Diversification of a Thieno[2,3-*d*]pyrimidin-4-one Scaffold via Regioselective Alkylation Reactions

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The 2-aryl-2,3,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-ones and 2-aryl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones have been diversified by alkylation reactions, applying benzylchlorides and N-substituted 2-chloroacetamides as alkylating agents. Under the found uniform conditions the substitution direction does not depend on the structure of the alkylating agent and gives monoalkylated products in high yields with simple workup. The alkylation of the 2,3-dihydropyrimidin-4(1*H*)-one derivatives proceeds onto the N1-position; however, in the case of pyrimidin-4(3*H*)-ones the O-alkylated products are formed selectively. An alternative strategy for the synthesis of the N1-benzyl-2,3-dihydropyrimidin-4(1*H*)-one derivatives is also developed. It applies the redaction of N2-substituted Gewald's amides with aromatic aldehydes and allows simple introduction of various substituents in the final molecule.

Introduction

Synthesis of fused thieno[2,3-*d*]pyrimidine derivatives has been widely reported over the last years. They were shown to possess antiviral[1,2] and antibacterial activity.[3−6] Their remarkable medicinal properties cover also anti-inflammatory[7−9] and antihistaminic[10] action. Moreover, among other thieno[2,3-*d*]pyrimidin-4-ones of these family, the compound **1** was recently identified as inhibitor of tumor cells proliferation.[11] Diversification of this scaffold using its cyclohexane moiety afforded another potent derivative **2** displaying IC_{50} of 91 nM in the p21-deficient cell line[12] (Chart 1). The same core compound are found to be phosphodiesterase PDE9 inhibitors, for example, **3**.[13,14] Such inhibitors can be applied for treating memory deficits that are associated with aging and neurodegenerative disorders such as Alzheimer's disease.[15] Thereby, a combinatorial approach to structural analogs of the compound **3** was recently developed.[16] This route applies reactivity of corresponding 2-aminothiophen-3,5-dicarboxylates in reactions with (hetero)aromatic and aliphatic nitriles.

Another strategy for the construction of the thieno[2,3-*d*]pyrimidine skeleton, applying reactivity of Gewald's Amide with aromatic aldehydes, has been also suggested by our group (Scheme 1).[17] The application of aldehydes under different conditions allows isolation of three possible products **4**−**6** from these reactions, including the dihydropyrimidin-4-one derivatives **5** that have not been described before. In the current work, we aimed to develop efficient protocols for diversification of the scaffolds **5** and **6** via regioselective alkylation reactions.

A literature survey about the alkylation of such thieno[2,3-*d*]pyrimidin-4-ones **5** showed ambiguous results. Structurally they have three nucleophilic centers: two nitrogen atoms of pyrimidine fragment and one carbonyl oxygen. All of them turned out can be attacked by a variety of alkylating agents under different conditions. In the case of structurally similar quinazolin-4-ones, N3/O-alkylation proceeds preferably. A steric effect of bulky C2-substituents in such quinazolones has often been claimed as a reason for hindering the N-alkylation.[18−20] Substitution on the N3-atom can be easily carried out for 2-benzyl[18] and 2-chloromethyl[21] derivatives. 2-Allylthioquinazolinones and thieno[2,3-*d*]pyrimidinones undergo both N3- and N1-alkylation and two kinds of products can be obtained under different conditions.[22] Preferable intramolecular N1-alkylation is also proved for 4-chloro-3-oxo-2-(4-oxo-1,2,4,5-tetrahydro-2-quinazolinylidene)-butanenitrile.[23] Though, the direction of such electrophilic substitution is known to depend on both the steric and electronic factors. It is rather difficult to take them into account and undoubtedly predict the correct reaction pathway. Thus, the structural elucidation of such products often requires evidence additional to routine for novel reactions.

Results and Discussion

In continuation of our study on Gewald's Amide transformations in the reactions with carbonyl compounds as an efficient strategy for diverse thieno[2,3-*d*]pyrimidine derivatives,[17] we have investigated regioselectivity of their alkylation by various alkylating reagents, substituted benzylchlorides **7**, and chloroacetoanilides **11**, which were suitable

