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HETEROCYCLES IN FOCUS

Recent approaches to the synthesis of thieno[2,3-*b*]pyridines (microreview)

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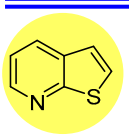


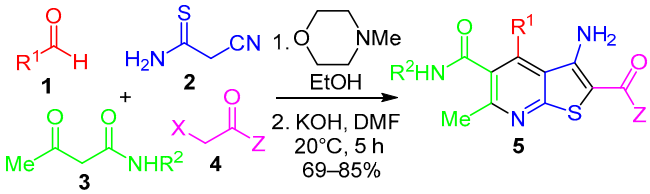
This microreview describes recent approaches to the synthesis of thieno[2,3-*b*]pyridine derivatives. Selected works published in 2015–2019 are reviewed.

Introduction

Thieno[2,3-*b*]pyridine derivatives are an important class of heterocyclic compounds due to their pharmacological and biological utility, including anticancer, antidermatophytic, antimalarial, anti-Alzheimer's, antifungal, anti-inflammatory, insecticidal, and antiviral activities.[1] Thieno[2,3-*b*]pyridines were also reported as Pim-1 kinase inhibitors and multidrug resistance modulators.[2] Therefore, many efforts have been made to synthesize these important heterocycles.[3]

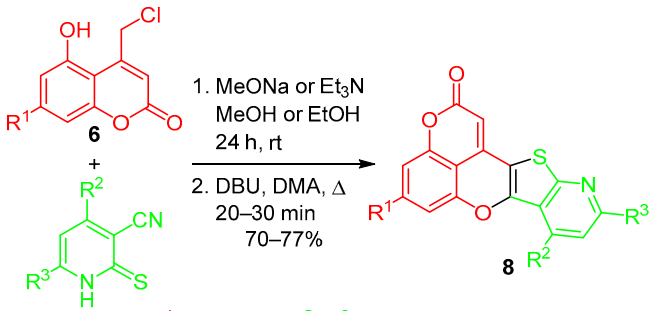
2-Thioxopyridine-3-carbonitrile-based reactions

There are many recent papers devoted to the synthesis of thieno[2,3-*b*]pyridines using substituted 2-thioxopyridine-3-carbonitrile or 3-cyanopyridine-2-thiolate as starting material or key intermediate.[4] Dyachenko et al. described multicomponent synthesis of functionalized thieno[2,3-*b*]-pyridines **5** starting from compounds **1**–**4** through 3-cyanopyridine-2-thiolate intermediate.[5]



R^1 = 3-Me-thiophen-2-yl, furan-2-yl, 2-ClC_6H_4
R^2 = Ph, 4-ClC_6H_4, 2-$MeOC_6H_4$; X = Br, Cl
Z = 4-MeC_6H_4, 4-BrC_6H_4NH, 4-$MeOC_6H_4$, NH_2, *n*-BuO, *i*-PrO

The reaction between 4-(chloromethyl)-5-hydroxycoumarins **6** and 2-thioxopyridine-3-carbonitriles **7** in the presence of a base leads to pyrano[4",3",2":4',5']chromeno[2',3':4,5]-thieno[2,3-*b*]pyridin-2-ones **8** in two synthetic steps.[6]



R^1 = OH, Me; R^2, R^3 = H, Me

Seyed Sajad Sajadikhah was born in 1982 in Mamasani, Fars province, Iran. He obtained his BSc in pure chemistry from the University of Isfahan in 2006, MSc and PhD in organic chemistry under supervision of Prof. M. T. Maghsoodlou from the University of Sistan and Baluchestan, Zahedan in 2009 and 2013, respectively. Currently he is an assistant professor at the Department of Chemistry at the Payame Noor University, Iran. His research focuses on organic synthesis, heterocyclic chemistry and catalysts.

Ghasem Marandi was born in 1973 in Khoy, Iran, and received his BSc degree in chemistry from the Payame Noor University in 1999. To complete MSc degree in organic chemistry, he joined the University of Sistan and Baluchestan in 2002. He earned PhD degree in organic chemistry in 2009. His research projects for MSc and PhD degrees were supervised by Prof. M. T. Maghsoodlou. From 2011, he is an assistant professor at the Science Faculty of Urmia University. His research interests focus on synthesis and methodology, he is a coauthor of more than 50 papers.

