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Modulating the Reactivity of Functionalized *N,S*-Ketene Acetal in MCR: Selective Synthesis of Tetrahydropyridines and Thiochromeno[2,3-*b*]pyridines via DABCO-Catalyzed Tandem Annulation

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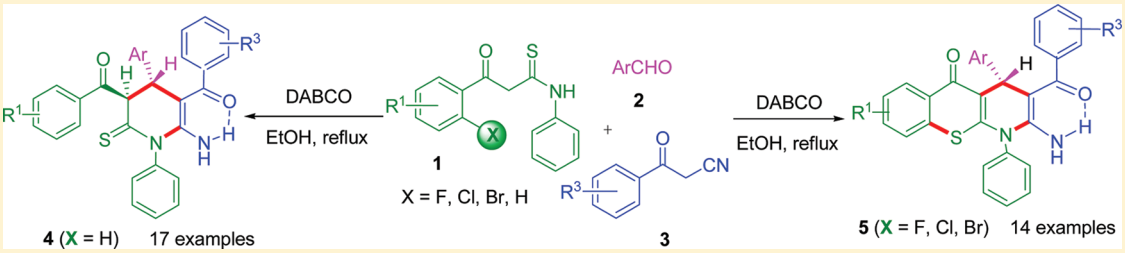
Supporting Information



ABSTRACT: An efficient and straightforward three-component synthetic protocol was developed to synthesize 1,2,3,4-tetrahydropyridine derivatives or thiochromeno[2,3-*b*]pyridine derivatives from *β*-aroylthioacetanilides or *β*-(2-haloaroyl)-thioacetanilides, aldehydes, and aroyl acetonitriles via DABCO-catalyzed tandem [3 + 2 + 1] annulation and S_NAr reaction. This synthetic approach has the prominent features of high chemo-, stereo- (or enantio-), and unusual regioselectivity. In the domino processes, at least seven reactive sites were involved, and up to three covalent bonds and one functionalized pyridine ring were generated. This facile and efficient reaction is a quite general for the preparation of tetrahydropyridine derivatives or thiochromeno[2,3-*b*]pyridine derivatives.

INTRODUCTION

A major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds with interesting properties.[1] Multicomponent reactions (MCRs) have manifested themselves as a powerful tool for the rapid introduction and expansion of molecular diversity.[2] An important asset of the approach is the significant increase of the combinatorial possibilities, since a modification of the final product is easily accomplished by implementing minor changes in the reaction setup; this obviously allows considerable savings in time and resources. These advantages are of particular interest in pharmaceutical research for the construction of libraries of biologically active compounds.[3] Consequently, the design and development of new MCR routes for the generation of heterocycles receive growing interest.[4]

The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry.[5] 1,4-Dihydropyridines, as the important "privileged scaffold", are very attractive targets for combinatorial library synthesis due to their wide range of pharmaceutical activities, which have been reported to be vasodilators, antihypertensives, and bronchodilators, and to possess antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, antidiabetic, geroprotective, and photosensitizing activities.[6] They are also important reducing agents toward the application of the nicotinamide adenine dinucleotide coenzyme [NAD(P)H] models.[7] Many examples of "privileged medicinal scaffolds" have the 1,4-dihydropyridine scaffolds, such as nifedipine,[8] which has been in clinical medicine since 1975. Quite recently, many novel second-generation calcium antagonists have emerged with improved bioavailability and tissue selectivity/stability (such as Benidipine and Lacidipine),[9] and calcium agonists (such as BAY K 8644) have been also discovered.[10]

A rapidly increasing recognition of the rich and fascinating chemistry of the *N,S*- ketene acetals in organic synthesis has been brought out in the past decades. Functionalized *α*-oxoketene *N,S*-acetals with general structure **1** (Figure 1) have been proven to be important building blocks in the construction of heterocyclic systems.[11] Three or four active centers determine the chemical properties of *α*-oxoketene *N,S*-acetals. One of them is attributed to the nitrogen atom with an unshared electron pair, the second one, to the sulfur atom, the third potential center, to the *α*-carbon due to the highly polarized push (HS and RNH)−pull (C═O) interaction on the C═C bond, and the last one, particularly significant, to a

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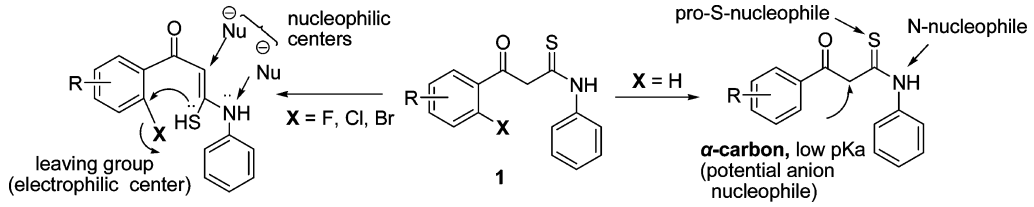
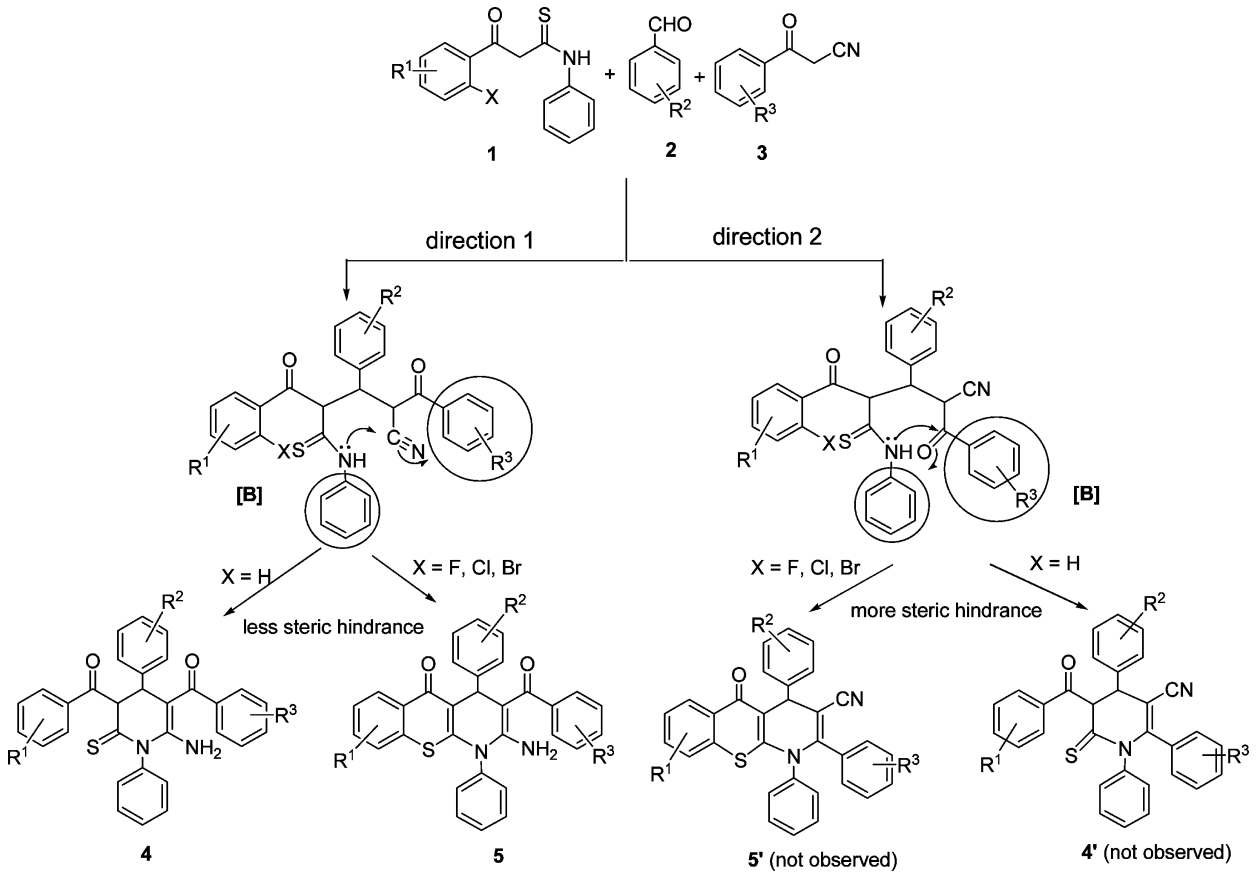