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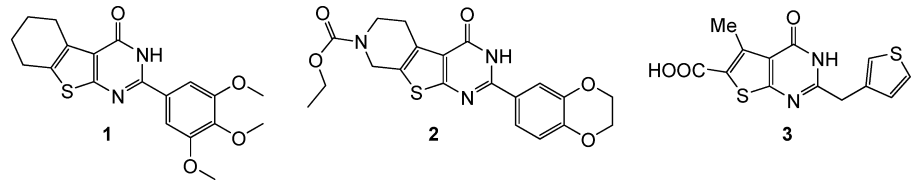
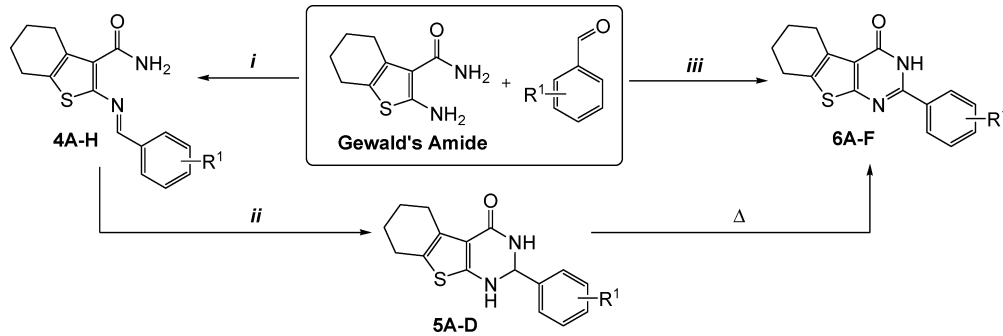
Chart 1



Scheme 1. Preparation of the Initial Substances **4**−**6** (Table 1)[a]



[a] Reagents and conditions: (i) 2-PrOH, piperidine, MW 120 °C, 300 s; (ii) NaH, DMF, rt, 1−2 min; (iii) DMF, KOH, MW 180 °C, 300 s or reflux, 20 min.

Table 1. Individual Initial Compounds **4**−**6** (Scheme 1)

compound	R^1	yield[a], %
4A	4-NMe_2	91
4B	4-OMe	95
4C	H	95
4D	4-Me	98
4E	3-F	92
4F	3,4-di-OMe	98
4G	5-Br-2-OH	87
4H	4-OH-3-OMe	90
5A	4-NMe_2	84
5B	4-OMe	86
5C	H	79
5D	4-Me	83
6A	4-OMe	81
6B	4-Me	75
6C	4-Br	79
6D	4-NO_2	85
6E	4-F	69
6F	4-Cl	65

[a] The isolated yields are calculated on the initial Gewald's Amide.

Table 2. Initial Benzylchlorides **7** and 2-Chloro-N-R^4-acetamides **11**

compound	R^2
7a	3,4-di-OMe
7b	4-OMe
7c	H
7d	4-Me
7e	3-F
7f	3-Me
7g	3-CF_3
	R^4
11a	3,5-di-MeO-C_6H_3
11b	4-Me-C_6H_4−CH_2
11c	C_6H_5
11d	4-NO_2−C_6H_4
11e	4-MeO-C_6H_4
11f	4−F-C_6H_4
11g	3-MeS-C_6H_4
11h	2-EtO-C_6H_4
11i	Cyclohexyl

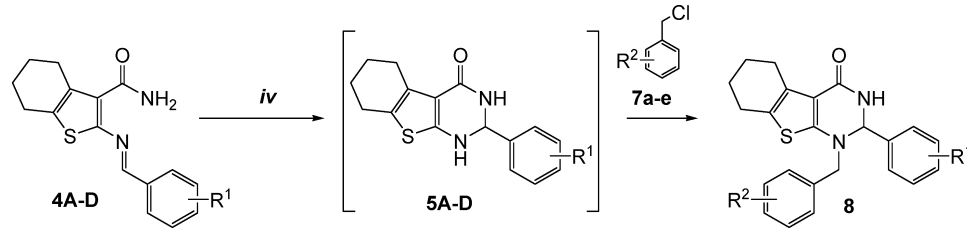
because they had similar reactivity and could be applied under uniform reaction conditions in parallel synthesis.[19]

The initial compounds **4**−**6** (Table 1) were obtained in high yields according to our previously described procedures[17] (Scheme 1).

We began our study from alkylation of the 2-aryl-2,3,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **5** using the benzylchlorides **7** (Table 2). We have already noticed the capability of the dihydropyrimidin-4-ones **5** to undergo oxidation into the corresponding pyrimidin-4-ones **6** even under mild heating.[17] To avoid such side transformations an appropriate reaction medium had to be chosen for the alkylation (solvent and base). It was necessary that the initial reagents could be easily dissolved and the final product simply isolated. As our first attempt, we tested reaction conditions similar to that applied for the cyclization of the azomethenes **4** into the starting dihydropyrimidin-4-ones **5** (DMF/NaH). Thus, stirring a solution of the dihydropyrimidin-4-ones **5** in DMF in the presence of 3.0 equiv of sodium hydride and 1.1 equiv of the benzylchlorides **7** (Table 2) at room temperature led to formation of N1-substituted dihydropyrimidin-4(1*H*)-one derivatives **8** in good yields (52−58% calculated on azomethenes **4**). Even slight increase of the reaction temperature resulted in formation of the oxidated byproduct **6**. Other model reactions using Et_3N/DMF, $NaHCO_3$/DMF, 1,4-dioxane/NaH also led to significant amounts of the byproduct formation or gave much lower yields. The selected reaction conditions (NaH/DMF) allowed the synthesis of the products **8** in one-pot starting from the azomethenes **4** without isolation of the intermediate compounds **5** and, thereby, with higher total transformation yields (Method A, Scheme 2, Table 3).

