# 2-Amino-4,5-dihydrothiophene-3-carbonitriles: A New Synthesis, Quantum Chemical Studies, and Mannich-Type Reactions Leading to New Hexahydrothieno[2,3-d]pyrimidines

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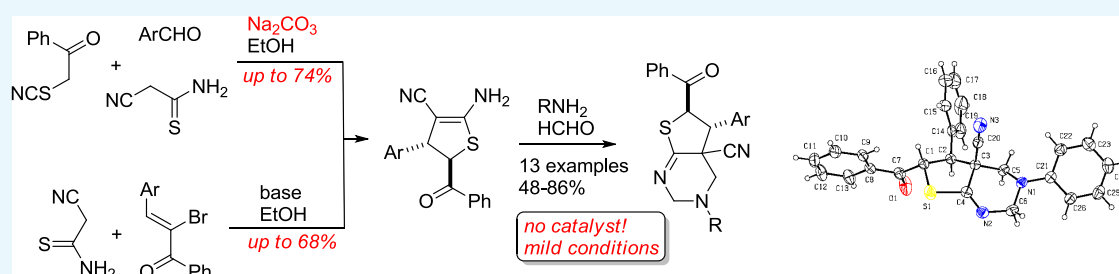
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**ABSTRACT:** *trans*-2-Amino-4-aryl-5-benzoyl-4,5-dihydrothiophene-3-carbonitriles were prepared either by the reaction of 3-aryl-2-cyanothioacrylamides with $\alpha$-thiocyanatoacetophenone or by the Michael-type addition of cyanothioacetamide to $\alpha$-bromochalcones followed by intramolecular cyclization. The mechanism of the first reaction was studied using high-level quantum chemical calculations. Density functional theory (DFT) studies were carried out to determine the mechanism of the first reaction. A new approach toward the construction of the thieno[2,3-d]pyrimidine core system was demonstrated by the reaction of the prepared dihydrothiophenes with HCHO and RNH₂ under noncatalyzed Mannich conditions.

## INTRODUCTION

2-Aminothiophenes and related molecules are of particular interest, especially within the realm of medicinal chemistry (for reviews, see refs 1−7). Many of the compounds based on the 2-aminothiophene structural motif show a broad range of biological properties and were recognized as potent pan-serotype dengue virus inhibitors,[8] antitubercular agents,[9−11] allosteric modulators of the A1 adenosine receptor (A₁R),[12] antiproliferative agents,[13,14] antimicrobials,[15] inhibitors of influenza virus polymerase,[16] GluR6-antagonists,[17] and protein-tyrosine phosphatase 1B (PTP1B) inhibitors[18] (Figure 1). Some 2-aminothiophenes are traded drugs and were subjected to extensive pharmacological studies. Among them, strontium ranelate (Protelos/Osseor, useful for the treatment of osteoporosis,[19−25] as a dental pulp-like cell proliferation agent,[26] and as a radiopaque agent for calcium phosphate cement[27]), tinoridine (old but still useful anti-inflammatory drug with a strong antiperoxidative and hepatoprotective activity),[28−30] and olanzapine[31−33] (Zyprexa, used to treat certain mental disorders such as schizophrenia and bipolar disorder) should be noted (Figure 1). In addition, the 2-aminothiophene motif is present in drugs and bioactive molecules such as T-62 (a selective allosteric modulator of the adenosine A receptor),[34] bentazepam (Tiadipona),[35] and brotizolam (Lendormin);[36−38] anxiolytic/anticonvulsant agents

and skeletal muscle relaxants; and the anticancer drug raltitrexed (Tomudex)[39−41] (Figure 1). 2-Aminothiophenes are able to act as starting points for the synthesis of a variety of thiophene-containing heterocycles and polycyclic hybrid molecules.[3−6,42] Moreover, as shown recently, 2-aminothiophenes might find an application in the preparation of functional materials such as electrochemically color switching azomethines,[43−46] liquid crystalline materials,[47] oligothiophene-BODIPY hybrids as NIR dyes,[48] organic photovoltaic cells,[49] azodyes,[50] nonlinear optical materials,[51] and azomethine-bridged polythiophenefer-rocenes.[52]

Such a diversity of available structures and applications is due to the synthetic availability of 2-aminothiophenes. The most widely used synthetic approach toward 2-aminothiophenes is based on the Gewald reaction of methylene active nitriles with elemental sulfur and methylene active ketones/aldehydes.[1−6] However, this approach provides an access to aromatic 2-aminothiophenes only. Less is known on the chemistry of
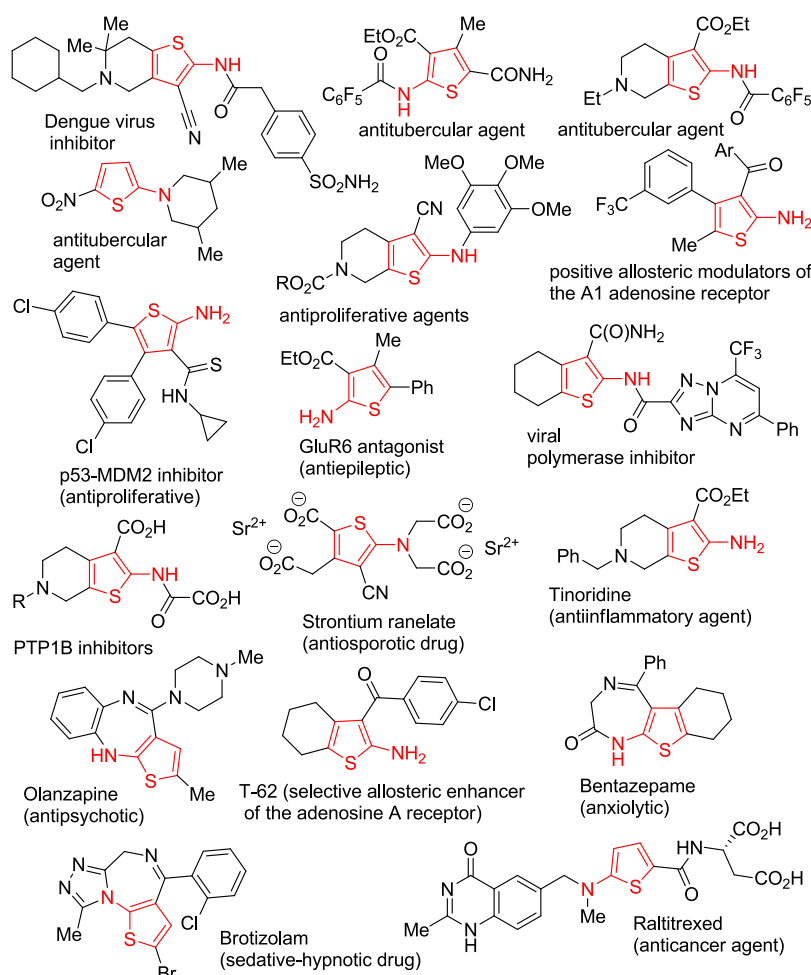
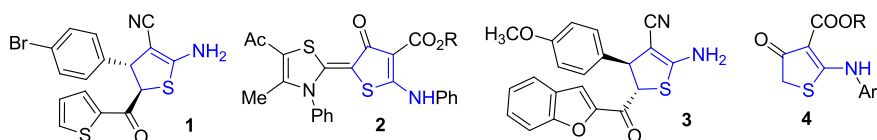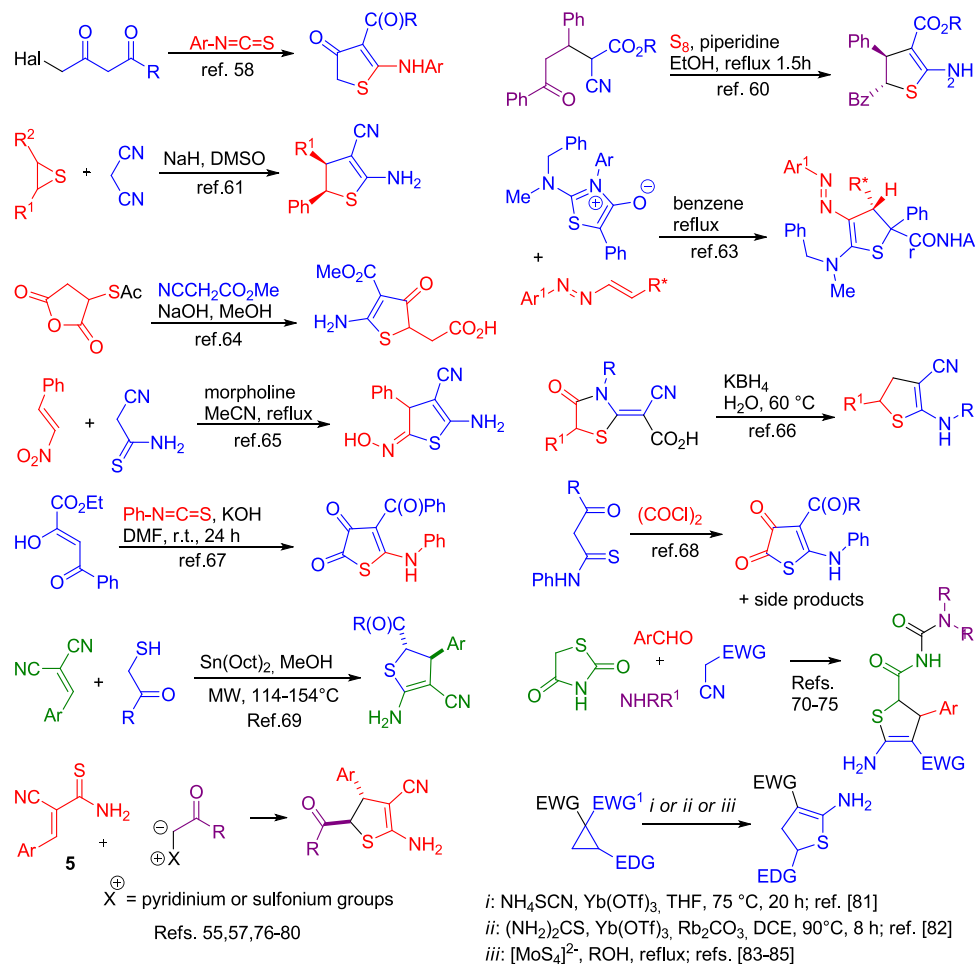**Figure 1.** Selected biologically active 2-aminothiophenes.



**Figure 2.** Biologically active compounds featuring an ADHT scaffold.

partially saturated analogs such as 2-amino-4,5-dihydrothiophenes (ADHTs). In general, 2,3(4,5)-dihydrothiophenes have a rich synthetic application, and dihydrothiophene ring systems have been incorporated into a variety of biologically active molecules (for reviews, see refs 53, 54). For instance, ADHT **1** (Figure 2) was reported as a moderately active microbicide and fungicide,[55] ADHT-thiazoline hybrids **2** showed good anticancer activity against colon carcinoma (HCT-116),[56] and benzofurane-ADHT hybrid **3** showed an antinociceptive effect.[57] Some esters of ADHT-3-carboxylic acids **4** were recognized as specific inhibitors of malaria agent *Plasmodium falciparum* dihydroorotate dehydrogenase.[58]
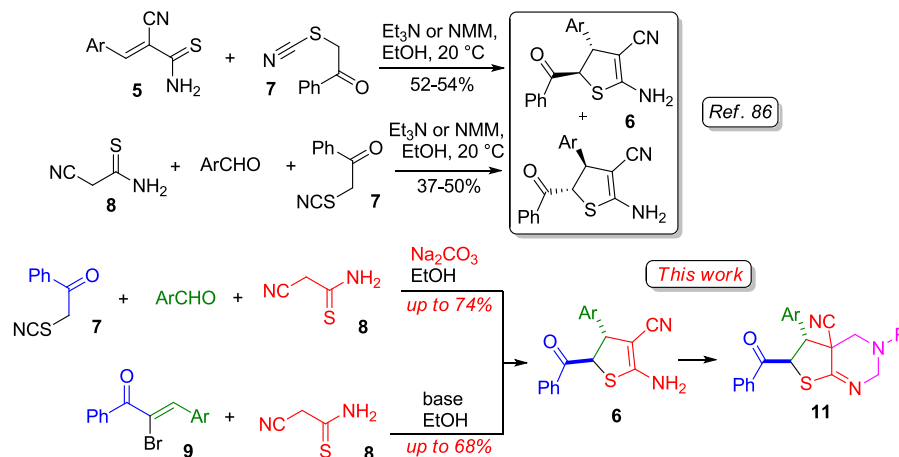
However, the available methods for the synthesis of ADHTs are somewhat limited and the studies are somewhat hampered by the lack of common practical procedures and by the narrow scope of useful substrates. ADHTs can be prepared (Scheme 1) by the reaction of γ-haloacetoacetic acid derivatives with isothiocyanates,[58,59] treatment of Michael adducts prepared from cyanoacetic esters and chalcone with elemental sulfur,[60] recyclization of thiiranes,[61,62] diastereoselective cycloadditions

of aminothioisomünchnones with chiral 1,2-diaza-1,3-butadienes,[63] condensation of S-acetylmercaptosuccinic anhydride with methyl cyanoacetate,[64] reaction of cyanothioacetamide with β-nitrostyrene,[65] reductive recyclization of functionalized thiazolidinones,[66] and cyclocondensation of benzoylpyruvate with PhNCS[67] or β-ketothioamides with oxalyl chloride.[68] Very recently, the organotin-catalyzed reaction of arylmethylene malononitriles with α-mercaptoketones was reported to produce ADHTs as a mixture of diastereomers.[69] Most of the reported procedures either require the use of expensive/exotic reagents and harsh reaction conditions or are accompanied by the formation of side products. The domino reaction of 1,3-thiazolidinedione, active methylene nitriles, amines, and aromatic aldehydes[70−75] demonstrates a common approach to functionalized ADHTs. Another useful approach leading to *trans*-4,5-disubstituted ADHT-3-carbonitriles is the reaction of 2-cyanothioacrylamide **5** with pyridinium[55,57,76,77] or sulfonium[76,78,79] ylides. However, the ylide method suffers from some drawbacks such as the temperature-dependent cyclopropane or pyridine byproduct formation,[80] elimination of foul-

## Scheme 1. The Reported Methods for the Preparation of ADHTs



*i*: NH$_4$SCN, Yb(OTf)$_3$, THF, 75 °C, 20 h; ref. [81]
*ii*: (NH$_2$)$_2$CS, Yb(OTf)$_3$, Rb$_2$CO$_3$, DCE, 90 °C, 8 h; ref. [82]
*iii*: [MoS$_4$]$^{2-}$, ROH, reflux; refs. [83–85]

## Scheme 2. Different Approaches toward the Synthesis of ADHTs 6



smelling dimethyl sulfide, and relatively low atom economy. Recent approaches consist of the Lewis acid catalyzed recyclizations of donor−acceptor cyclopropanes upon treatment with NH$_4$SCN,[81] thiourea,[82] or tetrathiomolybdates[83−85] (Scheme 1). These reactions are also not free from disadvantages such as long reaction times and difficult-to-obtain starting materials and catalysts. Given the practical significance of 2-aminothiophenes and ADHTs, the search for conceptually

new rational methodologies for their synthesis, as well as an extension of the range, is of particular importance.

