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RECENT ADVANCES IN THE SYNTHESIS OF 1,2,4-TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLE COMPOUNDS: A MINI-REVIEW

Jin Luo,* Puqing Chen, and Chonghu Song

Analytical and Testing Center, Jiangxi Normal University, Nanchang, Jiangxi
330022, China, jinluo@jxnu.edu.cn

Abstract – 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazoles are important sulphur- and nitrogen-containing fused heterocycles that can act as promising scaffolds exhibiting outstanding biological activities. Herein, we focused on the major synthetic pathways and methodologies for the synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds in an attempt to facilitate the discovery of unique 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives with improved biological activities.

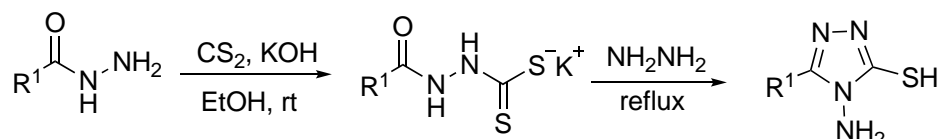
1. INTRODUCTION

The 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds, which were first reported by Kanaoka in 1956,¹ have been received much attention due to their remarkable biological activities. For instance, some of these derivatives were reported to exhibit antimicrobial,²⁻⁵ anticonvulsant,⁶ antiviral,⁷ fungicidal,⁸ anti-inflammatory and analgesic activities,⁹ whereas others displayed antituberculous,^{10,11} anticancer,¹² anti-HIV,¹³ and SIRT1 inhibitor properties.¹⁴

In view of their significant biological activities, numerous approaches have been developed to synthesize 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives. In generally, there are two strategies for the preparation of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles. The most common route to 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds occurs via reaction of 4-amino-1,2,4-triazole-3-thiols with different electrophiles such as carboxylic acids, carbon disulfide, aromatic aldehydes, acetic anhydride, cyanide, acyl chlorides, isothiocyanates, urea and ethyl chloroformate. The other route uses 1,3,4-thiadiazol-2-ylhydrazine as materials to prepare the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds. In this review, we discuss chemists' efforts in developing general synthetic protocols to synthesize 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds from 2000 to the present.

2. SYNTHESIS OF 1,2,4-TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLE COMPOUNDS FROM 4-AMINO-1,2,4-TRIAZOLE-3-THIOLS

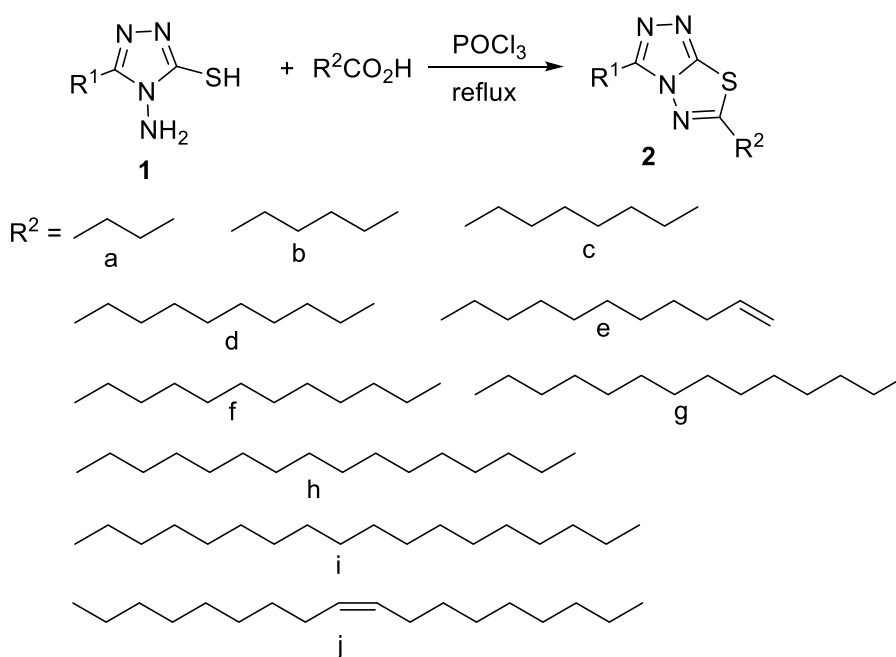
The substrate 4-amino-1,2,4-triazole-3-thiols were usually prepared from potassium dithiocarbazate (Scheme 1).