It is important that being alkylated the dihydropyrimidin-4-ones **8** becomes much more stable toward the oxidation and can be recrystallized from hot solvents and stored in solid state. Their NMR spectra were measured in DMSO-d_6 solutions and no traces of decomposition were observed during storage of these solutions or mild heating during the sample preparation. ^{1}H NMR spectra of the compounds **8** are characterized by singlets corresponded to the methylene

Scheme 2. One-Pot Transformation of Azomethenes **4** into N1-alkylated dihydropyrimidin-4-ones **8** (Method A, Table 3)[a]



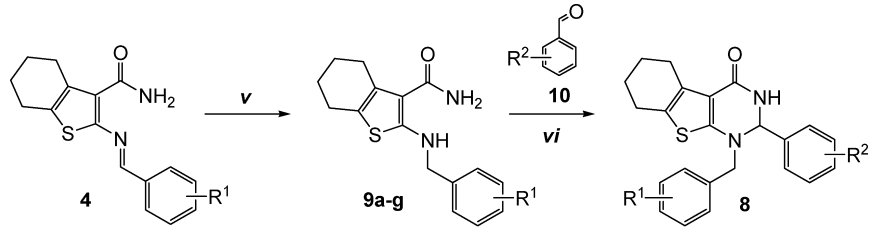
[a] Reagents and conditions: (iv) NaH, DMF, rt, 40 min.

Table 3. Novel 1-Benzyl-2-aryl-2,3,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **8** (Schemes 2 and 3)

compound	R^1	R^2	yield[a], %
8Cb	H	4-OMe	72 (79)
8Bc	4-OMe	H	64 (81)
8Bd	4-OMe	4-Me	68 (84)
8Ae	4-NMe_2	3-F	61 (75)
8 Da	4-Me	3,4-di-OMe	(87)
8Cf	H	5-Br-2-OH	(69)
8Bg	4-OMe	4-OH-3-OMe	(73)

[a] The isolated yields are calculated on the azomethenes **4** and given for Method A (B).

Scheme 3. Benzaldehyde Strategy for the Compounds **8** (Method B, Tables 3 and 4)[a]



The aldehydes **10**: R^2 = H; 4-Me; 4-OMe; 4-NMe_2

[a] Reagents and conditions: (v) $NaBH_4$, 2-PrOH, rt, 30 min; (vi) NaH, dioxane, reflux, 5 min.

Table 4. Novel 2-(Benzylamino)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamides **9** (Scheme 3)

compound	R^1	yield[a], %
9a	3,4-di-OMe	94
9b	4-OMe	91
9c	H	86
9d	4-Me	87
9e	3-F	83
9f	5-Br-2-OH	76
9g	4-OH-3-OMe	81

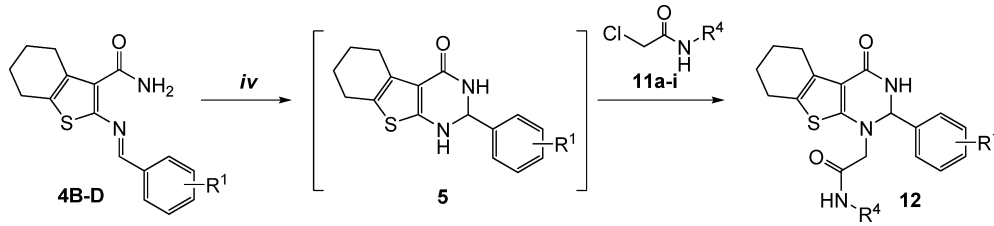
[a] The isolated yields are calculated on the azomethenes **4**.

CH_2 group of benzyl fragment at δ 4.24−4.38 ppm, the methene CH proton signal at δ 5.61−5.71 ppm, and a broad singlet of the NH at δ 7.76−7.98 ppm. The presence of the dihydropyrimidine methene group can be easily identified in ^{13}C NMR spectra by the free-standing signal at δ 70.0−75.0 ppm. These data fully confirm the introduction of the benzyl substituent into the dihydropyrimidin-4-one scaffold, however, it cannot allow estimation of the process direction. As mentioned above, the dihydropyrimidin-4-one fragment of the starting molecules **5** has at least three possible centers for the electrophilic attacks. To determine undoubtedly the structures **8**, we have carried out a counter-synthesis of these compounds **8** (Method B, Scheme 3).