Figure 1. Functionalized α-oxoketene *N*,*S*-acetals.

Scheme 1. Two Directions of the Reaction



potential leaving halogen group on aromatic ring. Therefore, precursors **1** could be used to develop a new strategy for the synthesis of 1,2,3,4-tetrahydropyridine and thiochromeno[2,3-*b*]pyridine derivatives.

As part of our ongoing studies on the chemistry of functionalized α-oxoketene *N*,*S*-acetals,[12] we wish to report herein a highly efficient three-component reaction based on β-aroylthioacetanilides **1**, aromatic aldehydes **2**, and 3-oxo-3-aryl propanenitriles **3**, which provides high regio- and stereoselectively a straightforward entry to fully substituted thiochromenopyridine derivatives and fully substituted 2-thioxo-1,2,3,4-tetrahydropyridine derivatives, which are potential 1,4-dihydropyridine compounds due to tautomeric isomers referring to thioenol or thione. To the best of our knowledge, this synthetic strategy for 2-thioxo-1,2,3,4-tetrahydropyridine and thiochromenopyridine derivatives has not been reported before using functionalized *N*,*S*-ketene acetals as building blocks and DABCO as a catalyst via MCR.

RESULTS AND DISCUSSION

Our approach toward the design and development of new domino and multicomponent procedures involves the use of building block **1** that contains a number of chemically distinct functionalities, which could be selectively reacted to generate diversity with aldehydes **2** and 3-oxo-3-arylpropanenitriles **3**. So, the reaction may proceed in two directions (Scheme 1).

In direction 1, the intermediate [**B**] undergoes the intramolecular *N*-cyclization by amino group attacking the cyano group to produce **4** (X = H) and S_NAr of the mercapto group to give **5** (X = F, Cl, Br). In direction 2, the intermediate [**B**] undergoes the intramolecular *N*-cyclization by amino group attacking the carbonyl group to produce **4′** (X = H) and S_NAr of the amino group to give **5′** (X = F, Cl, Br). Surprisingly, during our investigation, we did not detect **4′** or **5′**, and only **4** and **5** were obtained exclusively. This observation is rare and very interesting in organic chemistry. Our experimental results demonstrated that the three-component reactions described show high regioselectivity.

The initial attempt to perform a reaction of 3-oxo-*N*,3-diphenylpropanethioamide **1a** and 4-chlorobenzaldehyde **2a**

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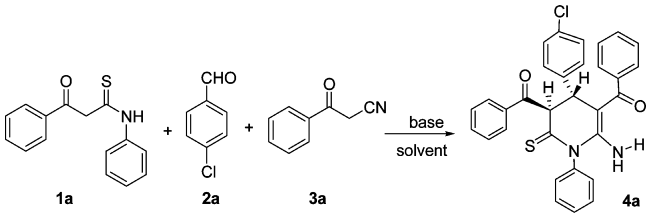
with 3-oxo-3-phenylpropanenitrile **3a** was focused on the optimization of the reaction conditions (Table 1). Initially,

Table 1. Optimization of Reaction Conditions for the Synthesis of 4a[a]



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

entry	catalyst/mmol %	solvent	time/h	yield[b]/%
1	–[c]	EtOH	20	–[d]
2	Et_3N (1.0)	EtOH	20[e]	–[d]
3	Et_3N (0.5)	EtOH	15	54
4	Et_3N (1.0)	EtOH	14	62
5	Et_3N (1.5)	EtOH	14	64
6	DABCO (0.2)	EtOH	20[e]	–[d]
7	DABCO (0.2)	EtOH	13	68
8	DABCO (0.5)	EtOH	5.5	85
9	DABCO (1.0)	EtOH	10	71
10	DABCO (0.5)	THF	14	55
11	DABCO (0.5)	CH_3CN	14	56
12	DABCO (0.5)	DMF	10	53
13	pyridine (0.5)	EtOH	21	30
14	DBU (0.5)	EtOH	20	35
15	DMAP (0.5)	EtOH	9	60
16	K_2CO_3 (0.5)	EtOH	20	–[d]
17	KOH (0.5)	EtOH	20	–[d]

[a]Unless otherwise noted, reactions were carried out using **1a** (1 mmol), **2a** (1.2 mmol), and **3a** (1 mmol) under refluxing. [b]Isolated yield. [c]No base. [d]No reaction. [e]At room temperature.

triethylamine was selected as a base in this reaction. The reaction was carried out in the presence of 50 mmol % triethylamine, affording the product **4a** successfully in 54% yield within 15 h (Table 1, entry 3). However, an additional increase of the amount of Et_3N to 100 or 150 mmol % did not improve the yield of the product (Table 1, entries 4 and 5), and no product was observed in the absence of a catalyst (Table 1, entry 1). These results revealed that a base is favored to this MCR. Then, other bases also were employed for this MCR. First, DABCO (1,4-diazabicyclic[2,2,2]octane) was examined at room temperature or under reflux condition (Table 1, entries 6 and 7), and the results suggested that DABCO in refluxing EtOH as a catalyst was superior to Et_3N. Furthermore, when raising the amount of DABCO up to 50 mmol %, the yield of **4a** reached 85%, and reaction time was shortened to 5.5 h (Table 1, entry 8). However, further raising the amount of DABCO did not obviously increase the yield (Table 1, entry 9). Next, pyridine, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), or DMAP as a catalyst for this reaction also were investigated, but the results were unsatisfactory (Table 1, entries 13–15). In addition, the inorganic bases such as K_2CO_3 and KOH were both ineffective for this reaction (Table 1, entries 16 and 17). Screening of the solvents revealed that ethanol turned out to be an appropriate solvent, which provided not only a shorter reaction time, but also a higher yield than other examined solvents such as DMF, CH_3CN, THF (Table 1, entries 8 and 10–12). Therefore, the reaction conditions of 50 mmol % DABCO as a catalyst in refluxing EtOH were best for the preparation of **4a**. Compared to other bases, DABCO has been regarded as an unhindered and nucleophilic base, and considered one of the best versatile amine catalysts because of its unique properties.[13]

