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Novel four-component reaction towards diastereoselective synthesis of tetrahydropyrimidinthiones

Jie-Ping Wan [a,b], Chunping Wang [a], Yuanjiang Pan [b,*]

[a] College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, China
[b] Department of Chemistry, Zhejiang University, Hangzhou 310027, China

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ABSTRACT

The first multicomponent synthesis of tetrahydropyrimidinthiones has been realized via the four-component assembly of aromatic aldehyde, enaminone, aromatic amine, and thiourea. The reaction was performed at room temperature and the products were obtained in excellent diastereoselectivity.

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1. Introduction

Creating molecular diversity in organic reactions is one of the main goals of organic synthesis due to the urgent requirement on compound libraries in drug discovery process.[1] The central issue to achieve this goal is to develop fast and efficient synthetic technologies, which exclude the drawbacks embedded in traditional step-by-step synthesis, such as tedious repeated work-up, long cyclic period, low total yield, and continuous production of organic wastes. Multicomponent reaction (MCR), known to construct complex products in one-pot by the assembly of three or more substrates, provided an ideal solution to the contradiction between low efficiency of tradition linear synthesis and the high requirement of candidate compounds for drug discovery.[2]

Tetrahydropyrimidinthiones (THPMs) could be regarded as the reduced derivatives of dihydropyrimidinones (DHPMs) and represent a class of highly valuable heterocylic identities in the study of medicinal chemistry. Properly elaborated THPMs have been reported to possess a broad range of bioactivities: HIV protease inhibiting activity,[3] antineoplastic activity,[4] antiproleferative,[5] and herbicidal activity,[6] to name but a few. Presently, THPMs are generally synthesized by the annulation reaction of ureas and 1,3-dihalides.[7] The Pd-catalyzed ring expansion reaction of *N*-alkyl-2-vinylazetidine with isocyanate was also reported to afford THPMs.[8] However, in the viewpoint of molecular diversity and complexity, multicomponent reaction is arguably the most ideal strategy for the synthesis of these heterocyclic scaffolds. The presently known MCR protocols for the synthesis of THPMs are using Biginelli-like transformation. Unfortunately, controlling the Biginelli-like process to provide THPMs is rather difficult since the THPMs prone to dehydrate to give more stable DHPMs (Biginelli reaction). It is possible to obtain THPMs as products using this methodology only when substrates with particular functional groups, such as fluorinated 1,3-dicarbonyl[9] compounds or trichloromethylated 1,3-dicarbonyl compounds[10] were employed. Or alternatively, using the two-step operation of Knoevenagel condensation and (thio)urea annulation.[11] To the best of our knowledge, not a multicomponent protocol for the synthesis of THPMs tolerating conventional and simple reactants is presently available. It is therefore highly desirable to develop MCR methods for the generous synthesis of THPMs. As our continuous efforts in developing novel MCRs for the synthesis of useful heterocyclic scaffolds[12] we wish to report herein the first four-component synthesis of THPMs by using aromatic aldehyde, emaminone, aromatic amine, and thiourea.

2. Results and discussion

In the initial study, we tentatively employed enaminone **1a**, benzaldehyde **2a**, aniline **3a**, and thiourea for the synthesis of THPM **5a** in the manner of four-component reaction at the presence of trimethylsilyl chloride (TMSCl). To our delight, albeit in low yield,

* Corresponding author. Tel.: +86 571 8795 1264; fax: +86 571 8795 1629; e-mail address: cheyjpan@zju.edu.cn (Y. Pan).

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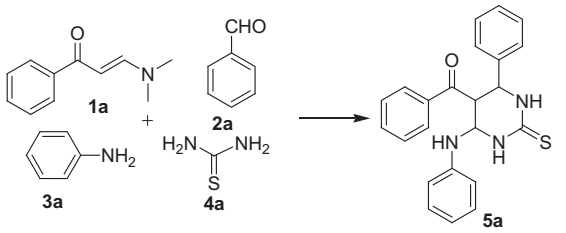
THPM **5a** was provided in the reaction as expected (entry 1, Table 1). This result encouraged us to further investigate proper reaction conditions to enhance the reaction efficiency. Typical results on condition optimization were summarized in Table 1. It is interesting that significantly higher yield of **5a** could be obtained when employing a co-catalyst, such as $FeCl_3$ or cerium (IV) ammonium nitrate (CAN) to promote the reaction, and CAN is better favored by this four-component reaction (entries 2 and 3, Table 1). The loading of catalysts as well as reaction solvent has also been briefly examined. Finally, it was found that the co-catalyst of TMSCl/CAN in the loading of 0.5/0.5 equiv in EtOH gave the best result among the performed entries (entry 3, Table 1). The transformation gave significantly better yield under co-catalyst system may be attributed to the water scavenging effect of TMSCl as well as the Lewis acid function of CAN or $FeCl_3$.[13]