Scheme 1. The commonly route for synthesis of 4-amino-1,2,4-triazole-3-thiols

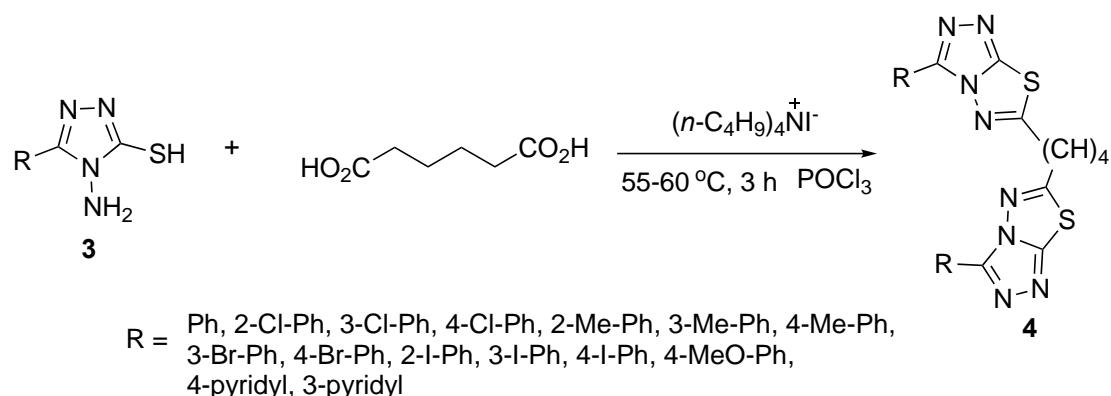
2-1. Fatty acids as electrophiles

4-Amino-1,2,4-triazole-3-thiols (**1**) reacted with several fatty acids in refluxing phosphorus oxychloride to afford 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole analogues (**2**) in moderate to good yields (Scheme 2).^{15,16} The results from biological evaluation showed that some 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds exhibited promising antimicrobial and antidepressant activities.



Scheme 2. Synthesis of compounds **2**

Moreover, 1,4-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]butanes (**4**) can also be synthesized via the cyclization of 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiol (**3**) with hexanedioic acid in the presence of phosphorus oxychloride and tetrabutylammonium iodide as a catalyst in good yields (Scheme 3).¹⁷