Earlier, we reported[86] the unusual synthesis of highly functionalized ADHTs **6** as a mixture of trans isomers based on the tertiary base catalyzed reaction of α-thiocyanato acetophenone **7** with aldehydes and cyanothioacetamide **8** (or with 3-aryl-2-cyanothioacrylamides **5**) (Scheme 2).

Despite the availability of the starting reagents and low-cost, easy-to-handle synthesis, the reported procedures give only

**Scheme 3. Synthesis of ADHTs 6a–d**
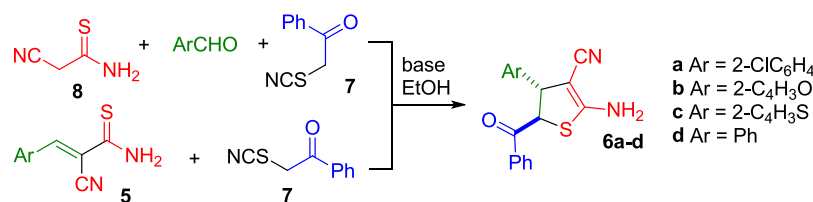


moderate (up to 54%) yields. In addition, the reaction mechanism still remains unclear. Herein, we report two modified superior procedures for the synthesis of ADHTs 6 affording higher yields across the range of substrates (Scheme 2). Also, we present the detailed quantum-chemical study to indicate the reaction mechanism. In addition, we also report the Mannich-type double aminomethylation reactions of ADHTs 6, providing an efficient approach to the synthesis of new functionalized thieno[2,3-d]pyrimidines 11.

## ■ RESULTS AND DISCUSSION

To optimize the procedure for the preparation of ADHTs 6, we used 2-chlorobenzaldehyde/furfural, α-thiocyanatoacetophenone 7,[87] and cyanothioacetamide 8[88] as the model reagents and examined the effect of catalyst and conditions (Scheme 3). We found that the use of 10% aq KOH instead of tertiary amines[86] dramatically shortened the reaction time to within 1–2 min. However, it had no effect on the yields as the target product 6a was isolated in only a modest yield of 37% (Table 1, entry 1). Similarly, product 6b was prepared in 37% yield from furfural (Scheme 3 and Table 1, entry 5). The use of pre-prepared Knoevenagel products 5a,b had no advantages over the three-component approach since the yields were only slightly improved (38–40%; Table 1, entries 7 and 13). Potassium carbonate showed much better results as a catalyst to afford

yields of ADHTs 6a,b up to 70% (Table 1, entries 2, 3, 8, 9, 14, and 15).

Finally, the best yields (62–74%) were achieved when aq Na$_2$CO$_3$ was taken as a catalyst and the reaction was conducted at 40–50 °C (Table 1, entries 4, 6, 12, and 17–20). As we found (see the discussion on the quantum-chemical calculations of the mechanism below), one of the possible reaction pathways include the Michael-type addition of phenacylthiocyanate 7 to thioacrylamide 5 followed by the intramolecular S$_N$2 substitution of the SCN group.

Inspired by this, here we proposed a new approach to ADHTs 6 based on the tandem Michael addition–intramolecular S$_N$2 substitution of thioamide 8 to easily available[89] α-bromochalcones 9a,d (Scheme 4).

Optimization of the reaction of 8 with 9d showed that the yields of ADHTs 6 strongly depend on the reaction conditions and the base used (Table 2). The lowest yield of 6d was observed when the mixture of thioamide 8 and bromochalcone 9d was treated with excessive Et$_3$N at 25 °C (Table 2, entry 1). The best results were achieved when the reaction mixture was gently refluxed with KOH (1 equiv) for 0.5 h (Table 2, entry 5). Compound 9a gave similar results (Table 2, entry 6).

**Quantum-Chemical Calculations of the Mechanism of the Reaction of 5 and 7.** A quantum-chemical study of possible mechanisms of the reaction between thioacrylamides 5 and α-thiocyanatoacetophenone 7 was performed using the ORCA 5.0.1 software package.[90−92] The search for the transition state, determination of reaction routes, and calculation of vibrational frequencies and Gibbs free energy were performed using DFT and the new Grimme composite approach r$^2$SCAN-3c.[93] This approach is a combination of r$^2$SCAN functional with mTZVPP basis, including atom-pairwise dispersion correction based on tight binding partial charges D4[94] and geometrical counterpoise correction gCP.[95] The found geometry of transition states was confirmed by the presence of an imaginary vibrational frequency corresponding to the reaction coordinate. All the calculations were performed with the correction for the influence of nonspecific solvation (EtOH) using the CPCM model.[96] We used the Gabedit 2.5 software[97] to generate the input files and the ChemCraft 1.8 software[98] to visualize the molecular geometry and vibrational frequencies.

At a first glance at the overall reaction, it seems likely that the first step is the formation of the Michael adducts 10 (Scheme 5). However, further intramolecular cyclization of the Michael adducts 10 can proceed by two different mechanisms (Scheme 5, pathways A and B). In the first case (pathway A), one-step intramolecular nucleophilic substitution of the thiocyanate group at the carbon atom (C1) by the sulfur atom (S14) can occur. The literature data on the nucleofugality of pseudohalide NCS$^-$ anion are rather scarce, though some substitution reactions with thiocyanate as a leaving group were reported.[99−106] It is likely that trans stereochemistry of the

**Table 1. Optimization of the Conditions for the Synthesis of ADHTs 6a–d (Scheme 3)[a]**

| entry | reagents | conditions | product (yield, %) |
|---|---|---|---|
| 1 | 2-ClC$_6$H$_4$CHO, 7, 8 | 10% aq KOH, rt | 6a (37) |
| 2 | 2-ClC$_6$H$_4$CHO, 7, 8 | 10% aq K$_2$CO$_3$, 40–50 °C | 6a (64) |
| 3 | 2-ClC$_6$H$_4$CHO, 7, 8 | 10% aq K$_2$CO$_3$, rt | 6a (60) |
| 4 | 2-ClC$_6$H$_4$CHO, 7, 8 | 10% aqNa$_2$CO$_3$, 40–50 °C | 6a (68) |
| 5 | furfural, 7, 8 | 10% aq KOH, rt | 6b (37) |
| 6 | furfural, 7, 8 | 10% aqNa$_2$CO$_3$, 40–50 °C | 6b (62) |
| 7 | 5a, 7 | 10% aq KOH, rt | 6a (38) |
| 8 | 5a, 7 | 10% aq K$_2$CO$_3$, rt | 6a (61) |
| 9 | 5a, 7 | 10% aq K$_2$CO$_3$, 40–50 °C | 6a (70) |
| 10 | 5a, 7 | 10% aq K$_2$CO$_3$, reflux | 6a (31) |
| 11 | 5a, 7 | 10% aq Na$_2$CO$_3$, rt | 6a (57) |
| 12 | 5a, 7 | 10% aqNa$_2$CO$_3$, 40–50 °C | 6a (74) |
| 13 | 5b, 7 | 10% aq KOH, rt | 6b (40) |
| 14 | 5b, 7 | 10% aq K$_2$CO$_3$, rt | 6b (56) |
| 15 | 5b, 7 | 10% aq K$_2$CO$_3$, 40–50 °C | 6b (62) |
| 16 | 5b, 7 | 10% aq Na$_2$CO$_3$, rt | 6b (58) |
| 17 | 5b, 7 | 10% aq Na$_2$CO$_3$, 40–50 °C | 6b (63) |
| 18 | 5c, 7 | 10% aq Na$_2$CO$_3$, 40–50 °C | 6c (67) |
| 19 | 2-C$_3$H$_4$S-CHO, 7, 8 | 10% aq Na$_2$CO$_3$, 40–50 °C | 6c (69) |
| 20 | PhCHO, 7, 8 | 10% aq Na$_2$CO$_3$, 40–50 °C | 6d (64) |

[a]Entries 1–6, 19, and 20: molar ratio aldehyde/7/8 = 1:1:1, EtOH. Entries 7–18: molar ratio 5/7 = 1:1, EtOH.
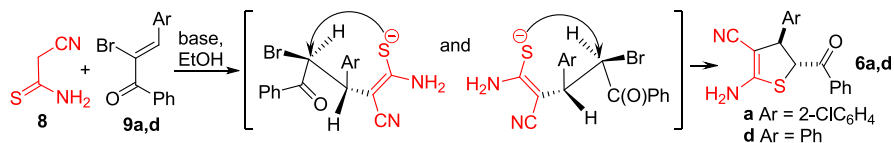
**Scheme 4. Preparation of ADHTs 6 from α-Bromochalcones 9**



**Table 2. The Reaction Conditions and the Yields for the Synthesis of ADHTs 6a,d from α-Bromochalcones 9 and Cyanothioacetamide 8 (Scheme 4)**

| entry | reagents[a] | conditions | product (yield, %) |
|---|---|---|---|
| 1 | 8, 9d | Et₃N (1.5 equiv), EtOH, rt, 6 days | 6d (25) |
| 2 | 8, 9d | Et₃N 1.5 equiv, EtOH, reflux | 6d (46) |
| 3 | 8, 9d | K₂CO₃, EtOH, 40–50 °C | 6d (42) |
| 4 | 8, 9d | Na₂CO₃, EtOH, 40–50 °C | 6d (37) |
| 5 | 8, 9d | KOH (1 equiv), EtOH, reflux | 6d (61) |
| 6 | 8, 9a | KOH (1 equiv), EtOH, reflux | 6a (57) |

[a]Molar ratio **8/9** = 1:1.

**Scheme 5. Possible Mechanisms of the Formation and Stereochemistry of ADHTs 6**
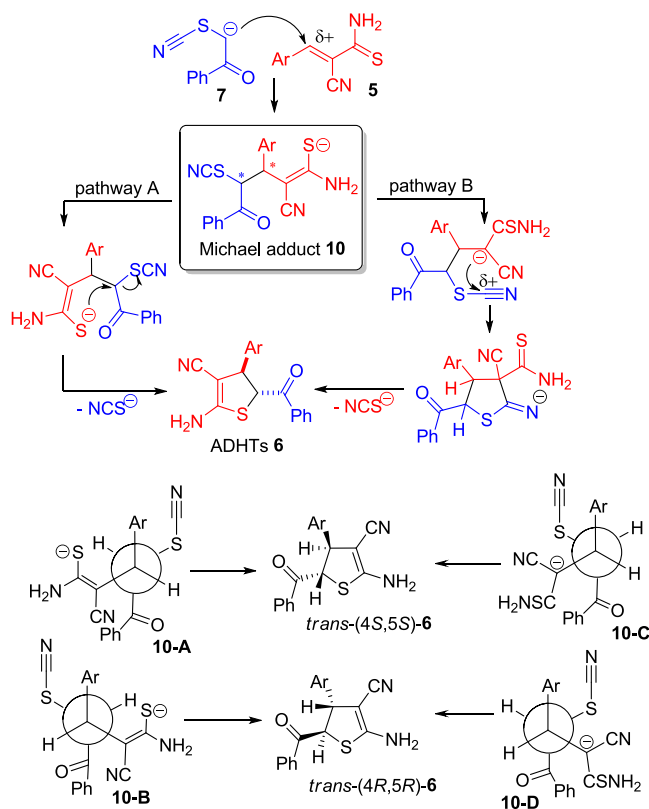


target ADHTs **6** should be determined at the formation of the Michael adducts **10** since bulky benzoyl and (het)aryl substituents would occupy a sterically favorable trans relationship. Therefore, two enantiomeric pairs of the Michael adducts **10A,10B** and **10C,10D** (Scheme 5) with an *anti-periplanar* orientation of (het)aryl and benzoyl groups appear to be the most stable.