To further demonstrate the scope and versatility of this procedure for regiospecific synthesis of 1,2,3,4-tetrahydropyridines **4**, 11 *β*-aroylthioacetanilides **1** and 14 variously substituted aldehydes **2** were examined for their reactions with three aroyl acetonitriles **3** under the optimized conditions (Table 2). As can be seen from Table 2, for precursors **1** and **2** bearing either electron-donating or electron-withdrawing substituents on the aroyl group (for **1**) or on the aromatic ring (for **2**), the reactions all proceeded very smoothly to provide the corresponding pyridine derivatives. With regard to the reactivities of precursors **1** and **2**, it is very clear that the reactions of various aromatic aldehydes **2** containing electron-withdrawing substituents provided generally higher yields than those containing an electron-donating substituent. For example, the yields of **4a–f** were obviously higher than the corresponding ones of **4h–k**, respectively (Table 2, entries 1–6 and 8–11). Aromatic aldehydes bearing an *ortho* substituent showed certain steric hindrance (Table 2, entries 2 and 3), which led to a lower yield of the product. However, when 3- or 4-nitrobenzaldehydes were employed, the reaction system became disordered and did not give desired products. The property of substituents on the aroyl group of *β*-aroylthioacetanilides **1** did not assert an obvious effect on the reaction yield (Table 2, entries 12–16). Our attempt to use aliphatic aldehydes such as *n*-butanalaldehydes in this MCR was unsuccessful, with no separable product being formed; instead, significant tarring was observed, which was caused most likely by self-condensation of the aliphatic aldehydes under this reaction condition.

In this domino process, two C–C bonds, one C–N bond, and one six-membered ring were formed with the concomitant creation. Importantly, this three-component reaction for tetrahydropyridines **4** generates two chirality centers, but only one stereoisomer was observed through ^1H NMR and ^{13}C NMR spectra, and X-ray diffraction analysis of **4i** reveals that the products **4** adopt *trans* configuration.

Functionalized thiochromones and their fused analogues are of interest because they represent an important class of heterocycles, many of them exhibit useful biological activities, and many have been tested and applied as drugs.[14] Although a few known methods have been developed for thiochromone structural motifs, partly because it is difficult to access,[15] it is still challenging to explore efficient synthetic routes for this class of compounds.

Conducting a postcondensation reaction can generate more complicated molecules.[2e] On the basis of the results as described above and in continuation of our ongoing research toward the discovery of new reactions for the synthesis of heterocycles containing pyridine-based frameworks, we designed a novel protocol by simply introducing an *o*-halo group into the aryl ring of *β*-aroylthioacetanilides for the preparation of thiochromeno[2,3-*b*]pyridine derivatives **5**.

The broad tolerance for various R^1 and R^2 substituents to the formation of **5** was investigated (Table 2, entries 18–31). The results showed that whether it is electron-donating or electron-withdrawing substituents on the aromatic ring of precursors **2**, the reaction could afford the corresponding thiochromeno[2,3-*b*] pyridines **5** in good to excellent yields. Different to the formation of **4**, 4-nitrobenzaldehyde could react well with

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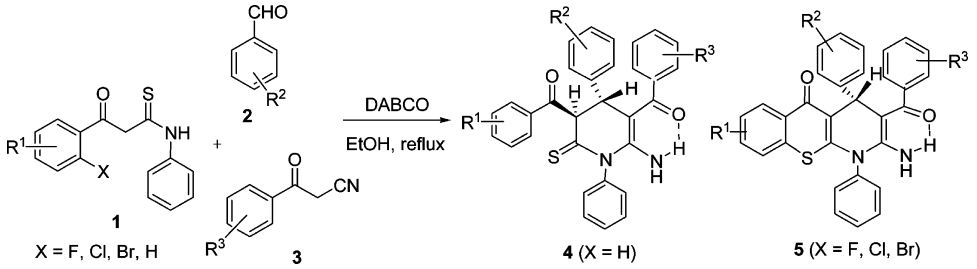
Table 2. Synthesis of Products 4 and 5 from Thioacetanilides[a]



entry	1, R^1	X	2, R^2	3, R^3	4/5	time/h	yield[b]/%
1	**1a**, H	H	**2a**, 4-Cl	**3a**, H	**4a**	5.5	85
2	**1a**, H	H	**2b**, 2-Cl	**3a**, H	**4b**	7.5	78
3	**1a**, H	H	**2c**, 2, 4-Cl_2	**3a**, H	**4c**	7	81
4	**1a**, H	H	**2d**, 3-Br	**3a**, H	**4d**	6.5	82
5	**1a**, H	H	**2e**, 3-F	**3a**, H	**4e**	6	78
6	**1a**, H	H	**2f**, 4-F	**3a**, H	**4f**	5.5	84
7	**1a**, H	H	**2g**, H	**3a**, H	**4g**	8	80
8	**1a**, H	H	**2h**, 3,4-OCH_2O	**3a**, H	**4h**	7.5	77
9	**1a**, H	H	**2i**, 4-CH_3	**3a**, H	**4i**	8	77
10	**1a**, H	H	**2j**, 4-OCH_3	**3a**, H	**4j**	8.5	76
11	**1a**, H	H	**2k**, 3-OCH_3	**3a**, H	**4k**	8	75
12	**1b**, 4-F	H	**2a**, 4-Cl	**3a**, H	**4l**	7	83
13	**1c**, 4-Cl	H	**2a**, 4-Cl	**3a**, H	**4m**	7.5	80
14	**1d**, 4-Br	H	**2a**, 4-Cl	**3a**, H	**4n**	7.5	83
15	**1e**, 4-CH_3	H	**2a**, 4-Cl	**3a**, H	**4o**	7	82
16	**1f**, 4-OCH_3	H	**2a**, 4-Cl	**3a**, H	**4p**	8	82
17	**1a**, H	H	**2c**, 2, 4-Cl_2	**3b**, 4-CH_3	**4q**	8.5	75
18	**1g**, 4-Cl	Cl	**2a**, 4-Cl	**3a**, H	**5a**	5.5	82
19	**1g**, 4-Cl	Cl	**2b**, 2-Cl	**3a**, H	**5b**	7	76
20	**1g**, 4-Cl	Cl	**2l**, 4-Br	**3a**, H	**5c**	6	85
21	**1g**, 4-Cl	Cl	**2e**, 3-F	**3a**, H	**5d**	6	88
22	**1g**, 4-Cl	Cl	**2m**, 2-F	**3a**, H	**5e**	7.5	79
23	**1g**, 4-Cl	Cl	**2n**, 4-NO_2	**3a**, H	**5f**	8	73
24	**1g**, 4-Cl	Cl	**2g**, H	**3a**, H	**5g**	6.5	75
25	**1g**, 4-Cl	Cl	**2i**, 4-CH_3	**3a**, H	**5h**	8	76
26	**1g**, 4-Cl	Cl	**2j**, 4-OCH_3	**3a**, H	**5i**	8	75
27	**1h**, 4-F	F	**2a**, 4-Cl	**3a**, H	**5j**	6	83
28	**1i**, H	Br	**2a**, 4-Cl	**3a**, H	**5k**	7	82
29	**1j**, 4-(4-ClC_6H_4O)	Cl	**2a**, 4-Cl	**3a**, H	**5l**	6	88
30	**1k**, 6-Cl-3-F	Cl	**2l**, 4-Br	**3c**, 4-Cl	**5m**	7	76
31	**1g**, 4-Cl	Cl	**2h**, 3,4-OCH_2O	**3c**, 4-Cl	**5n**	8	76