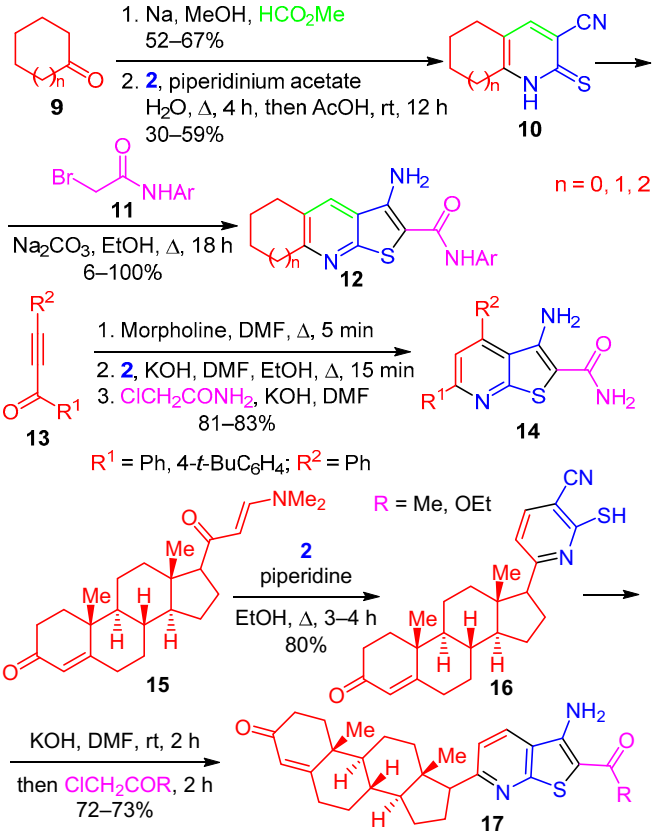
2-Thioxopyridine-3-carbonitrile-based reactions (continued)

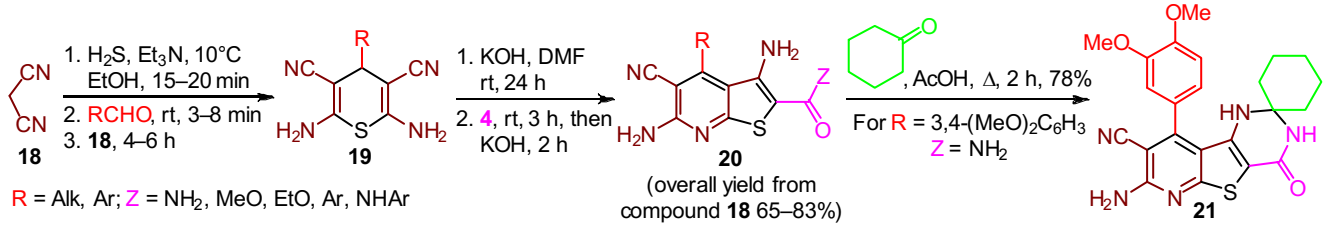
Leung et al. developed a practical synthesis of cycloalkylthienopyridine-2-carboxamides **12** starting from cycloalkanones **9**, methyl formate, 2-cyanoethanethioamide (**2**), followed by the reaction of 2-thioxopyridine-3-carbonitrile intermediate **10** with *N*-aryl-2-bromoacetamides **11**. Anticancer activity of compounds **12** was investigated.[7]

The Bohlmann–Rahtz reaction of α,β-acetylenic ketones **13** with 2-cyanothioacetamide **2** followed by a tandem *S*-alkylation/Thorpe–Ziegler cyclization reaction with chloroacetamide leads to thieno[2,3-*b*]pyridines **14**.[8]