Table 1
Screening on the reaction conditions for the four-component THPM synthesis[a]



Entry	Solvent	Catalyst(s)	Cat. (%)	Yield[b] (%)
1	EtOH	TMSCl	50	28
2[c]	EtOH	TMSCl/$FeCl_3$	50/50	40
3[d]	EtOH	TMSCl/CAN	50/50	63
4	EtOH	CAN	50	Trace
5	EtOH	TMSCl/CAN	100/50	29
6	EtOH	TMSCl/CAN	50/70	35
7	EtOH	TMSCl/CAN	50/30	19
8	$ClCH_2CH_2Cl$	TMSCl/CAN	50/50	Messy
9	Toluene	TMSCl/CAN	50/50	30

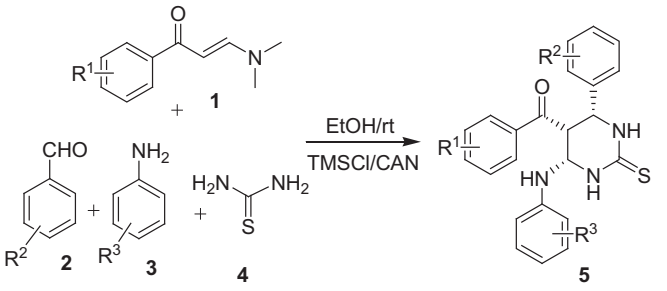
[a] All reactions were carried out at 0.30 mmol scale (thiourea was used in 0.35 mmol) in 2 mL solvent and stirred at room temperature for 16 h.
[b] Isolated yield.
[c] Iron chloride was used in the form of commercial $FeCl_3 \cdot 6H_2O$.
[d] CAN: cerium (IV) ammonium nitrate.

Subsequently, we performed the experiments using various substrates, including enaminones, aldehydes, and primary aromatic amines with different functional groups. The results of different THPMs synthesis are outlined in Table 2. It can be found in the results that this reactions system tolerates a wide range of functional groups of different properties. The products are generally furnished in moderate to good yields, and the present data on product yields implied that the factors affecting the reaction efficiency are complex. Notably, all the entries in our THPMs synthesis provided single racemate products based on their ^1H NMR results, which demonstrates that this four-component assembly proceeds in the manner of specific diastereoselectivity. However, urea was found incompatible to this kind of reaction when used as the alternative substrate of thiourea.

The stereochemistry of products **5** was assigned based on the NOE NMR analysis on **5q**. As exhibited in Fig. 1, the relative configuration of the three chiral centers formed in **5q** was identified via the NOE signal interactions between protons H^a to H^f. First, clear NOE signals of H^a/H^b and H^b/H^c were observed in the NMR spectrum; secondary, no NOE interaction signal between H^a/H^e, H^b/H^d, H^b/H^f or H^c/H^e were observed. Therefore, the stereostructure of **5q** was established as shown in Fig. 1.

Following the examination on the application scope of this new four-component reaction, we sought to survey if this type of transformation is applicable for classical Biginelli reaction to synthesize corresponding THPMs. We then employed typical acetyl ethyl acetate

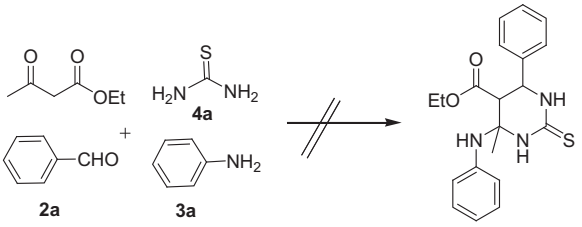
Table 2
Various THPMs synthesized by four-component reactions[a]