In the second case (pathway B), a four-stage process is assumed, including the nucleophilic addition of the carbon atom (C3) to the nitrile fragment (C6-N7) of the thiocyanate group followed by the transfer of a proton from the nitrogen atom (N13) to the nitrogen atom (N7) and by the elimination of

HNCS and transfer of the second proton from nitrogen atom (N13) to nitrogen atom (N7). Arguments in favor of the pathway B involving the nucleophilic attack of a carbanion on the carbon atom of the SCN group come from numerous examples of the reactions of organic thiocyanates with active methylene compounds.[87,107]

To determine the most plausible mechanism, a quantum-chemical study of the reaction trajectories was carried out. Molecular geometries and Gibbs energies for intermediates and transition states were calculated.

The optimized molecular structures of most stable conformations, all transition states, and intermediates are shown in Figures 3−6, and the calculated energy diagrams are shown in Figure 7. Since the starting anionic intermediate **10** contains two asymmetric carbon atoms (C1 and C2), it can exist as four diastereomers or two enantiomeric pairs: *R,S/S,R* and *S,S/R,R*. Using *S,S*- and *R,S*-structures, we have calculated possible reaction pathways for each diastereomeric channel. A preliminary conformational analysis was performed for the studied isomers, and the most stable conformations **R1** (for the *S,S*-isomer) and **R2** (for the *R,S*-isomer) were found (Figure 3). It is noteworthy that the difference in energy between the most stable conformations of these isomers is extremely small (less than 1.5 kJ/mol; the *R,S*-isomer is more stable).

First, proper conformational changes of the intermediate **10** are required for successful intramolecular nucleophilic substitution since S14, C1, and S4 atoms should occupy suitable relative positions in the molecule to permit a nucleophilic attack. The rotation barrier around the C1−C2 bond was calculated as 31.8 kJ/mol for the *S,S*-isomer and 34.0 kJ/mol for the *R,S*-isomer. The transition states of the indicated conformational changes (**TS1c** and **TS2c**) and the processes of subsequent nucleophilic substitution (**TS1** and **TS2**) are shown in Figure 4.

As a result of calculations, it was found that intramolecular nucleophilic substitution (pathway A, Scheme 5) can be realized successfully only in the *S,S/R,R*-diastereomeric channel. In the *R,S*-isomer, S14, C1, and S4 atoms cannot occupy a configuration suitable for the S_N2 process due to spatial difficulties caused by the bulky benzoyl group that prevents the sulfur S14 from approaching the C1 carbon from the rear side. Thereby, the process of synchronous substitution is disrupted, which leads to a sharp increase in the activation energy up to 298.8 kJ/mol. At the same time, the calculated activation energy of nucleophilic substitution for the *S,S*-isomer is even slightly lower (27.9 kJ/mol) than that of the previous conformational transition.

As for the alternative mechanism (pathway B, Scheme 5), the entire process can be presented as a sequence of the following four steps (the optimized molecular structures of transition states are shown in Figure 5):

1. Nucleophilic addition of C3 atom to C6 atom of the SCN group through the formation of transition states **TS1.1** (for the *S,S*-isomer) and **TS2.1** (for the *R,S*-isomer), leading to the closure of the thiophene ring and the formation of anionic intermediates **I1.1** and **I2.1**.
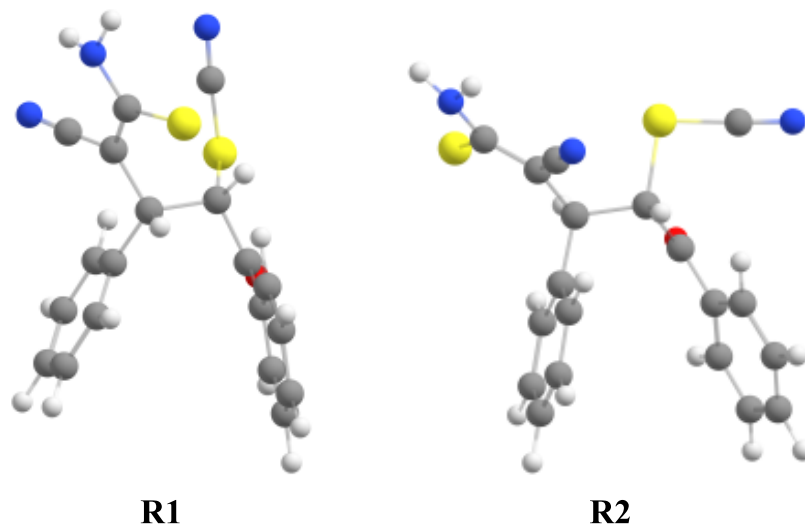
**Figure 3.** The most stable conformations **R1** (for the *S,S*-isomer) and **R2** (for the *R,S*-isomer). Geometry optimized at the r²SCAN-3c level.
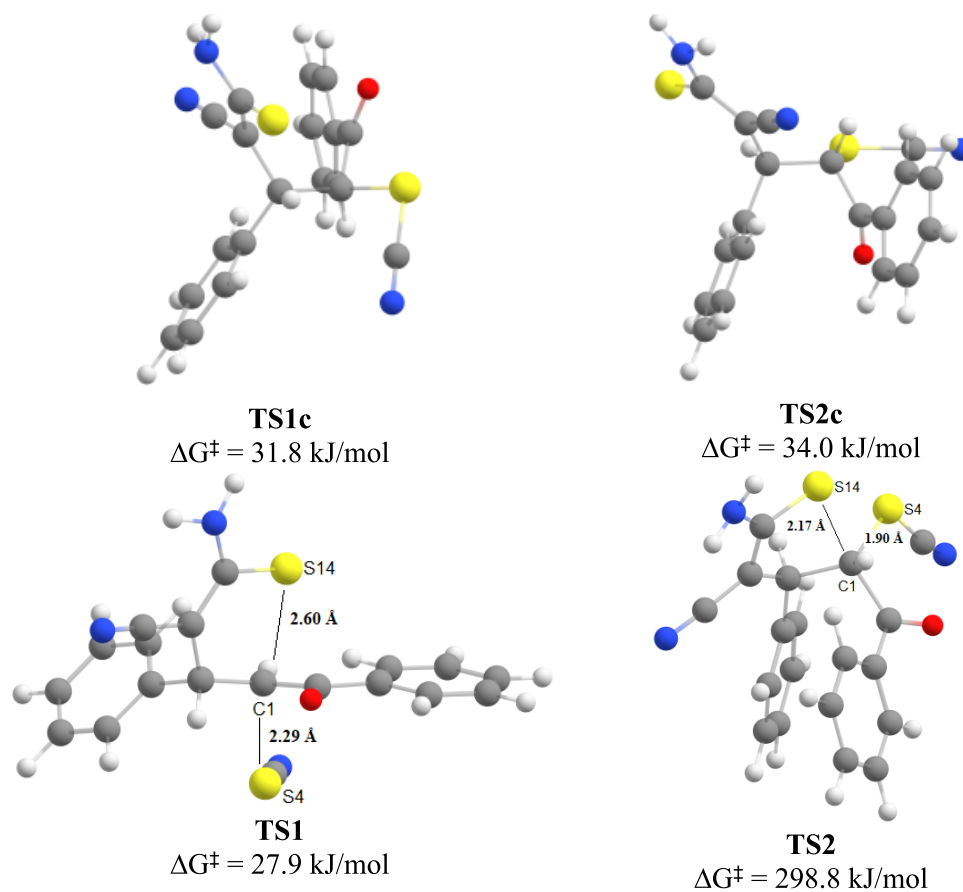


**TS1c**
ΔG‡ = 31.8 kJ/mol

**TS2c**
ΔG‡ = 34.0 kJ/mol

**TS1**
ΔG‡ = 27.9 kJ/mol

**TS2**
ΔG‡ = 298.8 kJ/mol

**Figure 4.** The optimized molecular structures of S_N transition states (**TS**) for *S,S*-(**TS1c**, **TS1**) and *R,S*-isomers (**TS2c**, **TS2**) (geometry optimized at the r²SCAN-3c level).

According to the calculated data, the activation energy of this process is 54.5 kJ/mol for the *S,S*-isomer and 46.6 kJ/mol for the *R,S*-isomer. It should be noted that the process does not require preliminary conformational changes and can be realized directly from the most stable conformers **R1** and **R2**.

2. Transfer of H28 proton from N13 nitrogen atom to N7 atom with the formation of transition states **TS1.2** (for

the *S,S*-isomer) and **TS2.2** (for the *R,S*-isomer) with the formation of intermediate products **I1.2** and **I2.2**.

3. The elimination of HNCS with the cleavage of the C3—C10 bond. This stage has the highest activation energy (63.4 kJ/mol for the *S,S*-isomer and 77.2 kJ/mol for the *R,S*-isomer) and therefore should be considered as the rate-limiting step.

4. Transfer of the second proton H29 from N13 atom of the HNCS molecule to N7 atom with the formation of
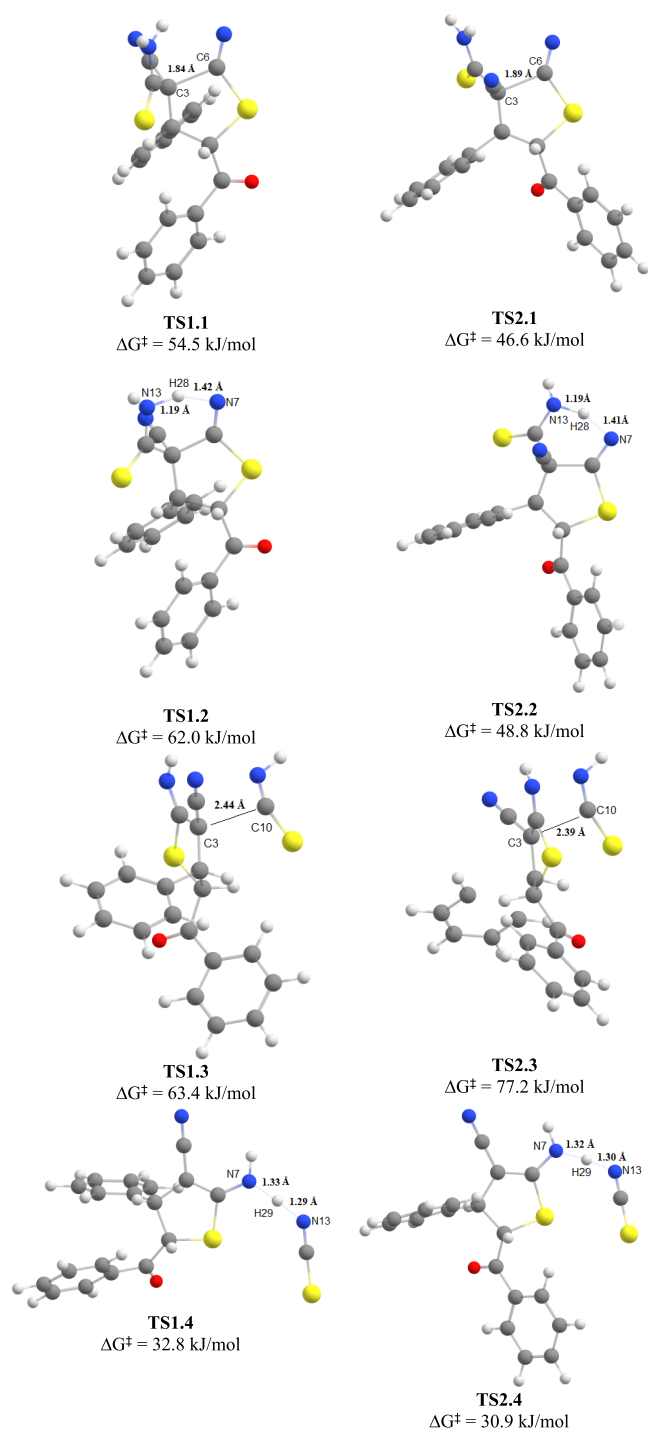
**TS1.1**
$\Delta G^{\ddagger} = 54.5$ kJ/mol

**TS2.1**
$\Delta G^{\ddagger} = 46.6$ kJ/mol

**TS1.2**
$\Delta G^{\ddagger} = 62.0$ kJ/mol

**TS2.2**
$\Delta G^{\ddagger} = 48.8$ kJ/mol

**TS1.3**
$\Delta G^{\ddagger} = 63.4$ kJ/mol

**TS2.3**
$\Delta G^{\ddagger} = 77.2$ kJ/mol

**TS1.4**
$\Delta G^{\ddagger} = 32.8$ kJ/mol

**TS2.4**
$\Delta G^{\ddagger} = 30.9$ kJ/mol

**Figure 5.** The optimized molecular structures of transition states formed during the thiophene ring formation through the addition−elimination mechanism starting from *S,S*- (**TS1.1**, **TS1.2**, **TS1.3**, **TS1.4**) and *R,S*-isomers (**TS2.1**, **TS2.2**, **TS2.3**, **TS2.4**) (geometry optimized at the r²SCAN-3c level).

transition states **TS1.4** (for the *S,S*-isomer) and **TS2.4** (for the *R,S*-isomer), leading to the formation of final dihydrothiophenes **6**.