A reduction of the azomethenes **4** with sodium tetrahydroborate ($NaBH_4$) in 2-propanol led to 2-benzylamino Gewald's Amide derivatives **9a**−**g** (Table 4). Further refluxing a mixture of the **9** with sodium hydride and aromatic aldehydes **10** (Scheme 3) in 1,4-dioxane for 5 min resulted in formation of the compounds **8** even in higher isolated yields (Table 3) than by the Method A (Scheme 2) over two reaction steps (Scheme 3). All spectroscopic data, including their IR, ^1H and ^{13}C NMR, and mass-spectrometry spectra, indicate the identity of the substances formed by different methods A and B, which fully confirms the drawn structure of the alkylated dihydropyrimidin-4-ones **8**. In addition to the higher isolated yields, the alternative Method B allows introduction into this novel dihydropyrimidin-4(1*H*)-one scaffold various aldehyde derived substituents. This makes the preparation of the diverse compounds **8** more synthetically and economically flexible. For instance, the aldehyde approach allows the direct synthesis of the compounds **8Cf** and **8Bg** with nucleophilic hydroxyl groups (Table 3), which is not possible, following the Method A, without protection−deprotection stages. In addition, Method B eliminates the environmentally unfavorable HCl formation. Finally, the diversified vicinal amino-amides **9** as reactive 1,5-binucleophiles, and this strategy for easy introduction of the alkyl substituent into 2-aminothiophens, can be utilized in many other synthetic schemes.

The dihydropyrimidin-4-one derivatives **5** were also alkylated by deferent 2-chloro-N-arylacetamides **11** (Table 2), a variety of which hinges on the diversity of available aromatic or aliphatic amines. The reactions were carried out under the same reaction conditions used for the benzylchlorides **7** (NaH/DMF, room temperature, and workup with water, Scheme 4, Table 5).

Scheme 4. Alkylation of Compounds **5** by 2-Chloro-N-arylacetamides **11** (Table 5)[a]



[a] Reagents and conditions: (iv) NaH, DMF, rt, 40 min.

Table 5. Novel 2-(4-Oxo-2-aryl-3,4,5,6,7,8-hexahydro[1]-benzothieno[2,3-*d*]pyrimidin-1(2*H*)-yl)acetamides **12** (Scheme 4).

compound	R^1	R^4	yield[a], %
12Ba	4-OMe	3,5-di-MeO-C_6H_3	76
12Bb	4-OMe	4-Me-C_6H_4−CH_2	73
12Ca	H	3,5-di-MeO-C_6H_3	69
12Ce	H	4-MeO-C_6H_4	64
12De	4-Me	4-MeO-C_6H_4	70

[a] The isolated yields are calculated on the azomethenes **4**.

Since a counter synthesis of the compounds **12** appeared to be not reliable, determination of the regioselectivity for the reaction (Scheme 4) was carried out on the base of NMR correlation experiments (HMQC and HMBC), and comparing the chemical shifts in ^{1}H NMR spectra of the obtained benzothieno[2,3-*d*]pyrimidinones of the series **5**, **8**, and **12**. Thus, the presence of mutual correlations between protons and carbons of methylene CH_2 and methene CH groups in HMBC spectrum of the compound **12Ce** shows that the reaction proceeded onto one of the pyrimidine nitrogen (structures **I** or **II**, Chart 2). Otherwise, in the case of the O-alkylation (structure **III**), such correlations across five bonds would not be observed. Another crucial correlation of the CH_2 protons signal at δ 3.88 ppm and a downfield carbon signal at δ 158.5 ppm was also found. However, it appeared to be impossible to distinguish the structures **I** and **II** from the HMQC and HMBC data, since there were not possibilities to recognize correctly two low field carbon signals of the pyrimidin-4-one carbonyl group and the 2-thiophene carbon at 158.5 and 161.9 ppm (Chart 2). Therefore, the correlation between the CH_2 proton singlet and one of these carbons could be expected for both structures **I** and **II**.

To correctly assign the structures **I** or **II** to the compound **12Ce** we compared the NH proton chemical shifts of the dihydropyrimidin-4-one system for the initial compound **5**, benzyl derivatives **8**, and the problematic case **12** (Table 6). The introduction of the benzyl substituent into the 1-position of the pyrimidine cycle in the compounds **5B** resulted in disappearance of the upfield NH signal and the downfield NH signal was only slightly shifted (about 0.1 ppm, compounds **8**). In the case of acetamide derivatives **12**, such shift was even smaller (0.01 ppm for **12Ba**, **12Ce**, and 0.04 ppm for **12Ca** comparing with **5B** and **5C**, correspondingly). Thus, the downfield NH signal for these three ranges of compounds is unambiguously assigned to the 3-NH and the upfield to the 1-NH correspondingly. It indicates that the electrophilic substitution for both the benzylchlorides **7** and the 2-chloro-N-arylacetamides **12** proceeds onto the 1-amino function of the initial dihydropyrimidin-4-ones **5**. Thereby, the product **12Ce** has the structure **I**. This assignment also gives a possibility to correlate inversely the downfield ^{13}C NMR signals at 158.5 and 161.9 ppm to the 2-thiophene carbon and the pyrimidone carbonyl group, correspondingly (Chart 2).