[a]Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), and **3** (1 mmol), refluxing EtOH, DABCO (0.5 equiv) for products **4** or DABCO (1.0 equiv) for products **5**. [b]Isolated yield.

precursors **1** to yield the desired product (Table 2, entry 23). Moreover, *β*-aroylthioacetanilides **1** bearing an electron-donating substituent provided higher yields than ones with an electron-withdrawing substituent. For example, the yield of **5l** was higher than **5a** (Table 2, entries 18 and 29), presumably because of the higher electron density of the methylene, making it easy to attack the carbonyl group of the aldehydes.

It is worthy to note that all isolated products only need recrystallization rather than column chromatography. This ease of purification makes this methodology facile, practical, and rapid to execute.

The structures of all new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopy. The regio- and stereoselectivity outcome of the cycloaddition was unambiguously ascertained by X-ray diffraction analysis of single crystals of **4i** and **5a** (see Figure S1 in the Supporting Information).

Unfortunately, however, the results were unsatisfactory when the *N*,*S*-ketene acetal **1** bearing either electron-donating or electron-withdrawing substituents on the *N*-aryl group at *p*-position, such as CH_3, OEt, and CF_3, were employed to react with **2a** and **3a** to prepare compounds **4**. The three *N*-(4-substituted-phenyl)-3-oxo-3-phenylpropanethioamides only gave an unexpected mixture, which could not be separated by the conventional methods such as column chromatography and recrystallization. On the basis of the fact that the *N*,*S*-ketene acetal **1** bearing the CH_3 and OEt on the *N*-aryl ring at *p*-position, which should be helpful to arylamino group attacking the cyano group, could not provide the expected products, we inferred that the steric hindrance of the *N*-aryl ring might have a great effect on the intramolecular *N*-cyclization by arylamino group attacking the cyano group.

The possible mechanism for the formation of products **4**/**5** is shown in Scheme 2. The Knoevenagel-type reaction of

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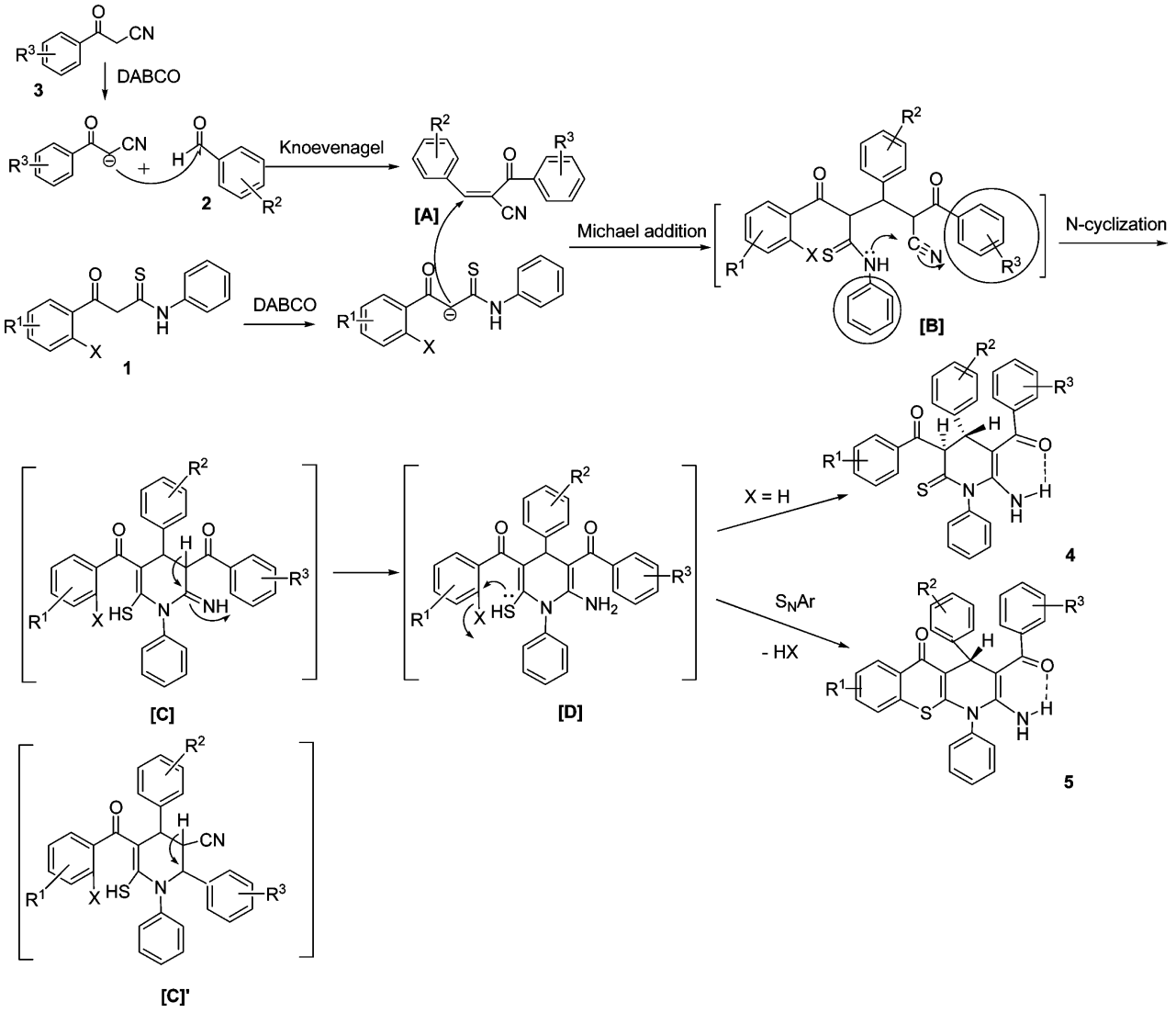
Scheme 2. Plausible Mechanism for the Formation of Products 4 and 5



aldehydes **2** with 3-oxo-3-arylpropanenitriles **3** results in the formation of intermediates [**A**]. Then, the *β*-aroylthioacetanilides **1** undergo Michael addition to intermediates [**A**] to generate in situ the intermediates [**B**], which successively form [**C**] via the novel intramolecular N-cyclization by arylamino group attacking the cyano group with less steric hindrance between the arylamino and cyano groups, rather than [**C**]′, which could be given by amino group attacking the carbonyl carbon of aroyl group as in previous reports.[16] Next, the intermediates [**C**] would undergo a rapid imine−amine tautomerization to give [**D**], and 1,2,3,4-tetrahydropyridines **4** are obtained. Finally, an intramolecular S_NAr reaction of the *ortho*-halogen by attack of mercapto group leads to a new and highly functionalized thiochromenopyridines **5** with elimination of a molecular HX. X-ray analysis of **4i** and **5a** reveals that there exist intramolecular hydrogen bonds between amino on the pyridine ring and carbonyl from **3**, helping to further stabilize the structures of the products, which further corroborate our proposed mechanism.

