Tetrahedron 71 (2015) 6196–6203

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile synthesis of pyrido[2,3-*d*]pyrimidines via cyclocondensation of 4,6-dichloro-2-methylsulfanylpyrimidine-5-carbaldehyde with β-substituted β-aminoacrylic esters

Maria E. Chizhova, Olga Yu. Bakulina, Alexander Yu. Ivanov, Pavel S. Lobanov, Dmitrii V. Dar'in *

St. Petersburg State University, 198504 St. Petersburg, Russian Federation

ARTICLE INFO

Article history:
Received 10 May 2015
Received in revised form 14 June 2015
Accepted 22 June 2015
Available online 30 June 2015

Keywords:
Push–pull enamines
Pyrido[2,3-*d*]pyrimidines
Cyclocondensation
4,6-Dichloropyrimidine-5-carbaldehyde
β-substituted β-aminoacrylic esters

ABSTRACT

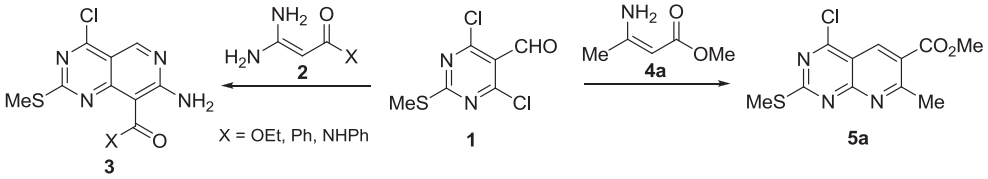
A new facile synthesis of pyrido[2,3-*d*]pyrimidin-4-ones via cyclocondensation of 4,6-dichloro-2-methylsulfanylpyrimidine-5-carbaldehyde with β-alkyl and β-aryl-β-aminoacrylic esters followed by hydrolysis of chlorine atom at position 4 of pyridopyrimidine ring has been developed. The cyclocondensation was found to be accelerated by acid.

1. Introduction

4,6-Dichloropyrimidine-5-carbaldehydes have proved to be very convenient building blocks for the synthesis of various fused pyrimidines.[1] Recently we have studied the reactions of 4,6-dichloro-2-methylsulfanylpyrimidine-5-carbaldehyde (**1**) with geminal push–pull enediamines **2**, giving pyrido[4,3-*d*]pyrimidines **3** in good yields (Scheme 1).[2] At the same time in our previous work we have reported the reaction of aldehyde **1** with methyl aminocrotonate (**4a**) to proceed with another chemoselectivity and to lead to pyrido[2,3-*d*]pyrimidine **5a**.[3]

In the present work we investigated the reactions of aldehyde **1** with push–pull enamines more thoroughly. These studies led to a novel convenient method for the synthesis of highly functionalized pyrido[2,3-*d*]pyrimidines.

Pyrido[2,3-*d*]pyrimidine derivatives demonstrate a wide range of biological properties that are now actively studied, such as analgesic,[4] antiviral,[5] *anti*-inflammatory,[6] antimicrobial,[5d,7] antifungal,[5d,8] anticancer activity[9] and some others.[10] Therefore, the synthesis of diverse structures belonging to this class of compounds is very important.



Scheme 1. Cyclocondensation of aldehyde **1** with enediamines **2** and enamine **4a** (previous works).

2. Results and discussion

The reaction of aldehyde **1** with enamine **4a** was carried out in DMF at ambient temperature. The twofold excess of enamine was

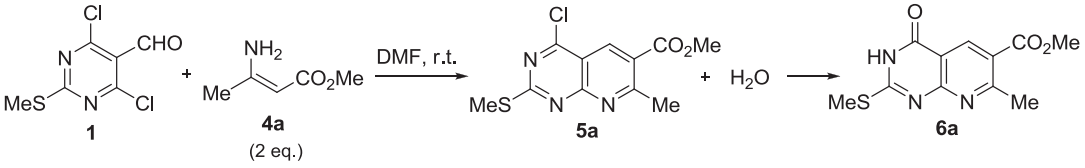
* Corresponding author. Tel.: +7 981 787 1252; fax: +7 812 428 6733; e-mail address: d.dariin@spbu.ru (D.V. Dar'in).

http://dx.doi.org/10.1016/j.tet.2015.06.085
0040-4020/

used for scavenging HCl evolved during the process. The cyclocondensation product—chloride **5a**—precipitated in 15 min and was isolated in pure form after filtration. However it was also shown that slow hydrolysis of **5a** leading to compound **6a** took place under the reaction conditions (Scheme 2). According to ^{1}H NMR spectroscopy monitoring, the cyclocondensation was found to be accelerated by acid. These experiments are illustrated by Fig. 1a and b. When the reaction was carried out with enamine only, an incubation period (over 10 min) was observed (Fig. 1a); the addition of a catalytic amount of HCl increased the rate of cyclocondensation product (**5a**) accumulation significantly from the very beginning (Fig. 1b). Noteworthy, in both cases the hydrolysis reaction (accumulation of compound **6a**) was quite slow.

the hydrolysis of the compound **5b** (leading to pyridopyrimidone **6b**) was found to be accelerated. Apparently, this was due to the increased acidity of the media caused by the absence of another equivalent of enamine, acting as a weak base. The acceleration of hydrolysis of chloride **5b** relative to the rate of its formation from aldehyde **1** and enamine **4b** was demonstrated using NMR-monitoring of this reaction (Fig. 2).

Thus, the preparation of chloride **5b** from aldehyde **1** and aminocinnamic ester **4b** in one step proved to be difficult. At the same time, the product of its hydrolysis in the applied reaction conditions—pyridopyrimidone **6b**—can be isolated in good yield. However, the chloride **5b** can be easily obtained by treating compound **6b** with phosphorus oxychloride (Scheme 4).



Scheme 2. Formation of chloride **5a** and its hydrolisys to pyridopyrimidone **6a**.

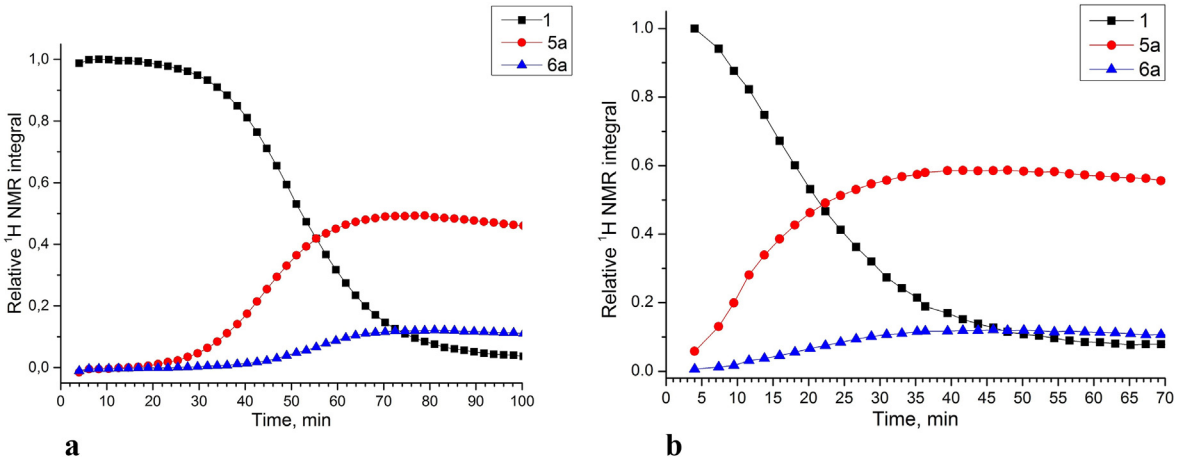
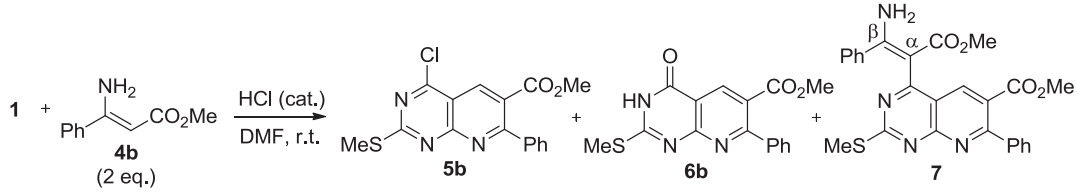


Fig. 1. a ^{1}H NMR monitoring of reaction of aldehyde **1** and enamine **4a** (no HCl added), b ^{1}H NMR monitoring of reaction of aldehyde **1** and enamine **4a** (HCl added).