The next part of our work was directed to diversification of the thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** by the alkylation. From the literature data we could expect formation of two most probable products of N3- and O-electrophilic substitution of the pyrimidin-4-one fragment. The reactions of the compounds **6** with the benzylchlorides **7** (Scheme 5) were found to proceed selectively being carried out by stirring with sodium bicarbonate (2.0 equiv) in DMF at 50 °C for 30 min, giving the individual products **13** in very good isolated yields (Table 7). An application of stronger alkali bases as potassium carbonate K_2CO_3 and sodium hydride NaH resulted in formation of two different regioisomers. The product structures **13** were confirmed by disappearing the absorption bands of the C═O group in IR spectra, which were presented at 1670−1640 cm^{-1} for the starting compounds **6**. The data of the HMQC and HMBC experiments also proved the regioselective O-alkylation of the pyrimidin-4(3*H*)-ones **6**. Thus, in the case of the alternative N3- or N1-substitution, in the HMBC plot for the representative **13Fg**, a correlation between the benzyl CH_2 protons and the quaternary C2 would be observed, but it is absent. And a cross-peak between the CH_2 proton singlet and the C4 carbon signal was presented instead (structure **IV**, Chart 3). Thereby, the IR and correlation NMR data undoubtedly testifies in favor of the O-alkylation.

Alkylation of pyrimidin-4(3*H*)-one derivatives **6** by the 2-chloroacetamides **11** (Scheme 6) was carried out under the same conditions as in the case of the benzylchlorides **7**. Thus, stirring a solution of the initial compounds **6** with the mixture of the alkylating agents **11** (1.1 equiv) in DMF in the presence of $NaHCO_3$ (2.0 equiv) led to formation of N-aryl-2-[(pyrimidin-4-yl)oxy]acetamides **14** in good yields without additional purification stage (Scheme 6, Table 8). The use of stronger alkali bases NaH or K_2CO_3 did not favor the selectivity.

In addition to the routine spectral and analytical methods, the selective O-alkylation (Scheme 6) was proved by the single crystal X-ray diffraction study of the nitro derivative **14Ad** (Chart 4). ^{1}H NMR spectrum of this compound has a characteristic singlet of the CH_2 protons at δ 5.23 ppm, and all the other representatives of the row **14** also have such singlets ranged from δ 5.14 to 5.23 ppm. In light of these facts and the selective formation of the O-benzyl derivatives **13** under the same reaction conditions (Scheme 5), it is

Chart 2. Results of HMBC Experiment for the Compounds 12Ce Excluding O-Alkylation

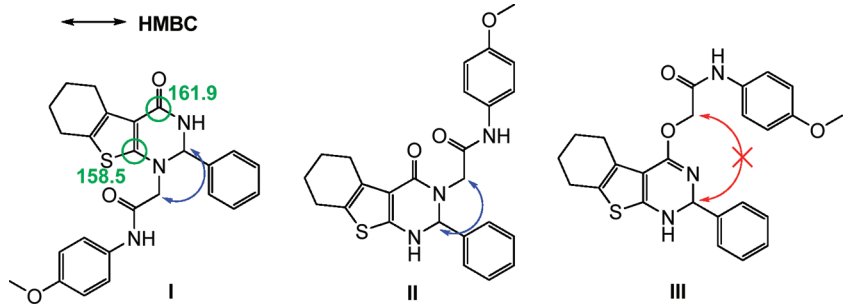
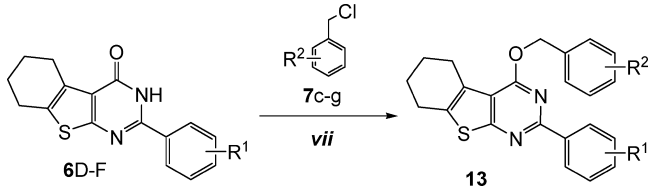


Table 6. Comparison of Chemical Shifts of the NH Protons for the Compounds **5**, **8**, and **12**

compound	R^1	R^2	R^4	NH (downfield) δ, ppm	NH (upfield) δ, ppm
5B	4-OMe			7.68	7.46
8Bc	4-OMe	H		7.83	
8Bd	4-OMe	4-Me		7.83	
12Ba	4-OMe		3,5-di-MeO-C_6H_3	7.66	
5C	H			7.81	7.62
8Cb	H	4-OMe		7.94	
12Ca	H		3,5-di-MeO-C_6H_3	7.85	
12Ce	H		4-MeO-C_6H_4	7.81	

Scheme 5. Synthesis of the O-Alkylated Benzothieno-[2,3-*d*]pyrimidines **13** (Table 7)[a]



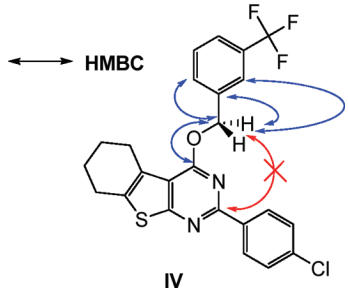
[a] Reagents and conditions: (vii) $NaHCO_3$, DMF, 50 °C, 30 min.