Overall, the reaction of thioacrylamides **5** with α-thiocyana-toacetophenone **7** can proceed through the cyclization of the Michael adducts **10** by two alternative pathways: intramolecular S$_N$2 substitution of the SCN group (pathway A, Scheme 5) and nucleophilic addition/elimination of HNCS sequence (pathway
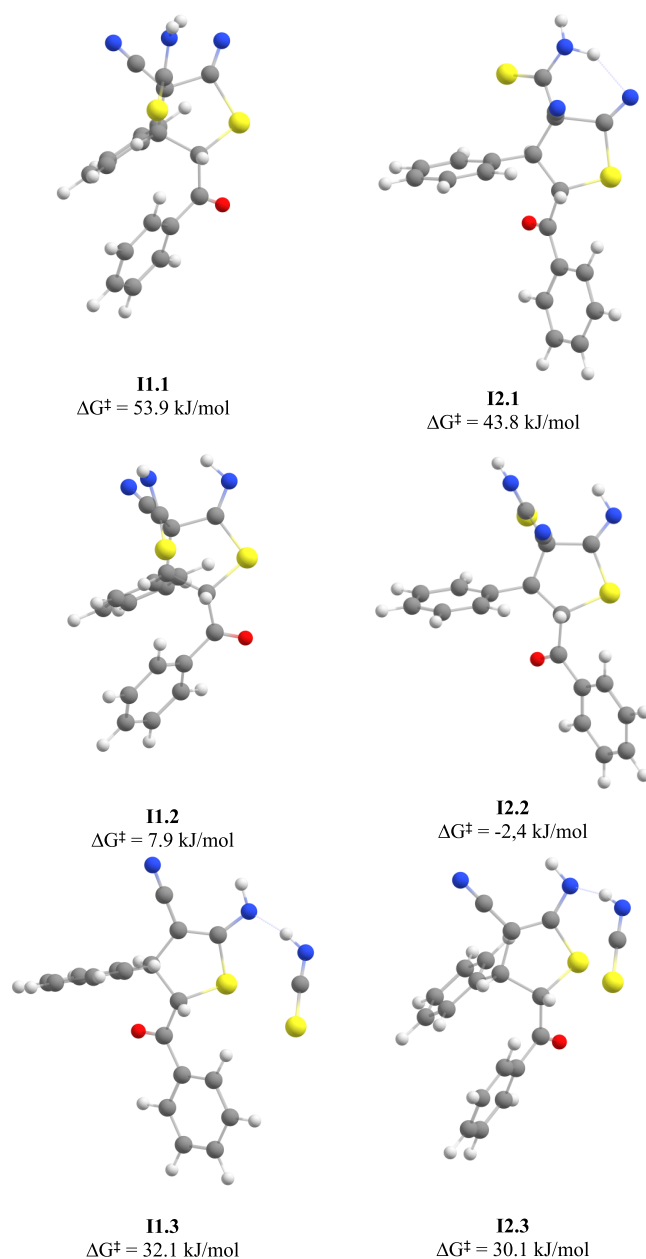
**I1.1**
$\Delta G^{\ddagger} = 53.9$ kJ/mol

**I2.1**
$\Delta G^{\ddagger} = 43.8$ kJ/mol

**I1.2**
$\Delta G^{\ddagger} = 7.9$ kJ/mol

**I2.2**
$\Delta G^{\ddagger} = -2,4$ kJ/mol

**I1.3**
$\Delta G^{\ddagger} = 32.1$ kJ/mol

**I2.3**
$\Delta G^{\ddagger} = 30.1$ kJ/mol

**Figure 6.** The optimized molecular structures of intermediates formed during the thiophene ring formation through the addition−elimination mechanism starting from *S,S*- (**I1.1**, **I1.2**, **I1.3**) and *R,S*-isomers (**I2.1**, **I2.2**, **I2.3**) (geometry optimized at the r²SCAN-3c level).

B, Scheme 5). For *S,S/R,R*-diastereomers, both variants are possible, but nucleophilic substitution (pathway A) seems to be more likely due to the lower activation energy. Moreover, from the stereochemical point of view, the intramolecular nucleo-philic substitution for the *S,S*-isomer should lead to the formation of trans isomers of **6**, while the realization of the alternative addition−elimination process should give only cis isomers that were not observed experimentally. In contrast, the intramolecular S$_N$2 reaction cannot be realized with *R,S/S,R*-diastereomers of **10** due to steric hindrance. Therefore, in this case, cyclization can proceed only through the addition−elimination mechanism (pathway B) with the formation of trans isomers of dihydrothiophenes **6**. The calculations performed are thus consistent with the experimental results pointing to the formation of trans isomers of dihydrothiophenes **6**.
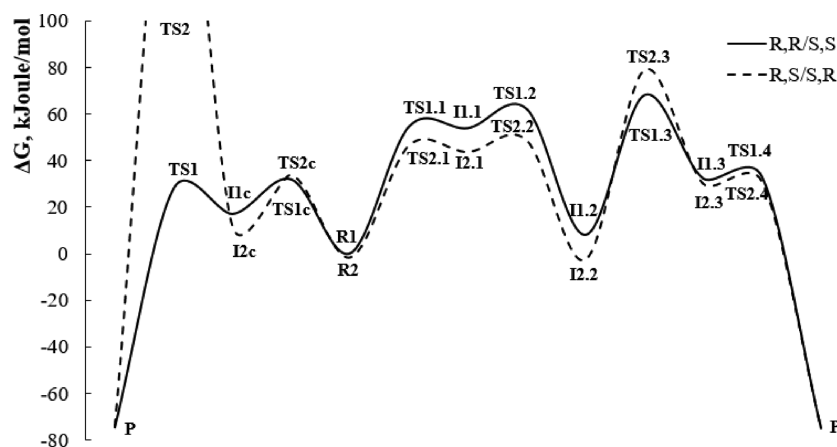
**Figure 7.** Energy diagrams of the proposed cyclization mechanisms: intramolecular nucleophilic substitution of thiocyanate anion (*S,S/R,R*-diastereomeric channel, pathway A) or nucleophilic addition at the SCN nitrile fragment with subsequent elimination of thiocyanate anion (*R,S/S,R*-diastereomeric channel, pathway B). The calculated Gibbs energies are given relative to the energy of the most stable conformation of the *S,S*-isomer (**R1**).

**Scheme 6. The Aminomethylation of ADHTS 6**
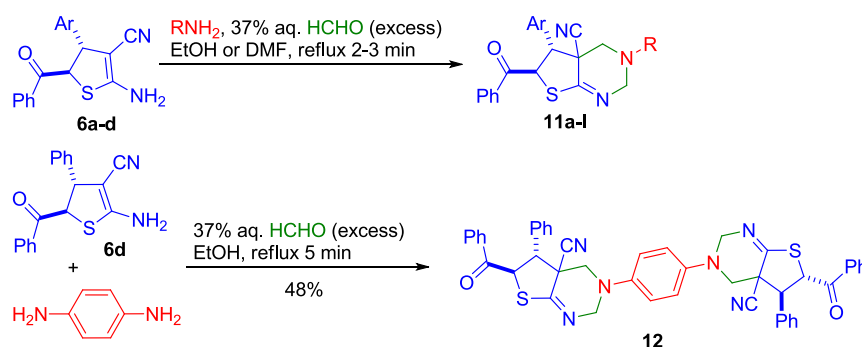


### The Noncatalyzed Aminomethylation of ADHTs Leading to Thieno[2,3-d]pyrimidines.

Thieno[2,3-d]-pyrimidines are purine bioisosteres coming to the center of interest due to their high structural diversity and well-documented spectrum of biological activity (for reviews, see refs 108−115). Much less is known on the preparation and reactions of partially saturated thieno[2,3-d]pyrimidines.[116−120] To study the reactivity of the prepared ADHTs **6** under Mannich conditions, their behavior upon treatment with a series of primary amines and HCHO was examined here.

We found that ADHTs **6** react with RNH$_2$ and excessive HCHO resulted in double aminomethylation to afford new 2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidines **11** (Scheme 6). To optimize the reaction conditions, *p*-toluidine and ADHT **6b** were chosen as model reagents. We found that EtOH was a superior solvent compared to DMF, MeOH, or *i*-PrOH (Table 3, entries 1−2 and 4−5). This is probably connected with the better solubility of either products or starting ADHTs **6** in a solvent. However, the use of DMF or DMF−EtOH mixtures as solvents is also effective in the case of less soluble ADHT **6a**. Doubling the amount of the amine component did not affect the yields of product **11e** (Table 3, entry 3).

With the optimized conditions, good yields (60−86%) of new 2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidines **11a−l** were achieved (Scheme 6 and Figure 8). Also, when *p*-phenylenediamine was reacted with 2 equiv of ADHT **6d** and excessive HCHO, polycyclic compound **12** was isolated in 48% yield. It is

**Table 3. Optimization of the Conditions for the Synthesis of Thienopyrimidines 11**

| entry | reagents[a] | conditions | product (yield, %) |
|---|---|---|---|
| 1 | **6b**, 4-MeC$_6$H$_4$NH$_2$ (1.05 equiv) | EtOH, reflux | **11e** (69) |
| 2 | **6b**, 4-MeC$_6$H$_4$NH$_2$ (1.05 equiv) | DMF, reflux | **11e** (44) |
| 3 | **6b**, 4-MeC$_6$H$_4$NH$_2$ (2 equiv) | DMF, reflux | **11e** (43) |
| 4 | **6b**, 4-MeC$_6$H$_4$NH$_2$ (1.05 equiv) | MeOH, reflux | **11e** (63) |
| 5 | **6b**, 4-MeC$_6$H$_4$NH$_2$ (1.05 equiv) | *i*-PrOH, reflux | **11e** (61) |

[a]At least 10-fold excess of aq 37% HCHO used in each entry.

noteworthy that the reaction required no catalysts. It should be noted that ADHTs **6** play here an unusual role of 1,3-dinucleophilic β-enaminonitrile species. In general, the Mannich-type reactions of β-enaminocarbonyls and related enamines with HCHO and primary amines leading to tetrahydropyrimidines are well known;[121−134] however, as far as we know, no cyclic enaminonitriles were reported as substrates in the Mannich reaction prior to our studies.

The structure of the products was supported by IR, ^{1}H NMR, ^{13}C APT NMR, HPLC−MS, and elemental analysis.^{1}H NMR spectra of compounds **11,12** revealed the presence of signals of the =NCH$_2$NCH$_2$− fragment: two doublets (or AB-quartet) of methylene protons C(4)H$_2$ at δ 2.87−3.69 and δ 3.03−4.20 ppm ($^2J$ = 11.4−12.6 Hz) and two doublets (or AB-quartet) of methylene protons C(2)H$_2$ at δ 4.05−4.79 ppm and δ 4.50−5.37 ppm ($^2J$ = 16.7−17.4 Hz). The doublet of C(5)H was observed at δ 4.04−4.64 ppm, and C(6)H appeared as doublet
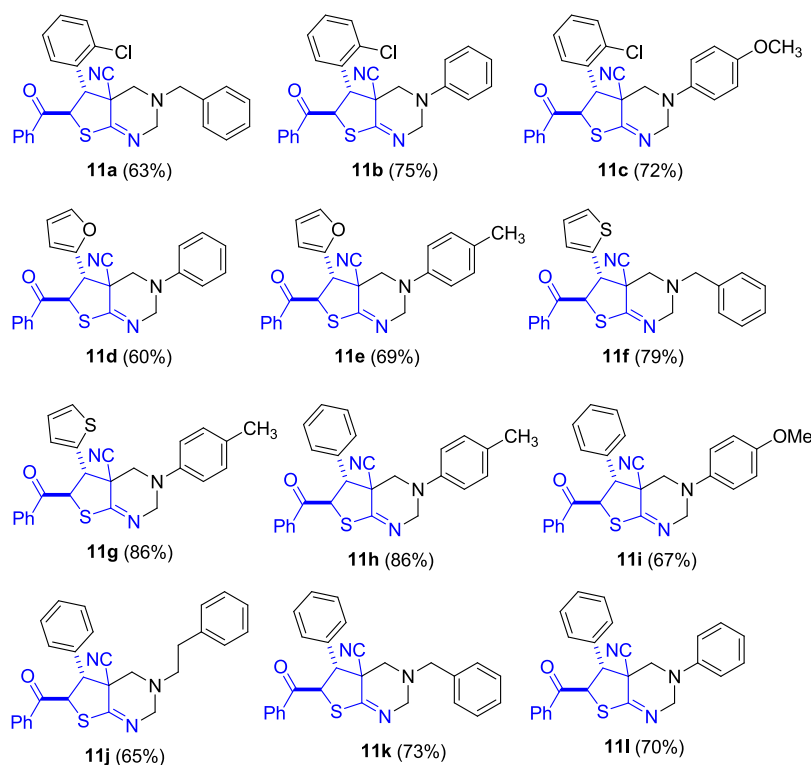
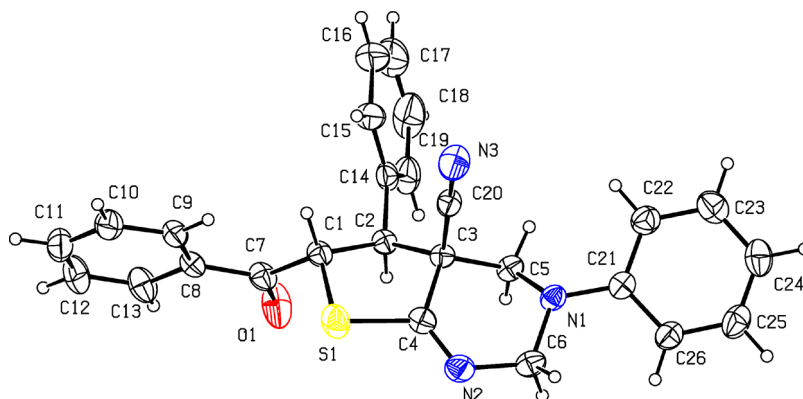**Figure 8.** The scope and yields of products **11**.