The reaction of aldehyde **1** with methyl aminocinnamate (**4b**) was conducted under the same conditions (with twofold excess of enamine). Enamine **4b** proved to be less reactive: without the addition of acid no conversion was observed after 2 h. When a catalytic amount of HCl was added, the consumption of starting material was achieved in 1.5 h. Herein, the chloride **5b** (unlike **4b**) did not precipitate, and therefore, considering the slower aldehyde **1** conversion, it underwent hydrolysis much more readily forming pyridopyrimidone **6b** (Scheme 3). Besides, in these conditions the formation of compound **7** was observed as a result of the substitution of chlorine atom in compound **5b** by *C*-nucleophilic center of enamine.

The structure of pyridopyrimidone **6b** was confirmed by a series of chemical transformations. An alkaline hydrolysis yielded acid **8** followed by its decarboxylation accompanied by hydrolytic removal of methylsulfanyl group to give compound **9** (Scheme 4). ^{1}H NMR spectrum of compound **9** revealed pyridine ring protons (5-H and 6-H) signals as a pair of doublets with coupling constant of 8.1 Hz. That would be impossible for structure **9'** (in case of alternative cyclocondensation product).

In order to investigate the effect of substituents in the enamine and determine the scope and limitations of the method, we tested in the reaction with aldehyde **1** various β-aminoacrylic esters **4a**–**l,** which are readily available from corresponding β-ketoesters. The



Scheme 3. Reaction of aldehyde **1** and enamine **4b** (2 eq.).

In order to prevent the formation of side-product **7**, the reaction was carried out with an equimolar amount of enamine. In this case, reactions were performed using standard conditions: ambient temperature, DMF as solvent, catalytic amount of HCl (Table 1).

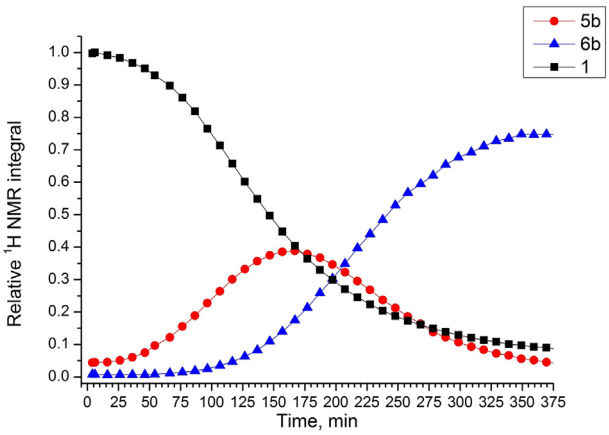
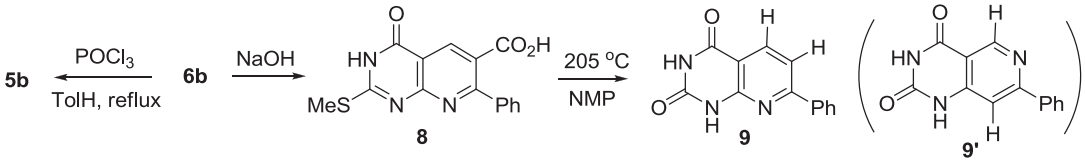


Fig. 2. ^{1}H NMR monitoring of reaction of aldehyde **1** and enamine **4b**.

atom nucleophilicity, so the pyridine nitrogen is able to compete with other nucleophilic centers of enamine **4l**. When chlorine atom in aldehyde **1** (or in pyridopyrimidine **5**) is substituted by the pyridine nitrogen atom, a pyridinium cation is formed, being readily involved in further unpredictable transformations.

The full assignment of signals in ^{13}C NMR spectrum of the obtained compounds **6** was made, based on 2D-NMR spectroscopy HSQC and HMBC. In most cases the signals of pyrimidine ring carbon atoms are significantly broadened that may arise from prototropic tautomerism. Moderate heating (60 °C) simplifies the spectrum view due to acceleration of molecular dynamic processes, which leads to averaging signals and lines narrowing.

Smooth proceeding of the reaction between aldehyde **1** and most enamines bearing an ester group encouraged us to involve in this procedure some push–pull enamines with another 'pull' group, namely nitriles **10** and ketones **11** and **12** (Scheme 5). The aldehyde was found to be consumed within 1–3 h when reacted



Scheme 4. Transformations of pyridopyrimidone **6b**.

Since the synthesis of compounds **6** comprises two subsequent reactions: cyclocondensation of enamine **4** with aldehyde **1** giving chloride **5** and its further hydrolysis *in situ*,—the consumption of both the starting aldehyde and the intermediate compound **5** were controlled by TLC. In some cases by the moment of full aldehyde **1** conversion the hydrolysis process has been also accomplished (Table 1, entries 2, 4, 8–10). In other cases this process has been 'delayed' and reaction mixture was left stirring for additional few hours until complete disappearance of chloride **5** (Table 1, entries 1, 3, 5–7). Especially this was typical for the synthesis with enamine **4a** (Table 1, entry 1), when chloride **5a** precipitated and its hydrolysis proceeded in heterogeneous conditions (a stirring suspension).

Replacement of methyl group in enamine **4a** to isopropyl one did not affect the product yield but only slightly increased the reaction time (Table 1, entry 3). However, in case of enamine **4d** (bearing *tert*-butyl group) the situation turned completely different: the reaction time increased significantly and the yield of compound **6d** proved to be much lower (Table 1, entry 4). Enamine **4e** containing the electron withdrawing triflouromethyl group did not react with aldehyde **1** at all (Table 1, entry 5). While, the enamine itself was being gradually consumed in side processes.

The full conversion time and the yield of the reaction were found to be not influenced by the nature of substitution in phenyl ring of β-aminocinnamic esters **4f**–**j** (Table 1, entries 6–10). For substrates containing either electron withdrawing or electron donating groups, high yields were observed and the full conversion of aldehyde **1** took 2–3 h on average. Apparently, the absence of obvious influence of substituent electronic effect can be attributed to the lack of sufficiently effective conjugation between the aromatic π-system and double C=C bond of enamine. This conjugation is probably prevented by more effective direct polar conjugation between amino group and ester carbonyl group.

The reaction of enamine **4k** bearing thiophene moiety afforded corresponding pyridopyrimidine in high yield (Table 1, entry 11). However, in case of enamine **4l** containing pyridine ring the result was completely different (Table 1, entry 12). The aldehyde **1** was fully consumed, but a complex mixture of unidentified products was obtained. This result is likely to be caused by pyridine nitrogen

with enamines **10** and **11**. However, unfortunately, the target transformations were accompanied with multiple side processes and only the unidentified complex mixtures were obtained in these cases. Meanwhile the enamine **12** showed much more positive result giving the pyridopyrimidone **13** in 46% yield after 5 h (Scheme 5). In this case, the pyrido[2,3-*d*]pyrimidine structure was confirmed by X-ray analysis.