CONCLUSION

In summary, we have developed an efficient method for the synthesis of tetrahydropyridine or thiochromeno[2,3-*b*]-pyridine derivatives from readily accessible starting materials. The three-component reaction of *β*-aroylthioacetanilides or *β*-(2-haloaroyl)thioacetanilides, aldehydes, and aroylacetonitriles proceeds smoothly under DABCO-catalyzed conditions. This synthetic approach has the prominent features of high chemo-, regio-, and stereoselectivity, high efficiency, good yields, as well as broad scope of substrate tolerance. This study not only adds a useful entry to increasingly demanding multicomponent reactions, but also provides plenty of novel tetrahydropyridine or thiochromeno[2,3-*b*]pyridine compounds with structural diversity for further bioassay.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Products 4 and 5 (4a). A mixture of 3-oxo-*N*,3-diphenylpropanethioamide **1a** (1 mmol, 0.255 g), 4-chlorobenzaldehyde **2a** (1.2 mmol, 0.169 g), and 3-oxo-3-phenylpropanenitrile **3a** (1 mmol, 0.145 g) was refluxed for 5.5 h in EtOH (15 mL) containing DABCO (0.5 mmol, 0.110 g). After completion of the reaction as indicated by TLC (petroleum ether−EtOAc, 2:1, v/v), the mixture was cooled to room temperature, and the solid product was filtered, washed with EtOH, and subsequently dried and recrystallized from EtOH to give the pure product **4a**.

((3*R*,4*R*)-6-Amino-4-(4-chlorophenyl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-diyl)bis(phenylmethanone)

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(4a). Yellow powder: mp 243−245 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.16 (s, 1H), 5.58 (d, J = 2 Hz, 1H), 6.35−8.08 (m, 19H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 40.9, 67.9, 88.1, 125.0, 128.0, 128.7, 128.9, 129.2, 129.4, 129.7, 130.1, 130.3, 130.8, 132.1, 134.3, 134.9, 138.7, 140.4, 141.4, 156.5, 192.3, 196.3, 201.8; IR (KBr) υ 3440, 3059, 2924, 1673, 1615, 1597, 1489, 1459, 1305, 1195, 1124, 774, 701, 604 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{24}ClN_2O_2S$, 523.1247, found 523.1262.

((3*R*,4*S*)-6-Amino-4-(2-chlorophenyl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-diyl)bis(phenylmethanone) (4b). Yellow powder: mp 258−259 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.33 (d, J = 1.5 Hz, 1H), 5.28 (d, J = 1.5 Hz, 1H), 6.37−7.96 (m, 19H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 39.0, 65.8, 88.6, 124.9, 128.0, 128.4, 128.5, 128.8, 129.3, 129.6, 129.8, 130.2, 130.4, 130.9, 132.3, 134.1, 135.7, 138.2, 138.7, 141.4, 157.2, 192.2, 196.9, 201.4; IR (KBr) υ 3408, 3060, 2926, 1674, 1615, 1580, 1489, 1461, 1359, 1312, 1262, 1194, 1122, 978, 756, 693, 601 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{24}ClN_2O_2S$, 523.1247, found 523.1251.

((3*R*,4*S*)-6-Amino-4-(2,4-dichlorophenyl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-diyl)bis(phenylmethanone) (4c). Yellow powder: mp 247−249 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.26 (d, J = 2 Hz, 1H), 5.24 (d, J = 2 Hz, 1H), 6.34−7.93 (m, 18H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 38.7, 65.6, 88.3, 124.8, 128.1, 128.5, 128.8, 129.4, 129.8, 130.3, 130.9, 131.3, 133.2, 133.3, 134.1, 135.6, 137.5, 138.7, 141.3, 157.1, 192.2, 196.7, 201.2; IR (KBr) υ 3435, 3061, 2927, 1671, 1616, 1490, 1456, 1301, 1193, 1123, 697, 604 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{23}Cl_2N_2O_2S$, 557.0857, found 557.0853.

((3*R*,4*R*)-6-Amino-4-(3-bromophenyl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-diyl)bis(phenylmethanone) (4d). Yellow powder: mp 244−245 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (d, J = 2 Hz, 1H), 5.41 (d, J = 2 Hz, 1H), 6.59−7.96 (m, 19H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.3, 67.4, 88.8, 123.1, 125.3, 125.5, 127.7, 128.1, 128.4, 128.6, 129.1, 129.8, 130.1, 130.2, 130.6, 130.8, 133.7, 134.8, 138.2, 140.9, 144.0, 155.8, 193.8, 194.8, 200.4; IR (KBr) υ 3395, 3052, 2988, 1685, 1612, 1458, 1294, 1201, 1123, 694, 601 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{24}BrN_2O_2S$, 567.0742, found 567.0742.

((3*R*,4*R*)-6-Amino-4-(3-fluorophenyl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-diyl)bis(phenylmethanone) (4e). Yellow powder: mp 233−235 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.17 (d, J = 2 Hz, 1H), 5.61 (d, J = 2 Hz, 1H), 6.34−8.07 (m, 19H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 41.1, 67.7, 88.1, 114.2, 114.4, 114.6, 123.5, 125.1, 127.9, 128.7, 128.9, 129.7, 130.1, 130.8, 131.3, 134.3, 134.9, 138.7, 141.4, 144.5, 156.5, 161.8, 163.8, 192.3, 196.2, 201.8; IR (KBr) υ 3447, 3396, 3060, 2985, 1683, 1612, 1489, 1458, 1357, 1303, 1198, 1123, 693, 601 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{24}FN_2O_2S$, 507.1543, found 507.1533.

((3*R*,4*R*)-6-Amino-4-(4-fluorophenyl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-diyl)bis(phenylmethanone) (4f). Yellow powder: mp 248−249 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.14 (s, 1H), 5.56 (d, J = 1.5 Hz, 1H), 6.34−8.06 (m, 19H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 40.7, 68.1, 88.4, 115.9, 116.1, 125.1, 127.9, 128.7, 128.9, 129.4, 129.5, 129.7, 130.1, 130.8, 134.3, 134.9, 137.5, 138.7, 141.4, 156.3, 156.4, 160.6, 162.5, 192.4, 196.3, 201.9; IR (KBr) υ 3424, 3062, 2914, 1677, 1621, 1581, 1504, 1460, 1354, 1308, 1198, 1122, 696, 603 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{24}FN_2O_2S$, 507.1543, found 507.1521.