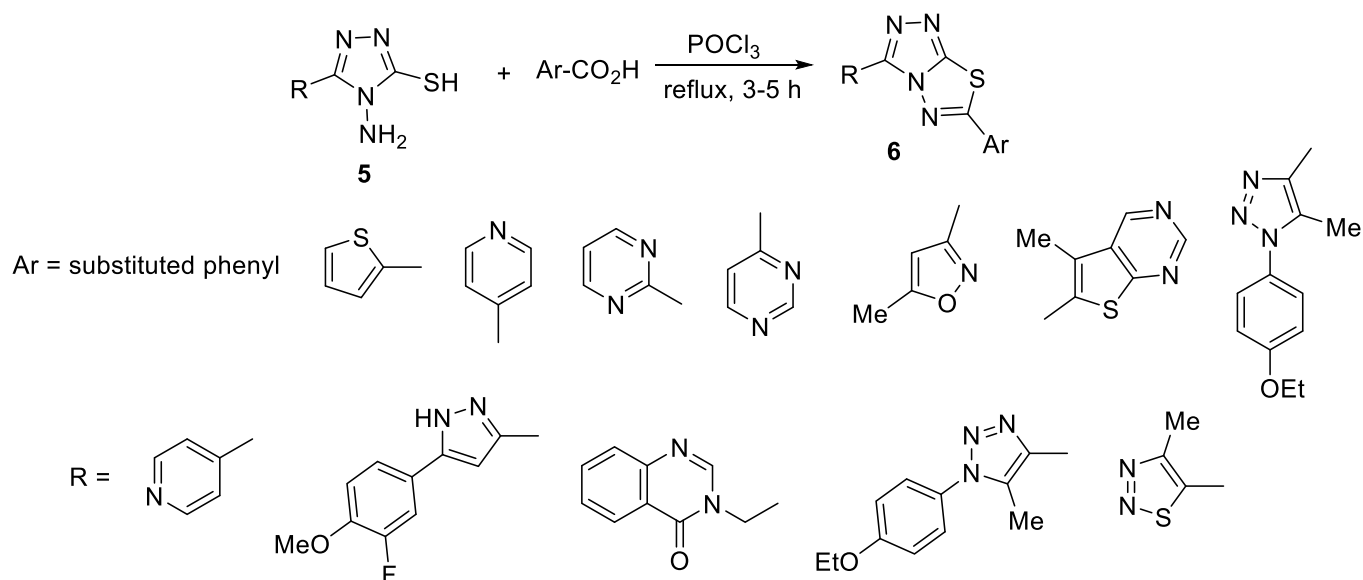


Scheme 3. Synthesis of compounds 4

2-2. Aromatic acids as electrophiles

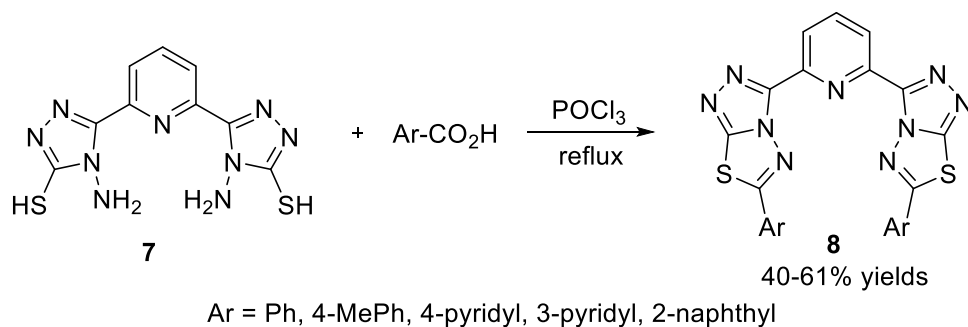
Apart from fatty acids, aromatic acids were demonstrated to be applicable partner, which reacted with 4-amino-1,2,4-triazole-3-thiols to provide 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives.

4-Amino-1,2,4-triazole-3-thiols bearing kinds of functional groups (**5**) were refluxed with aromatic acid in the presence of phosphorus oxychloride to provide a great deal of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives (**6**) (Scheme 4).¹⁸⁻²⁷ Many compounds were found to have potential anti-inflammatory, analgesic, antimicrobial, and antibacterial activities.

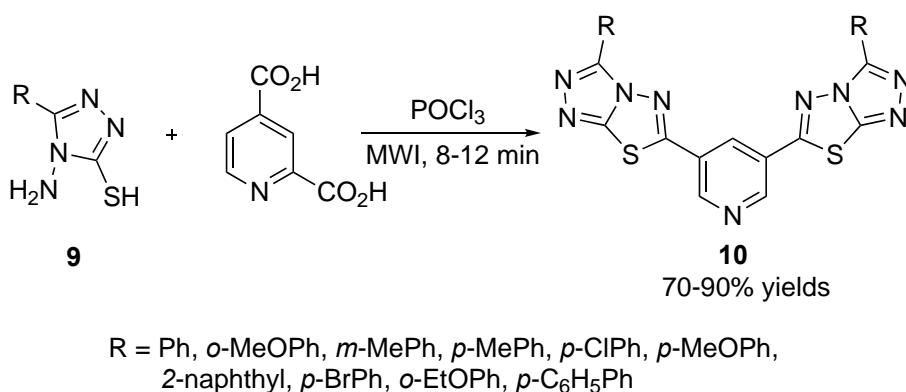


Scheme 4. Synthesis of compounds 6

In addition, the condensation of 2,6-bis(4-amino-5-mercapto-1,2,4-triazol-2-yl)pyridine (**7**) with aromatic acid gave 2,6-bis(6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)pyridines (**8**) in 40-61% yields (Scheme 5).²⁸