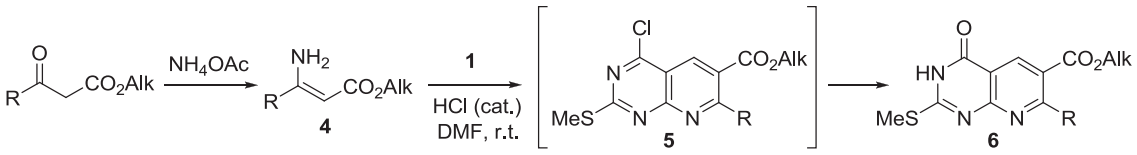
Our attempts to extend the range of electrophilic substrates employing compounds structurally similar to aldehyde **1**, but bearing other acyl group, failed. Enamine **4a** was treated with acetylpyrimidine **14**[11] (Scheme 6), but no conversion of starting materials was observed neither when catalytic amount of acid was added nor under heating (60 °C). The ester **15** did not react with enamine **4a** too and the only result of heating was slow destruction of the starting materials. More electrophilic (π-deficient) ester **16**, synthesized from **15** by oxidation of methylsulfanyl group, also failed to react with aminocrotonic ester (**4a**). Nevertheless such electrophiles are readily transformed into corresponding pyrido[4,3-*d*]pyrimidines, when treated with geminal enediamines **2**.[11,12]

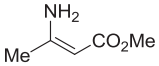
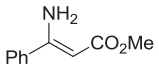
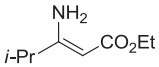
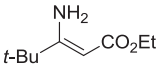
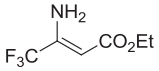
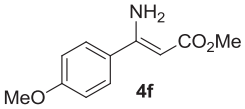
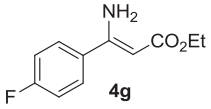
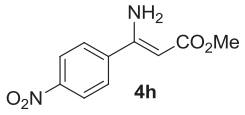
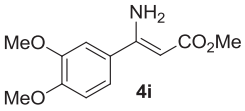
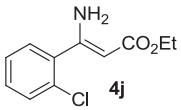
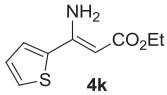
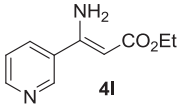
Some interesting and apparently interrelated questions should be considered. How does the acidic catalysis work in the reaction of aldehyde **1** and enamines **4**? What is the sequence of the cyclocondensation reaction steps? What factors control cyclocondensation chemoselectivity in case of enamines **4** in contrast to geminal push–pull enediamines **2** (Scheme 1)? Our assumptions, based on experimental data and the literature, will be discussed below.

The reactivity (nucleophilicity) of push–pull enamines is significantly lower in comparison to analogous enediamines (bearing the same 'pull-group'). The direct (non-catalytic) aromatic nucleophilic substitution of halogen may be considered as a common and well known reaction in case of enediamines.[13] Herein the latter act as *C*-nucleophiles, whereas such reactions are not typical for push–pull enamines. In the case of enamines only highly π-deficient arenes can be involved in the reaction and the yields are usually low.[14] Such substitution may proceed smoothly only intramolecularly.[15]

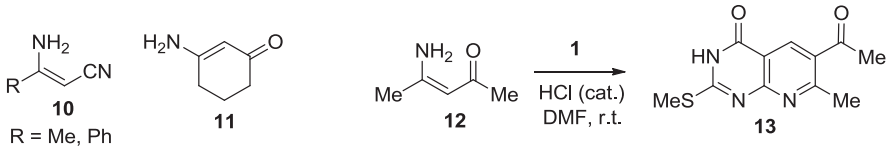
However, the reactions with aromatic aldehydes occurring in acidic media are common for push–pull enamines. These reactions

Table 1
Reaction of aldehyde **1** with enamines **4**. Synthesis of pyrido[2,3-*d*]pyrimidones **6**

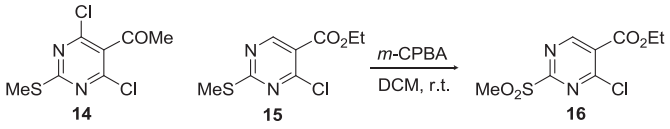


Entry	4	Time[a]	Yield[b] of 6/%
1	 **4a**	3 h (0.5 h)	96 (75)
2	 **4b**	2 h	95
3	 **4c**	3 h (2 h)	92
4	 **4d**	5 days	32[c]
5	 **4e**	24 h	0[d]
6	 **4f**	1.5 h (1 h)	96
7	 **4g**	2.5 h (1.5 h)	92
8	 **4h**	2.5 h (2 h)	92
9	 **4i**	1.5 h	86
10	 **4j**	2 h	89
11	 **4k**	2 h	95
12	 **4l**	1 h	—[e]

[a] Total time of reaction, after which both cyclocondensation and hydrolisys processes were completed (step 1+step 2); time of the aldehyde **1** consumption (step 1) is given in parenthesis (controlled by TLC).
[b] Isolated yields before purification (purity ≥94%); the yield after recrystallization from DMF is given in parenthesis.
[c] Yield after column chromatography.
[d] No convertion of aldehyde **1** was observed.
[e] Unidentified mixture of products was obtained.



Scheme 5. Cyanoenamines **10** and ketoenamines **11**, **12**. Formation of pyridopyrimidone **13**.



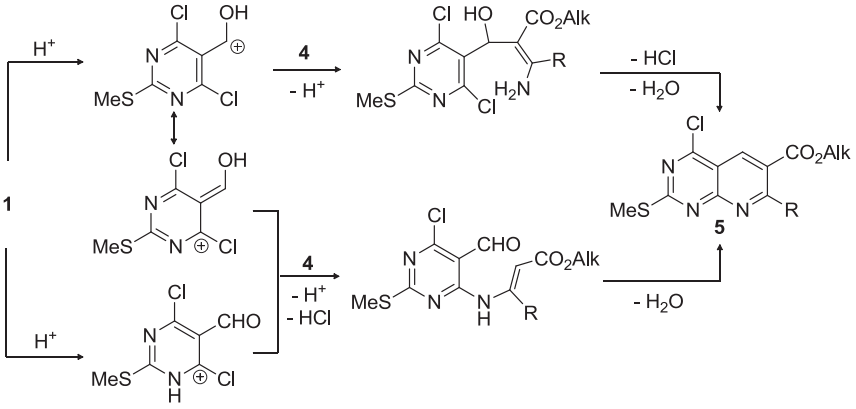
Scheme 6. Electrophilic substrates structurally similar to aldehyde **1**.

lead to dihydropyridines formation (Hantzsch's synthesis) via *C*-nucleophilic attack of two enamine molecules on the formyl function.[16]

The studied cyclocondensation of aldehyde **1** with enamines proceeds relatively fast: in case of enamine **4a** the full conversion is achieved within 20–30 min. These values are comparable to the ones observed for cyclocondensation of aldehyde **1** with ethyl 3,3-diaminoacrylate (**2** X=OEt, 5–10 min). Such a small difference was shown to be caused by acidic catalysis in case of enamine reaction. There may be supposed two possible reaction pathways for the cyclocondensation process (Scheme 7). They differ by the nature of the initial step (interaction between enamine *C*-nucleophilic center and formyl group or attacking the pyrimidine ring by *N*-nucleophilic center).

adjacent chlorine atoms shielding it. The formyl group is unavailable for attack by the C-nucleophilic center of the enediamine, which is sensitive to steric hindrance. Along with this, the high nucleophilicity of the latter makes possible for it to substitute the chlorine atom easily, when the attack on pyrimidine ring takes place.