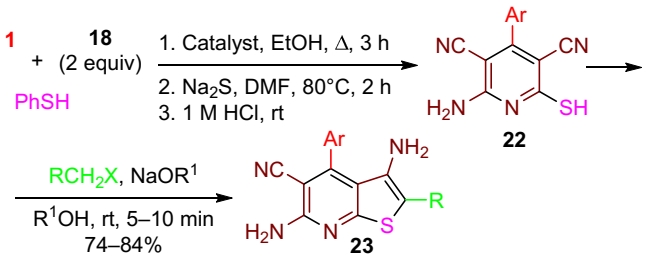
Yahya et al. reported the synthesis of new progesterone derivatives **17** bearing thieno[2,3-*b*]pyridine substituent. Starting enaminone **15** was obtained from the reaction of progesterone with dimethylformamide–dimethylacetal in dry xylene under reflux. Condensation of compound **15** with 2-cyanoethanethioamide (**2**) gave 2-thioxopyridine-3-carbonitrile **16**. Subsequent *S*-alkylation and cyclization produced thienopyridine **17**. Synthesized products **17** were tested for the cytotoxic effect against human breast cancer cells.[9]

The reaction of malononitrile (**18**), H_2S, and aldehydes in the presence of Et_3N afforded 4*H*-thiopyran **19**. Recyclization of compound **19** under alkaline conditions led to 3-cyanopyridine-2-thiolate intermediate. Its *S*-alkylation with α-halocarbonyl compounds **4** and subsequent intramolecular cyclization afforded thieno[2,3-*b*]pyridines **20**. Further reaction of the vicinal amino and carbamoyl groups with cyclohexanone in glacial AcOH gave spiro compound **21**.[10]



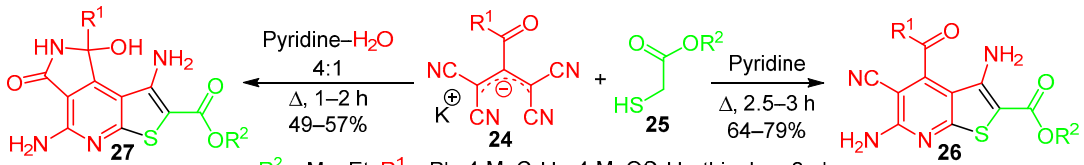


An efficient route for the synthesis of thieno[2,3-*b*]pyridines **23** was reported by Alinaghizadeh et al.[11] One-pot three-component reaction of aldehydes **1**, malononitrile (**18**), and thiophenol in the presence of catalysts (Et_3N, high surface area or nanosized MgO) in EtOH led to 2-amino-4-aryl-6-(phenylsulfanyl)pyridine-3,5-dicarbonitrile, which was reduced by Na_2S to compounds **22**. Sodium alkoxide-catalyzed *S*-alkylation of 2-amino-4-aryl-6-mercaptopyridine-3,5-dicarbonitriles **22** followed by cyclization reaction gave thienopyridines **23**.



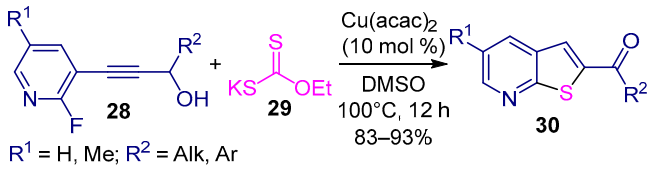
Cascade heterocyclization of tetracyanopropenide

Highly substituted thieno[2,3-*b*]pyridines **26** were obtained through cascade heterocyclization of 2-acyl-1,1,3,3-tetracyanopropenide salts **24** with mercaptoacetate **25** in refluxing pyridine.[12] Use of a mixture of pyridine–H_2O, 4:1, as a solvent led to pyrrolo[3,4-*d*]thieno[2,3-*b*]pyridines **27** in 49–57% yields.[13]