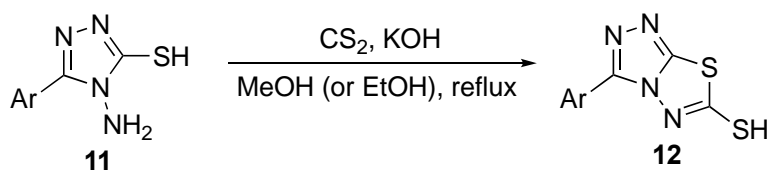
Scheme 5. Synthesis of compounds **8**

Moreover, 2,4-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]pyridines (**10**) were synthesized in 70-90% yields by reacting of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol (**9**) with 2,4-pyridinedicarboxylic acid under microwave irradiation (Scheme 6).²⁹

Scheme 6. Synthesis of compounds **10**

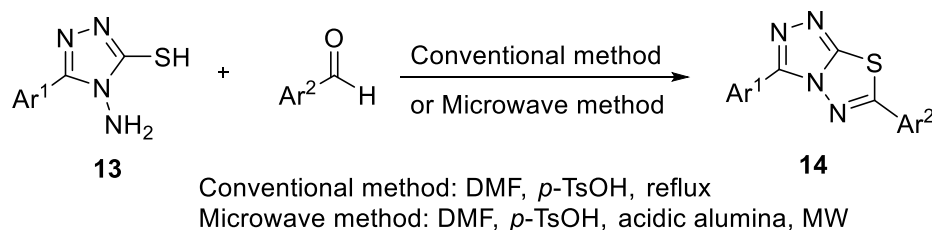
2-3. Carbon disulfide as an electrophile

The 3-substituted-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiols (**12**) were achieved by refluxing 4-amino-5-substituted-phenyl-4*H*-1,2,4-triazole-3-thiol (**11**) with carbon disulfide using MeOH and KOH as a catalyst (Scheme 7).³⁰⁻³³ Further derivatization of compounds **12** exhibited antiproliferative, antibacterial, and fungicidal activities.

Scheme 7. Synthesis of compounds **12**

2-4. Aromatic aldehydes as electrophiles

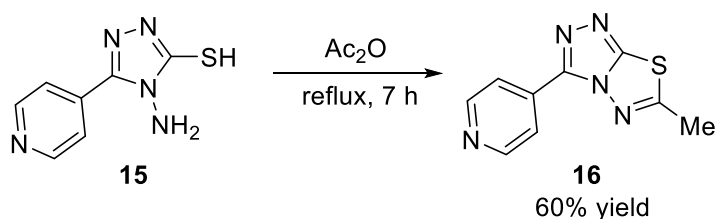
Many 5,6-dihydro-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (**14**) were prepared from 1,2,4-triazoles (**13**) with heteroaromatic aldehydes by microwave-assisted and conventional methods (Scheme 8).³⁴⁻³⁶



Scheme 8. Synthesis of compounds **14**

2-5. Acetic anhydride as an electrophile

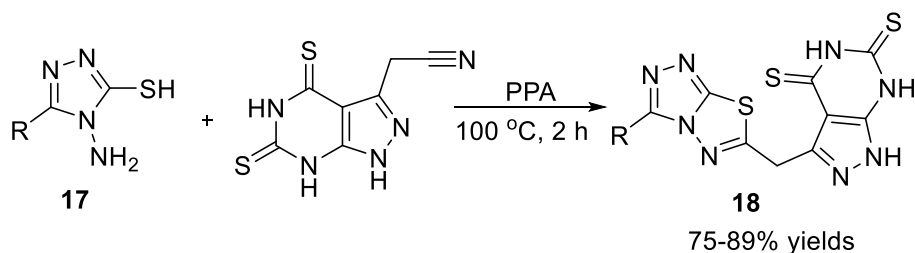
A mixture of 4-amino-5-(pyridin-4-yl)-1,2,4-triazole-3-thiol (**15**) and acetic anhydride was heated under reflux for 7 h to produce novel compound 6-methyl-3-(pyridin-4-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole (**16**) with anticancer activity (Scheme 9).³⁷