Table 7. Novel 4-(Benzyloxy)-2-phenyl-5,6,7,8-tetrahydro[1]-benzothieno[2,3-*d*]pyrimidines **13** (Scheme 5)

Compound	R^1	R^2	yield,[a] %
13Dc	4-NO_2	H	91
13De	4-NO_2	3-F	86
13Df	4-NO_2	3-Me	89
13Ed	4-F	4-Me	75
13Fg	4-Cl	3-CF_3	72

[a] The isolated yields.

Chart 3. HMBC Results for the Representative 13Fg Confirming O-Alkylation

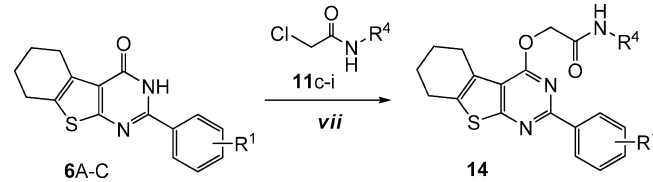


possible to conclude that the alkylation with all applied 2-chloroacetamides **11** also gives the O-alkylated pyrimidones **14** (Scheme 6).

Conclusion

In the present work, we have developed several protocols for diversification of the parent dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-one **5** and thieno[2,3-*d*]pyrimidin-4(3*H*)-one **6**

Scheme 6. O-Alkylation of the Benzothieno-[2,3-*d*]pyrimidines **6** by the 2-Chloro-*N*-acetamides (Table 8)[a]



[a] Reagents and conditions: *vii* $NaHCO_3$, DMF, 50 °C, 30 min.

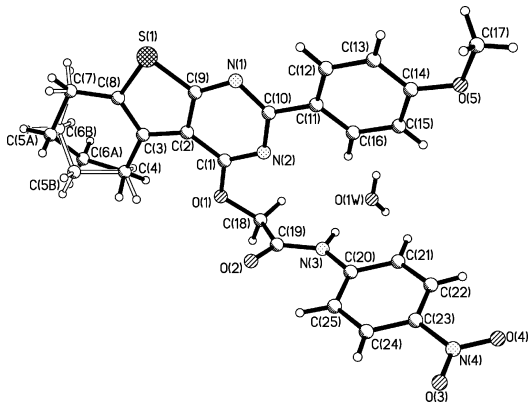
Table 8. Novel *N*-Aryl-2-[(2-aryl-5,6,7,8-tetrahydro[1]-benzothieno[2,3-*d*]pyrimidin-4-yl)oxy]acetamides **14** (Scheme 6)

compound	R^1	R^4	yield,[a] %
14Ad	4-OMe	4-NO_2-C_6H_4	79
14Af	4-OMe	4-F-C_6H_4	65
14Ag	4-OMe	3-MeS-C_6H_4	73
14Bc	4-Me	C_6H_5	71
14Bh	4-Me	2-EtO-C_6H_4	62
14Bi	4-Me	cyclohexyl	76
14Ce	4-Br	4-MeO-C_6H_4	75

[a] The isolated yields.

scaffolds, both available from reactions of Gewald's Amide with the benzaldehydes previously described by us.[17] In the case of unstable initial compounds **5**, the alkylation is carried out in one-pot starting from the azomethenes **4** (Scheme 2), that gives selectively the N1-alkylated products **8** and **12** in good yields and with improved stability. Alternatively, the synthesis of the benzyl derivatives **8** is performed by the aldehyde strategy via N2-benzyl Gewald's Amides **9** (Scheme 3), which can be considered also as useful building-blocks for diversity-orientated studies. The second protocol gives even better overall yields, and it can be applied for substrates containing nucleophilic groups, e.g. hydroxyl. The alkylation of the pyrimidin-4(3*H*)-one ring by both the benzylchlorides **7** and the 2-chloroacetamides **11** is found to proceed selectively as O-electrophilic substitution under the found conditions. Such reaction pathways often cannot be undoubtedly predicted from the published literature on analogous reactions, and the question of the reaction directions requires

Chart 4. Molecular Structure of Compound 14Ad



certain structural investigations in addition to the routine methods for every novel reaction scheme of this kind. Finally, the developed protocols apply the uniform reaction conditions with high yields, simple workup and the substituent tolerance. Therefore, they are suitable for parallel/automated synthesis of diverse libraries for further bioscreening.