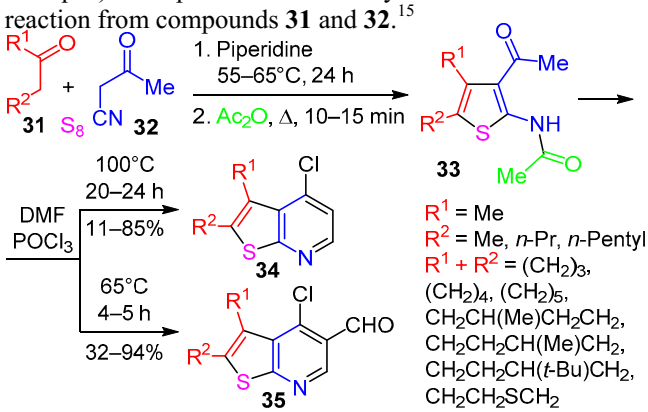
Cu-catalyzed cyclization

Li et al. reported an efficient approach to 2-acylthieno-pyridines **30** from (2-fluoropyridin-3-yl)alkynols **28** through nucleophilic thiolation, Cu-catalyzed thioester cleavage, *5-endo-dig* cyclization, and oxidation reaction cascade. Two equivalents of potassium ethyl xanthate (**29**) were used as sulfur source and probably as facilitator of oxidation process *via* coordination with Cu complexes.[14]

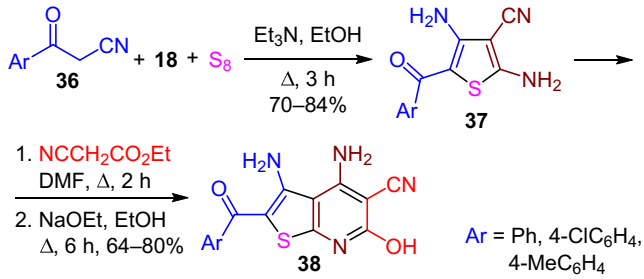


Thiophene-based reactions

Vilsmeier–Haack reagent was used to produce 4-chloro-thieno[2,3-*b*]pyridines **34** and formylated 4-chlorothieno-[2,3-*b*]pyridines **35** from *N*-protected 3-acetyl-2-amino-thiophenes **33**. The reaction was performed at 65 or 100°C with different amounts of Vilsmeier–Haack reagent (6 and 12 equiv). Thiophenes **33** were synthesized *via* Gewald reaction from compounds **31** and **32**.[15]



Mohareb and Ibrahim reported another strategy for the synthesis of thieno[2,3-*b*]pyridine derivatives **38**.[16] Thiophenes **37**, synthesized from 3-oxo-3-propanenitriles **36**, were reacted with ethyl cyanoacetate affording 2-(*N*-cyano-acetamido)thiophene. The latter underwent cyclization in the presence of NaOEt to give the final products **38**. Compounds **38** were tested for anticancer activity and showed good results.



