FACILE AND EFFICIENT ONE-POT PROCEDURE FOR THIENO[2,3-e][1,2,3]TRIAZOLO[1,5-a]PYRIMIDINES PREPARATION

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GRAPHICAL ABSTRACT

Abstract Base-catalyzed cycloaddition reactions of heterocyclic azides with activated nitriles were studied. Convenient, efficient, and high-yield synthetic method for thieno [2,3-e][1,2,3]triazolo[1,5-a]pyrimidines preparation from available starting reagents without complicated protocols was elaborated. Such an approach allows creation of broad combinatorial libraries for drug discovery.

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Keywords Domino reaction; thieno[2,3-d]pyrimidin-4(3H)-one; thiophene; triazole

INTRODUCTION

Thienopyrimidines are significant because of their application in technical aims and wide-ranging biological activities, including anticancer and antiviral agents.[1–6] In addition, it is wellknown that triazoles are also very attractive targets for combinatorial library synthesis because of their broad range of pharmaceutical activities.[7–10] Therefore, new methodology for the preparation of these compounds with both heterocyclic frameworks is of interest and utility. However, synthesis of diverse heterocyclic molecules from the readily available starting materials in a cost- and time-effective manner is an enduring challenge for organic chemists. Recently,

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Pokhodylo and coworkers have reported base-catalyzed cycloaddition reactions of new heterocyclic azides with activated methylene compounds providing new ring systems of thieno[3,2-e][1,2,3]triazolo[1,5-a]pyrimidines. Alternatively, Ivachtchenko et al. have described the preparation of a number of 3-(phenylsulfonyl)thieno[2,3-e][1,2,3]triazolo[1,5-a]pyrimidines as new potent and selective 5-HT6 receptor antagonists. Moreover, such sulfonyl-thieno[2,3-e][1,2,3]triazolo[1,5-a]pyrimidine derivatives have been identified as potent HIV-1 replication inhibitors. To develop new medicinally active compounds with the thienotriazolopyrimidine core and to find the application of the described synthetic approach, we continued investigation of the syntheses of such heterocycles which were accessible by 1,3-dipolar cycloaddition reactions and could be used to broaden the combinatorial libraries.

Herein, we report a convenient and mild method for the synthesis of thieno[2,3-e][1,2,3]triazolo[1,5-a]pyrimidinones from thiophene-3-yl-azides and activated methylene nitriles via 1,3-dipolar cycloaddition reaction.

RESULTS AND DISCUSSION

The presented synthetic route is summarized in Scheme 1. In the first step 3-aminothiophenes were prepared from the β-chloroacetonitriles; the latest ones could be easily obtained from commercially available carbonyl compounds via the known procedure. In contrast to Gewald 2-aminothiophenes, 3-aminothiophenes were transformed into the corresponding azides without any complicated procedures. Hence, diazotization of amino derivatives was performed in concentrated hydrochloric acid and conversion of the obtained diazonium salts into azides by the reaction with sodium azide led to the formation of stable crystalline 3-azidothiophenes. Heterocyclic azides as 1,3-dipolar agents proved to be feasible and highly reactive substances for the novel polycyclic ring system construction.

The anionic domino reaction of 3-azidothiophenes with nitriles occurred in the presence of sodium methoxide in methanol at room temperature, leading to the

![Scheme 1. Synthetic route of thieno[2,3-e][1,2,3]triazolo[1,5-a]pyrimidine 7 construction.](image-url)
formation of thieno[2,3-e][1,2,3]triazolo[1,5-a]pyrimidines. Under these conditions, the cycloaddition reaction proceeded smoothly to completion and thienotriazolopyrimidines were isolated in good yields and purity. The mechanism of such reactions involves two stages. The azido group is supposed to attack the dipolarophile in the same way the anion of methylene active acetonitrile does. The intermediate triazole 6, obtained from 1,3-dipolar cycloaddition reaction, contains an amino group, which has a tendency to further the reaction with the carboxylate function, providing formation of the pyrimidine ring.

It is known that such a cyclization can take place in two ways (Scheme 2). The direction of the reaction depends on the nature of R2-group in activated nitriles II.

Nitriles II with electron-donating heterocycles (for example 5c) react with azides I without formation of Dimroth-type rearrangement products; only one regioisomer III B was observed (path B). However, this method has a limitation. In the case of nitriles with electron-withdrawing substituents (ex. R2 = Ph) (path A) the mixture of regioisomers was detected with a favor of regioisomer III A, which is not mentioned in the work and should be considered.

The structure of the polycyclic ring system was determined from the NMR spectroscopic data.

CONCLUSION

In summary, we have described a simple, efficient, one-pot, regioselective synthesis of the substituted thieno[2,3-e][1,2,3]triazolo[1,5-a]pyrimidines, which are suitable for the evaluation of biological activity and further drug discovery.

EXPERIMENTAL

1H NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for 1H) with tetramethylsilane (TMS) or deuterated solvent as an internal reference. Mass spectra were run using Agilent 1100 series LC/MSD with an
API-ES/APCI ionization mode. Satisfactory elemental analyses were obtained for new compounds (C ± 0.17, H ± 0.21, N ± 0.19).

**General Procedure for the Preparation of Azides 4a–c**

Appropriate 3-aminothiophene 1 (0.02 mol) was dissolved in concentrated hydrochloric acid (5 mL), and ice (15 g) was added. When the mixture was cooled to 0 °C, saturated sodium nitrite (1.73 g, 0.025 mol) aqueous solution was added keeping the temperature below 5 °C. After 10 min, resinous sediment (if it was formed) should be filtered. To the filtrated solution of the diazonium salt, sodium azide (1.3 g; 0.02 mol) in 5 mL of water was added dropwise. The solution was left for 15 min at room temperature and the azide was filtered. Azides were used without subsequent cleaning.