((3*R*,4*R*)-6-Amino-1,4-diphenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-diyl)bis(phenylmethanone) (4g). Yellow powder: mp 244−245 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.21 (d, J = 1 Hz, 1H), 5.60 (d, J = 1 Hz, 1H), 6.89−8.09 (m, 20H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 41.4, 68.1, 88.4, 125.2, 127.4, 127.5, 127.9, 128.6, 128.8, 129.3, 129.7, 130.1, 130.8, 134.3, 135.0, 138.8, 141.5, 156.2, 156.3, 156.4, 192.4, 196.3, 201.9; IR (KBr) υ 3439, 3066, 2856, 1673, 1617, 1596, 1459, 1351, 1312, 1296, 1193, 1124, 697, 604 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{25}N_2O_2S$, 489.1637, found 489.1619.

((3*R*,4*R*)-6-Amino-4-(benzo[*d*][1,3]dioxol-5-yl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-diyl)bis(phenylmethanone) (4h). Yellow powder: mp 240−242 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.11 (d, J = 2 Hz, 1H), 5.59 (d, J = 2 Hz, 1H), 6.04 (s, 2H), 6.41−8.09 (m, 18H); ^{13}C NMR (125 MHz DMSO-d_6) δ 41.1, 68.2, 88.7, 101.6, 107.8, 108.7, 120.4, 125.2, 127.9, 128.6, 128.8, 129.6, 130.0, 130.8, 134.2, 135.0, 135.2, 138.8, 141.5, 146.7, 148.2, 156.4, 192.3, 196.3, 202.0; IR (KBr) υ 3437, 3057, 2891, 1683, 1620, 1483, 1462, 1356, 1298, 1196, 1121, 1040, 775, 700, 601 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{32}H_{25}N_2O_4S$, 533.1535, found 533.1538.

((3*R*,4*R*)-6-Amino-1-phenyl-2-thioxo-4-*p*-tolyl-1,2,3,4-tetrahydropyridine-3,5-diyl)bis(phenylmethanone) (4i). Yellow powder: mp 251−252 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.29 (s, 3H), 4.16 (s, 1H), 5.56 (s, 1H), 6.39−8.07 (m, 19H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.0, 41.0, 68.3, 88.4, 125.2, 127.3, 127.9, 128.6, 128.8, 129.7, 129.9, 130.1, 130.3, 130.7, 134.3, 134.9, 136.5, 138.4, 138.8, 141.5, 156.5, 192.3, 196.4, 202.0; IR (KBr) υ 3439, 3066, 2856, 1673, 1617, 1596, 1459, 1351, 1312, 1296, 1193, 1124, 697, 604 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{32}H_{27}N_2O_2S$, 503.1788, found 503.1780.

((3*R*,4*R*)-6-Amino-4-(4-methoxyphenyl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyridine-3,5-diyl)bis(phenylmethanone) (4j). Yellow powder: mp 223−225 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.73 (s, 3H), 4.11 (d, J = 2 Hz, 1H), 5.53 (d, J = 2 Hz, 1H), 6.37−8.04 (m, 19H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 55.5, 68.4, 88.8, 114.6, 125.3, 127.9, 128.5, 128.7, 128.8, 129.7, 130.1, 130.8, 133.3, 134.3, 135.1, 138.9, 141.6, 156.4, 158.6, 192.4, 196.3, 202.1; IR (KBr) υ 3412, 3066, 2920, 1683, 1611, 1508, 1457, 1305, 1199, 1123, 696, 669, 604 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{32}H_{27}N_2O_3S$, 519.1733, found 519.1742.

((3*R*,4*R*)-6-Amino-4-(3-methoxyphenyl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyridine-3,5-diyl)bis(phenylmethanone) (4k). Yellow powder: mp 225−226 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 4.27 (d, J = 2 Hz, 1H), 5.48 (d, J = 2 Hz, 1H), 6.64−7.97 (m, 19H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.5, 55.3, 67.6, 89.4, 111.9, 113.6, 119.2, 125.5, 127.7, 128.2, 128.5, 129.1, 129.9, 130.1, 130.5, 130.7, 133.6, 134.9, 138.4, 141.1, 143.4, 155.7, 160.1, 194.0, 195.1, 201.0; IR (KBr) υ 3401, 2921, 2851, 1682, 1614, 1456, 1304, 1198, 1123, 695, 669, 602 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{32}H_{27}N_2O_3S$, 519.1743, found 519.1742.

((4*R*,5*R*)-2-Amino-4-(4-chlorophenyl)-5-(4-fluorobenzoyl)-1-phenyl-6-thioxo-1,4,5,6-tetrahydropyridin-3-yl)(phenyl)-methanone (4l). Yellow powder: mp 233−234 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (d, J = 2 Hz, 1H), 5.38 (d, J = 2 Hz, 1H), 6.63−7.99 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.1, 67.4, 88.9, 116.2, 116.4, 125.2, 127.7, 128.2, 128.7, 129.2, 129.7, 130.2, 130.6, 131.1, 133.3, 138.1, 140.0, 140.9, 155.7, 165.1, 167.0, 193.2, 193.8, 200.1; IR (KBr) υ 3447, 2852, 1682, 1615, 1457, 1294, 1198, 1124, 701, 669, 602 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{23}ClFN_2O_2S$, 541.1153, found 541.1162.

((4*R*,5*R*)-2-Amino-5-(4-chlorobenzoyl)-4-(4-chlorophenyl)-1-phenyl-6-thioxo-1,4,5,6-tetrahydropyridin-3-yl)(phenyl)-methanone (4m). Yellow powder: mp 223−224 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (d, J = 2 Hz, 1H), 5.36 (d, J = 2 Hz, 1H), 6.61−7.87 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.1, 67.5, 88.8, 125.2, 127.8, 128.2, 128.7, 129.3, 129.4, 129.7, 130.2, 130.6, 133.1, 133.3, 138.1, 139.9, 140.3, 140.8, 155.7, 193,7, 200.0; IR (KBr) υ 3423, 3061, 2927, 1684, 1613, 1457, 1356, 1304, 1199, 1124, 700, 604 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{23}Cl_2N_2O_2S$, 557.0868, found 557.0857.

((4*R*,5*R*)-2-Amino-5-(4-bromobenzoyl)-4-(4-chlorophenyl)-1-phenyl-6-thioxo-1,4,5,6-tetrahydropyridin-3-yl)(phenyl)-methanone (4n). Yellow powder: mp 240−242 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (d, J = 2 Hz, 1H), 5.34 (d, J = 2 Hz, 1H), 6.60−7.77 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.0, 67.5, 88.8, 125.2, 127.8, 128.2, 128.7, 129.0, 129.3, 129.7, 129.8, 130.2, 130.6, 132.4, 133.3, 133.5, 138.0, 139.9, 155.7, 193.7, 193.9, 200.0; IR (KBr) υ 3428, 2923, 2852, 1684, 1615, 1457, 1357, 1305, 1199, 1124, 700, 604 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{23}BrClN_2O_2S$, 601.0352, found 601.0359.