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References

1. (a) Abdelriheem, N. A.; Ahmad, S. A.-K.; Abdelhamid, A. O. *Molecules* **2015**, *20*, 822. (b) Liu, H.; Zaplishnyy, V.; Mikhaylichenko, L. *J. Chem. Educ.* **2016**, *93*, 1785. (c) Masch, A.; Nasereddin, A.; Alder, A.; Bird, M. J.; Schweda, S. I.; Preu, L.; Doering, C.; Dzikowski, R.; Gilberger, T. W.; Kunick, C. *Malar. J.* **2019**, *18*, 89.
2. (a) Naguib, B. H.; El-Nassan, H. B. *J. Enzyme Inhib. Med. Chem.* **2016**, *31*, 1718. (b) Gao, L.-J.; Kovachova, S.; Šála, M.; Ramadori, A. T.; De Jonghe, S.; Herdewijn, P. *J. Med. Chem.* **2014**, *57*, 7624. (c) Krauze, A.; Grinberga, S.; Krasnova, L.; Adlere, I.; Sokolova, E.; Domracheva, I.; Shestakova, I.; Andzans, Z.; Duburs, G. *Bioorg. Med. Chem.* **2014**, *22*, 5860.
3. El-Sayed, H. A. *J. Iran. Chem. Soc.* **2014**, *11*, 131.
4. (a) Kumar, G. S.; Poornachandra, Y.; Reddy, K. R.; Kumar, C. G.; Narsaiah, B. *Synth. Commun.* **2017**, *47*, 1864. (b) Sanad, S. M. H.; Hawass, M. A. E.; Ahmed, A. A. M.; Elneairy, M. A. A. *Synth. Commun.* **2018**, *48*, 1847. (c) Elsayed, M. A.; Hafez, N. A. A.; Elshahawi, M. M.; Ali, K. A. *J. Heterocycl. Chem.* **2019**, *56*, 172. (d) Dotsenko, V. V.; Krivokolysko, S. G.; Krivokolysko, B. S.; Frolov, K. A. *Russ. J. Gen. Chem.* **2018**, *88*, 682. [*Zh. Obshch. Khim.* **2018**, *88*, 599.] (e) El-Dean, A. M. K.; Abd-Ella, A. A.; Hassanien, R.; El-Sayed, M. E. A.; Abdel-Raheem, S. A. A. *ACS Omega* **2019**, *4*, 8406. (f) Sanad, S. M. H.; Abdel-Fattah, A. M.; Attaby, F. A.; Elneairy, M. A. A. *J. Heterocycl. Chem.* **2019**, *56*, 651.
5. Dyachenko, I. V.; Dyachenko, V. D.; Dorovatovskii, P. V.; Khrustalev, V. N.; Nenajdenko, V. G. *Chem. Heterocycl. Compd.* **2019**, *55*, 442. [*Khim. Geterotsikl. Soedin*. **2019**, *55*, 442.]
6. Bondarenko, S. P.; Zhitnetskyi, I. V.; Semenov, S. V.; Frasinyuk, M. S. *Chem. Heterocycl. Compd.* **2016**, *52*, 262. [*Khim. Geterotsikl. Soedin*. **2016**, *52*, 262.]
7. (a) Leung, E.; Pilkington, L. I.; van Rensburg, M.; Jeon, C. Y.; Song, M.; Arbshahi, H. J.; De Zoysa, G. H.; Sarojini, V.; Denny, W. A.; Reynisson, J.; Barker, D. *Bioorg. Med. Chem.* **2016**, *24*, 1142. (b) Arabshahi, H. J.; van Rensburg, M.; Pilkington, L. I.; Jeon, C. Y.; Song, M.; Gridel, L.-M.; Leung, E.; Barker, D.; Vuica-Ross, M.; Volcho, K. P.; Zakharenko, A. L.; Lavrik, O. I.; Reynisson, J. *Med. Chem. Commun.* **2015**, *6*, 1987.
8. Buryi, D. S.; Dotsenko, V. V.; Levashov, A. S.; Lukina, D. Yu.; Strelkov, V. D.; Aksenov, N. A.; Aksenova, I. V.; Netreba, E. E. *Russ. J. Gen. Chem.* **2019**, *89*, 886. [*Zh. Obshch. Khim.* **2019**, *89*, 690.]
9. Yahya, S. M. M.; Abdelhamid, A. O.; Abd-Elhalim, M. M.; Elsayed, G. H.; Eskander, E. F. *Steroids* **2017**, *126*, 15.
10. Dyachenko, I. V.; Dyachenko, V. D.; Dorovatovskii, P. V.; Khrustalev, V. N.; Nenajdenko, V. G. *Russ. J. Org. Chem.* **2018**, *54*, 1435. [*Zh. Org. Khim.* **2018**, *54*, 1423.]
11. Alinaghizadeh, F.; Zahedifar, M.; Seifi, M.; Sheibani, H. *J. Braz. Chem. Soc.* **2016**, *27*, 663.
12. Grigor'ev, A. A.; Karpov, S. V.; Kayukov, Y. S.; Nasakin, O. E.; Gracheva, I. A.; Tafeenko, V. A. *Chem. Heterocycl. Compd.* **2017**, *53*, 230. [*Khim. Geterotsikl. Soedin*. **2017**, *53*, 230.]
13. Grigor'ev, A. A.; Karpov, S. V.; Kayukov, Y. S.; Gracheva, I. A.; Tafeenko, V. A. *Synlett* **2017**, 1592.
14. Li, Y.; Luo, X.; Shao, Y.; Chen, L. *J. Org. Chem.* **2018**, *83*, 8768.
15. (a) Abdelwahab, A. B.; Hanna, A. G.; Kirsch, G. *Synthesis* **2017**, 2971. (b) Abdelwahab, A. B.; Hanna, A. G.; Kirsch, G. *Synthesis* **2016**, 2881.
16. Mohareb, R. M.; Ibrahim, R. A. *Med. Chem. Res.* **2017**, *26*, 587.