Chemistry

FACILE SYNTHESIS OF 5(6)-PHENYL SUBSTITUTED THIENO[2,3-d]PYRIMIDIN-4-ONES

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New enamines of Gewald’s 4(5)-phenyl substituted thiophenes interaction with primary amines allowed to obtain 5(6)-phenylthieno[2,3-d]pyrimidin-4-ones with variable N³-substituents.

Keywords: amines, cyclocondensation, enamines, Gewald’s reaction, thieno[2,3-d]pyrimidin-4-ones.

Thienopyrimidines, particularly aromatically substituted have been shown to possess a variety of pharmacological activities like analgesic, anti-inflammatory, antipyretic, antimicrobial, fungicidal, antiplatelet [1, 2], CNS affecting activities [3], inhibitors of Cyclin D1-CDK4 [4]. It seems to be actual to propose a facile synthesis of 5(6)-phenyl-3(N)-substituted-thieno[2,3-d]pyrimidinones.

Earlier was proposed a new method for obtaining aliphatic substituted thieno[2,3-d]pyrimidin-4-ones [5–7] with practically unlimited possibilities to introduce the willing substitute at the position N³. Biological investigations of several obtained compounds as proteasome inhibitors were realized in Laboratory of Molecular and Functional Enzimologie and demonstrated that investigations are promising [8]. In this paper we enlarged proposed method for 5(6)-aromatically substituted thieno[2,3-d]pyrimidin-4-ones synthesis.

Gewald’s 2-aminothiophenes (1) [9] are easily reacting with DMF/DMA in boiling anhydrous xylene within 7 h with formation of the corresponding new β-dimethylaminomethyleneamino derivatives (2), bearing easily leaving dimethylamino group in high yields (up to 95%).

The obtained 2 in one stage leads to the novel 5(6)-Ph-3-R-thieno[2,3-d]-pyrimidin-4-ones (3) by refluxing in anhydrous xylene with various aliphatic substituted primary amines (see Scheme). The best yields were obtained, when reaction was realized with 1:3 molar ratio of dimethylaminomethyleneamino intermediates to the primary amines. The realization of reaction was detected by gaseous dimethylamine elimination.

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The diversity of amines used for cyclocondensations is connected with expected biological investigations. Several synthesized compounds are twice aromatic substituted, that can be interesting from the point of possible biological activity.

Reaction seems to be realized through the interaction of amine with dimethylaminomethyleneamino group with gaseous dimethylamine elimination and further intramolecular ring formation with elimination of ethanol.

Condensation with anilines of analogous dimethylaminovinyl derivatives usually is realized in the ambiance of glacial acetic acid for rising of nucleophilic reactivity of amines. In declared case thiophenes dimethylaminomethyleneamino derivative was condensed with several aromatic amines in proposed conditions and instead of expected thienopyrimidinone the reactions completely led to the initial aminothiophenes.

We have demonstrated the utility of enamines for synthesis of various N3-substituted 5(6)-phenylthieno[2,3-d]pyrimidin-4-ones from the common dimethylaminomethyleneamino intermediates in one stage.

**Experimental Part.**

**General Procedures.** Mp were determined on a SMP-10 melting point apparatus and are uncorrected. 1H NMR spectra were obtained on a Varian Mercury 300 VX spectrometer at 300 MHz with TMS as internal reference in DMSO-d6 solution at 303 K. IR spectra were measured by Nicolet FTIR NEXUS spectrophotometers in Nujol, recorded in KBr pellets. TLC analysis was performed on Silurol UV-254 plates, eluent acetone/benzene (1:3), visualization with iodine vapors. The elemental analyses matched the calculated composition.

3-component Gewald’s reaction for 2-amino-thiophene (1a) synthesis was realized using phenylacetaldehyde, ethyl cyanoacetate and sulphur. For 1b synthesis preliminary condensed aryldenecyanoacetates were used in 2-component reaction [9].
General Procedure for Synthesis of 2-(Dimethylaminomethyleneamino-thiophene-3-carboxylate (2 a, b). A mixture of corresponding thiophene (1 a, b), (10 mmol) and DMF/ DMA (1.56 mL, 12 mmol) in an anhydrous xylene (20 mL) was heated under reflux for 7 h. After cooling to room temperature 5 mL, light petroleum was added, precipitated crystals were filtered, washed with diethyl ether, and dried.

Ethyl 2-(dimethylamino-methyleneamino)-5-phenyl-thiophene-3-carboxylate (2 a).

Yield 94%; mp 80°C; 1H NMR, δ, ppm: 1.05 t (J=7.1 Hz, 3H); 3.04 s (3H); 3.11 s (3H); 4.01 q (J=7.1 Hz, 2H); 6.44 s (1H); 7.15–7.38 m (5H); 7.76 s (1H).