Scheme 9. Synthesis of compound **16**

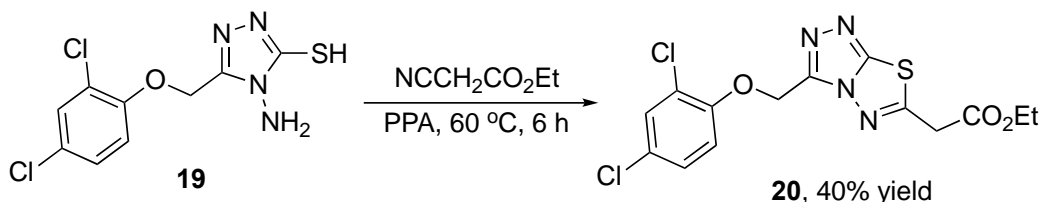
2-6. Cyanide as electrophiles

Reacting 4-amino-5-substituted-1,2,4-triazole-3-thiol (**17**) with (1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6-dithion-3-yl)acetonitrile in polyphosphoric acid (PPA) at 100 °C for 2 h provided 3-(3-substituted-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6-dithione derivatives (**18**) in good yields (Scheme 10).³⁸



Scheme 10. Synthesis of compounds **18**

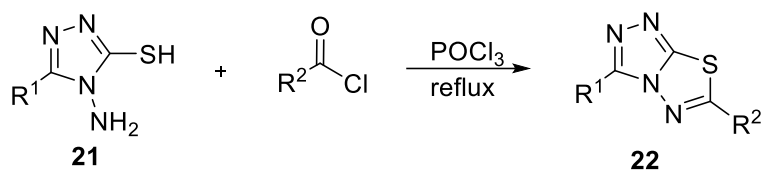
The reaction of 4-amino-5-((2,4-dichlorophenoxy)methyl)-4*H*-1,2,4-triazole-3-thiol (**19**) with ethyl cyanoacetate in PPA at 60 °C for 6 h afforded ethyl-2-(3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)acetate (**20**) in 40% yield (Scheme **11**).³⁹



Scheme 11. Synthesis of compound **20**

2-7. Acyl chlorides as electrophiles

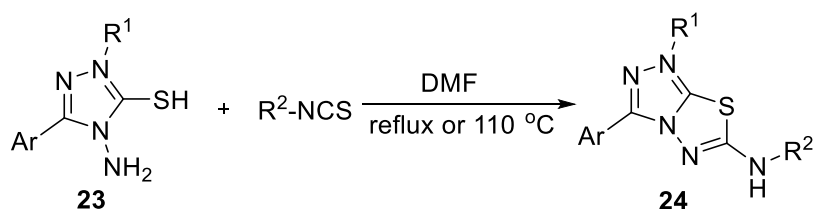
An efficient synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds (**22**) was developed by the cyclo-condensation of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol (**21**) with acyl chloride in refluxing POCl₃ (Scheme **12**).⁴⁰⁻⁴³