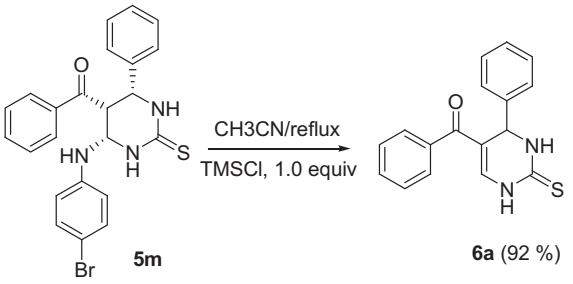
Entry	R^1	R^2	R^3	Product[b]	Yield[c] (%)
1	H	H	H	**5a**	63
2	H	4-Me	H	**5b**	57
3	H	4-MeO	H	**5c**	72
4	H	4-F	H	**5d**	66
5	H	4-Cl	H	**5e**	48
6	H	3-MeO	H	**5f**	42
7	H	3-NO_2	H	**5g**	50
8	H	2-F	H	**5h**	37
9	4-Me	H	H	**5i**	40
10	4-MeO	H	H	**5j**	53
11	H	H	4-Me	**5k**	57
12	H	H	4-Cl	**5l**	73
13	H	H	4-Br	**5m**	75
14	4-MeO	4-Me	H	**5n**	47
15	4-Cl	4-Br	H	**5o**	64
16	4-Me	4-MeO	H	**5p**	55
17	4-Me	H	4-Cl	**5q**	70
18	4-MeO	H	4-Cl	**5r**	69
19	4-Me	4-MeO	4-Cl	**5s**	47

[a] Reactions conditions: 0.30 mmol **1**, **2**, and **3** as well 0.35 mmol **4** located in 2 mL EtOH in the presence of 0.5 equiv mol of TMSCl and 0.5 equiv mol of CAN, stirred at room temperature for 16 h.
[b] The stereochemistry of the products were assigned by NOE NMR experiment (see below).
[c] Isolated yield

to react with benzaldehyde, aniline, and thiourea for one-pot reaction under identical conditions as described above. However, the target product was not formed even though we repeated the operation (Eq. 1), which further confirmed that the four-component protocol developed in our study is uniquely applicable for the synthesis of THPMs.



Finally, to investigate the stability and potential transformation property of the THPMs synthesized in our research, product **5m** (0.1 mmol) was selected and subjected to the acidic environment. In the presence of 1 equiv mol of TMSCl in reflux CH_3CN, **5m** was completely transformed to corresponding DHPM **6a** by undergoing a deamination process (Eq. 2).



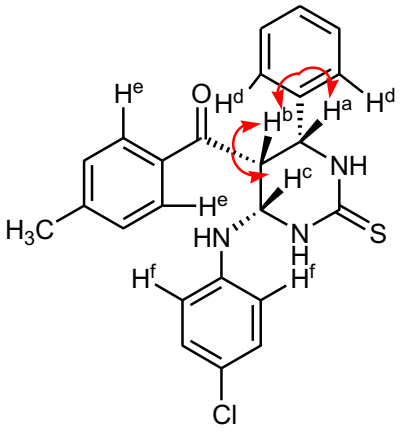


Fig. 1. NOE analysis of **5q**.

3. Conclusion

Through the design of multicomponent reactions using simple starting materials, the first four-component synthesis of THPMs has been achieved. The reactions proceeded in mild reaction conditions to give unprecedented THPMs in specific diastereoslectivity. This approach is therefore potentially useful for the synthesis of structurally diversified heterocyclic compounds with the THPM backbone for the sake of medicinal or biological research.

4. Experimental section

4.1. Four-component synthesis of THMPs (5a–s)

Aldehyde (0.30 mmol), 0.30 mmol enaminone, 0.30 mmol aromatic amine, and 0.35 mmol thiourea were located in a 25 mmol round bottom flask. Then, 2 mL EtOH and 0.15 mmol CAN were added. Finally, 0.15 mmol TMSCl was injected into the flask, and the reaction was stirred at room temperature for 16 h to complete (TLC). The THPMs products directly precipitated from the reaction and were filtrated. Generally, analytically pure products were obtained by simply washing the residue with EtOH (3×3 mL) and drying in vacuum. Further purification of recrystallization in EtOH/DMF/H_2O was employed when necessary.