**Methyl 3-Azidothiophene-2-carboxylate 4a**

Yield: 81%; mp: 72 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 7.34 (d, J = 4.9 Hz, 1H, ThH-5), 6.71 (d, J = 5.0 Hz, 1H, ThH-4), 3.21 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 164.34 (CO), 134.10 (C-3), 132.99 (C-2), 126.16 (C-5), 123.55 (C-4). MS (m/z): 170 (M⁺ + 1). Anal. calcd. for C₅H₃N₃O₂S: C, 35.50; H, 1.79; N, 24.84. Found: C, 35.67; H, 1.91; N, 24.73.

**General Procedure for the Preparation of [2,3-e][1,2,3]Triazolo[1,5-a]pyrimidines 7a–h**

Sodium (0.23 g, 0.01 mol) was added to 20 mL of absolute methanol. Nitrile 5 (0.01 mol) and the appropriate azide 4 (0.01 mol) were slowly added to the obtained sodium methylate solution. The mixture was kept for 30 min. The obtained solid was filtered, washed with water, and crystallized from ethanol.

**SUPPORTING INFORMATION**

¹H and ¹³C NMR spectra of all new compounds can be found via the “Supplementary Content” section of this article’s Web page.

**REFERENCES**

1. Jordan, A.; Bedford, S.; Burkhard, K.; Yule, I.; Poullennec, K. Thienopyrimidine compounds and compositions. US Patent 0298349 A1, 2010.
2. Babu, Y.; Chand, P.; Wu, M.; Kotian, P. L.; Kumar, V. S.; Lin, T.-H.; El-Kattan, Y.; Ghosh, A. K. Therapeutic furopyrimidines and thienopyrimidines. WO Patent 050161, 2006.
3. McClellan, W. J.; Dai, Y.; Abad-Zapatero, C.; Albert, D. H.; Bouska, J. J.; Glaser, K. B.; Magoc, T. J.; Marcotte, P. A.; Osterling, D. J.; Stewart, K. D.; Davidsen, S. K.; Michaelides, M. R. Bioorg. Med. Chem. Lett. 2011, 21, 5620–5624.
4. Edgar, K. A.; Wallin, J. J.; Berry, M.; Lee, L. B.; Prior, W. W.; Sampath, D.; Friedman, L. S.; Belvin, M. Cancer Res. 2010, 70, 1164–1172.
5. Heffron, T. P.; Wei, B. Q.; Olivero, A.; Staben, S. T.; Tsui, V.; Do, S.; Dotson, J.; Folkes, A. J.; Goldsmith, P.; Goldsmith, R.; Gunzner, J.; Lesnick, J.; Lewis, C.; Mathieu, S.; Nonomiya, J.; Shuttleworth, S.; Sutherland, D. P.; Wan, N. C.; Wang, S.; Wiesmann, C.; Zhu, B.-Y. J. Med. Chem. 2011, 54, 7815–7833.
6. Bowers, S.; Truong, A. P.; Neitz, R. J.; Hom, R. K.; Sealy, J. M.; Probst, G. D. et al. Bioorg. Med. Chem. Lett. 2011, 21, 5521–5527.
7. Olesen, P. H.; Sorensen, A. R.; Urso, B.; Kurtzhals, P.; Bowler, A. N.; Ehrbar, U.; Hansen, B. F. J. Med. Chem. 2003, 46, 3333–3341.
8. Bascal, Z.; Holdén-Dye, L.; Willis, R. J.; Smith, S. W. G.; Walker, R. J. Parasitology 1996, 112, 253–269.
9. Biagi, G.; Giorgi, I.; Livi, O.; Lucacchini, A.; Martini, C.; Scartoni, V. J. Pharm. Sci. 1993, 82, 893–896.
10. Moltzen, E. K.; Pedersen, H.; Bogeso, K. P.; Meier, E.; Frederiksen, K.; Sanchez, C.; Lembol, K. L. J. Med. Chem. 1994, 37, 4085–4099.
11. Pokhodylo, N. T.; Matiychuk, V. S.; Obushak, M. D. Tetrahedron 2009, 65, 2678–2683.
12. Ivachtchenko, A. V.; Golovina, E. S.; Kadieva, M. G.; Koryakova, A. G.; Kovalenko, S. M.; Mitkin, O. D.; Okun, I. M.; Ravnyeyko, I. M.; Tkachenko, S. E.; Zaremba, O. V. Bioorg. Med. Chem. 2010, 18, 5282–5290.
13. Kim, J.; Kwon, J.; Lee, D.; Jo, S.; Park, D. S.; Choi, J.; Park, E.; Hwang, J. Y.; Ko, Y.; Choi, I.; Ju, M. K.; Ahn, J. Y.; Kim, J.; Han, S. J.; Kim, T.-H.; Cechetto, J.; Name, J.; Ahn, S.; Sommer, P.; Liuzzi, M.; No, Z.; Lee, J. Bioorg. Med. Chem. Lett. 2013, 23, 153–157.
14. (a) Liebscher, J.; Neumann, B.; Hartmann, H. J. Prakt. Chem. 1983, 325 (6), 915–918; (b) Gewald, K.; Hain, U. Monatsh. Chem. 1992, 123, 455–459.
15. Pokhodylo, N. T.; Shyyka, O. Y.; Savka, R. D.; Obushak, M. D. Phosphorus, Sulfur Silicon Relat. Elem. 2010, 185 (10), 2092–2100.
16. Pokhodylo, N. T.; Teslenko, Y. O.; Matiychuk, V. S.; Obushak, M. D. Synthesis 2009, 17, 2741–2748.