((4*R*,5*R*)-2-Amino-4-(4-chlorophenyl)-5-(4-methylbenzoyl)-1-phenyl-6-thioxo-1,4,5,6-tetrahydropyridin-3-yl)(phenyl)-methanone (4o). Yellow powder: mp 224−225 °C; ^{1}H NMR (500

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MHz, $CDCl_3$) δ 2.48 (s, 3H), 4.28 (d, J = 2 Hz, 1H), 5.41 (d, J = 2 Hz, 1H), 6.60−7.85 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 41.1, 67.3, 89.0, 125.3, 127.7, 128.1, 128.2, 128.6, 129.2, 129.8, 130.2, 130.7, 132.1, 133.1, 138.2, 140.2, 140.9, 144.8, 155.7, 193.8, 194.5, 200.9; IR (KBr) υ 3423, 2925, 2854, 1675, 1618, 1457, 1356, 1305, 1195, 1126, 701, 603 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{32}H_{26}ClN_2O_2S$, 537.1404, found 537.1400.

((4*R*,5*R*)-2-Amino-4-(4-chlorophenyl)-5-(4-methoxybenzoyl)-1-phenyl-6-thioxo-1,4,5,6-tetrahydropyridin-3-yl)(phenyl)-methanone (4p). Yellow powder: mp 245−246 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.28 (d, J = 1.5 Hz, 1H), 5.41 (d, J = 1.5 Hz, 1H), 6.63−7.95 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.2, 55.6, 67.1, 89.1, 114.3, 125.4, 127.5, 127.7, 128.1, 128.2, 128.5, 129.1, 129.8, 130.1, 130.6, 130.8, 133.1, 138.3, 140.3, 141.0, 155.7, 164.1, 193.1, 193.8, 201.0; IR (KBr) υ 3424, 2922, 2851, 1670, 1613, 1600, 1458, 1306, 1199, 1171, 1125, 702, 603 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{32}H_{26}ClN_2O_3S$, 553.1353, found 553.1372.

((3*R*,4*S*)-6-Amino-4-(2,4-dichlorophenyl)-5-(4-methylbenzoyl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyridin-3-yl)(phenyl)-methanone (4q). Yellow powder: mp 243−244 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (s, 3H), 4.52 (d, J = 2 Hz, 1H,), 5.35 (d, J = 2 Hz, 1H), 6.47−8.01 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 38.7, 65.1, 89.1, 125.0, 127.5, 128.0, 128.4, 128.5, 128.7, 129.7, 130.0, 130.1, 130.2, 130.6, 130.7, 133.4, 133.5, 133.9, 135.5, 137.1, 137.8, 138.1, 138.6, 156.5, 193.8, 195.9, 200.6; IR (KBr) υ 3448, 3063, 2923, 1677, 1612, 1453, 1303, 1195, 1122, 1048, 750, 696, 599 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{32}H_{25}Cl_2N_2O_2S$, 571.1008, found 571.1013.

(*R*)-2-Amino-3-benzoyl-8-chloro-4-(4-chlorophenyl)-1-phenyl-1*H*-thio-chromeno[2,3-*b*]pyridin-5(4*H*)-one (5a). Pale yellow powder: mp 265−267 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.55 (s, 1H), 6.95−7.24 (m, 6H), 7.39−8.19 (m, 11H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 36.9, 88.9, 117.6, 126.6, 126.9, 127.6, 128.6, 128.7, 128.9, 129.4, 130.3, 131.1, 131.2, 131.5, 132.0, 134.4, 134.9, 137.2, 142.2, 145.8, 148.3, 155.2, 176.8, 192.9; IR (KBr) υ 3462, 3062, 1612, 1581, 1487, 1446, 1389, 1271, 1223, 1137, 699 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{21}Cl_2N_2O_2S$, 555.0701, found 555.0720.

(*R*)-2-Amino-3-benzoyl-8-chloro-4-(2-chlorophenyl)-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5b). Yellow powder: mp 170−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (s, 1H), 6.65−6.98 (m, 3H), 7.15−8.23 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.4, 88.5, 115.1, 125.1, 125.7, 126.7, 127.4, 127.6, 128.0, 128.5, 129.1, 130.2, 130.4, 131.1, 131.8, 132.9, 133.7, 134.2, 137.6, 141.7, 141.8, 148.1, 153.7, 177.6, 195.3; IR (KBr) υ 3455, 3060, 1617, 1583, 1489, 1446, 1390, 1266, 1226, 1138, 757, 699 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{21}Cl_2N_2O_2S$, 555.0701, found 555.0728.

(*R*)-2-Amino-3-benzoyl-4-(4-bromophenyl)-8-chloro-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5c). Yellow powder: mp 275−277 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.53 (s, 1H), 6.89−7.17 (m, 4H), 7.35−8.18 (m, 13H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 36.9, 88.8, 126.6, 126.9, 127.5, 128.5, 129.2, 129.4, 130.3, 131.0, 131.4, 131.6, 131.9, 134.3, 134.9, 137.2, 142.1, 146.1, 148.3, 155.2, 170.7, 176.7, 192.8; IR (KBr) υ 3463, 3062, 1621, 1579, 1484, 1445, 1388, 1266, 1273, 1223, 1137, 698 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{21}BrClN_2O_2S$, 599.0196, found 599.0188.

(*R*)-2-Amino-3-benzoyl-8-chloro-4-(3-fluorophenyl)-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5d). Yellow powder: mp 244−245 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.57 (s, 1H), 6.52−6.93 (m, 3H), 7.17−8.19 (m, 14H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 37.2, 88.7, 113.4, 113.6, 113.7, 117.2, 123.0, 126.6, 126.9, 127.4, 128.6, 129.4, 130.3, 130.9, 131.0, 131.5, 132.0, 134.3, 134.9, 137.2, 142.1, 148.4, 149.7, 155.1, 161.3, 163.2, 176.8, 192.8; IR (KBr) υ 3454, 3053, 1610, 1581, 1541, 1484, 1445, 1388, 1351, 1271, 1220, 1136, 697 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{21}ClFN_2O_2S$, 539.0996, found 539.0981.

(*S*)-2-Amino-3-benzoyl-8-chloro-4-(2-fluorophenyl)-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5e). Yellow powder: mp 251−253 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.65 (s, 1H), 6.51−6.99 (m, 3H), 7.09−8.11 (m, 14H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 35.3, 88.0, 115.0, 115.9, 116.1, 123.8, 126.5, 126.9, 127.4, 128.4, 128.5, 129.2, 130.1, 131.0, 131.1, 131.4, 131.9, 132.5, 132.6, 134.6, 134.8, 137.1, 142.3, 148.7, 154.6, 154.7, 160.4, 162.4, 176.5, 193.1; IR (KBr) υ 3458, 3055, 1620, 1580, 1542, 1487, 1444, 1388, 1352, 1269, 1228, 1139, 752, 696 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{21}ClFN_2O_2S$, 539.0996, found 539.0983.