*4.1.1. 4-Phenyl-5-benzoyl-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5a**).* Pale yellow solid; mp 228–230 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.60 (s, 1H), 8.14 (s, 1H), 7.61 (d, 2H, J=7.6 Hz), 7.43 (t, 2H, J=7.0 Hz), 7.27 (t, 2H, J=7.7 Hz), 7.20–7.11 (m, 5H), 7.04 (t, 2H, J=7.8 Hz), 6.60–6.54 (m, 3H), 6.07 (d, 1H, J=10.6 Hz), 5.39 (t, 1H, J=10.0 Hz), 4.72 (d, 1H, J=10.2 Hz), 4.19 (t, 1H, J=9.7 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=200.4, 177.9, 146.9, 139.1, 138.2, 134.4, 130.1, 129.6, 129.4, 129.3, 129.2, 128.3, 118.8, 114.8, 65.4, 60.2, 51.7; HRMS: calcd for $C_{23}H_{21}N_3OSNa$ $[M+Na]^+$ 410.1298; found: 410.1293.

*4.1.2. 4-p-Tolyl-5-benzoyl-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5b**).* White solid; mp 287–289 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.50 (s, 1H), 8.09 (s, 1H), 7.65 (d, 2H, J=7.5 Hz), 7.45 (t, 1H, J=7.7 Hz), 7.29 (t, 2H, J=7.7 Hz), 7.09 (d, 2H, J=8.0 Hz), 7.05–6.95 (m, 4H), 6.60–6.54 (m, 3H), 6.07 (d, 1H, J=10.6 Hz), 5.36 (t, 1H, J=9.9 Hz), 4.71 (d, 1H, J=10.0 Hz), 4.19 (t, 1H, J=9.7 Hz), 2.14 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=200.5, 177.8, 146.9, 138.4, 138.2, 136.1, 134.4, 130.1, 129.5, 129.3, 128.2, 118.8, 114.8, 65.5, 59.9, 51.5, 21.8; HRMS: calcd for $C_{24}H_{23}N_3OSNa$ $[M+Na]^+$ 424.1454; found: 424.1461.

*4.1.3. 4-(p-Methoxylphenyl)-5-benzoyl-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5c**).* White solid; mp 221–222 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.46 (s, 1H), 8.05 (s, 1H), 7.65 (d, 2H, J=7.7 Hz), 7.46 (t, 1H, J=7.5 Hz), 7.29 (t, 2H, J=7.6 Hz), 7.12 (d, 2H, J=8.5 Hz), 7.04 (t, 2H, J=7.6 Hz), 6.75 (d, 2H, J=8.5 Hz), 6.60–6054 (m, 3H), 6.06 (d, 1H, J=10.5 Hz), 5.36 (t, 1H, J=10.0 Hz), 4.68 (d, 1H, J=10.2 Hz), 4.18 (t, 1H, J=9.7 Hz), 3.61 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=200.1, 177.3, 159.6, 146.4, 137.8, 133.9, 130.3, 129.6, 129.1, 129.0, 128.8, 118.4, 114.6, 114.4, 65.0, 59.1, 55.7, 51.1; HRMS: calcd for $C_{24}H_{23}N_3O_2SNa$ $[M+Na]^+$ 440.1403; found: 440.1393.

*4.1.4. 4-(p-Fluorophenyl)-5-benzoyl-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5d**).* White solid; mp 249–251 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.62 (s, 1H); 8.16 (s, 1H), 7.64 (d, 2H, J=7.6 Hz), 7.47 (t, 1H, J=7.3 Hz), 7.30 (t, 2H, J=7.3 Hz), 7.25–7.22 (m, 2H), 7.06–6.99 (m, 4H), 6.60–6.55 (m, 3H), 6.09 (d, 1H, J=10.5 Hz), 5.39 (t, 1H, J=10.0 Hz), 4.74 (d, 1H, J=10.2 Hz), 4.19 (t, 1H, J=10.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=200.4, 177.9, 146.9, 138.2, 135.2, 134.5, 130.5, 130.1, 129.5, 129.2, 118.8, 116.4, 116.3, 114.8, 65.4, 59.5, 51.6; HRMS: calcd for $C_{23}H_{20}FN_3OSNa$ $[M+Na]^+$ 428.1203; found: 428.1200.