In case of reaction with enamines, the formyl group is also unavailable and the nucleophilicity of enamine is insufficient for attacking the pyrimidine ring and substituting of chlorine atom with observable rate. Nevertheless, such attack is likely to occur (resulting in formation of traces of HCl), although very slowly. When the acid emerge in the reaction media and protonation of the formyl group takes place the formyl carbon atom becomes much more electrophilic (carbocationic center), which permits the nucleophilic attack on it to occur readily. Furthermore, due to the same steric hindrance caused by two chlorine atoms this electrophilic center (after first nucleofilic attack) proves to be unavailable for attack by another enamine molecule (as it happens in dihydropyridine synthesis in case of other aromatic aldehydes). Meanwhile the high electrophilicity of the pyrimidine ring allows the cyclization via intramolecular aromatic nucleophilic sub-



Scheme 7. Possible pathways for cyclocondensation of aldehyde **1** and enamines **4**.

Protonation of aldehyde **1** leads to significant increase of its electrophilicity. The first step of cyclocondensation is assumed to be an interaction between enamine carbon atom and protonated formyl group. This assumption is consistent with the fact that other pyrimidine electrophiles similar to aldehyde **1** (ketone **14** and ester **15**), do not react with enamines. If the first step was the attack on pyrimidine ring (the substitution of chlorine atom by the enamine amino group), the similar reactivity for ketone **14** and likely ester **15** would rather be expected.

Taking these considerations into account we suggest the following explanation of different chemoselectivity of cyclocondensation reaction of aldehyde **1** with enamines **4** (acid catalysis; pyrido[2,3-*d*]pyrimidines are formed) on one hand and geminal enediamines **2** (no catalysis; pyrido[4,3-*d*]pyrimidines are formed) on the other. The acid catalysis (protonation of aldehyde molecule) is unable to work in case of enediamines because of their high (in contrast to enamines) basicity. The reactivity of non-protonated formyl group is low due to the presence of two stitution of chlorine atom by nitrogen atom to occur easily. Such influence of adjacent chlorine atoms on the reactivity of chlorine-substituted quinoline-3-carbaldehydes in the reaction with ethyl 3,3-diaminoacrylate (**2** X=OEt) was reported in one of our previous works.[17]

3. Conclusions

In conclusion, the developed method for the synthesis of pyrido-[2,3-*d*]pyrimidines is very efficient for preparative use, considering the easy availability of starting materials, short reaction times and high yields of the target compounds. Although there are some limitations in the type of substrates, different β-substituted β-acrylic esters are suitable for the described procedure. It should be also noted that the heterocycles obtained may be considered as having wide perspectives for potential modifying of the bicyclic system periphery.

4. Experimental part

4.1. General considerations

The NMR spectra were recorded on a Bruker Avance III 400 spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; chemical shifts are reported as parts per million (δ, ppm); the residual solvent peaks were used as internal standards: 7.28 and 2.51 ppm for ^{1}H in $CDCl_3$ and DMSO-d_6 respectively, 39.7 ppm for ^{13}C in $CDCl_3$ and DMSO-d_6; multiplicities are abbreviated as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad; coupling constants, *J*, are reported in Hz). Mass spectra were recorded on a Bruker micrOTOF spectrometer (ESI ionisation). IR spectra were recorded on an FT-spectrometer Spectrum BX (KBr pellets). Melting points were determined in open capillary tubes on Stuart SMP30 Melting Point Apparatus. The ethereal HCl solution was prepared by saturating of ether with gaseous HCl under ice-cooling.

4.2. General procedure for synthesis of pyrido[2,3-*d*]pyrimidones 6

To a stirred solution of aldehyde **1** (1.0 mmol, 1 equiv) in 3 mL DMF was added enamine **2** (1.15 equiv) followed by addition of a few drops of satd ethereal HCl.

Except for **6d**: Mixture was stirred at ambient temperature for period of time indicated in Table 1. After removing of solvent (50 °C/5 Torr) the residue was stirred with water (10 mL) for 1 h, crystals were filtered and dried at 110 °C/5 Torr to give compound **6** with purity≥94%. Recrystallization from DMF can be used for purification, if necessary.

For **6d**: After stirring for 20 h the additional portion of enamine **4d** (0.15 equiv) was added and the mixture was left at ambient temperature for 4 days. After removing of solvent (50 °C/5 Torr) the residue was dissolved in $CHCl_3$ (30 mL), washed with water, satd $NaHCO_3$ and brine. Compound **6d** was isolated using column chromatography on silica (EtOAc–*n*Hexane 1:1, R_f~0.25).

4.3. Methyl 7-methyl-2-(methylsulfanyl)-4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate (6a)

Light pink powder, mp 261–263 °C (DMF; decomp.); ν_{max}(KBr) 3006–2800, 1735, 1673, 1604, 1578, 1539, 1416, 1283, 1261, 1236, 1121, 1056; δ_H (400 MHz, DMSO-d_6) 12.99 (1H, s, NH), 8.69 (1H, s, 5-H), 3.88 (3H, s, CO_2CH_3), 2.79 (3H, s, 7-CH_3), 2.60 (3H, s, SCH_3); δ_C (100.6 MHz, DMSO-d_6) 165.9 (7-C), 165.7 (CO_2CH_3), 164.2 (2-C), 161.7 (8a-C), 158.7 (4-C), 138.9 (5-C), 122.5 (6-C), 113.0 (4a-C), 52.9 (CO_2CH_3), 25.5 (7-CH_3), 13.6 (SCH_3); HRMS (ESI): MH^+, found 266.0599. $[C_{11}H_{12}N_3O_3S]^+$ requires 266.0594.

4.4. Methyl 2-(methylsulfanyl)-4-oxo-7-phenyl-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate (6b)

Colorless powder, mp 276–278 °C (DMF); ν_{max}(KBr) 3008, 2919–2800 (br), 1731, 1669, 1595, 1559, 1417, 1400, 1243, 1118, 1099, 989; δ_H (400 MHz, DMSO-d_6) 13.09 (1H, s, NH), 8.70 (1H, s, 5-H), 7.59–7.47 (5H, m, H(Ph)), 3.71 (3H, s, CO_2CH_3), 2.63 (3H, s, SCH_3); δ_C (100.6 MHz, DMSO-d_6, 60 °C) 167.1 (CO_2CH_3), 164.1 (2-C), 163.7 (7-C), 161.5 (8a-C), 158.6 (4-C), 139.6 (*ipso*-Ph), 138.7 (5-C), 129.7 (*p*-Ph), 129.0 (*o*-Ph), 128.5 (*m*-Ph), 124.2 (6-C), 113.6 (4a-C), 52.8 (CO_2CH_3), 13.5 (SCH_3); HRMS (ESI): MH^+, found 328.0758. $[C_{16}H_{14}N_3O_3S]^+$ requires 328.0750.

4.5. Ethyl 7-isopropyl-2-(methylsulfanyl)-4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate (6c)

Colorless powder, mp 270–271 °C (DMF); ν_{max}(KBr) 3071–2800, 1729, 1677, 1600, 1567, 1513, 1406, 1276, 1260, 1240, 1119; δ_H (400 MHz, DMSO-d_6) 12.97 (1H, s, NH), 8.66 (1H, s, 5-H), 4.35 (2H, *q*, OCH_2CH_3, *J* 7.1), 3.97–3.87 (1H, m, $CH(CH_3)_2$), 2.64 (3H, s, SCH_3), 1.35 (3H, *t*, OCH_2CH_3, *J* 7.1), 1.26 (6H, d, $CH(CH_3)_2$, *J* 6.7); δ_C (100.6 MHz, DMSO-d_6) 173.2 (7-C), 165.8 ($CO_2CH_2CH_3$), 163.9 (2-C), 161.6 (8a-C), 159.1 (4-C), 138.7 (5-C), 122.8 (6-C), 112.9 (4a-C), 61.8 (OCH_2CH_3), 32.9 ($CH(CH_3)_2$), 22.5 ($CH(CH_3)_2$), 14.5 (OCH_2CH_3), 13.6 (SCH_3); HRMS (ESI): MH^+, found 308.1073. $[C_{14}H_{18}N_3O_3S]^+$ requires 308.1063.