**Figure 9.** The structure of compound **11l** according to X-ray data. Thermal ellipsoids of nonhydrogen atoms are shown at the 30% probability level.

at δ 5.97−6.38 ppm ($^3J$ = 10.4−10.9 Hz). The IR spectra of compounds **11,12** revealed the absence of absorption bands of NH$_2$ and conjugated C≡N groups. Instead, a weak band appears at ν 2235−2245 cm$^{-1}$ (nonconjugated C≡N). The absorption bands corresponding to the vibrations of C=O and C=N groups are found at ν 1680−1690 and 1647−1664 cm$^{-1}$. In addition, the structure of compound **11l** was confirmed by X-ray studies (Figure 9).

The independent part of the unit cell contains two molecules of compound **11l**: **A** and **B** with a close conformation. The tetrahydropyrimidine ring has a distorted *half-chair* conformation with an almost planar fragment C6-N2-C4-C3 (torsion angle 4.7(3)° in molecule **11l-A** and 3.2(3)° in molecule **11l-B**). Atoms N1 and C5 deviate from this plane by 0.243(4) and −0.516(4) Å (molecule **11l-A**) and by 0.276(4) and −0.496(4) Å (molecule **11l-B**). The tetrahydrothiophene ring is in the *twist* conformation with the deviation of the C2 and C3 atoms from the plane of the rest of the ring atoms by −0.469(4) and

0.250(4) Å (**11l-A**) and by −0.258(4) and 0.396(4) Å (**11l-B**). The nitrogen atom N1 has a pyramidal configuration; the sum of the bond angles centered on the atom is 344.7° (**11l-A**) or 349.8° (**11l-B**). The substituents at C1, C2, and N1 atoms have an equatorial orientation (torsion angles C4-S1-C1-C7 139.98(15)° (**11l-A**) and 131.00(15)° (**11l-B**), S1-C1-C2-C14 −172.61(14)° (**11l-A**) and −163.25(14)° (**11l-B**), and N2-C6-N1-C21 178.98(18)° (**11l-A**) and 169.30(17)° (**11l-B**)). The nitrile group is in the axial position (torsion angle N2-C4-C3-C20 −101.5(2)° (**11l-A**) and −100.4(2)° (**11l-B**)). Molecules **11l-A** and **11l-B** differ in the orientation of the phenyl substituent at the N1 atom, which is in the −*ac* conformation in molecule **11l-A** and in the −*sc* conformation in molecule **11l-B** relative to the idealized position of the lone pair (Lp) of electrons of the nitrogen atom (torsion angle C22-C21-N2-Lp(N1) −122° (**11l-A**) and −61° (**11l-B**)). The rotation of the substituent is facilitated by the repulsion between hydrogen atoms in the ortho positions (shortened intramolecular contacts

H26...H6a 2.19 Å (**11l-A**) and 2.23 Å (**11l-B**), and H22...H5a 2.17 Å (**11l-A, 11l-B**) (sum of van der Waals radii 2.32 Å[135])). The molecule also contains shortened intramolecular contacts between the hydrogen atom at C1 and hydrogen atoms in the ortho positions of the phenyl substituents at C2 and C7 (H1...H9 2.22 Å (**11l-A**) and 2.13 Å (**11l-B**), and H1...H15 2.29 Å (**11l-A**) and 2.24 Å (**11l-B**)).

Crystals of compound **11l** consist of alternating layers of molecules **11l-A** and **11l-B** parallel to the plane (0 0 1). In this case, layers **11l-A** and **11l-A** have different structures. A common feature of molecules **11l-A** and **11l-B** is the formation of centrosymmetric dimers due to hydrogen bonds between the carbonyl group and methylene hydrogen atoms (C5-H5a...O1$^i$ [i: $-x$, $1 - y$, $1 - z$] (H...O 2.31 Å, C−H...O 152°) in layer **A** and C6-H6b...O1$^{ii}$ [ii: $1 - x$, $1 - y$, $-z$] (H...O 2.45 Å, C−H...O 141°)). Also in layer **A**, molecules are linked by hydrogen bonds C16-H16...N3$^{ii}$ [ii: $1 - x$, $-y$, $1 - z$] (H...N 2.58 Å, C−H...N 136°) and C−H...$\pi$ contacts C6-H6b...C11$^{iii}$ [iii: $-1 + x$, $y$, $z$] (H...C 2.89 Å, C−H...C 135°) and C12-H12...C16$^{iv}$ [iv: $1 - x$, $1 - y$, $1 - z$] (H...C 2.89 Å, C−H...C 158°). In layer **B**, the molecules are linked by intermolecular hydrogen bonds C1-H1...N3$^v$ [v: $2 - x$, $1 - y$, $-z$] (H...N 2.53 Å, C−H...N 158°) and C9-H9...N3$^v$ (H...N 2.52 Å, C−H...N 157°) and C−H...$\pi$ contacts C13-H13...C26$^{ii}$ (H...C 2.87 Å, C−H...C 179°), C26-H26...C10$^{vi}$ [vi: $-1 + x$, $1 + y$, $z$] (H...C 2.87 Å, C−H...C 154°), and C6-H6b...C24$^{vii}$ [vii: $1 - x$, $2 - y$, $-z$] (H...C 2.78 Å, C−H...C 133°).

The copies of IR and NMR spectra as well as LCMS and X-ray data for new compounds are given in the Supporting Information.

## CONCLUSIONS

In summary, we have optimized synthetic procedures for the preparation of highly functionalized, useful building blocks, *trans*-2-amino-4-aryl-5-benzoyl-4,5-dihydrothiophene-3-carbonitriles **6** (ADHTs), starting from easily available $\alpha$-thiocyanatoacetophenone **7** and cyanothioacetamide **8**. The reaction mechanism was studied on the r$^2$SCAN-3c level of theory. The reaction of $\alpha$-thiocyanatoacetophenone **7** with 3-aryl-2-cyanothioacrylamides **5** proceeds through the formation of the corresponding Michael adduct that undergoes further cyclization. The cyclization can proceed by two different mechanisms: by intramolecular S$_N$2 substitution of the SCN group (only for *S,S/R,R*-diastereomers of the Michael adduct **10**) or through intramolecular nucleophilic addition to the SCN carbon atom followed by elimination of the HNCS molecule (only for *S,R/R,S*-diastereomers of the Michael adduct **10**), as it was supported by quantum chemical calculations performed on the r$^2$SCAN-3c level of theory.

In addition, a new approach for the preparation of ADHTs **6** was developed, starting from cyanothioacetamide **8** and available $\alpha$-bromochalcones **9**. We have also demonstrated that a small library of new 2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitriles **11** could be synthesized by noncatalyzed double Mannich-type cyclization, starting from ADHTs **6**, primary amines, and aq HCHO. The work demonstrates a new approach to the formation of pharmacologically interesting thieno[2,3-d]pyrimidines. The procedure has certain advantages such as mild reaction conditions, short reaction time, and a diversity of useful starting building blocks and provides pure target products in good yields. All the reported procedures preclude volatile, foul smelling, or toxic solvents or byproducts. The formation of both starting ADHTs

**6** and thieno[2,3-d]pyrimidines **11** proceeds in an atom-economical way with a broad substrate scope under metal-free conditions.

## EXPERIMENTAL SECTION

Solvents and starting reagents were purified according to common procedures. Melting points were determined on a Kofler hot stage and reported uncorrected. IR spectra were recorded on an IKS-29 spectrometer in Nujol mulls or a Thermo Nicolet Avatar 370 FT-IR spectrometer in KBr pellets. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DRX-500 (500.13 MHz for $^1$H and 125.74 MHz for $^{13}$C) or Bruker DPX-400 (400.40 MHz for $^1$H) spectrometer at room temperature in DMSO-$d_6$. Chemical shifts are given in parts per million (ppm) with reference to TMS or to the residual solvent signals; coupling constants are given in Hz; and multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), m (multiplet), and br (broad). LC−MS data were obtained using the LC−MS system consisting of the high-performance liquid chromatograph Agilent 1100 equipped with diode-matrix and mass-selective detector Agilent LC/MSD SL (APCI ionization in positive and negative modes) and on a PE SCIEX API 150EX mass spectrometer following separation on a Shimadzu LC-10 AD liquid chromatography system equipped with a Shimadzu SP D-10AUV−vis detector (254 nm) and Sedex 75 ELSD detector (ES-API ionization). The elemental analysis (C, H, N) was performed using a Carlo Erba Strumentazione 1106 analyzer. The analytical results were within ±0.4% of the theoretical values. Thin-layer chromatography (TLC) was performed on Silufol UV-254 plates using EtOAc, EtOAc−hexane, or acetone−hexane 1:1 mixture as eluents; the spots were visualized with iodine vapors, UV light, or KMnO$_4$−H$_2$SO$_4$ solution. Cyanothioacetamide **8** was prepared by bubbling H$_2$S gas through a malononitrile solution in EtOH containing a catalytic amount of Et$_3$N at 10−15 °C for 6−8 h.[136] 3-Aryl-2-cyanothioacrylamides **5** were prepared by the Knoevenagel condensation of cyanothioacetamide **8** with aromatic aldehydes in the presence of catalytic amounts of Et$_3$N (EtOH, 20 °C).[137] $\alpha$-Bromochalcones **9a,d** were prepared by dehydrobromination of the corresponding chalcone dibromide.[138,139]

**$\alpha$-Thiocyanatoacetophenone 7** was prepared as follows: the mixture of $\alpha$-bromoacetophenone (23.5 g, 0.118 mol) and dry KSCN (12.6 g, 0.13 mol) in anhydrous acetone (70 mL) was boiled under vigorous stirring for 1 h and evaporated to one-half of the volume. The slurry obtained was cooled to 25 °C and treated with 50 mL of cold water. The precipitate formed was filtered off and washed with water and twice with cold 40% aq EtOH to give 20.6 g (98.5%) of thiocyanate **7** as colorless crystals, mp 74−75 °C [lit.:[140] 72.5−73.5 °C].

**General Procedures for the Synthesis of 2-Amino-5-benzoyl-4-(het)aryl-4,5-dihydrothiophene-3-carbonitriles (6).** *A. KOH-Catalyzed Reaction of Aldehydes, Cyanothioacetamide 8, and Phenacyl Thiocyanate 7 (Table 1, Entries 1 and 5).* To a suspension of 0.5 g (5 mmol) of cyanothioacetamide **8** in 20 mL of EtOH, 5 mmol of the corresponding aldehyde and one drop of 10% aq KOH were successively added with stirring. The mixture was stirred for 0.5 h, and then 0.89 g (5 mmol) of $\alpha$-thiocyanatoketone **7** and an excess (4 mL) of 10% aq KOH were added. The mixture was stirred for 0.5 h, diluted with water (10 mL), and then kept for 0.5 h at 25 °C. The precipitate of dihydrothiophenes **6a** or **6b** was filtered off and purified by recrystallization from EtOH−acetone.

*B. KOH-Catalyzed Reaction of Thioacrylamides 5a,b and Phenacyl Thiocyanate 7 (Table 1, Entries 7 and 13).* To a suspension of 2.5 mmol of α,β-unsaturated thioamide **5a,b** (0.55 g of **5a** or 0.45 g of **5b**) and 0.44 g (2.5 mmol) of α-thiocyanatoketone **7** in 10 mL of EtOH, an excess (2.0 mL) of 10% aq KOH was added dropwise with vigorous stirring. The mixture immediately turned red, and the starting reagents dissolved. The reaction mixture quickly turned yellow, and a yellow solid precipitated within 30−60 s. The mixture was stirred for 0.5 h, diluted with 5 mL of water, and then allowed to stand for another 0.5 h. The precipitate was filtered off, washed with water and cold EtOH, and recrystallized from EtOH−acetone. The yields were 323 mg (38%, **6a**) and 300 mg (40%, **6b**).

*C. Na₂CO₃-Catalyzed Reaction of Thioacrylamides 5a−c and Phenacyl Thiocyanate 7 (Table 1, Entries 12, 17, and 18).* To a suspension of 2.25 mmol of unsaturated thioamides **5a−c** and 400 mg (2.26 mmol) of α-thiocyanatoketone **7** in 10 mL of alcohol, 2.4 mL of 10% aq Na₂CO₃ solution was added with stirring (Na₂CO₃ partially precipitated). The reaction mixture was stirred under gentle heating (40−50 °C) until the starting reagents had dissolved. The solution turned light brown, and CO₂ was evolved. The mixture was allowed to cool to 25 °C and diluted with 3−4 mL of water (a yellow solid precipitated). After 72 h, the precipitate was filtered off, washed with water and cold EtOH, and purified (if appropriate) by recrystallization from EtOH−acetone.

*D. Na₂CO₃-Catalyzed Reaction of Aldehydes, Cyanothioacetamide 8, and Phenacyl Thiocyanate 7 (Table 1, Entries 4, 6, 19, and 20).* To a suspension of 0.5 g (5 mmol) of cyanothioacetamide **8** in 10 mL of EtOH, 5 mmol of the corresponding aldehyde and one drop of 10% aq Na₂CO₃ were successively added with stirring. The mixture was stirred for 0.5 h, and then 0.89 g (5 mmol) of α-thiocyanatoketone **7** and an excess (4 mL) of 10% aq Na₂CO₃ were added. The mixture was stirred for 0.5 h, diluted with water (10 mL), and then kept for 0.5 h at 25 °C. The precipitate of dihydrothiophenes **6a−d** was filtered off and purified (if appropriate) by recrystallization from EtOH−acetone.