(*R*)-2-Amino-3-benzoyl-8-chloro-4-(4-nitrophenyl)-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5f). Yellow powder: mp 203−206 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.65 (s, 1H), 7.14−7.17 (m, 4H), 7.39−8.16 (m, 13H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 37.8, 88.2, 116.5, 124.1, 126.6, 126.8, 127.3, 128.3, 128.7, 129.4, 130.2, 131.1, 131.4, 132.0, 134.1, 134.9, 137.3, 142.0, 146.3, 148.9, 154.2, 155.0, 176.6, 192.8; IR (KBr) υ 3455, 3061, 1615, 1583, 1518, 1446, 1389, 1346, 1267, 1223, 700 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{21}ClN_3O_4S$, 566.0941, found 566.0961.

(*R*)-2-Amino-3-benzoyl-8-chloro-1,4-diphenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5g). Yellow powder: mp 217−220 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.59 (s, 1H), 6.96−8.19 (m, 18H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 37.3, 89.4, 118.0, 126.6, 126.7, 127.0, 127.1, 127.6, 128.6, 128.8, 129.4, 130.3, 131.0, 131.5, 131.9, 134.5, 134.9, 137.2, 142.2, 146.9, 148.0, 155.3, 176.8, 192.8; IR (KBr) υ 3435, 3051, 2923, 1612, 1585, 1489, 1442, 1391, 1355, 1218, 1135, 832, 747, 700 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{22}ClN_2O_2S$, 521.1091, found 521.1098.

(*R*)-2-Amino-3-benzoyl-8-chloro-1-phenyl-4-p-tolyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5h). Yellow powder: mp 247−248 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.17 (s, 3H), 5.57 (s, 1H), 6.88−6.99 (m, 4H), 7.21−8.19 (m, 13H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.0, 36.7, 89.3, 118.2, 126.5, 126.8, 127.0, 127.6, 128.4, 129.3, 130.2, 130.9, 131.4, 131.8, 134.5, 134.9, 135.6, 137.1, 142.2, 143.9, 147.7, 155.3, 176.8, 192.7; IR (KBr) υ 3409, 3048, 1616, 1580, 1536, 1489, 1445, 1395, 1353, 1274, 1226, 1136, 700 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{32}H_{24}ClN_2O_2S$, 535.1247, found 535.1255.

(*R*)-2-Amino-3-benzoyl-8-chloro-4-(4-methoxyphenyl)-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5i). Yellow powder: mp 234−235 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3H), 5.69 (s, 1H), 6.70−8.34 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.5, 55.1, 90.5, 113.6, 119.1, 125.2, 126.7, 127.9, 128.0, 128.1, 128.2, 129.1, 130.5, 130.6, 131.0, 131.6, 134.3, 134.4, 137.6, 138.6, 141.4, 146.3, 154.2, 158.1, 177.5, 195.0; IR (KBr) υ 3448, 2929, 1614, 1582, 1507, 1490, 1447, 1265, 1224, 1137, 831, 701 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{32}H_{24}ClN_2O_3S$, 551.1213, found 551.1196.

(*R*)-2-Amino-3-benzoyl-4-(4-chlorophenyl)-8-fluoro-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5j). Yellow powder: mp 238−240 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (s, 1H), 6.97−8.45 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.0, 89.9, 111.9, 112.1, 115.8, 116.0, 118.1, 126.1, 126.7, 128.3, 128.4, 128.7, 129.3, 130.6, 131.1, 131.8, 132.0, 132.0, 134.2, 135.0, 135.1, 141.3, 144.8, 146.7, 154.3, 162.8, 164.9, 177.4, 195.0; IR (KBr) υ 3467, 2925, 1618, 1592, 1480, 1447, 1271, 1224, 1136, 700, 608 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{21}ClFN_2O_2S$, 539.0996, found 539.0986.

(*R*)-2-Amino-3-benzoyl-4-(4-chlorophenyl)-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5k). Yellow powder: mp 247−248 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.59 (s, 1H), 6.97−8.23 (m, 18H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 36.9, 70.5, 89.0, 117.6, 127.0, 127.3, 128.3, 128.4, 128.6, 128.7, 128.9, 129.4, 131.1, 131.4, 131.9, 132.3, 133.2, 134.6, 136.7, 142.2, 146.0, 148.3, 155.4, 177.5, 192.8; IR (KBr) υ 3443, 3065, 2922, 1615, 1590, 1488, 1439, 1364, 1268, 1223, 1137, 701 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{31}H_{22}ClN_2O_2S$, 521.1075, found 521.1091.

(*R*)-2-Amino-3-benzoyl-8-(4-chlorophenoxy)-4-(4-chlorophenyl)-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5l). Yellow powder: mp 248−250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (s, 1H), 6.83−8.39 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.9, 89.9, 112.7, 118.1, 121.6, 124.7, 126.7, 128.3, 128.6, 129.2, 130.2, 130.5, 131.0, 131.3, 131.7, 131.9, 134.2, 135.0, 141.3, 144.8, 146.5, 153.7, 154.3, 159.9, 177.5, 194.8; IR (KBr) υ 3450, 2927, 1615, 1582, 1487, 1447, 1248, 1220, 1090, 701 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{37}H_{25}Cl_2N_2O_3S$, 647.0963, found 647.0975.

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(*R*)-2-Amino-4-(4-bromophenyl)-6-chloro-3-(4-chlorobenzoyl)-9-fluoro-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5m). Yellow powder: mp 278−279 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.61 (s, 1H), 6.96−7.67 (m, 15H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 36.9, 89.5, 116.4, 116.6, 119.0, 120.4, 124.6, 126.7, 128.1, 128.6, 128.9, 130.4, 131.3, 131.5, 132.0, 133.6, 135.2, 139.5, 140.2, 143.8, 144.9, 154.4, 155.0, 156.9, 177.2, 193.4; IR (KBr) υ 3443, 2927, 1617, 1592, 1487, 1445, 1263, 1225, 1137, 824, 775, 700 cm^{-1}; HRMS (ESI-TOF, [M + Na]$^+$) calcd for $C_{31}H_{18}BrCl_2FN_2O_2SNa$, 672.9526, found 672.9533.

(*R*)-2-Amino-4-(benzo[*d*][1,3]dioxol-5-yl)-8-chloro-3-(4-chlorobenzoyl)-1-phenyl-1*H*-thiochromeno[2,3-*b*]pyridin-5(4*H*)-one (5n). Yellow powder: mp 279−280 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (s, 1H), 5.89 (d, 2H), 6.59−8.38 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.8, 90.1, 100.8, 107.7, 107.9, 118.7, 120.1, 125.3, 127.8, 128.0, 128.3, 128.4, 130.5, 131.1, 131.7, 134.0, 134.3, 135.2, 137.7, 139.6, 140.0, 146.1, 146.5, 147.6, 154.4, 177.5, 193.3; IR (KBr) υ 3448, 2924, 1615, 1582, 1487, 1444, 1268, 1223, 1134, 928, 797, 698 cm^{-1}; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{32}H_{21}Cl_2N_2O_4S$, 599.0594, found 599.0591.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, ORTEP drawings of compounds **4i** and **5a**, ^{1}H and ^{13}C NMR spectra of all new compounds, and X-ray data for compounds **4i** and **5a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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