 4.20 (2H, *q*, CH_2), 4.59(1H, *s*, CH), 6.46-7.01(9H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 171.1, 165.5, 160.1, 147.6, 139.6, 134.5, 128.8, 128.1, 113.9, 102.2, 59.9, 56.0, 54.9, 15.4, 13.5. Anal. Calcd (%) for $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.32; found C, 65.89; H, 5.77; N, 7.30.

5-Ethoxycarbonyl-1-(2-chloroyphenyl)-6-methyl-4-(3-hydroxyphenyl)-3,4-dihydro-pyrimidin 2(1*H*)-thione *(4f)*
M.p.155-157°C; IR (KBr, *v max, cm*$^{-1}$); 3381, 3270, 1725, 1632, 1215, 1014. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.33 (3H, *t*, CH_3), 1.68(3H, *s*, CH_3), 2.2 (1H, *s*, NH), 4.16 (2H, *q*, CH_2), 4.55(1H, *s*, CH),5.08(1H,*s*, OH), 6.36-7.18(8H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 171.0, 165.5, 147.2, 142.7,130.8, 129.1, 128.5, 127.3, 126.7, 102.5, 59.5, 56.0, 15.4, 13.5. Anal. Calcd (%) for $C_{20}H_{19}ClN_2O_3S$: C, 59.62; H, 4.75; N, 6.95; found C, 59.55; H, 4.71; N, 6.94.

5-Ethoxycarbonyl-1-(2-chloroyphenyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione*(4g)*
M.p.151-153°C; IR (KBr, *v max, cm*$^{-1}$); 3280, 1739, 1622, 1235, 1035, 1018. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.30 (3H, *t*, CH_3), 1.71(3H, *s*, CH_3), 2.1 (1H, *s*, NH), 4.19 (2H, *q*, CH_2), 4.59(1H, *s*, CH), 6.40-7.14(9H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 171.5, 165.3, 147.5, 142.4,130.6, 129.2, 128.3, 127.1, 126.9, 125.9, 102.2, 59.9, 56.0, 54.9, 15.4, 13.7. Anal. Calcd (%) for $C_{20}H_{19}ClN_2O_2S$: C, 62.09; H, 4.95; N, 7.24; found C, 62.00; H, 4.91; N, 7.26.

5-Ethoxycarbonyl-1-(2-chloroyphenyl)-4-(4-methyl-phenyl)-6-methyl-3,4-dihydro-pyrimidin-2(1*H*)-thione *(4h)*
M.p.191-193°C; IR (KBr, *v max, cm*$^{-1}$); 3277, 1747, 1614,1365, 1231, 1038. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.29 (3H, *t*, CH_3), 1.73(3H, *s*, CH_3), 2.0 (1H, *s*, NH), 2.35(3H, *s*, CH_3), 4.18 (2H, *q*, CH_2), 4.55(1H, *s*, CH), 6.40-7.1(8H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ (ppm): 171.3, 165.5, 147.3, 139.8, 135.6, 130.6, 129.1, 127.0, 126.7,125.9, 102.3, 59.5, 56.2, 54.8, 20.9, 15.2, 13.5. Anal. Calcd (%) for $C_{21}H_{21}ClN_2O_2S$: C, 62.91; H, 5.28; N, 6.99; found C, 62.86; H, 5.22; N, 6.95.

5-Ethoxycarbonyl-1-(2-chloroyphenyl)–4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione *(4i)*
M.p.243-245°C ; IR (KBr, *v max, cm*$^{-1}$); 3287, 1731, 1624, 1223, 1023, 1017. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.33 (3H, *t*, CH_3), 1.71(3H, *s*, CH_3), 2.10 (1H, *s*, NH), 4.17 (2H, *q*, CH_2), 4.59(1H, *s*, CH), 6.41-7.16(8H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ (ppm): 171.5, 165.3, 147.5, 139.5, 131.8, 128.7, 126.6, 125.7, 102.0, 59.9, 54.2, 15.4, 13.7. Anal.Calcd (%) for $C_{20}H_{18}Cl_2N_2O_2S$: C, 57.01; H, 4.31; N, 6.65; found C, 56.96; H, 4.28; N, 6.61.

5-Ethoxycarbonyl-1-(2-chloroyphenyl)–4-(4-methoxyphenyl)-6-methyl-3,4-dihydro-pyrimidin-2(1*H*)-thione *(4j)*
M.p.167-169°C; IR (KBr, *v max, cm*$^{-1}$); 3271, 1729, 1607, 1234, 1045, 1011. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.31 (3H, *t*, CH_3), 1.69(3H, *s*, CH_3), 2.15 (1H, *s*, NH), 3.71(3H, *s*, OCH_3), 4.23 (2H, *q*, CH_2), 4.60(1H, *s*, CH), 6.40-7.02(8H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 171.1, 165.0, 160.3, 147.3, 139.9, 137.4, 130.8, 129.2, 128.1, 126.2, 125.3, 113.9, 102.2, 59.5, 54.4, 15.1, 13.4. Anal. Calcd (%) for $C_{11}H_{21}ClN_2O_3S$: C, 60.50; H, 5.08; N, 6.72; found C, 60.44; H, 5.00; N, 6.65.