*E. Synthesis of ADHTs 6a,d from Cyanothioacetamide 8 and α-Bromochalcones 9a,d (Table 2, Entries 5 and 6).* The mixture of 400 mg (4.0 mmol) of cyanothioacetamide **8**, 4.0 mmol of the corresponding α-bromochalcone **9a,d**, and EtOH (20 mL) was treated with 2.4 mL (4 mmol) of 10% aq KOH. The resulting red solution was slowly brought to reflux under vigorous stirring and kept for 0.5 h. The mixture was cooled; after 24 h, the precipitate was filtered off, washed with 50% EtOH and ether, and purified by recrystallization from acetone/*n*-BuOH (2:1) to give **6a,d** as yellow crystalline solids.

**trans-2-Amino-5-benzoyl-4-(2-chlorophenyl)-4,5-dihydrothiophene-3-carbonitrile (6a).** Recrystallization from 1:1 acetone/EtOH gave bright yellow crystals, mp 243−245 °C (dec.). IR (Nujol, cm⁻¹) $\nu_{max}$ 3415, 3310, 3200 (NH₂), 2195 (C≡N), 1675 (C═O).¹H NMR (400 MHz, DMSO-$d_6$) δ 4.83 (1H, d, ³*J* = 2.9 Hz, H-4), 5.19 (1H, d, ³*J* = 2.9 Hz, H-4), 7.00 (2H, br s, NH₂), 7.20−7.52 (7H, m, H−Ar), 7.85 (2H, d, ³*J* = 7.1 Hz, H-2 and H-6 benzoyl). ¹³C NMR (126 MHz, DMSO-$d_6$) δ 46.9 (C-4), 55.9 (C-5), 71.2 (C-3), 119.0 (C≡N), 128.0 (C−Ar), 129.0 (C−Ar), 129.3 (C−Ar), 129.9 (C−Ar), 131.8 (C−Ar), 132.1 (C−Ar), 133.5 (C−Ar), 134.0 (C−Ar), 135.1 (C−Ar), 140.5 (C−Ar), 161.3 (C-2), 193.0 (C═O). Anal. Calcd for C₁₈H₁₃ClN₂OS: C, 63.43; H, 3.84; N, 8.22. Found C, 63.31; H, 3.93; N, 8.18.

**trans-2-Amino-5-benzoyl-4-(2-furyl)-4,5-dihydrothiophene-3-carbonitrile (6b).** Recrystallization from 1:1 EtOH/1,4-dioxane gave dark yellow crystals, mp 208−210 °C. IR (KBr, cm⁻¹) $\nu_{max}$ 3405, 3290, 3170 (NH₂), 2200 (C≡N), 1670 (C═O).¹H NMR (400 MHz, DMSO-$d_6$) δ 4.90 (1H, d, ³*J* = 3.0 Hz, H-4), 5.17 (1H, d, ³*J* = 3.0 Hz, H-5), 6.29−6.30 (1H, m, H-3 furyl), 6.34−6.35 (1H, m, H-4 furyl), 6.97 (2H, br s, NH₂), 7.45−7.63 (4H, m, 3 H−Ar and H-5 furyl overlapped), 7.92 (2H, d, ³*J* = 7.1 Hz, H-2 and H-6 benzoyl).¹³C NMR (126 MHz, DMSO-$d_6$) δ 46.0 (C-4), 54.9 (C-5), 71.0 (C-3), 104.0 (C-4 furyl), 109.1 (C-3 furyl), 118.7 (C≡N), 128.3 (C−Ar), 131.0 (C−Ar), 133.6 (C−Ar), 135.1 (C−Ar), 142.9 (C-5 furyl), 161.1 (C-2), 163.2 (C-2 furyl), 192.7 (C═O). Anal. Calcd for C₁₆H₁₂N₂O₂S: C, 64.85; H, 4.08; N, 9.45. Found C, 64.80; H, 4.16; N, 9.43.

**trans-2-Amino-5-benzoyl-4-(2-thienyl)-4,5-dihydrothiophene-3-carbonitrile (6c).** Recrystallization from 1:1 acetone/EtOH gave yellow crystals, mp 211−213 °C. IR (KBr, cm⁻¹) $\nu_{max}$ 3405, 3290, 3175 (NH₂), 2202 (C≡N), 1670 (C═O).¹H NMR (400 MHz, DMSO-$d_6$) δ 4.84 (1H, d, ³*J* = 3.0 Hz, H-4), 5.24 (1H, d, ³*J* = 3.0 Hz, H-5), 7.07 (2H, br s, NH₂), 7.10−7.11 (1H, m, H-3 thienyl), 7.40−7.41 (1H, m, H-4 thienyl), 7.51−7.52 (1H, m, H-5 thienyl), 7.55−7.65 (3H, m, H-3, H-4, H-5 benzoyl), 7.90 (2H, d, ³*J* = 7.3 Hz, H-2 and H-6 benzoyl).¹³C NMR (126 MHz, DMSO-$d_6$) δ 50.8 (C-4), 55.5 (C-5), 71.3 (C-3), 119.1 (C≡N), 123.1 (C−Ar), 125.0 (C−Ar), 128.6 (C−Ar), 130.8 (C−Ar), 131.1 (C−Ar), 133.0 (C−Ar), 135.1 (C−Ar), 144.6 (C−Ar), 160.9 (C-2), 193.0 (C═O). Anal. Calcd for C₁₆H₁₂N₂OS₂: C, 61.51; H, 3.87; N, 8.97. Found C, 61.57; H, 4.00; N, 8.90.

**trans-2-Amino-5-benzoyl-4-phenyl-4,5-dihydrothiophene-3-carbonitrile (6d).** Recrystallization from 1:2 n-BuOH/acetone gave yellow crystals, mp 207−209 °C. IR (KBr, cm⁻¹) $\nu_{max}$ 3412, 3300, 3184 (NH₂), 2201 (C≡N), 1670 (C═O).¹H NMR (400 MHz, DMSO-$d_6$) δ 4.75 (1H, d, ³*J* = 3.0 Hz, H-4), 5.21 (1H, d, ³*J* = 3.0 Hz, H-5), 7.13 (2H, br s, NH₂), 7.27−7.32 (1H, m, H−Ph), 7.37−7.38 (4H, m, H−Ph), 7.49−7.59 (2H, m, H-3, H-5 benzoyl), 7.62−7.66 (1H, m, H-4 benzoyl), 7.90 (2H, d, ³*J* = 7.5 Hz, H-2 and H-6 benzoyl).¹³C NMR (126 MHz, DMSO-$d_6$) δ 50.8 (C-4), 56.0 (C-5), 70.9 (C-3), 118.2 (C≡N), 127.3 (C-4 Ph), 127.4 (C-3, C-5 Ph), 128.61 (C-2, C-6 Ph), 128.62 (C-3, C-5 benzoyl), 128.8 (C-2, C-6 benzoyl), 133.6 (C-4 benzoyl), 134.5 (C-1 benzoyl), 141.8 (C-1 Ph), 161.1 (C-2), 193.0 (C═O). LCMS (*m/z*, ES-API) 307.5 [M + H]⁺, 613.3 [2 M + 1]⁺, 919.3 [3 M + 1]⁺. Anal. Calcd for C₁₈H₁₄N₂OS: C, 70.56; H, 4.61; N, 9.14. Found C, 70.60; H, 4.70; N, 9.08.

General Procedure for the Synthesis of 2,3,4,4a,5,6-Hexahydrothieno[2,3-d]pyrimidine-4a-carbonitriles (**11a−i**)

The corresponding ADHTs **6a-d** (0.6−0.8 mmol) and a primary amine (1.05 equiv, 0.65−0.85 mmol) were dissolved in EtOH (10−12 mL) (for less soluble ADHTs **6a,b**, DMF (2 mL) or DMF−EtOH mixture (2 + 8 mL) is also useful), and an excess (1.0 mL) of 37% aq HCHO was added to the resulting solution. The reaction mixture was heated to reflux under vigorous stirring for 2−3 min (in some cases, a colorless crystalline solid started to separate). The reaction mixture was allowed to stand for 24 h at 20 °C, and the crystals were filtered off, washed with EtOH and hexane, and purified (if appropriate) by recrystallization to give thieno[2,3-d]pyrimidines **11** as colorless crystals.

**6-Benzoyl-3-benzyl-5-(2-chlorophenyl)-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile**

**(11a).** Recrystallization from acetone gave colorless crystals, yield 63%, mp 208−210 °C. IR (KBr, cm$^{-1}$) $\nu_{max}$ 2235 (C≡N), 1680 (C=O), 1657 (C=N).$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.87 (1H, d, $^2J$ = 11.4 Hz, H-4), 3.03 (1H, d, $^2J$ = 11.4 Hz, H-4), 3.65 (1H, d, $^2J$ = 13.7 Hz, CH$_2$Ph), 3.77 (1H, d, $^2J$ = 13.7 Hz, CH$_2$Ph), 4.11 (1H, d, $^2J$ = 17.1 Hz, H-2), 4.49−4.56 (2H, m, two doublets overlapped: 1H, d, H-2 and 1H, d, H-5), 6.30 (1H, d, $^3J$ = 10.9 Hz, H-6), 7.20−7.22 (1H, m, H-4 Ph), 7.26−7.37 (6H, m, H−Ar), 7.50 (1H, d, $^3J$ = 7.3, H−Ar), 7.55−7.58 (2H, m, H−Ar), 7.68−7.71 (1H, m, H−Ar), 8.03 (1H, d, $^3J$ = 7.8, H−Ar), 8.07 (2H, d, $^3J$ = 7.8, H-2 and H-6 benzoyl).$^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 47.1 (C-5), 49.7 (C-6), 52.2 (C-4a), 53.1 (CH$_2$Ph), 56.3 (C-4), 70.6 (C-2), 116.8 (C≡N), 127.3 (C−Ar), 127.5 (C−Ar), 128.27 (C−Ar), 128.31 (C−Ar), 128.9 (C−Ar), 129.1 (C−Ar), 129.75 (C−Ar), 129.79 (C−Ar), 130.0 (C−Ar), 131.3 (C−Ar), 134.2 (C−Ar), 134.68 (C−Ar), 134.73 (C−Ar), 137.0 (C−Ar), 161.7 (C=N), 192.9 (C=O). LCMS ($m/z$, ES-API) 120.7 [PhCH$_2$N = CH$_2$ + H]$^+$, 472.6 [M + H]$^+$, 945.8 [2M + H]$^+$. Anal. Calcd for C$_{27}$H$_{22}$ClN$_3$OS: C, 68.71; H, 4.70; N, 8.90. Found C, 68.70; H, 4.76; N, 8.88.

**6-Benzoyl-5-(2-chlorophenyl)-3-phenyl-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile (11b).** Recrystallization from DMF/H$_2$O 1:1 gave a snow-white fine crystalline powder, yield 75%, mp 261−263 °C. IR (KBr, cm$^{-1}$) $\nu_{max}$ 2235 (C≡N), 1682 (C=O), 1651 (C=N).$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 3.64 (1H, d, $^2J$ = 12.6 Hz, H-4), 3.91 (1H, d, $^2J$ = 12.6 Hz, H-4), 4.63 (1H, d, $^3J$ = 10.6 Hz, H-5), 4.79 (1H, d, $^2J$ = 17.4 Hz, H-2), 5.35 (1H, d, $^2J$ = 17.4 Hz, H-2), 6.38 (1H, d, $^3J$ = 10.6 Hz, H-6), 6.83−6.87 (1H, m, H-4 Ph), 6.91 (2H, d, $^3J$ = 7.9, H−Ph), 7.20−7.24 (2H, m, H−Ar), 7.39−7.41 (2H, m, H−Ar), 7.56−7.60 (3H, m, H−Ar), 7.70−7.74 (1H, m, H-4 benzoyl), 8.07−8.11 (3H, m, H−Ar).$^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 47.2 (C-5), 49.5 (C-6), 50.9 (C-4a), 51.4 (C-4), 66.7 (C-2), 116.2 (C−Ar), 116.3 (C≡N), 120.4 (C−Ar), 127.5 (C−Ar), 128.9 (C−Ar), 129.1 (C−Ar), 129.2 (C−Ar), 129.8 (C−Ar), 129.9 (C−Ar), 130.1 (C−Ar), 131.3 (C−Ar), 134.4 (C−Ar), 134.7 (C−Ar), 134.8 (C−Ar), 146.9 (C-1 NPh), 161.7 (C=N), 192.9 (C=O). Anal. Calcd for C$_{26}$H$_{20}$ClN$_3$OS: C, 68.19; H, 4.40; N, 9.17. Found C, 68.15; H, 4.48; N, 9.16.