*4.1.5. 4-(p-Chlorophenyl)-5-benzoyl-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5e**).* White solid; mp 238–241 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.64 (s, 1H), 8.18 (s, 1H), 7.66 (d, 2H, J=7.7 Hz), 7.48 (t, 1H, J=7.6 Hz), 7.30 (t, 2H, J=7.6 Hz), 7.26–7.21 (m, 4H), 7.04 (t, 2H, J=7.7 Hz), 6.60–6.55 (m, 3H), 6.07 (d, 1H, J=10.2 Hz), 5.39 (t, 3H, J=9.6 Hz), 4.75 (d, 1H, J=10.1 Hz), 4.20 (t, 1H, J=9.7 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=200.3, 177.9, 146.9, 138.1, 138.0, 134.6, 133.6, 130.3, 130.0, 129.5, 129.2, 118.8, 114.8, 65.4, 59.5, 51.4; HRMS: calcd for $C_{23}H_{20}ClN_3OSNa$ $[M+Na]^+$ 444.0908; found: 444.0902.

*4.1.6. 4-(m-Methoxylphenyl)-5-benzoyl-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5f**).* White solid; mp 205–207 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.55 (s, 1H), 8.11 (s, 1H), 7.65 (d, 2H, J=7.8 Hz), 7.46 (t, 1H, J=7.6 Hz), 7.30 (t, 2H, J=7.6 Hz), 7.10 (t, 1H, J=7.8 Hz), 7.03 (t, 2H, J=7.5 Hz), 6.77 (d, 1H, J=7.6 Hz), 6.73 (s, 1H), 6.67 (d, 1H, J=7.6 Hz), 6.61–6.54 (m, 3H), 6.00 (d, 1H, J=10.3 Hz), 5.37 (t, 1H, J=9.6 Hz), 4.70 (d, 1H, J=9.9 Hz), 4.21 (t, 1H, J=10.3 Hz), 3.64 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=200.4, 177.8, 160.2, 146.8, 140.6, 138.2, 134.4, 130.7, 130.1, 129.4, 129.2, 120.5, 118.9, 114.8, 113.9, 65.3, 60.0, 56.2, 51.5; HRMS: calcd for $C_{24}H_{23}N_3O_2SNa$ $[M+Na]^+$ 440.1403; found: 440.1394.

*4.1.7. 4-(m-Nitrophenyl)-5-benzoyl-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5g**).* Pale yellow solid; mp 268–270 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.83 (s, 1H), 8.35 (s, 1H), 8.08 (s, 1H), 7.97 (d, 1H, J=7.9 Hz), 7.66 (t, 3H, J=8.2 Hz), 7.48–7.43 (m, 2H), 7.28 (t, 2H, J=7.7 Hz), 7.04 (t, 2H, J=7.8 Hz), 6.61–6.55 (m, 3H), 6.01 (d, 1H, J=10.1 Hz), 5.41 (t, 1H, J=10.1 Hz), 4.93 (d, 1H, J=9.8 Hz), 4.31 (t, 1H, J=9.6 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=200.0, 178.0, 148.6, 146.8, 141.4, 138.0, 135.3, 134.7, 131.2, 130.6, 129.6, 129.2, 124.1, 123.2, 118.8, 114.8, 65.2, 59.0, 51.3; HRMS: calcd for $C_{23}H_{20}N_4O_3SNa$ $[M+Na]^+$ 455.1148; found: 455.1143.

*4.1.8. 4-(o-Fluorophenyl)-5-benzoyl-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5h**).* White solid; mp 242–244 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.67 (s, 1H), 8.12 (s, 1H), 7.70 (d, 2H, J=7.8 Hz), 7.47 (t, 1H, J=7.3 Hz), 7.31 (t, 3H, J=7.3 Hz), 7.19–7.14 (m, 1H), 7.08–6.97 (m, 3H), 6.95 (t, 1H, J=9.5 Hz), 6.58 (t, 3H, J=8.3 Hz), 6.16 (d, 1H, J=10.5 Hz), 5.41 (t, 1H, J=9.7 Hz), 4.94 (d, 1H, J=10.2 Hz), 4.39 (t, 1H, J=10.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=199.9,

177.7, 162.1, 160.2, 146.9, 138.0, 134.6, 131.4, 130.8, 130.6, 129.5, 129.1, 125.7, 118.8, 116.8, 116.6, 114.8, 65.4, 54.6, 49.4; HRMS: calcd for $C_{23}H_{20}FN_3OSNa$ $[M+Na]^+$ 428.1203; found: 428.1206.