5-Ethoxycarbonyl-6-methyl-4-(3-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione *(4k)*M.p.211-213°C; IR (KBr, *v max, cm*$^{-1}$); 3413, 3325, 3250, 1733, 1615, 1345, 1219, 1020. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.26 (3H, *t*, CH_3), 1.71(3H, *s*, CH_3), 2.01 (1H, *s*, NH), 2.09(1H, *s*, NH), 4.14 (2H, *q*, CH_2), 4.62(1H, *s*, CH), 5.08(1H,*s*, OH), 7.10-7.15(4H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ (ppm): 178.5, 165.3,152.3,145.2, 128.3,127.1, 126.5, 104.2, 59.9, 54.9, 17.9, 13.7. Anal. Calcd (%) for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; found C, 57.46; H, 5.50; N, 9.46.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione *(4l)*
M.p.207-209°C; IR (KBr, *v max, cm*$^{-1}$); 3360, 3280, 1740, 1619, 1365,1229, 1020. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.28 (3H, *t*, CH_3), 1.73(3H, *s*, CH_3), 2.03 (1H, *s*, NH), 2.08(1H, *s*, NH), 4.17 (2H, *q*, CH_2), 4.63(1H, *s*, CH), 7.06-7.14(5H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 178.5, 165.3, 152.3, 145.2, 128.3, 127.1, 126.5, 104.2, 59.9, 54.8, 17.7, 13.7. Anal. Calcd (%) for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14; found C, 60.80; H, 5.80; N, 10.10.

5-Ethoxycarbonyl-4-(4-methyl-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione*(4m)*
M.p.149-151°C; IR (KBr, *v max, cm*$^{-1}$); 3354,3279, 1742, 1620, 1230, 1019. ^{1}H NMR (DMSO-d_6) δ(ppm): 1.34 (3H, *t*, CH_3), 1.71(3H, *s*, CH_3), 2.00 (1H, *s*, NH), 2.05(1H, *s*, NH), 2.34 (3H, *s*, CH_3), 4.22 (2H, *q*, CH_2), 4.58(1H, *s*, CH), 6.94-6.99(4H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 178.5, 165.3, 152.3, 139.4, 135.6, 129.1, 127.0, 104.2, 59.5, 54.6, 17.7, 13.7. Anal. Calcd (%)for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65; found C, 62.00; H, 6.21; N, 9.67.

5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione*(4n)*
M.p.190-192°C; IR (KBr, *v max, cm*$^{-1}$); 3357, 3269, 1739, 1610, 1241,1010. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.35 (3H, *t*, CH_3), 1.73(3H, *s*, CH_3), 2.02 (1H, *s*, NH), 2.08(1H, *s*, NH), 4.19 (2H, *q*, CH_2), 4.55(1H, *s*, CH), 7.00-7.15(4H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ(ppm): 178.3, 165.1, 152.1, 139.6, 131.8, 128.7, 104.2, 59.6, 54.4, 17.9, 13.9. Anal. Calcd (%) for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N, 9.01; found C, 54.06; H, 4.80; N, 9.04.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione *(4o)*
M.p.150-152°C; IR (KBr, *v max, cm*$^{-1}$); 3345, 3255, 1725, 1608, 1247, 1045, 1019.^{1}H NMR (DMSO-d_6) δ(ppm): 1.31 (3H, *t*, CH_3), 1.70(3H, *s*, CH_3), 2.00 (1H, *s*, NH), 2.05(1H, *s*, NH), 3.73(3H, *s*, OCH_3), 4.17 (2H, *q*, CH_2),4.58(1H, *s*, CH), 6.65-4.95(4H, *m*, H-Ar), ^{13}C NMR (DMSO-d_6) δ (ppm): 178.5, 165.3, 160.2, 152.3, 134.7, 128.1, 113.9, 104.2, 59.8, 56.0, 54.6, 17.7, 13.5. Anal. Calcd (%) for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14; found C, 58.75; H, 5.89; N, 9.16.

CONCLUSION

In conclusion, a rapid and highly efficient approach to structurally diverse 3,4-dihydropyrimidin-2(1*H*)-thiones derivatives has been developed via *p*-TSA-promoted one-pot reaction of ethyl acetoacetate with substituted thiourea/phenyl thiourea and aryl aldehydes in ethanol. The mild conditions, short reaction time, easy purification and easy available starting materials make the protocol interesting for academic research.

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