Scheme 12. Synthesis of compounds **22**

2-8. Isothiocyanates as electrophiles

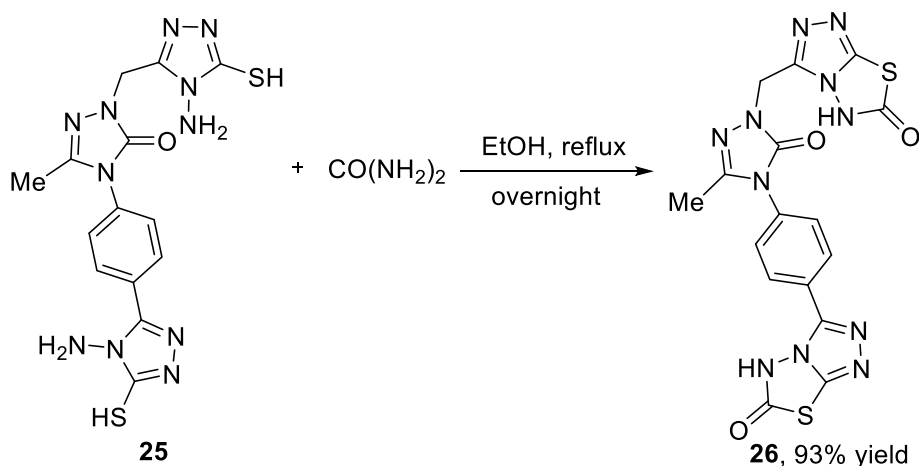
A range of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives (**24**) were prepared by the reaction of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol (**23**) with various isothiocyanates in the presence of DMF (Scheme **13**).⁴⁴⁻⁴⁸ It was worth noting that aliphatic, aryl, and glycosyl isothiocyanates were suitable for this methodology. Moreover, the results from biological activities screening indicated that some 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds displayed anti-inflammatory, antibacterial, antifungal, and acetylcholinesterase inhibitory activities.



Scheme 13. Synthesis of compounds **24**

2-9. Urea as an electrophile

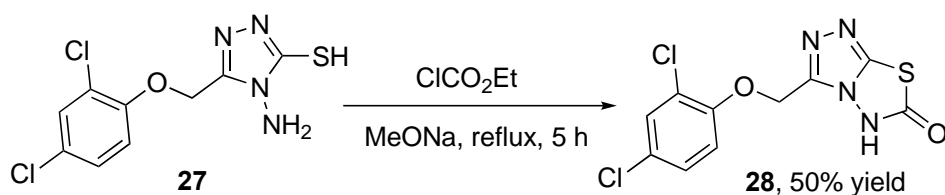
The cyclization of compound (**25**) with urea in EtOH under reflux gave a new compound 3-(4-{3-methyl-5-oxo-1-[(6-oxo-5,6-dihydro-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)methyl]-1,5-dihydro-4*H*-1,2,4-triazol-4-yl}phenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-6(5*H*)-one (**26**) (Scheme 14).⁴⁹



Scheme 14. Synthesis of compound **26**

2.10. Ethyl chloroformate as an electrophile

The treatment of compound (**27**) with ethyl chloroformate in the presence of sodium methoxide under reflux conditions afforded 3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazol-6(5*H*)-one (**28**) (Scheme 15).³⁹



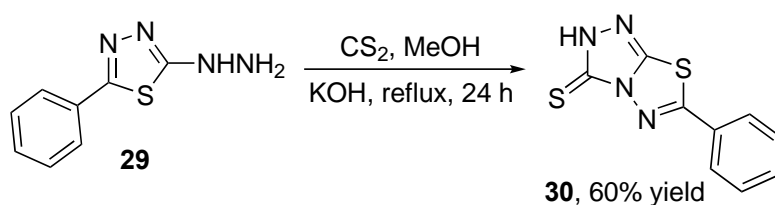
Scheme 15. Synthesis of compound **28**

3. SYNTHESIS OF 1,2,4-TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLE COMPOUNDS FROM (1,3,4-THIADIAZOL-2-YL)HYDRAZINE

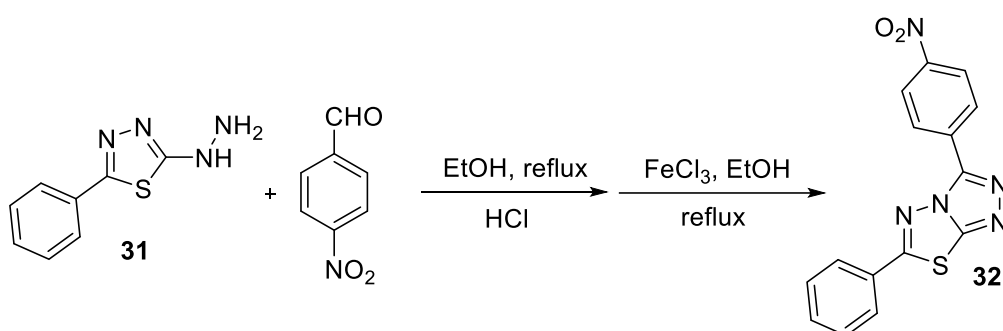
There are several reports on the preparation of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds from (1,3,4-thiadiazol-2-yl)hydrazine. (5-Phenyl-1,3,4-thiadiazol-2-yl)hydrazine (**29**) was treated with carbon disulfide in xylene under reflux to give 3,5-diphenyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole (**30**) (Scheme 16).⁵⁰ 6-Phenyl-3(4-nitrophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole (**32**) was synthesized via cyclocondensation of (5-phenyl-1,3,4-thiadiazol-2-yl)hydrazine (**31**) with 4-nitrobenzaldehyde (Scheme 17).⁵¹