*4.1.9. 4-Phenyl-5-(p-methylbenzoyl)-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5i**).* Pale yellow solid; mp 250–253 °C; ^1H NMR (500 MHz, DMSO-d_6): δ=8.56 (s, 1H), 8.08 (s, 1H), 7.54 (d, 2H, J=8.5 Hz), 7.20 (s, 4H), 7.14–7.12 (m, 1H), 7.09–7.02 (m, 4H), 6.60–6.54 (m, 3H), 6.03 (d, 1H, J=10.5 Hz), 5.35 (t, 1H, J=8.6 Hz), 4.73 (d, 1H, J=10.2 Hz), 4.15 (t, 1H, J=9.7 Hz), 2.24 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=199.8, 177.8, 146.9, 145.0, 139.2, 135.8, 130.1, 130.0, 129.6, 129.4, 129.3, 128.3, 118.8, 114.8, 65.4, 60.2, 51.4, 22.2; HRMS: calcd for $C_{24}H_{23}N_3OSNa$ $[M+Na]^+$ 424.1454; found: 424.1449.

*4.1.10. 4-Phenyl-5-(p-methoxylbenzoyl)-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5j**).* Pale yellow solid; mp 213–215 °C; ^1H NMR (500 MHz, DMSO-d_6): δ=8.54 (s, 1H), 8.05 (s, 1H), 7.64 (d, 2H, J=7.7 Hz), 7.20 (s, 4H), 7.15–7.12 (m, 1H), 7.04 (t, 2H, J=7.7 Hz), 6.79 (d, 2H, J=7.4 Hz), 6.60–6.54 (m, 3H), 6.03 (d, 1H, J=10.5 Hz), 5.35 (t, 1H, J=9.8 Hz), 4.71 (d, 1H, J=10.2 Hz), 4.13 (t, 1H, J=10.2 Hz), 3.75 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=198.3, 177.8, 164.3, 146.9, 139.2, 131.7, 131.3, 130.1, 129.5, 129.2, 128.3, 118.8, 114.8, 114.7, 65.4, 60.2, 56.6, 51.1; HRMS: calcd for $C_{24}H_{23}N_3O_2SNa$ $[M+Na]^+$ 440.1403; found: 440.1409.

*4.1.11. 4-Phenyl-5-benzoyl-6-(p-methylphenyl)amino-1,4,5,6-tetrahydropyrimidine-2-thione (**5k**).* Pale yellow solid; mp 238–239 °C; ^1H NMR (500 MHz, DMSO-d_6): δ=8.59 (s, 1H), 7.94 (s, 1H), 7.62 (d, 2H, J=7.8 Hz), 7.44 (t, 1H, J=7.5 Hz), 7.28 (t, 2H, J=7.7 Hz), 7.20 (s, 4H), 7.12 (br s, 1H), 6.86 (d, 2H, J=8.0 Hz), 5.84 (d, 2H, J=8.1 Hz), 5.84 (d, 1H, J=10.1 Hz), 5.34 (t, 1H, J=9.8 Hz), 4.72 (d, 1H, J=10.1 Hz), 4.18 (t, 1H, J=10.0 Hz), 2.12 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=200.4, 177.8, 144.4, 139.1, 138.2, 134.4, 130.5, 129.6, 129.4, 129.3, 129.2, 128.3, 127.5, 115.1, 65.9, 60.2, 51.7, 21.2; HRMS: calcd for $C_{24}H_{23}N_3OSNa$ $[M+Na]^+$ 424.1454; found: 424.1455.

*4.1.12. 4-Phenyl-5-benzoyl-6-(p-chlorophenyl)amino-1,4,5,6-tetrahydropyrimidine-2-thione (**5l**).* White solid; mp 251–252 °C; ^1H NMR (500 MHz, DMSO-d_6): δ=8.56 (s, 1H), 8.36 (s, 1H), 7.59–7.04 (m, 12H), 2.56 (2H), 6.27 (1H), 5.37 (1H), 4.72 (1H), 4.16 (1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=200.4, 177.9, 146.0, 139.0, 138.2, 134.4, 129.6, 129.5, 129.4, 129.3, 129.1, 128.3, 122.0, 116.2, 65.4, 60.2, 51.7; HRMS: calcd for $C_{23}H_{20}ClN_3OSNa$ $[M+Na]^+$ 444.0908; found: 444.0901.