**6-Benzoyl-5-(2-chlorophenyl)-3-(4-methoxyphenyl)-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile (11c).** Recrystallization from acetone gave a beige crystalline solid, yield 72%, mp 218−220 °C. IR (Nujol mulls, cm$^{-1}$) $\nu_{max}$ 2240 (C≡N), 1685 (C=O), 1650 (C=N).$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 3.55 (1H, d, $^2J$ = 12.5 Hz, H-4), 3.65 (1H, d, $^2J$ = 12.5 Hz, H-4), 3.68 (3H, s, MeO), 4.60 (1H, d, $^3J$ = 10.6 Hz, H-5), 4.64 (1H, d, $^2J$ = 17.0 Hz, H-2), 5.23 (1H, d, $^2J$ = 17.0 Hz, H-2), 6.36 (1H, d, $^3J$ = 10.6 Hz, H-6), 6.85 (4H, AB-q, $^3J$ = 8.9, H-Ar 4-MeOC$_6$H$_4$) 7.33−7.50 (3H, m, H−Ar), 7.59−7.70 (4H, m, H−Ar), 8.09 (2H, d, $^3J$ = 7.8, H-2 and H-6 benzoyl).$^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 47.2 (C-5), 50.1 (C-6), 51.5 (C-4a), 52.1 (C-4), 55.4 (MeO), 68.9 (C-2), 114.0 (C−Ar), 116.7 (C≡N), 119.0 (C−Ar), 128.7 (C−Ar), 129.0 (C−Ar), 129.2 (C−Ar), 129.7 (C−Ar), 129.9 (C−Ar), 130.2 (C−Ar), 131.3 (C−Ar), 134.4 (C−Ar), 134.7 (C−Ar), 134.8 (C−Ar), 141.3 (C-1 NAr), 154.0 (C−OMe), 162.1 (C=N), 193.0 (C=O). Anal. Calcd for C$_{27}$H$_{22}$ClN$_3$O$_2$S: C, 66.45; H, 4.54; N, 8.61. Found C, 66.39; H, 4.60; N, 8.56.

**6-Benzoyl-5-(2-furyl)-3-phenyl-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile (11d).** Recrystallization from EtOH−acetone 1:3 gave a beige crystalline solid, yield 60%, mp 187−189 °C. IR (KBr, cm$^{-1}$)

$\nu_{max}$ 2241 (C≡N), 1688 (C=O), 1664 (C=N). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 3.69 (1H, d, $^2J$ = 12.5 Hz, H-4), 4.20 (1H, d, $^2J$ = 12.5 Hz, H-4), 4.34 (1H, d, $^3J$ = 10.4 Hz, H-5), 4.73 (d, $^2J$ = 17.1 Hz, H-2), 5.37 (d, $^2J$ = 17.1 Hz, H-2), 5.97 (1H, d, $^3J$ = 10.4 Hz, H-6), 6.47−6.48 (1H, m, H-4 furyl), 6.64−6.65 (1H, m, H-3 furyl), 6.88−6.91 (1H, m, H-4 Ph), 6.99 (2H, d, $^3J$ = 7.8 Hz, H-2, H-6 Ph), 7.26−7.29 (2H, m, H-3, H-5 Ph), 7.59−7.62 (2H, m, H-3, H-5 benzoyl), 7.70−7.71 (1H, m, H-5 furyl), 7.73-7.76 (1H, m, H-4 benzoyl), 8.11 (2H, d, $^3J$ = 8.3 Hz, H-2, H-6 benzoyl). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 45.4 (C-5), 47.6 (C-6), 49.6 (C-4a), 51.1 (C-4), 66.8 (C-2), 109.0 (C-3 furyl), 110.8 (C-4 furyl), 116.4 (C-2, C-6 NPh and C≡N overlapped), 120.5 (C-4 NPh), 128.8 (C−Ar), 129.21 (C−Ar), 129.25 (C−Ar), 134.75 (C−Ar), 134.79 (C−Ar), 143.7 (C-5 furyl), 147.0 (C-1 NPh), 147.9 (C-2 furyl), 161.5 (C=N), 192.6 (C=O). Anal. Calcd for C$_{24}$H$_{19}$N$_3$O$_2$S: C, 69.71; H, 4.63; N, 10.16. Found C, 69.69; H, 4.70; N, 10.18.

**6-Benzoyl-5-(2-furyl)-3-(4-methylphenyl)-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile (11e).** Recrystallization from EtOH−DMF 4:1 gave colorless crystals, yield 69%, mp 199−201 °C. IR (Nujol mulls, cm$^{-1}$) $\nu_{max}$ 2240 (C≡N), 1690 (C=O), 1650 (C=N).$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.21 (3H, s, Me), 3.64 (1H, d, $^2J$ = 12.4 Hz, H-4), 4.10 (1H, d, $^2J$ = 12.4 Hz, H-4), 4.33 (1H, d, $^3J$ = 10.6 Hz, H-5), 4.67 (d, $^2J$ = 17.4 Hz, H-2), 5.30 (d, $^2J$ = 17.4 Hz, H-2), 5.97 (1H, d, $^3J$ = 10.6 Hz, H-6), 6.47−6.48 (1H, m, H-4 furyl), 6.64−6.65 (1H, d, $^3J$ = 3.3 Hz, H-3 furyl), 6.90 (2H, d, $^3J$ = 8.5 Hz, H-Ar), 7.08 (2H, d, $^3J$ = 8.5 Hz, H-Ar), 7.59−7.63 (2H, m, H-3, H-5 benzoyl), 7.70−7.71 (1H, m, H-5 furyl), 7.73−7.76 (1H, m, H-4 benzoyl), 8.10 (2H, d, $^3J$ = 7.9 Hz, H-2, H-6 benzoyl).$^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 20.0 (Me), 45.5 (C-5), 47.8 (C-6), 50.1 (C-4a), 51.5 (C-4), 67.0 (C-2), 109.2 (C-3 furyl), 110.8 (C-4 furyl), 116.6 (C≡N), 116.7 (C-2, C-6 NAr), 128.8 (C−Ar), 129.0 (C−Ar), 129.2 (C−Ar), 129.3 (C−Ar), 134.7 (C−Ar), 134.8 (C−Ar), 143.8 (C-5 furyl), 144.9 (C-1 NAr), 147.6 (C-2 furyl), 161.6 (C=N), 192.5 (C=O). LCMS ($m/z$, ES-API) 120.1 [ArN=CH$_2$ + H]$^+$. Anal. Calcd for C$_{25}$H$_{21}$N$_3$O$_2$S: C, 70.24; H, 4.95; N, 9.83. Found C, 70.26; H, 5.06; N, 9.77.

**6-Benzoyl-3-benzyl-5-(2-thienyl)-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile (11f).** Recrystallization from EtOH−acetone 1:3 gave colorless needles, yield 79%, mp 238−240 °C. IR (KBr, cm$^{-1}$) $\nu_{max}$ 2245 (C≡N), 1686 (C=O), 1659 (C=N). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.89 (1H, d, $^2J$ = 11.4 Hz, H-4), 3.11 (1H, d, $^2J$ = 11.4 Hz, H-4), 3.64 (1H, d, $^2J$ = 13.5 Hz, CH$_2$Ph), 3.83 (1H, d, $^2J$ = 13.5 Hz, CH$_2$Ph), 4.09 (1H, d, $^2J$ = 16.6 Hz, H-2), 4.34 (1H, d, $^3J$ = 10.4 Hz, H-5), 4.59 (1H, d, $^2J$ = 16.6 Hz, H-2), 5.99 (1H, d, $^3J$ = 10.4 Hz, H-6), 6.99−7.01 (1H, m, H-4 thienyl), 7.23−7.25 (1H, m, H-3 thienyl), 7.29−7.32 (5H, m, Ph), 7.45−7.46 (1H, dd, $^3J$ = 5.2 Hz,$^4J$ = 1.0 Hz, H-5 thienyl), 7.56−7.60 (2H, m, H-3 and H-5 benzoyl), 7.70−7.73 (1H, m, H-4 benzoyl), 8.07 (2H, d, $^3J$ = 8.3 Hz, H-2, H-6 benzoyl).$^{13}$C NMR APT (126 MHz, DMSO-$d_6$) $\delta$ 46.8* (C-5), 50.0* (C-6), 51.2 (C-4a), 53.0 (CH$_2$Ph), 56.3 (C-4), 70.7 (C-2), 117.1 (C≡N), 126.4* (CH Ar), 127.1* (CH Ar), 127.2* (CH Ar), 127.4* (CH Ar), 128.27* (CH Ar), 128.29* (CH Ar), 128.7* (CH Ar), 129.2* (CH Ar), 134.7* (C-4 benzoyl), 134.8 (C Ar), 135.3 (C Ar), 137.0 (C Ar), 161.6 (C=N), 192.5 (C=O). *Signals in antiphase. LCMS ($m/z$, APCI) 120.1 [PhCH$_2$N=CH$_2$ + H]$^+$, 365.0 [M−PhH + H]$^+$, 444.1 [M + 1]$^+$. Anal. Calcd for

$C_{25}H_{21}N_3OS_2$: C, 67.69; H, 4.77; N, 9.47. Found C, 67.73; H, 4.82; N, 9.40.

**6-Benzoyl-3-(4-methylphenyl)-5-(2-thienyl)-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile (11g).** Recrystallization from EtOH−acetone 1:1 gave a beige fine crystalline solid, yield 86%, mp 214−216 °C. IR (KBr, cm$^{-1}$) $\nu_{max}$ 2241 (C≡N), 1684 (C=O), 1651 (C=N).^{1}H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.20 (3H, s, Me), 3.64 (1H, d, $^2J$ = 12.4 Hz, H-4), 3.90 (1H, d, $^2J$ = 11.4 Hz, H-4), 4.47 (1H, d, $^3J$ = 10.4 Hz, H-5), 4.67 (1H, d, $^2J$ = 17.4 Hz, H-2), 5.31 (1H, d, $^2J$ = 17.4 Hz, H-2), 6.05 (1H, d, $^3J$ = 10.4 Hz, H-6), 6.85 (2H, d, $^3J$ = 8.3, H-2, H-6 ArN), 7.05−7.09 (3H, m, H-4 thienyl, H-3, H-5 ArN overlapped), 7.42−7.43 (1H, m, H-3 thienyl), 7.55 (1H, d, $^3J$ = 5.4 Hz, H-5 thienyl), 7.58−7.61 (2H, m, H-3 and H-5 benzoyl), 7.72−7.75 (1H, m, H-4 benzoyl), 8.11 (2H, d, $^3J$ = 7.9 Hz, H-2, H-6 benzoyl).^{13}C NMR (126 MHz, DMSO-$d_6$) $\delta$ 20.1 (Me), 46.8 (C-5), 49.7 (C-6), 50.2 (C-4), 51.6 (C-4a), 67.4 (C-2), 116.6 (C≡N), 116.8 (C−Ar), 126.5 (C−Ar), 127.3 (C−Ar), 127.6 (C−Ar), 128.8 (C−Ar), 129.2 (C−Ar), 129.6 (C−Ar), 129.7 (C−Ar), 134.8 (C−Ar), 134.9 (C−Ar), 135.3 (C−Ar), 144.8 (C−Ar), 161.6 (C=N), 192.6 (C=O). LCMS ($m/z$, ES-API) 120.2 [ArN=CH$_2$ + H]$^+$, 444.0 [M + H]$^+$. Anal. Calcd for $C_{25}H_{21}N_3OS_2$: C, 67.69; H, 4.77; N, 9.47. Found C, 67.70; H, 4.81; N, 9.45.

**6-Benzoyl-3-(4-methylphenyl)-5-phenyl-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile (11h).** Recrystallization from EtOH−acetone 1:2 gave a beige fine crystalline solid, yield 86%, mp 224−226 °C. IR (KBr, cm$^{-1}$) $\nu_{max}$ 2239 (C≡N), 1682 (C=O), 1655 (C=N).^{1}H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.18 (3H, s, Me), 3.64 (2H, AB-q, $^2J$ = 12.6 Hz, H-4), 4.19 (1H, d, $^3J$ = 10.6 Hz, H-5), 4.66 (1H, d, $^2J$ = 17.3 Hz, H-2), 5.29 (1H, d, $^2J$ = 17.3 Hz, H-2), 6.28 (1H, d, $^3J$ = 10.6 Hz, H-6), 6.80 (2H, d, $^3J$ = 8.3 Hz, H-2, H-6 ArN), 7.04 (2H, d, $^3J$ = 8.3 Hz, H-3, H-5 ArN), 7.33−7.42 (3H, m, H-Ph), 7.56−7.60 (2H, m, H-3 and H-5 benzoyl), 7.64 (2H, d, $^3J$ = 7.3 Hz, H-2 and H-6 Ph), 7.70−7.74 (1H, m, H-4 benzoyl), 8.10 (2H, d, $^3J$ = 8.1 Hz, H-2, H-6 benzoyl).^{13}C NMR (126 MHz, DMSO-$d_6$) $\delta$ 20.0 (Me), 48.4 (C-5), 50.4 (C-6), 51.6 (C-4 and C-4a overlapped), 67.5 (C-2), 116.7 (C≡N), 116.8 (C−Ar), 128.5 (C−Ar), 128.7 (C−Ar), 128.78 (C−Ar), 128.80 (C−Ar), 129.1 (C−Ar), 129.59 (C−Ar), 129.63 (C−Ar), 133.7 (C−Ar), 134.6 (C−Ar), 135.0 (C−Ar), 144.9 (C−Ar), 162.3 (C=N), 193.0 (C=O). LCMS ($m/z$, ES-API) 120.3 [ArN=CH$_2$ + H]$^+$, 426.9 [M-120 + HCO$_2$H + HCO$_2$NH$_4$], 438.0 [M + H]$^+$. Anal. Calcd for $C_{27}H_{23}N_3OS$: C, 74.11; H, 5.30; N, 9.60. Found C, 74.13; H, 5.34; N, 9.63.