4.6. Ethyl 7-*tert*-butyl-2-(methylsulfanyl)-4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate (6d)

Light yellow powder, mp 223–224 °C; ν_{max}(KBr) 3165–2800, 1733, 1670, 1603, 1567, 1536, 1402, 1278, 1250, 1114, 1026, 813; δ_H (400 MHz, $CDCl_3$) 11.10 (1H, br.s, NH), 8.53 (1H, s, 5-H), 4.44 (2H, *q*, CH_2CH_3, *J* 7.1), 2.80 (3H, s, SCH_3), 1.53 (6H, s, *t*-Bu), 1.45 (3H, *t*, CH_2CH_3, *J* 7.1); δ_C (100.6 MHz, $CDCl_3$) 173.4 (7-C), 169.1 ($CO_2CH_2CH_3$), 162.9 (2-C), 161.6 (8a-C), 157.5 (4-C), 137.5 (5-C), 127.0 (4a-C), 111.5 (6-C), 62.2 (CH_2CH_3), 40.5 ($C(CH_3)_3$), 29.8 ($C(CH_3)_3$), 14.1 (CH_2CH_3), 13.7 (SCH_3); HRMS (ESI): MH^+, found 322.1233. $[C_{15}H_{20}N_3O_3S]^+$ requires 322.1220.

4.7. Methyl 7-(4-methoxyphenyl)-2-(methylsulfanyl)-4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate (6f)

Colorless powder, mp 290–292 °C (DMF; decomp.); ν_{max}(KBr) 3013–2913 (br), 1730, 1655, 1596, 1572, 1402, 1259, 1181, 1116, 1099; δ_H (400 MHz, DMSO-d_6) 12.83 (1H, s, NH), 8.63 (1H, s, 5-H), 7.55 (2H, d, 2′,6′-H, *J* 8.7), 7.05 (2H, d, 3′,5′-H, *J* 8.7), 3.84 (3H, s, 4′-OCH_3), 3.74 (3H, s, CO_2CH_3), 2.63 (3H, s, SCH_3); δ_C (100.6 MHz, DMSO-d_6) 167.6 (CO_2CH_3), 164.0 (2-C), 162.8 (7-C), 161.6 (8a-C), 161.0 (4′-C), 158.5 (4-C), 138.7 (5-C), 131.4 (1′-C), 130.9 (2′,6′-C), 123.8 (6-C), 114.1 (3′,5′-C), 112.9 (4a-C), 55.8 (4′-OCH_3), 53.0 (CO_2CH_3), 13.6 (SCH_3); HRMS (ESI): MH^+, found 358.0860. $[C_{17}H_{16}N_3O_4S]^+$ requires 358.0856.

4.8. Ethyl 7-(4-fluorophenyl)-2-(methylsulfanyl)-4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate (6g)

Light yellow powder, mp 250–251 °C (DMF); ν_{max}(KBr) 3074–2880 (br), 1722, 1675, 1599, 1563, 1536, 1405, 1266, 1244, 1220, 1096; δ_H (400 MHz, DMSO-d_6) 13.09 (1H, s, NH), 8.69 (1H, s, 5-H), 7.61 (2H, dd, 2′,6′-H, *J* 8.7, 5.5), 7.32 (2H, *t*, 3′,5′-H, *J* 8.7), 4.18 (2H, *q*, OCH_2CH_3, *J* 7.1), 2.62 (3H, s, SCH_3), 1.11 (3H, *t*, OCH_2CH_3, *J* 7.1); δ_C (100.6 MHz, DMSO-d_6) 166.4 (7-C), 164.2 ($CO_2CH_2CH_3$), 163.3 (4′-C, d, *J* 146.5), 162.9 (2-C), 161.8 (8a-C), 158.7 (4-C), 138.9 (5-C), 136.1 (4′-C, d, *J* 2.8), 131.5 (2′,6′-C, d, *J* 8.7), 124.1 (6-C), 115.5 (3′,5′-C, d, *J* 21.8), 113.7 (4a-C), 61.8 (OCH_2CH_3), 14.1 (OCH_2CH_3), 13.6 (SCH_3); HRMS (ESI): MH^+, found 360.0825. $[C_{17}H_{15}FN_3O_3S]^+$ requires 360.0813.

4.9. Methyl 2-(methylsulfanyl)-7-(4-nitrophenyl)-4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate (6h)

Light yellow powder, mp 302–304 °C (DMF; decomp.); ν_{max}(KBr) 2926–2804 (br), 1735, 1683, 1598, 1568, 1517, 1408, 1352, 1279, 1251, 1122; δ_H (400 MHz, DMSO-d_6) 13.14 (1H, s, NH), 8.80 (1H, s, 5-H), 8.33 (2H, d, 3′,5′-H, *J* 8.6), 7.82 (2H, d, 2′,6′-H, *J* 8.6), 3.73 (3H, s, CO_2CH_3), 2.62 (3H, s, SCH_3); δ_C (100.6 MHz, DMSO-d_6) 166.0 (CO_2CH_3), 164.9 (2-C), 162.2 (7-C), 161.5 (8a-C), 158.7 (4-C), 148.2 (4′-C), 145.1 (1′-C), 139.5 (5-C), 130.6 (2′,6′-C), 123.6 (3′,5′-C), 123.5

(6-C), 114.4 (4a-C), 53.1 (CO_2CH_3), 13.6 (SCH_3); HRMS (ESI): MH^+, found 373.0610. $[C_{16}H_{13}N_4O_5S]^+$ requires 373.0601.

4.10. Methyl 7-(3,4-dimethoxyphenyl)-2-(methylsulfanyl)-4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate (6i)

Colorless powder, mp 278–280 °C (DMF); ν_{max}(KBr) 3071–2908, 1731, 1655, 1566, 1412, 1266, 1121, 1100, 1021, 871,; δ_H (400 MHz, DMSO-d_6, 60 °C) 13.02 (1H, br.s, NH), 8.62 (1H, s, 5-H), 7.20 (1H, d, 2′-H, *J* 2.0), 7.16 (1H, dd, 6′-H, *J* 8.3, 2.0), 7.08 (1H, d, 5′-H, *J* 8.3), 3.84 (3H, s, 4′-OCH_3), 3.81 (3H, s, 3′-OCH_3), 3.74 (3H, s, CO_2CH_3), 2.64 (3H, s, SCH_3); δ_C (100.6 MHz, DMSO-d_6, 60 °C) 167.6 (CO_2CH_3), 163.8 (2-C), 162.9 (7-C), 161.5 (4-C), 158.6 (8a-C), 151.0 (4′-C), 149.0 (3′-C), 138.4 (5-C), 131.9 (1′-C), 124.4 (6-C), 122.5 (6′-C), 113.3 (2′-C), 113.1 (4a-C), 112.2 (5′-C), 56.4 (4′-OCH_3), 56.3 (3′-OCH_3), 52.9 (CO_2CH_3), 13.5 (SCH_3); HRMS (ESI): MH^+, found 388.0967. $[C_{18}H_{18}N_3O_5S]^+$ requires 388.0962.