*4.1.13. 4-Phenyl-5-benzoyl-6-(p-bromophenyl)amino-1,4,5,6-tetrahydropyrimidine-2-thione (**5m**).* White solid; mp 240–241 °C; ^1H NMR (500 MHz, DMSO-d_6): δ=8.55 (s, 1H), 8.38 (s, 1H), 7.59 (d, 2H, J=7.6 Hz), 7.44 (t, 1H, J=7.8 Hz), 7.27 (t, 2H, J=7.7 Hz), 7.20–7.10 (m, 7H), 6.51 (d, 2H, J=8.8 Hz), 6.29 (d, 1H, J=10.5 Hz), 5.37 (t, 1H, J=9.9 Hz), 4.73 (d, 1H, J=10.2 Hz), 4.16 (t, 1H, J=9.9 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=200.4, 177.9, 146.5, 139.0, 138.2, 134.4, 132.5, 129.5, 129.4, 129.3, 129.1, 128.3, 116.7, 109.4, 65.3, 60.2, 51.7; HRMS: calcd for $C_{23}H_{20}BrN_3OSNa$ $[M+Na]^+$ 488.0403; found: 488.0411.

*4.1.14. 4-p-Tolyl-5-(p-methoxylbenzoyl)-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5n**).* Pale yellow solid; mp 207–209 °C; ^1H NMR (500 MHz, DMSO-d_6): δ=8.44 (s, 1H), 8.01 (s, 1H), 7.09 (d, 2H, J=8.7 Hz), 7.06–7.00 (m, 4H), 6.80 (d, 2H, J=8.3 Hz), 6.61–6.54 (m, 3H), 6.03 (d, 1H, J=10.3 Hz), 5.32 (t, 1H, J=9.4 Hz), 4.69 (d, 1H, J=10.2 Hz), 4.13 (t, 1H, J=10.3 Hz), 3.74 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=198.3, 177.7, 164.4, 146.9, 138.3, 136.2, 131.8, 131.3, 130.1, 128.2, 118.8, 114.8, 114.7, 65.5, 59.8, 56.6, 51.0, 21.8; HRMS: calcd for $C_{25}H_{25}N_3O_2SNa$ $[M+Na]^+$ 454.1560; found: 454.1560.

*4.1.15. 4-(p-Bromophenyl)-5-(p-chlorobenzoyl)-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5o**).* Pale yellow solid; mp 273–275 °C; ^1H NMR (500 MHz, DMSO-d_6): δ=8.64 (s, 1H), 8.22 (s, 1H), 7.67 (d, 2H, J=8.5 Hz), 7.39 (t, 4H, J=8.7 Hz), 7.16 (d, 2H, J=8.3 Hz), 7.03 (t, 2H, J=7.7 Hz), 6.60–6.54 (m, 3H), 6.06 (br s, 1H), 5.38 (br s, 1H), 4.74 (d, 1H, J=10.2 Hz), 4.16 (t, 1H, J=9.9 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=199.3, 177.9, 146.8, 139.7, 138.4, 136.8, 132.5, 131.1, 130.6, 130.0, 129.7, 122.3, 118.9, 114.8, 65.4, 59.4, 51.6; HRMS: calcd for $C_{23}H_{19}BrClN_3OSNa$ $[M+Na]^+$ 522.0013; found: 522.0037.

*4.1.16. 4-(p-Methoxylphenyl)-5-(p-methylbenzoyl)-6-phenylamino-1,4,5,6-tetrahydropyrimidine-2-thione (**5p**).* White solid; mp 228–230 °C; ^1H NMR (500 MHz, DMSO-d_6): δ=8. 43 (s, 1H), 8.01 (s, 1H), 7.58 (d, 2H, J=8.0 Hz), 7.14–7.09 (m, 4H), 7.03 (t, 2H, J=7.3 Hz), 6.76 (d, 2H, J=8.4 Hz), 6.60–6.54 (m, 3H), 6.04 (d, 1H, J=10.2 Hz), 5.33 (t, 1H, J=9.8 Hz), 4.69 (d, 1H, J=10.2 Hz), 4.15 (t, 1H, J=9.8 Hz), 3.62 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=199.9, 177.7, 160.0, 146.9, 145.0, 135.8, 130.9, 130.1, 129.6, 129.5, 118.8, 114.9, 114.8, 65.6, 59.6, 56.2, 51.3, 22.2; HRMS: calcd for $C_{25}H_{25}N_3O_2SNa$ $[M+Na]^+$ 454.1560; found: 454.1571.