Ethyl 2-(dimethylamino-methyleneamino)-4-phenyl-thiophene-3-carboxylate (2 b).

Yield 95%; mp 95°C; 1H NMR, δ, ppm: 1.05 t (J=7.1 Hz, 3H); 3.04 s (3H); 3.11 s (3H); 4.03 q (J=7.1 Hz, 2H); 6.48 s (1H); 7.17–7.37 m (5H); 7.73 s (1H).

General Procedure for Synthesis of Substituted Thiophene[2,3-d]pyrimidin-4(3H)-ones (3 a–n). A mixture of 2 a, b (5 mmol) and primary amine (15 mmol) in an anhydrous xylene (20 mL) was heated under reflux for 30 h (extra 3 h after cessation of gaseous dimethylaniline isolation), allowed to cool to room temperature; 8 mL of light petroleum was added. Precipitated crystals were filtered, washed with diethyl ether and dried. NMR and physicochemical data of synthesized compounds are presented below:

3-(4-Chlorobenzyl)-5-phenylthiopheno[2,3-d]pyrimidin-4(3H)-one (3 a): from 2 b and 4-chlorobenzylamin.

Yield 47.6%, mp 177°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.55 s (1H); 7.50–7.39 m (4H); 7.38–7.25 m (5H); 7.24 s (1H); 5.16 s (2H).

3-((1-Ethylpyrrolidin-2-yl)methyl)-5-phenylthiopheno[2,3-d]pyrimidin-4(3H)-one (3 b): from 2 b and 2-aminomethyl-1-ethylpyrrolidine.

Yield 37.6%, mp 132°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.22 s (1H); 7.51–7.46 m (2H); 7.38–7.29 m (3H); 7.18 s (1H); 3.90 ddd (J=41.7; 13.1; 5.6 Hz, 2H); 3.16–3.08 m (1H); 2.92–2.85 m (1H); 2.73–2.65 m (1H); 2.40–2.17 m (2H); 1.87–1.51 m (4H); 1.03 t (J=7.2 Hz, 3H).

3-(2-Hydroxyethyl)-5-phenylthiopheno[2,3-d]pyrimidin-4(3H)-one (3 c): from 2 b and 2-aminoethanol.

Yield 35.7%, mp 133–134°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.20 s (1H); 7.54–7.47 m (2H); 7.38–7.29 m (3H); 7.19 s (1H); 4.68 t (J = 5.2 Hz, 1H); 4.08 – 3.99 m (2H); 3.67dd (J = 9.5, 4.7 Hz, 2H).

5-Phenyl-3-(pyridin-3-ylmethyl)thiopheno[2,3-d]pyrimidin-4(3H)-one (3 d): from 2 b and 3-aminomethylpyridin.

Yield 77.7%, mp 200°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.66 d (J=2.2 Hz, 1H); 8.63 s (1H); 8.44 dd (J=4.8; 1.6 Hz, 1H); 7.78 dt (J=7.9; 2.0 Hz, 1H); 7.50–7.46 m (2H); 7.38–7.29 m (3H); 7.29–7.24 m (1H); 7.23 s (1H); 5.21 s (2H).
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3-(4-Methylbenzyl)-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one (3 e): from 2 b and 4-methylbenzylamin.

Yield 75.1%, mp150°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.45 s (1H); 7.51–7.46 m (2H); 7.39–7.30 m (3H); 7.29–7.24 m (2H); 7.21 s (1H); 7.12–7.06 m (2H); 5.13 s (2H); 2.31 s (3H).

3-(1H-Imidazol-1-yl)propyl-6-phenylthieno[2,3-d]pyrimidin-4(3H)-one (3 f): from 2 a and 1-(3-aminopropyl)imidazole.

Yield 29.9%, mp173°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.29 s (1H); 7.71–7.64 m (3H); 7.54 t (J=1.0 Hz, 1H); 7.45–7.37 m (2H); 7.36–7.29 m (1H); 7.07 t (J=1.1 Hz, 1H); 6.84 t (J=1.1 Hz, 1H); 4.06 dt (J=14.3; 7.3 Hz, 4H); 2.31–2.17 m (2H).

3-(Benzo[d][1,3]dioxol-5-ylmethyl)-6-phenylthieno[2,3-d]pyrimidin-4(3H)-one (3 g): from 2 a and piperonylamin.

Yield 49.8%, mp 188°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.45 s (1H); 7.68–7.63 m (3H); 7.44–7.28 m (3H); 7.00 d (J=1.6 Hz, 1H); 6.95 dd (J=7.9; 1.7 Hz, 1H); 6.75 d (J=7.9 Hz, 1H); 5.95 s (2H); 5.11 s (2H).