4.11. Ethyl 7-(2-chlorophenyl)-2-(methylsulfanyl)-4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate (6j)

Yellow powder, mp 214–215 °C (MeCN); ν_{max}(KBr) 3163–2800, 1718, 1685, 1601, 1567, 1400, 1266, 1249, 1107, 1056, 975, 814, 736; δ_H (400 MHz, DMSO-d_6, 60 °C) 13.04 (1H, br s, NH), 8.85 (1H, s, 5-H), 7.53–7.44 (4H, m, 2-Cl-C_6H_4), 4.12 (2H, *q*, OCH_2CH_3, *J* 7.1), 2.63 (3H, s, SCH_3), 1.04 (3H, *t*, OCH_2CH_3, *J* 7.1); δ_C (100.6 MHz, DMSO-d_6, 60 °C) 164.73 (2-C) 164.65 ($CO_2CH_2CH_3$), 162.7 (7-C), 161.5 (4-C), 159.2 (8a-C), 139.8 (2′-C), 138.8 (5-C), 131.5 (1′-C), 130.6 (6′-C), 130.4 (4′-C), 129.1 (5′-C), 127.3 (3′-C), 124.3 (6-C), 114.4 (4a-C), 61.6 (CH_2CH_3), 13.9 (CH_2CH_3), 13.5 (SCH_3); HRMS (ESI): MH^+, found 376.0523. $[C_{17}H_{15}{}^{35}ClN_3O_3S]^+$ requires 376.0517.

4.12. Ethyl 2-(methylsulfanyl)-4-oxo-7-(thiophen-2-yl)-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate (6k)

Colorless powder, mp 280–282 °C (DMF; decomp.); ν_{max}(KBr) 3063–2704, 1726, 1669, 1568, 1419, 1392, 1278, 1252, 1117, 851, 716; δ_H (400 MHz, DMSO-d_6, 60 °C) 12.84 (1H, br.s, NH), 8.55 (1H, s, 5-H), 7.82 (1H, dd, 5′-H, *J* 5.0, 1.0), 7.54 (1H, dd, 3′-H, *J* 3.8, 1.0), 7.20 (1H, dd, 4′-H, *J* 3.8, 5.0), 4.37 (2H, *q*, CH_2CH_3, *J* 7.1), 2.66 (3H, s, SCH_3), 1.30 (3H, *t*, CH_2CH_3, *J* 7.1); δ_C (100.6 MHz, DMSO-d_6, 60 °C) 167.2 ($CO_2CH_2CH_3$), 164.1 (2-C), 161.3 (4-C), 158.4 (8a-C), 154.9 (7-C), 141.9 (2′-C), 138.2 (5-C), 131.6 (5′-C), 130.1 (3′-C), 128.7 (4′-C), 123.5 (4a-C), 113.1 (6-C), 62.3 (CH_2CH_3), 14.2 (CH_2CH_3), 13.6 (SCH_3); HRMS (ESI): MH^+, found 348.0468. $[C_{15}H_{14}N_3O_3S_2]^+$ requires 348.0471.

4.13. Methyl 4-chloro-2-(methylsulfanyl)-7-phenylpyrido[2,3-*d*]pyrimidine-6-carboxylate (5b)

A mixture of compound **6b** (300 mg, 0.92 mmol), phosphorus oxychloride (310 mg, 2.02 mmol), dry toluene (20 mL) and dry 1,4-dioxane (4 mL) was stirred at reflux temperature for 3 h (controlled by TLC). After cooling to room temperature it was diluted with dichloromethane (25 mL) and passed through a short pad of silica. After evaporation of solvents the residue was thoroughly washed with warm hexane and dried in vacuo to give the title compound **5b** (187 mg, 59%) as a pale yellow powder; mp 137–139 °C, ν_{max}(KBr) 1737, 1599, 1565, 1510, 1429, 1351, 1250, 1140, 1102, 1041, 1024; δ_H (400 MHz, $CDCl_3$) 8.90 (1H, s, 5-H), 7.71–7.69 (2H, m, *o*-H(Ph)), 7.58–7.44 (3H, m, *m*,*p*-H(Ph)), 3.79 (3H, s, CO_2CH_3), 2.77 (3H, s, SCH_3); δ_C (100.6 MHz, $CDCl_3$) 175.1 (2-C); 166.88, 166.82 (7-C, CO_2CH_3); 162.4 (4-C), 158.8 (8a-C), 138.6 (5-C, *ipso*-Ph; overlapped); 130.2 (*p*-Ph), 128.9 (*o*-Ph), 128.4 (*m*-Ph); 126.6 (6-C), 114.1 (4a-C), 52.9 (CO_2CH_3), 14.9 (SCH_3); HRMS (ESI): MH^+, found 346.0414. $[C_{16}H_{13}ClN_3O_2S]^+$ requires 346.0412.

4.14. Methyl 4-(1-amino-3-methoxy-3-oxo-1-phenylprop-1-en-2-yl)-2-(methylsulfanyl)-7-phenylpyrido[2,3-*d*]pyrimidine-6-carboxylate (7)

To a solution of aldehyde **1** (500 mg, 2.25 mmol) and enamine **4b** (878 mg, 4.93 mmol) in DMF (3 mL) a few drops of satd ethereal HCl were added followed by stirring at room temperature for 2 h (controlled by TLC). Solvent was removed in vacuo (50 °C/5 Torr), the residue was treated with water (10 mL) and aqueous phase was separated. To the oily viscous residue was added DMSO (5 mL) and mixture was heated at 80 °C for 10 min. After cooling to room temperature formed crystals were filtered, washed with water and dried in air to give the mixture of compounds **6b** and **7** (515 mg, ~1:2.5). Compound **7** was isolated by column chromatography on *silica* (EtOAc-Hexane 1:1, R_f~0.5) to yield 214 mg (20%) as yellow powder, mp 204–205 °C; ν_{max}(KBr) 3400–3200, 1727, 1688, 1595, 1549, 1514, 1438, 1332, 1264, 1218, 1133, 1019, 773, 700; δ_H (400 MHz, DMSO-d_6) 9.08 (1H, br.s, NH), 8.67 (1H, s, 5-H), 8.32 (1H, br.s, NH), 7.66–7.47 (5H, m, 7-(Ph)), 7.29–7.06 (5H, m, β-(Ph)), 3.74 (3H, s, 6-(CO_2CH_3)), 3.54 (3H, s, α-(CO_2CH_3)), 2.40 (3H, s, SCH_3); δ_C (100.6 MHz, DMSO-d_6, 60 °C) 173.8, 170.3, 168.4, 167.2, 166.0, 164.0, 158.2, 140.3, 139.4, 137.1, 130.0, 129.8, 129.1, 128.6, 128.4, 125.0, 116.0, 92.3, 79.6, 53.0, 51.0, 14.1 (SCH_3); HRMS (ESI): MH^+, found 487.1444. $[C_{26}H_{23}N_4O_4S]^+$ requires 487.1435.

4.15. 2-(Methylsulfanyl)-4-oxo-7-phenyl-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid (8)

A mixture of compound **6b** (523 mg, 1.6 mmol) and aq KOH (263 mg, 4.7 mmol in 10 mL of water) was stirred at room temperature for 2 h. The solution was acidified with 3N citric acid to pH~6. The precipitate was filtered, washed with water and dried in air to give the titled compound (71%) as colourless powder, mp 296–297 °C (DMF; decomp.); ν_{max}(KBr) 3575–2600, 1735, 1678, 1600, 1568, 1403, 1266, 1124, 978, 815; δ_H (400 MHz, DMSO-d_6, 60 °C) 12.76 (2H, br s, NH, COOH), 8.68 (1H, s, 5-H), 7.64–7.59 (2H, m, *o*-H(Ph)), 7.51–7.46 (3H, m, *m*,*p*-H(Ph)), 2.65 (3H, s, SCH_3); δ_C (100.6 MHz, DMSO-d_6, 60 °C) 168.0 (7-C), 163.74 (CO_2H), 163.69 (2-C), 161.6 (8a-C), 158.4 (4-C), 139.9 (*ipso*-Ph), 138.3 (5-C), 129.6 (*p*-Ph), 129.2 (*o*-Ph), 128.3 (*m*-Ph), 125.7 (6-C), 113.43 (4a-C),13.5 (SCH_3); HRMS (ESI): $(M-H)^-$, found 312.0434. $[C_{15}H_{10}N_3O_3S]^+$ requires 312.0448.

