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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 N^3-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, anticonvulsant, 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 N^3. 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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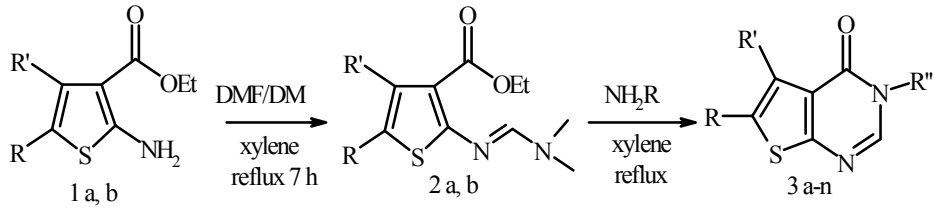
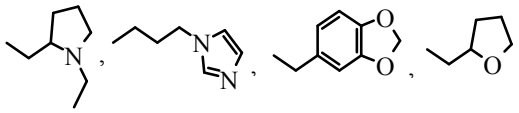
The diversity of amines used for cyclocondensations is connected with expected biological investigations. Several synthesized compounds are twice aromatic substituted, that can be interesting from the point of possible biological activity.

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.



R, R' = H,

R'' = -$(CH_2)_2OH$, -$(CH_2)_2N(CH_3)_2$, -$CH_2C_6H_5$, -$CH_2C_6H_4Cl$, -$CH_2C_6H_4CH_3$, -$CH_2C_6H_4OCH_3$,

-$(CH_2)_2C_6H_5Cl$, -CH_2Py, 

Scheme.

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 N^3-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. ^{1}H NMR spectra were obtained on a Varian Mercury 300 VX spectrometer at 300 *MHz* with TMS as internal reference in DMSO-d_6 solution at 303 *K*. IR spectra were measured by Nicolet FTIR NEXUS spectrophotometers in Nujol, recorded in KBr pellets. TLC analysis was performed on Silufol 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 (**1 a**) synthesis was realized using phenylacetaldehyde, ethyl cyanoacetate and sulphur. For **1 b** synthesis preliminary condensed arylidenecyanoacetates 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, dried.

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

Yield 94%; mp 80^0*C*; ^{1}H 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 95^0*C*; ^{1}H 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 Thieno[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 dimethylamine 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-phenylthieno[2,3-d]pyrimidin-4(3H)-one (**3 a**)*: from **2 b** and 4-chlorobenzylamin.

Yield 47.6%, mp177^0*C*. ^{1}H 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-phenylthieno[2,3-d]pyrimidin-4(3H)--one (**3 b**)*: from **2 b** and 2-aminomethyl-1-ethylpyrrolidine.

Yield 37.6%, mp 132^0*C*. ^{1}H 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-phenylthieno[2,3-d]pyrimidin-4(3H)-one (**3 c**)*: from **2 b** and 2-aminoethanol.

Yield 35.7%, mp 133–134^0*C*. ^{1}H 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)thieno[2,3-d]pyrimidin-4(3H)-one (**3 d**)*: from **2 b** and 3-aminomethylpyridin.

Yield 77.7%, mp 200^0*C*. ^{1}H 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).

*3-(4-Methylbenzyl)-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one (**3 e**)*: from **2 b** and 4-methylbenzylamin.

Yield 75.1%, mp150^0*C*. ^{1}H 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-(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%, mp173^0*C*. ^{1}H 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 188^0*C*. ^{1}H 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 159^0*C*. ^{1}H 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 ddd (*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 169^0*C*. ^{1}H 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 166^0*C*. ^{1}H 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 105^0*C*. ^{1}H 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 149^0*C*. ^{1}H 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 *Hz*, 2H); 3.20 t (*J*=7.2 *Hz*, 2H).

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

Yield 58.7%, mp 136^0*C*. ^{1}H NMR (300 *MHz*, DMSO), *δ*, *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 *Hz*, 2H); 2.58 t (*J*=6.0 *Hz*, 2H); 2.26 s (6H).

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

Yield 52.7%, mp 91^0*C*. ^{1}H NMR (300 *MHz*, DMSO), *δ*, *ppm*: 8.28 s (1H); 7.69–7.64 m (3H); 7.53 t (*J*=1.0 *Hz*, 1H); 7.44–7.37 m (2H); 7.35–7.28 m (1H); 7.06 t (*J*=1.2 *Hz*, 1H); 6.84 t (*J*=0.9 *Hz*, 1H); 4.07 dt (*J*=14.3; 7.2 *Hz*, 4H); 2.30–2.19 m (2H).

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REFERENCES

1. **Ibrachim J.A., Elwahy A.H.M., Kadry A.M.** Thienopyrimidines: Synthesis, Reactions and Biological Activity. // Advances in Heterocyclic Chemistry, 1996, v. 65, p. 235–281.
2. **Varvounis G., Giannopoulos T.** Synthesis, Chemistry, and Biological Properties of Thienopyrimidines. // Advances in Heterocyclic Chemistry, 1996, v. 66, p. 193–283.
3. **Sharma C., Terande S., Chavan R., Bhosale A.V.** Synthesis of Thienopyrimidines and their Antipsychotic Activity. // E-Journal of Chemistry, 2010, v. 7, № 2, p. 655–664. http://www.e-journals.net
4. **Horiuchi T., Chiba J., Uoto K., Soga T.** Discovery of Novel Thieno[2,3-d]pyrimidin-4-Yl hydrazone-Based Inhibitors of Cyclin D1-CDK4: Synthesis, Biological Evaluation and Structure-Activity Relationships. // Bioorg. & Med. Chem. Lett., 2009, v. 19, № 2, p. 305–308.
5. **Hovhannisyan A., Melikyan G., Avetisyan A.** Republic of Armenia, patent № 1469 A2, 06.07.2004.
6. **Melikyan G.S., Hovannisyan A.A., Aristakesyan L.A.** A New Approach to the Synthesis of 3*N*-Substituted Tthienopyrimidine-4-ones on the Base of Ethyl Aminothiophenecarboxilates. // Proceedings of the YSU. Cemistry and Biology, 2011, № 3 (226), p. 30–35 (in Russian).
7. **Hovhannisyan A., Aristakesyan L., Melikyan G.** Facile Approach to the Synthesis of Substituted Thieno[2,3-d]pyrimidin-4-Ones. // Het. Com., 2012, v. 18, № 5–6, p. 253–256, ISSN (Online) 2191-0197, ISSN (Print) 0793-0283, DOI: 10.1515/hc-2012-0095.
8. **Hovhannisyan A., Pham T.H., Bouvier D., Piroyan A., Dufau L., Qin L., Cheng Y., Melikyan G., Reboud-Ravaux M., Bouvier-Durand M.** New C4-and C1-Derivatives of Furo[3,4-c]pyridine-3-ones and New Furo- and Thieno-[2,3-d]pyrimidine-4-one Related Compounds. Discovery of Site-Specific Inhibitors of the Constitutive vs Immunoproteasome. // Bioorg. Med. Chem. Lett., 2013, v. 23, № 24.
9. **Gewald K., Schinke E., Böttcher H.** For the Synthesis of 2-Amino Thiophenes. // Chem. Ber., 1966, v. 99, p. 94–99.