Experimental Section

General Information. Initial compounds **4**−**6** were synthesized according to early published procedures.[17] All chemicals were obtained from commercially available sources and used without further purification. All solvents were used as acquired. Melting points were measured with a Buchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury VX 200 instrument using DMSO-d_6 as solvent and TMS as an internal standard. All ^{13}C NMR and 2D NMR experiments were performed using a Bruker AMX 500 spectrometer. IR spectra were recorded on a Specord M-82 instrument (pellets with potassium bromide KBr). The mass spectra were recorded on a Varian 1200 L GC-MS instrument with the use of direct exposure probe (DEP) method with EI at 70 eV. Elemental analysis was carried out on an EuroVector EA-3000 instrument. All the microwave-assisted reactions were carried out in an Emryse Creator EXP microwave system (Biotage, Uppsala) in sealed vessels for microwave synthesis (initial radiation power 300W corresponded to Normal option).

2-(Benzylamino)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamides 9 (General Procedure). A mixture of an appropriate 2-(1-arylmethylene)amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide **4** (2 mmol) and sodium tetrahydroborate (10 mmol) was stirred in 5 mL of 2-propanol for 30 min. To the stirring reaction mixture 2 mL of glacial acetic acid was poured. A yellowish precipitate formed was filtered off and washed with water and dried on air at 100 °C. No additional purification was required. Yields are listed in Table 4.

1-Benzyl-2-aryl-2,3,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-4(1H)-ones 8 (General Procedure). Method A. A mixture of the 2-(1-arylmethylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **4** (2 mmol), and sodium hydride (6 mmol, 60% in mineral oil) was dissolved in 2 mL of DMF at room temperature at stirring. A corresponding benzylchloride **7** (2.2 mmol) was added. The reaction mixture was stirred for 40 min keeping the temperature within range 15−20 °C (cold water bath) and, thereafter, poured into water (2 mL). A crystalline precipitate formed was filtered off and washed with 1,4-dioxane (1 mL) and hot hexane (2 × 2 mL). After drying on air at 100 °C the precipitate did not require additional purification.

Method B. A mixture of appropriate 2-(benzylamino)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamides **9** (2 mmol), aromatic aldehydes **10** (2.2 mmol), and sodium hydride (6 mmol, 60% in mineral oil) was placed into 2 mL of 1,4-dioxane. The reaction mixture was refluxed for 5 min. After the mixture was cooled, the yellowish crystalline precipitate formed was filtered off and washed with 1,4-dioxane (1 mL) and hot hexane (2 × 2 mL). After it was dried in air at 100 °C, the precipitate did not require additional purification. Yields are listed in Table 3.

2-(4-Oxo-2-aryl-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-1(2H)-yl)acetamides 12 (General Procedure). A mixture of an appropriate 2-(1-arylmethylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **4** (2 mmol) and sodium hydride (6 mmol, 60% in mineral oil) was dissolved in 2 mL of DMF at room temperature. The corresponding 2-chloro-*N*-arylacetamides **11** (2.2 mmol) was added. The reaction mixture was stirred for 40 min keeping the temperature within range 15−20 °C (cold water both) and, thereafter, poured into water (2 mL). A crystalline precipitate formed was filtered off and washed with 1,4-dioxane (1 mL) and hot hexane (2 × 2 mL). After drying on air at 100 °C no additional purification was required. Yields are listed in Table 5.

4-(Benzyloxy)-2-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidines 13 (General Procedure). A mixture of the 2-aryl-5,6,7,8-tetrahydro[1]benzothieno-[2,3-*d*]pyrimidin-4(3*H*)-one **6** (2 mmol), sodium bicarbonate (4 mmol), and an appropriate benzylchloride **7** (2.2 mmol) was stirred in 2 mL of DMF at 50 °C for 30 min. Thereafter, the reaction mixture was cooled and poured into water (2 mL). A crystalline precipitate formed was filtered off and washed with hot water (2 × 2 mL) and ethanol (1 mL) and dried on air at 100 °C. A yellowish precipitate obtained did not require additional purification. Yields are listed in Table 7.

***N*-Aryl-2-[(2-aryl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4-yl)oxy]acetamides 14 (General Procedure).** A mixture of the 2-aryl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one **6** (2 mmol), sodium bicarbonate (4 mmol), and an appropriate 2-chloro-*N*-acetamide **11** (2.2 mmol) was stirred in 2 mL of DMF at 50 °C for 30 min. Thereafter, the reaction mixture was cooled and poured into water (2 mL). A crystalline precipitate formed was filtered off and washed with hot water (2 × 2 mL) and ethanol (1 mL) and dried on air at 100 °C. The white precipitate obtained did not require additional purification. Yields are listed in Table 8.