4.16. 7-Phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9)

A mixture of acid **8** (169 mg, 0.54 mmol), Cu_2O (77 mg, 0.54 mmol) and *N*-methylpyrrolidone (1.5 mL) was heated at 205 °C for 12 h. The mixture was concentrated (85 °C/5 Torr) and the residue was treated with EtOAc (5 mL) and passed through SiO_2, washing out with EtOAc (R_f~0.5). After evaporation of solvent the residue was treated with ether (3 mL), ice-cooled and filtered to give the titled compound (23 mg, 18%) of~90% purity, beige powder, mp 278–280 °C (decomp.); ν_{max}(KBr) 3433, 3178, 3056, 2817, 1709, 1675, 1611, 1575, 1411, 1276; δ_H (400 MHz, DMSO-d_6) 11.53 (1H, br s, 1-NH), 11.28 (1H, br.s, 3-NH), 8.32 (1H, d, 5-H, *J* 8.1), 8.17–8.14 (2H, m, *o*-Ph), 7.81 (1H, d, 6-H, *J* 8.1), 7.58–7.53 (3H, m, *m*-, *p*-Ph); δ_C (100.6 MHz, DMSO-d_6, 60 °C) 162.6 (8a-C), 161.2 (7-C), 152.9 (4-C), 150.9 (2-C), 137.9 (5-C), 137.7 (*ipso*-Ph), 130.9 (*p*-Ph), 129.3 (*m*-Ph), 127.8 (*o*-Ph), 115.8 (6-C), 109.1 (4a-C); HRMS (ESI): MH^+, found 240.0769. $[C_{13}H_{10}N_3O_2]^+$ requires 240.0768.

4.17. 6-Acetyl-7-methyl-2-(methylsulfanyl)pyrido[2,3-*d*]pyrimidine-4(3*H*)-one (13)

To a stirred solution of aldehyde **1** (500 mg, 2.24 mmol) in 3.5 mL of DMF was added enamine **12** (250 mg, 2.52 mmol)

followed by addition of a few drops of satd ethereal HCl. Mixture was stirred at ambient temperature for 5 h. Crystals formed were filtered, washed thoroughly with MeCN (10 mL) and dried at 110 °C/5 Torr to give the titled compound (256 mg, 46%) as light pink powder, mp 265–267 °C (MeCN; decomp.); ν_{max}(KBr) 3417 (br), 3008, 2731, 2625, 1726, 1716, 1690, 1627, 1524, 1426, 1371, 1345, 1263, 1227, 1163, 1108, 960, 794; δ_H (400 MHz, DMSO-d_6, 60 °C) 10.40 (1H, s, NH), 8.77 (1H, s, 5-H), 2.76 (3H, s, 7-CH_3), 2.65 (3H, s, $COCH_3$), 2.63 (3H, s, SCH_3); δ_C (100.6 MHz, DMSO-d_6, 60 °C) 198.9 ($COCH_3$), 165.1 (2-C), 164.0 (7-C), 161.3 (4-C), 157.3 (8a-C), 138.8 (5-C), 130.5 (6-C), 113.2 (4a-C), 29.8 (7-CH_3), 24.6 ($COCH_3$), 13.6 (SCH_3); HRMS (ESI): MH^+, found 250.0632. $[C_{11}H_{12}N_3O_2S]^+$ requires 250.0645.

Acknowledgements

This research was supported by the Russian Scientific Fund (project grant 14-50-00069). NMR studies, IR and mass spectrometry studies were performed at Research Centre for Magnetic Resonance and Centre for Chemical Analysis and Materials Research of Saint Petersburg State University.

Supplementary data

Supplementary data (Supplementary file contains the synthetic procedures and NMR data for compounds **1**, **4a**–**l**, **12**, the NMR spectra for compounds **6a**–**d, f**–**k**, NMR-monitoring procedures (Figs. 1a, b, 2) and the X-ray data confirming the structure of compound **13**) related to this article can be found, online version at http://dx.doi.org/10.1016/j.tet.2015.06.085.