**6-Benzoyl-3-(4-methoxyphenyl)-5-phenyl-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile (11i).** Recrystallization from EtOH−acetone 1:3 gave a pale yellow crystalline solid, yield 67%, mp 213−215 °C. IR (KBr, cm$^{-1}$) $\nu_{max}$ 2245 (C≡N), 1682 (C=O), 1655 (C=N).^{1}H NMR (400 MHz, DMSO-$d_6$) $\delta$ 3.52 (1H, d, $^3J$ = 12.5 Hz, H-4), 3.62 (1H, d, $^3J$ = 12.5 Hz, H-4), 3.67 (3H, s, MeO), 4.18 (1H, d, $^3J$ = 10.6 Hz, H-5), 4.63 (1H, d, $^2J$ = 17.1 Hz, H-2), 5.19 (1H, d, $^2J$ = 17.1 Hz, H-2), 6.26 (1H, d, $^3J$ = 10.6 Hz, H-6), 6.83 (2H, d, $^3J$ = 8.8 Hz, 4-MeOC$_6$H$_4$), 6.89 (2H, d, $^3J$ = 8.8 Hz, 4-MeOC$_6$H$_4$), 7.34−7.41 (3H, m, H-Ph), 7.56−7.60 (2H, m, H-3, H-5 benzoyl), 7.64 (2H, d, $^3J$ = 7.3 Hz, H-2, H-6 Ph), 7.70−7.73 (1H, m, H-4 benzoyl), 8.09 (2H, d, $^3J$ = 7.3 Hz, H-2, H-6 benzoyl).^{13}C APT NMR (126 MHz, DMSO-$d_6$) $\delta$ 48.4* (C-5), 50.4 (C-4a), 51.6* (C-6), 52.7 (C-4), 55.2* (MeO), 68.4 (C-2), 114.5* (CH Ar), 116.7 (C≡N), 119.2* (CH Ar), 128.5* (CH Ar), 128.6* (CH Ar), 128.7* (CH Ar), 128.8* (CH Ar), 129.1*

(CH Ar), 133.6 (C-1 Ph), 134.6* (C-4 benzoyl), 135.0 (C-1 Ph), 141.0 (C-OMe), 154.2 (C-1 Ar), 162.2 (C-2), 193.0 (C=O). *Signals in antiphase. LCMS ($m/z$, ES-API) 136.1 [ArN=CH$_2$ + H]$^+$, 453.9 [M + H]$^+$, 906.7 [2 M + 1]$^+$. Anal. Calcd for $C_{27}H_{23}N_3O_2S$: C, 71.50; H, 5.11; N, 9.26. Found C, 71.47; H, 5.17; N, 9.20.

**6-Benzoyl-3-phenethyl-5-phenyl-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-arbonitrile (11j).** Recrystallization from EtOH−acetone 1:1 gave colorless needles, yield 65%, mp 167−169 °C. IR (KBr, cm$^{-1}$) $\nu_{max}$ 2237 (C≡N), 1684 (C=O), 1647 (C=N).^{1}H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.66−2.78 (4H, m, CH$_2$CH$_2$Ph), 2.92 (1H, d, $^3J$ = 11.4 Hz, H-4), 3.03 (1H, d, $^3J$ = 11.4 Hz, H-4), 4.04 (1H, d, $^3J$ = 10.6 Hz, H-5), 4.11 (1H, d, $^2J$ = 16.9 Hz, H-2), 4.64 (1H, d, $^2J$ = 16.9 Hz, H-2), 6.19 (1H, d, $^3J$ = 10.6 Hz, H-6), 7.15−7.21 (5H, m, Ph), 7.32−7.39 (3H, m, Ph), 7.55−7.59 (4H, m, Ph), 7.69−7.72 (1H, m, H-4 benzoyl), 8.07 (2H, d, $^3J$ = 7.8 Hz, H-2, H-6 benzoyl).^{13}C NMR (126 MHz, DMSO-$d_6$) $\delta$ 32.5 (CH$_2$CH$_2$Ph), 48.6 (C-5), 51.0 (C-6), 51.7 (C-4a), 53.8 (CH$_2$Ph), 54.3 (C-4), 70.6 (C-2), 117.2 (C≡N), 125.8 (C−Ar), 128.1 (C−Ar), 128.4 (C−Ar), 128.60 (C−Ar), 128.64 (C−Ar), 128.67 (C−Ar), 128.73 (C−Ar), 129.1 (C−Ar), 133.7 (C−Ar), 134.6 (C−Ar), 135.0 (C−Ar), 139.7 (C−Ar), 162.1 (C=N), 193.0 (C=O). LCMS ($m/z$, ES-API) 105.3 [PhCHCH$_3$]$^+$, 134.1 [PhCH$_2$CH$_2$N=CH$_2$ + H]$^+$, 452.0 [M + H]$^+$. Anal. Calcd for $C_{28}H_{25}N_3OS$: C, 74.47; H, 5.58; N, 9.31. Found C, 74.44; H, 5.67; N, 9.27.

**6-Benzoyl-3-benzyl-5-phenyl-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile (11k).** Recrystallization from EtOH−acetone 1:1 gave colorless needles, yield 73%, mp 188−190 °C. IR (KBr, cm$^{-1}$) $\nu_{max}$ 2243 (C≡N), 1689 (C=O), 1655 (C=N).^{1}H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.90 (2H, br s, H-4), 3.61 (1H, d, $^2J$ = 14.0 Hz, CH$_2$Ph), 3.78 (1H, d, $^2J$ = 14.0 Hz, CH$_2$Ph), 4.05−4.09 (2H, m: 1H, d, H-2 and 1H, d, H-5 overlapped), 4.56 (1H, d, $^2J$ = 16.7 Hz, H-2), 6.21 (1H, d, $^3J$ = 10.8 Hz, H-6), 7.20−7.22 (1H, m, H-4 Ph), 7.25−7.35 (7H, m, Ph), 7.55−7.58 (4H, m, Ph), 7.68−7.72 (1H, m, H-4 benzoyl), 8.06 (2H, d, $^3J$ = 7.5 Hz, H-2, H-6 benzoyl).^{13}C APT NMR (126 MHz, DMSO-$d_6$) $\delta$ 48.7* (C-5), 51.3 (C-4a), 51.6* (C-6), 53.3 (CH$_2$Ph), 56.4 (C-4), 70.8 (C-2), 117.2 (C≡N), 127.2* (CH Ph), 128.3* (CH Ph), 128.4* (CH Ph), 128.6* (CH Ph), 128.7* (CH Ph), 128.8* (CH Ph), 129.1* (CH Ph), 133.7 (C Ph), 134.6* (C-4 benzoyl), 135.0 (C Ph), 137.1 (C Ph), 162.4 (C=N), 193.0 (C=O). *Signals in antiphase. LCMS ($m/z$, ES-API) 120.4 [PhCH$_2$N=CH$_2$ + H]$^+$, 438.5 [M + H]$^+$, 875.5 [2 M + H]$^+$. Anal. Calcd for $C_{27}H_{23}N_3OS$: C, 74.11; H, 5.30; N, 9.60. Found C, 74.10; H, 5.36; N, 9.57.

**6-Benzoyl-3,5-diphenyl-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile (11l).** Recrystallization from EtOH−acetone 1:1 gave large colorless cubes, yield 70%, mp 214−216 °C. IR (KBr, cm$^{-1}$) $\nu_{max}$ 2239 (C≡N), 1682 (C=O), 1666 (C=N).^{1}H NMR (400 MHz, DMSO-$d_6$) $\delta$ 3.66 (1H, d, $^2J$ = 12.5 Hz, H-4), 3.76 (1H, d, $^2J$ = 12.5 Hz, H-4), 4.21 (1H, d, $^3J$ = 10.6 Hz, H-5), 4.72 (1H, d, $^2J$ = 17.3 Hz, H-2), 5.37 (1H, d, $^2J$ = 17.3 Hz, H-2), 6.29 (1H, d, $^3J$ = 10.6 Hz, H-6), 6.84−6.90 (3H, m, Ph), 7.21−7.25 (2H, m, Ph), 7.36−7.43 (3H, m, Ph), 7.56−7.60 (2H, m, H-3 and H-5 benzoyl), 7.64 (2H, d, $^3J$ = 7.3 Hz, H-2 and H-6 Ph), 7.70−7.74 (1H, m, H-4 benzoyl), 8.10 (2H, d, $^3J$ = 7.8 Hz, H-2, H-6 benzoyl).^{13}C APT NMR (126 MHz, DMSO-$d_6$) $\delta$ 48.5* (C-5), 50.3 (C-4), 51.2 (C-4a), 51.6* (C-6), 67.0 (C-2), 116.3* (C-2,

C-6 NPh), 116.6 (C≡N), 120.5* (C-4 N-Ph), 128.5* (CH Ph), 128.7* (CH Ph), 128.8* (CH Ph), 129.0* (CH Ph), 129.1* (CH Ph), 129.2* (CH Ph), 133.6 (C-1 Ph), 134.6* (C-4 benzoyl), 135.0 (C Ph), 147.0 (C-1 N-Ph), 162.4 (C=N), 193.0 (C=O). *Signals in antiphase. LCMS ($m/z$, ES-API) 129.4, 141.3, 149.6, 158.4, 214.4, 424.5 [M + H]$^+$, 847.0 [2 M + H]$^+$. Anal. Calcd for $C_{26}H_{21}N_3OS$: C, 73.73; H, 5.00; N, 9.92. Found C, 73.70; H, 5.06; N, 9.97.

**X-ray Studies of the Crystal of 11l.** Single crystals of 6-benzoyl-3,5-diphenyl-2,3,4,4a,5,6-hexahydrothieno[2,3-d]-pyrimidine-4a-carbonitrile $C_{26}H_{21}N_3OS$ (**11l**), $M$ = 423.52, were prepared by recrystallization from EtOH/acetone = 1:1. The crystals are triclinic at 298 K: $a$ = 11.9327(7) Å, $b$ = 12.7829(6) Å, $c$ = 16.4847(6) Å, $\alpha$ = 79.805(4)°, $\beta$ = 88.022(4)°, $\gamma$ = 62.234(6)°, $V$ = 2186.53(19) Å$^3$, $T$ = 839(2), space group P1 (no. 2), $Z$ = 4, $\mu$(Mo K$\alpha$) = 0.171 mm$^{-1}$, $d_{calc}$ = 1.29 g/cm$^3$, $F(000)$ = 888, 16,692 reflections measured, 9840 unique ($R_{int}$ = 0.0200) that were used in all calculations. The final $wR_2$ was 0.1243 (all data), and $R_1$ was 0.0582 (>2sigma($I$)). The unit cell parameters and the intensities of 16,692 reflections were measured on an Xcalibur 3 diffractometer (Mo K$\alpha$, graphite monochromator, CCD detector, $\omega$-scanning, $2\theta$max 57.52°). The structure was solved by the direct method with the SHELX-97 software package.[141] The hydrogen atoms were placed geometrically and refined with a riding model with $U$iso = 1.2 $U$eq for the supporting atom. The structure was refined on $F$2 by the full-matrix least-squares method with an anisotropic approximation for the nonhydrogen atoms to $wR2$ 0.124 at 9840 reflections ($R1$ 0.058 at 6619 reflections with $F > 4\sigma(F)$, $S$ = 1.03). A full set of crystallographic data has been deposited in the Cambridge Crystallographic Data Center (CCDC 1063909).

**3,3′-(1,4-Phenylene)-bis(6-benzoyl-5-phenyl-2,3,4,4a,5,6-hexahydrothieno[2,3-d]pyrimidine-4a-carbonitrile) (12).** The mixture of ADHT **6d** (151 mg, 0.49 mmol) and *p*-phenylenediamine (27 mg, 0.25 mmol) was dissolved in hot EtOH (10 mL). Then an excess (0.8 mL) of 37% aq HCHO was added, and the mixture was refluxed for 5 min under vigorous stirring. The precipitate formed upon cooling was filtered off after 4 h and triturated with boiling acetone for 2−3 min. Beige powder, yield 90 mg (48%), mp 164−166 °C. IR (Nujol mulls, cm$^{-1}$) $\nu_{max}$ 2245 (C≡N), 1685 (C=O), 1650 (C=N).$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 3.57 (4H, AB-q, $^2J$ = 11.9 Hz, H-4, H-4′), 4.17 (2H, d, $^3J$ = 10.6 Hz, H-5, H-5′), 4.61 (2H, d, $^2J$ = 17.3 Hz, H-2, H-2′), 5.20 (2H, d, $^2J$ = 17.3 Hz, H-2, H-2′), 6.26 (2H, d, $^3J$ = 10.6 Hz, H-6, H-6′), 6.84 (4H, br s, 1,4-NC$_6$H$_4$N), 7.34−7.39 (6H, m, Ph), 7.56−7.63 (8H, m, Ph), 7.70−7.73 (2H, m, H-4, H-4′ benzoyl), 8.09 (4H, d, $^3J$ = 7.5 Hz, H-2, H-6, H-2′, H-6′ benzoyl). Due to the poor solubility, the authors were unable to record $^{13}$C NMR spectra of **12**. LCMS ($m/z$, ES-API) 120.3 [H$_2$C=NC$_6$H$_4$N + H]$^+$, 426.8 [M + 2MeCN + 2H]$^{+2}$, 451.0 [thienopyrimidine-3-yl-C$_6$H$_4$-N=CH$_2$ + H]$^+$, 768.8 [M + H]$^+$. Anal. Calcd for $C_{46}H_{36}N_6O_2S_2$: C, 71.85; H, 4.72; N, 10.93. Found 71.74; H, 4.76; N, 11.00.

## ASSOCIATED CONTENT

**⊕ Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c04141.

    Copies of $^1$H, $^{13}$C NMR, FTIR, LCMS, and X-ray data of the synthesized compounds (PDF)

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**Notes**

## ACKNOWLEDGMENTS

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