In 2011, Batanero *et al.* reported the electrochemical synthesis of several 3,6-disubstituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (**34**) by anodic oxidation in acetonitrile of 2-arylidene-1-(5-aryl-1,3,4-thiadiazol-2-yl)hydrazine (**33**) at a platinum electrode (Scheme 18).⁵²

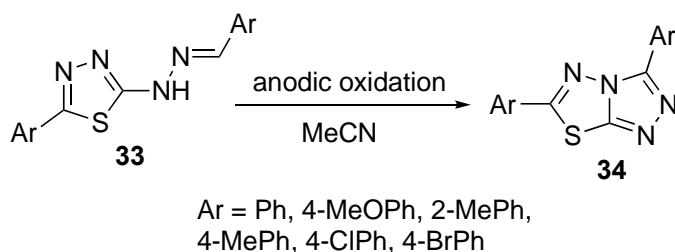
The synthesis of 3,6-bisubstituted phenyl-bi-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives (**37**) was described. The treatment of 2,5-bihydrazino-1,3,4-thiadiazole (**35**) with benzoyl chloride provided 2,5-biacylhydrazino-1,3,4-thiadiazole (**36**), which was further ring-closed by POCl₃ as the cyclization agent to produce compounds (**37**) (Scheme 19).⁵³



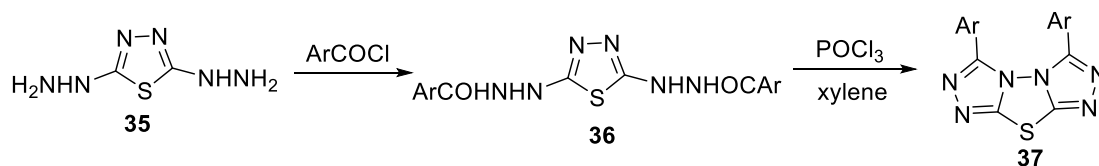
Scheme 16. Synthesis of compound **30**



Scheme 17. Synthesis of compound **32**



Scheme 18. Synthesis of compounds **34**



Ar = Ph, 4-ClPh, 4-NO₂Ph, Ar = 4-MePh, Ar = 4-MeOPh

Scheme 19. Synthesis of compounds **37**

4. CONCLUSION

This review not only concentrated on the recent advances in the synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds, but also revealed diverse approaches and strategies with their own characteristics and advantages in preparing of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives. Furthermore, the synthetic methods described in this article are useful to synthetic and medicinal chemists looking to functionalize the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole ring system. Researches are encouraged to design novel approaches to obtain 1,2,4-triazolo[3,4-*b*][1,3,4] thiadiazoles under mild conditions in excellent yield.

ACKNOWLEDGEMENTS

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Jin Luo was born in Jiangxi (China) in 1986. He obtained his PhD from Zhejiang University under the supervision of Professor Weilin Sun in 2014. Currently, he is a lecturer at Jiangxi Normal University. His research mainly focus on the synthesis and bioactivity of novel heterocyclic compounds.



Puqing Chen was born in Jiangxi (China) in 1983. He received his BS at Shanghai University in 2005. Currently, he is a lecturer at Jiangxi Normal University.



Chonghu Song was born in Jiangxi (China) in 1965. He obtained his BS from Jiangxi Normal University in 1988. Currently, he is an associate professor at Jiangxi Normal University.