References and notes

1. (a) Wainwright, P.; Maddaford, A.; Simms, M.; Forrest, N.; Glen, R.; Hart, J.; Zhang, X.; Pryde, D. C.; Stephenson, P. T.; Middleton, D. S.; Guyot, T.; Sutton, S. C. *Synlett* **2011**, 1900–1904; (b) Li, B.; Yue, Z.; Xiang, H.; Lv, L.; Song, S.; Miao, Z.; Yang, C. *RSC Adv.* **2014**, *4*, 358–364; (c) Babu, S.; Morrill, C.; Almstead, N. G.; Moon, Y.-C. *Org. Lett.* **2013**, *15*, 1882–1885; (d) Yan, H.; Boehm, J. C.; Jin, Q.; Kasparec, J.; Li, H.; Zhu, C.; Widdowson, K. L.; Callahan, J. F.; Wan, Z. *Tetrahedron Lett.* **2007**, *48*, 1205–1207; (e) Morrill, C.; Babu, S.; Almstead, N. G.; Moon, Y.-C. *Synthesis* **2013**, *45*, 1791–1806; (f) Evans, L. E.; Cheeseman, M. D.; Jones, K. *Org. Lett.* **2012**, *14*, 3546–3549; (g) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, *10*, 889–892; (h) Brough, P. A.; Barril, X.; Borgognoni, J.; Chene, P.; Davies, N. G. M.; Davis, B.; Drysdale, M. J.; Dymock, B.; Eccles, S. A.; Garcia-Echeverria, C.; Fromont, C.; Hayes, A.; Hubbard, R. E.; Jordan, A. M.; Jensen, M. R.; Massey, A.; Merrett, A.; Padfield, A.; Parsons, R.; Radimerski, T.; Raynaud, F. I.; Robertson, A.; Roughley, S. D.; Schoepfer, J.; Simmonite, H.; Sharp, S. Y.; Surgenor, A.; Valenti, M.; Walls, S.; Webb, P.; Wood, M.; Workman, P.; Wright, L. *J. Med. Chem.* **2009**, *52*, 4794–4809; (i) Vignaroli, G.; Mencarelli, M.; Sementa, D.; Crespan, E.; Kissova, M.; Maga, G.; Schenone, S.; Radi, M.; Botta, M. *ACS Comb. Sci.* **2014**, *16*, 168–175.
2. (a) Ryazanov, S. G.; Dar'in, D. V.; Lobanov, P. S.; Potekhin, A. A. *Russ. J. Org. Chem.* **2008**, *44*, 288–291; (b) Bakulina, O. Y.; Ivanov, A. Y.; Lobanov, P. S.; Dar'in, D. V. *Tetrahedron* **2014**, *70*, 7900–7905.
3. Bakulina, O. Y.; Ivanov, A. Y.; Dar'in, D. V.; Lobanov, P. S. *Mendeleev Commun.* **2014**, *24*, 163–164.
4. (a) Nash, M. S.; McIntyre, P.; Groarke, A.; Lilley, E.; Culshaw, A.; Hallett, A.; Panesar, M.; Fox, A.; Bevan, S. *J. Pharmacol. Exp. Ther.* **2012**, *342*, 389–398; (b) El-Gazzar, A.-R. B. A.; Hafez, H. N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3392–3397.
5. (a) Velthuisen, E. J.; Johns, B. A.; Gerondelis, P.; Chen, Y.; Li, M.; Mou, K.; Zhang, W.; Seal, J. W.; Hightower, K. E.; Miranda, S. R.; Brown, K.; Leesnitzer, L. *Eur. J. Med. Chem.* **2014**, *83*, 609–616; (b) Czodrowski, P.; Hölzemann, G.; Barnickel, G.; Greiner, H.; Musil, D. *J. Med. Chem.* **2015**, *58*, 457–465; (c) Lacbay, C. M.; Mancuso, J.; Lin, Y.-S.; Bennett, N.; Götte, M.; Tsantrizos, Y. S. *J. Med. Chem.* **2014**, *57*, 7435–7449; (d) Satasia, S. P.; Kalaria, P. N.; Raval, D. K. *Org. Biomol. Chem.* **2014**, *12*, 1751–1758.
6. (a) Huang, H.; Hutta, D. A.; Rinker, J. M.; Hu, H.; Parsons, W. H.; Schubert, C.; DesJarlais, R. L.; Crysler, C. S.; Chaikin, M. A.; Donatelli, R. R.; Chen, Y.; Cheng, D.; Zhou, Z.; Yurkow, E.; Manthey, C. L.; Player, M. R. *J. Med. Chem.* **2009**, *52*, 1081–1099; (b) Hayallah, A. M.; Abdel-Hamid, M. K. *D. Pharm. Chem.* **2014**, *6*, 45–54.
7. (a) El-Emary, T. I.; Abd El-Mohsen, S. A. *Molecules* **2012**, *17*, 14464–14483; (b) Ragab, M. N.; Talaat, El-Saidi, M. M.; Alia, Y. M.; Elnagdi, M. H. *Bioorg. Med. Chem.* **2007**, *15*, 6227–6235; (c) Saikia, L.; Das, B.; Bharali, P.; Thakur, A. J. *Tetrahedron Lett.* **2014**, *55*, 1796–1801; (d) Gangjee, A.; Namjoshi, O. A.; Raghavan, S.; Queener, S. F.; Kisliuk, R. L.; Cody, V. *J. Med. Chem.* **2013**, *56*, 4422–4441.
8. Farghaly, T. A.; Hassaneen, H. M. E. *Arch. Pharm. Res.* **2013**, *36*, 564–572.
9. (a) Gineinah, M. M.; Nasr, M. N. A.; Badr, S. M. I.; El-Husseiny, W. M. *Med. Chem. Res.* **2013**, *22*, 3943–3952; (b) Palopa, J. A.; Planoa, D.; Morenoa, E.; Sanmartin, C. *ARKIVOC* **2014**, *2*, 187–206; (c) Edupuganti, R.; Wang, Q.; Tavares, C. D. J.; Chitjian, C. A.; Bachman, J. L.; Ren, P.; Anslyn, E. V.; Dalby, K. N. *Bioorg. Med. Chem.* **2014**, *22*, 4910–4916; (d) Anderson, K.; Chen, Y.; Chen, Z.; Dominique, R.; Glenn, K.; He, Y.; Janson, C.; Luk, K.-C.; Lukacs, C.; Polonskai, A.; Qiao, Q.; Railkar, A.; Rossman, P.; Sun, H.; Xiang, Q.; Vilenchik, M.; Wovkulich, P.; Zhang, X. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6610–6615; (e) Han, F.; Lin, S.; Liu, P.; Tao, J.; Yi, C.; Xu, H. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4538–4541; (f) Zhang, J.-P.; Huang, J.; Liu, C.; Lu, X.-F.; Wu, B.-X.; Zhao, L.; Lu, N.; Guo, Q.-L.; Li, Z.-Y.; Jiang, C. *Chin. Chem. Lett.* **2014**, *25*, 1025–1028; (g) Fares, M.; Abou-Seri, S. M.; Abdel-Aziz, H. A.; Abbas, S. E.-S.; Youssef, M. M.; Eladwy, R. A. *Eur. J. Med. Chem.* **2014**, *83*, 155–166; (h) de la Bellacasa, R. P.; Roue, G.; Balsas, P.; Perez-Galan, P.; Teixido, J.; Colomer, D.; Borrell, J. I. *Eur. J. Med. Chem.* **2014**, *86*, 664–675; (i) Ramana, R. M. V.; Akula, B.; Cosenza, S. C.; Athuluridivakar, S.; Mallireddigari, M. R.; Pallela, V. R.; Billa, V. K.; Venkata, S. D. R. C.; Vijaya, Bharathi, E.; Vasquez-Del, Carpio, R.; Padgaonkar, A.; Baker, S. J.; Premkumar, Reddy, E. *J. Med. Chem.* **2014**, *57*, 578–599; (j) Alkorta, I.; Elguero, J. *J. Mol. Struct.* **2014**, 209–215; (k) Yang, T.; He, H.; Ang, W.; Yang, Y.-H.; Yang, J.-Z.; Lin, Y.-N.; Yang, H.-C.; Pi, W.-Y.; Li, Z.-C.; Zhao, Y.-L.; Luo, Y.-F.; Wei, Y. *Molecules* **2012**, *17*, 2351–2366.
10. (a) Jatczak, M.; Muylaert, K.; De Coen, L. M.; Keemink, J.; Wuyts, B.; Augustijns, P.; Stevens, C. V. *Bioorg. Med. Chem.* **2014**, *22*, 3947–3956; (b) DeGoey, D. A.; Betebenner, D. A.; Grampovnik, D. J.; Liu, D.; Pratt, J. K.; Tufanoa, M. D.; He, W.; Krishnan, P.; Pilot-Matias, T. J.; Marsh, K. C.; Molla, A.; Kempf, D. J.; Maring, C. J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3627–3630.
11. Bakulina, O. Y.; Igumnova, E. M.; Dar'in, D. V.; Lobanov, P. S. *Chem. Heterocycl. Compd.* **2013**, *49*, 466–471.
12. (a) Dar'in, D. V.; Ryazanov, S. G.; Selivanov, S. I.; Lobanov, P. S.; Potekhin, A. A. *Chem. Heterocycl. Compd.* **2008**, *44*, 461–465; (b) Dar'in, D. V.; Ivanov, A. Y.; Lobanov, P. S. *J. Heterocycl. Chem.* **2015**, *00*, 00, http://dx.doi.org/10.1002/jhet.2229
13. (a) Huang, C.; Yan, S.-J.; Zeng, X.-H.; Dai, X.-Y.; Zhang, Y.; Qing, C.; Lin, J. *Eur. J. Med. Chem.* **2011**, *46*, 1172–1180; (b) Yan, S.; Huang, C.; Su, C.; Ni, Y.; Lin, J. *J. Comb. Chem.* **2010**, *12*, 91–94; (c) Vypolzov, A. V.; Dar'in, D. V.; Lobanov, P. S. *Rus. Chem. Bull. Int. Ed.* **2012**, *61*, 877–880; (d) Igumnova, E. M.; Dar'in, D. V.; Selivanov, S. I.; Lobanov, P. S. *Chem. Heterocycl. Compd.* **2012**, *48*, 436–441.
14. (a) Hartman, G. D.; Hartman, R. D.; Cochran, D. W. *J. Org. Chem.* **1983**, *48*, 4119–4122; (b) Schnekenburger, J.; Riedel, H. *Arch. Pharm.* **1983**, *316*, 63–68.
15. Bunce, R. A.; Nammalwar, B.; Gnanasekaran, K. K.; Cain, N. R. *Tetrahedron* **2014**, *70*, 838–844.
16. (a) Yang, J.; Wang, C.; Xie, X.; Li, H.; Li, Y. *Eur. J. Org. Chem.* **2010**, 4189–4193; (b) Navarrete-Encina, P. A.; Squella, J. A.; Carbajo, J.; Conde, B.; Núñez-Vergara, L. J. *Synth. Commun.* **2007**, *37*, 2051–2060; (c) Di Stilo, A.; Visentin, S.; Cena, C.; Gasco, A. M.; Ermondi, G.; Gasco, A. *J. Med. Chem.* **1998**, *41*, 5393–5401.
17. Eliseev, I. I., Jr.; Dar'in, D. V.; Ryazanov, S. G.; Selivanov, S. I.; Lobanov, P. S.; Potekhin, A. A. *Chem. Heterocycl. Compd.* **2008**, *44*, 442–450.