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Supporting Information Available. General procedures for the synthesis of the initial compounds **4**-**6**, the ^{1}H and ^{13}C NMR, IR spectroscopic and mass-spectrometric data, the HMQC and HMBC plots, the X-ray analysis data, including a CIF file, and physicochemical properties of all the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Thakur, C. S.; Jha, B. K.; Dong, B.; Gupta, J. D.; Silverman, K. M.; Mao, H.; Sawai, H.; Nakamura, A. O.; Banerjee, A. K.; Gudkov, A.; Silverman, R. H. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104* (23), 9585–9590.

(2) Silverman, R. *Chem. Abstr.* **2007**, *147*, 496301; Patent WO 2007127212, 2007.

(3) Kapustina, M. V.; Kharizomenova, I. A.; Shvedov, V. I.; Radkevich, T. P.; Shipilova, L. D. *Pharm. Chem. J.* **1992**, *26* (1), 73–75.

(4) Hafez, H. N.; El-Gazzar, A. B. A *Bioorg. Med. Chem. Lett.* **2008**, *18* (19), 5222–5227.

(5) Balasubramanian, N.; Meena, K.; Nitin, J.; Avinash, D.; Chandrasekaran, S. *Bioorg. Med. Chem. Lett.* **2006**, *16* (18), 4951–4958.

(6) Prasad, M. R.; Prashanth, J.; Shilpa, K.; Kishore, D. P. *Chem. Pharm. Bull.* **2007**, *55* (4), 557–560.

(7) Alagarsamy, V.; Vijayakumar, S.; Solomon, V. R. *Biomed. Pharmacother.* **2007**, *61* (5), 285–291.

(8) Alagarsamy, V.; Shankar, D.; Solomon, V. R. *ARKIVOC* **2006**, *16*, 149–159.

(9) Manhas, M. S.; Sharma, S. D.; Amin, S. G. *J. Med. Chem.* **1972**, *15*, 106–107.

(10) Shishoo, C. J.; Shirsath, V. S.; Rathod, I. S.; Yande, V. D. *Eur. J. Med. Chem.* **2000**, *35* (3), 351–358.

(11) Wang, Y. D.; Johnson, S.; Powell, D.; McGinnis, J. P.; Miranda, M.; Rabindran, S. K. *Bioorg. Med. Chem. Lett.* **2005**, *15* (16), 3763–3766.

(12) Jennings, L. D.; Kincaid, S. L.; Wang, Y. D.; Krishnamurthy, G.; Beyer, C. F.; McGinnis, J. P.; Miranda, M.; Discafani, C. M.; Rabindran, S. K. *Bioorg. Med. Chem. Lett.* **2005**, *15* (16), 4731–4735.

(13) Gotanda, K.; Shinbo, A.; Nakano, Y.; Kobayashi, H.; Okada, M.; Asagarasu, A. *Chem. Abstr.* **2006**, *146*, 81884; Patent WO 2006135080, 2006.

(14) Gotanda, K.; Shinbo, A.; Nakano, Y.; Kobayashi, H.; Okada, M.; Asagarasu, A. *Chem. Abstr.* **2008**, *149*, 734240; Patent WO 2008072778, 2008.

(15) Van der Staay, F. J.; Rutten, K.; Barfacker, L.; DeVry, J.; Erb, C.; Heckroth, H.; Karthaus, D.; Tersteegen, A.; Van Kampen, M.; Blokland, A.; Prickaerts, J.; Reymann, K. G.; Schroder, U. H.; Hendrix, M. *Neuropharmacology* **2008**, *55*, 908–918.

(16) Bogolubsky, A. V.; Ryabukhin, S. V.; Plaskon, A. S.; Stetsenko, S. V.; Volochnyuk, D. M.; Tolmachev, A. A. *J. Comb. Chem* **2008**, *10* (6), 858–862.

(17) Dzhavakhishvili, S. G.; Gorobets, N. Yu.; Paponov, B. V.; Musatov, V. I.; Desenko, S. M. *J. Heterocycl. Chem.* **2008**, *45*, 573–577.

(18) Chen, G. S.; Kalchar, S.; Kuo, C.-W.; Chang, S.-C.; Usifoh, C. O.; Chern, J.-W. *J. Org. Chem.* **2003**, *68*, 2502–2505.

(19) Borisov, A. V.; Dzhavakhishvili, S. G.; Zhuravel, I. O.; Kovalenko, S. M.; Nikitchenko, V. M. *J. Comb. Chem.* **2007**, *9*, 5–8.

(20) Hori, M.; Ohtaka, H. *Chem. Pharm. Bull.* **1993**, *41* (6), 1114–1117.

(21) Kulik, S. N.; Kobko, A. S.; Tolmachev, A. A.; Tverdokhlebov, A. V.; Shishkin, O. V.; Chernegad, A. N. *Synthesis* **2007**, *10*, 1503–1508.

(22) Wippich, P.; Gutschow, M.; Leistner, S. *Synthesis* **2000**, *5*, 714–720.

(23) Volovenko, Yu. M.; Resnyanskaya, E. V. *Mendeleev Commun.* **2002**, *5*, 119–120.

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