*4.1.17. 4-Phenyl-5-(p-methylbenzoyl)-6-(p-chlorophenyl)amino-1,4,5,6-tetrahydropyrimidine-2-thione (**5q**).* White solid; mp 257–259 °C; ^1H NMR (500 MHz, DMSO-d_6): δ=8. 53 (s, 1H), 8.32 (s, 1H), 7.51 (d, 2H, J=7.9 Hz), 7.20 (s, 4H), 7.14–7.11 (m, 1H), 7.08–7.03 (m, 4H), 6.54 (d, 2H, J=8.5 Hz), 6.24 (d, 1H, J=10.4 Hz), 5.33 (t, 1H, J=9.8 Hz), 4.71 (d, 1H, J=10.2 Hz), 4.12 (t, 1H, J=9.7 Hz), 2.24 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=199.7, 177.9, 146.6, 145.0, 139.1, 135.8, 130.0, 129.6, 129.5, 129.3, 129.2, 128.2, 121.9, 116.2, 65.5, 60.1, 51.5, 22.2; HRMS: calcd for $C_{24}H_{22}ClN_3OSNa$ $[M+Na]^+$ 458.1064; found: 458.1061.

*4.1.18. 4-Phenyl-5-(p-methoxylbenzoyl)-6-(p-chlorophenyl)amino-1,4,5,6-tetrahydropyrimidine-2-thione (**5r**).* Pale yellow solid; mp 259–262 °C; ^1H NMR (500 MHz, DMSO-d_6, minor diastereoisomers included): δ=8. 51 (s, 1H), 8.30 (s, 1H), 7.61 (d, 2H, J=7.8 Hz), 7.20–7.12 (m, 5H), 7.03 (t, 3H, J=8.3 Hz), 6.78 (d, 1H, J=7.8 Hz), 6.54 (d, 2H, J=8.7 Hz), 6.24 (d, 1H, J=10.5 Hz), 5.32 (t, 1H, J=9.9 Hz), 4.69 (d, 1H, J=10.2 Hz), 4.09 (t, 1H, J=9.7 Hz), 3.73 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=198.3, 177.8, 164.4, 146.1, 139.2, 131.7, 130.6, 129.6, 129.4, 128.2, 121.9, 118.9, 116.2, 114.6, 65.3, 60.2, 56.6, 51.2; HRMS: calcd for $C_{24}H_{22}ClN_3O_2SNa$ $[M+Na]^+$ 474.0991; found: 474.1013.

*4.1.19. 4-(p-Methoxylphenyl)-5-(p-methylbenzoyl)-6-(p-chlorophenyl) amino-1,4,5,6-tetrahydropyrimidine-2-thione (**9s**).* Pale yellow solid; mp 249–251 °C; ^1H NMR (500 MHz, DMSO-d_6): δ=8. 42 (s, 1H), 8.28 (s, 1H), 7.55 (d, 2H, J=8.0 Hz), 7.11 (t, 4H, J=8.7 Hz), 7.04 (d, 2H, J=8.5 Hz), 6.75 (d, 2H, J=8.4 Hz), 6.54 (d, 2H, J=8.6 Hz), 6.26 (d, 1H, J=10.4 Hz), 5.31 (t, 1H, J=9.8 Hz), 4.66 (d, 1H, J=10.3 Hz), 4.11 (t, 1H, J=9.7 Hz), 3.62 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ=199.9, 177.7, 160.1, 146.1, 145.0, 135.8, 130.8, 130.1, 129.7, 129.6, 129.4, 121.9, 116.2, 114.9, 65.6, 59.6, 56.2, 51.4, 22.2; HRMS: calcd for $C_{25}H_{24}ClN_3O_2SNa$ $[M+Na]^+$ 488.1170; found: 488.1176.

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Supplementary data

General experiment details, copies of the ^1H, ^{13}C NMR spectra for products **5a**–**s**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.12.011. These data include MOL files and InChIKeys of the most important compounds described in this article.

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