6-Phenyl-3-(pyridin-2-ylmethyl)thieno[2,3-d]pyrimidin-4(3H)-one (3 h): from 2 a and 2-aminomethylpyridin.

Yield 46.8%, mp 159°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.49 ddd (J=4.9; 1.8; 1.0 Hz, 1H); 8.39 s (1H); 7.73 td (J=7.6; 1.8 Hz, 1H); 7.67–7.63 m (2H); 7.63 s (1H); 7.43–7.36 m (3H); 7.34–7.27 m (1H); 7.24 dd (J=7.5; 4.8; 1.0 Hz, 1H); 5.29 s (2H).

3-(3,4-Dimethoxybenzyl)-6-phenylthieno[2,3-d]pyrimidin-4(3H)-one (3 i): from 2 a and 3,4-dimethoxybenzylamin.

Yield 51.8%, mp 169°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.46 s (1H); 7.67 s (1H); 7.68–7.62 m (3H); 7.44–7.36 m (2H); 7.35–7.28 m (1H); 7.07 d (J=2.0 Hz, 1H); 6.97 dd (J=8.2; 2.0 Hz, 1H); 6.78 dd (J=13.0; 8.2 Hz, 2H); 5.12 s (2H); 3.81 s (3H); 3.77 s (3H).

3-Benzyl-6-phenylthieno[2,3-d]pyrimidin-4(3H)-one (3 j): from 2 a and benzylamin.

Yield 51.1%, mp 166°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.44 s (1H); 7.66 s (1H); 7.68–7.63 m (2H); 7.44–7.37 m (4H); 7.35–7.25 m (4H); 5.22 s (2H).

6-Phenyl-3-((tetrahydrofuran-2-yl)methyl)thieno[2,3-d]pyrimidin-4(3H)-one (3 k): from 2 a and tetrahydrofurfurylamin.

Yield 52.2%, mp 105°C. 1H NMR (300 MHz, DMSO), δ, ppm: 8.16 s (1H); 7.68–7.63 m (2H); 7.65 s (1H); 7.44–7.37 m (2H); 7.34–7.26 m (1H); 4.25 dd (J=13.4; 3.2 Hz, 1H); 4.14 ddd (J=14.6; 6.9; 3.1 Hz, 1H); 3.91–3.82 m (2H); 3.74–3.66 m (1H); 2.87 s (1H); 2.13–2.02 m (1H); 1.97–1.84 m (2H); 1.71–1.58 m (1H).

3-(2-Chlorophenethyl)-6-phenylthieno[2,3-d]pyrimidin-4(3H)-one (3 l): from 2 a and 2-chlorophenethylamin.

Yield 52.2%, mp 149°C. 1H NMR (300 MHz, DMSO), δ, ppm: 7.92 s (1H);
7.67 s (1H); 7.69–7.65 m (2H); 7.44–7.35 m (3H); 7.35–7.29 m (1H); 7.28–7.19 m (3H); 4.26 t \( (J=7.2 \text{ Hz}, 2\text{H}) \); 3.20 t \( (J=7.2 \text{ Hz}, 2\text{H}) \).

3-(2-(Dimethylamino)ethyl)-6-phenylthieno[2,3-d]pyrimidin-4(3H)-one \( (3 \text{ m}) \): from 2 a and 2-(dimethylamino)ethylamin.

Yield 58.7\%, mp 136\(^{\circ}\)C. \(^1\)H NMR (300 MHz, DMSO), \( \delta \) ppm: 8.18 s (1H); 7.68–7.63 m (3H); 7.43–7.36 m (2H); 7.34–7.27 m (1H); 4.07 t \( (J=6.0 \text{ Hz}, 2\text{H}) \); 2.58 t \( (J=6.0 \text{ Hz}, 2\text{H}) \); 2.26 s (6H).

3-\( (1\text{-H}-\text{Imidazol-1-yl})\text{propyl}\)-6-phenylthieno[2,3-d]pyrimidin-4(3H)-one \( (3 \text{ n}) \): from 2 a and 1-(3-aminopropyl)imidazole.

Yield 52.7\%, mp 91\(^{\circ}\)C. \(^1\)H NMR (300 MHz, DMSO), \( \delta \) ppm: 8.28 s (1H); 7.69–7.64 m (3H); 7.53 t \( (J=1.0 \text{ Hz}, 1\text{H}) \); 7.44–7.37 m (2H); 7.35–7.28 m (1H); 7.06 t \( (J=1.2 \text{ Hz}, 1\text{H}) \); 6.84 t \( (J=0.9 \text{ Hz}, 1\text{H}) \); 4.07 dt \( (J=14.3, 7.2 \text{ Hz}, 4\text{H}) \); 2.30–2.19 m (2H).

**REFERENCES**