HETEROCYCLES, Vol. 106, No. 3, 2023, pp. 411 - 422. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 15th August, 2022, Accepted, 17th October, 2022, Published online, 25th October, 2022
DOI: 10.3987/REV-22-992

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

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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.

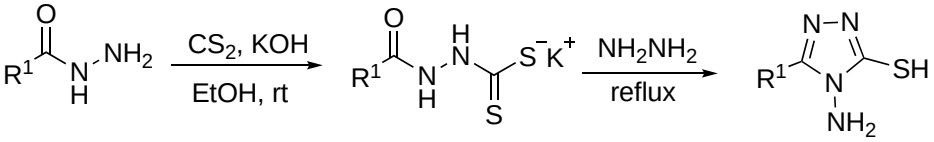
1. INTRODUCTION

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

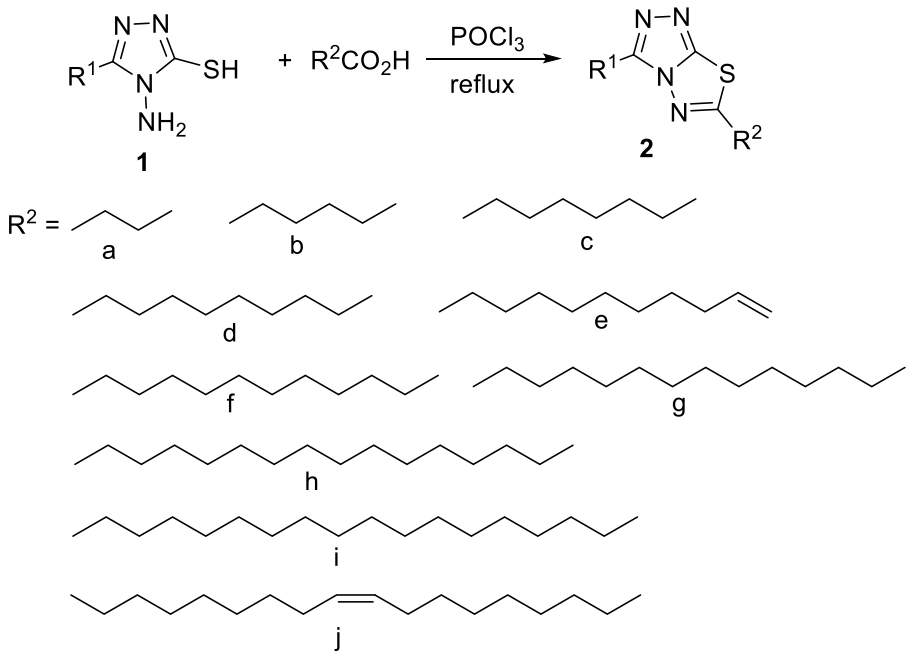
The substrate 4-amino-1,2,4-triazole-3-thiols were usually prepared from potassium dithiocarbazate (Scheme **1**).



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

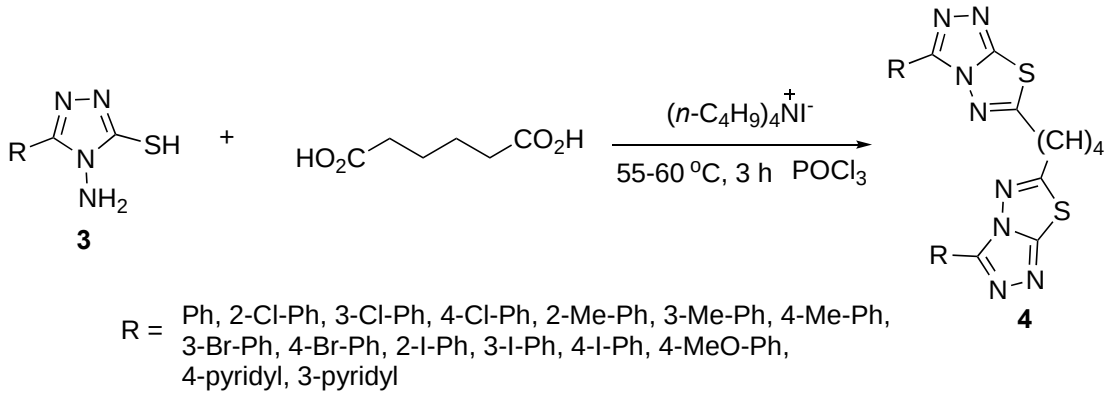
2-1. Fatty acids as electrophiles

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]

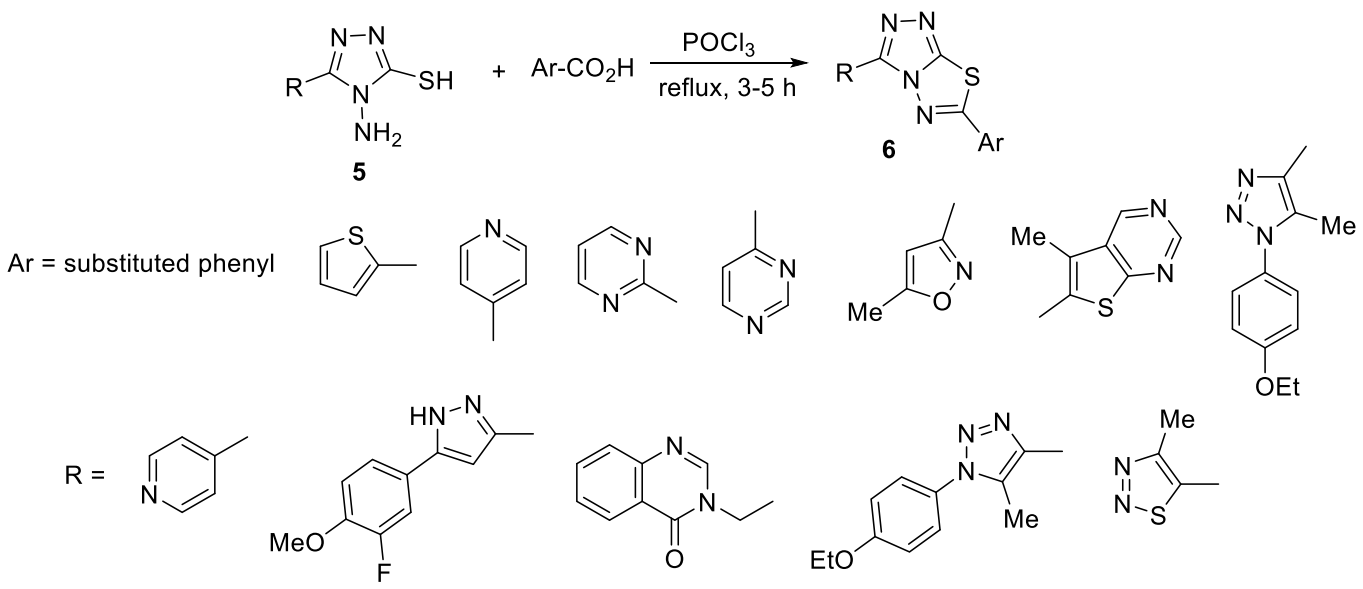


Scheme 3. Synthesis of compounds **4**

2-2. Aromatic acids as electrophiles

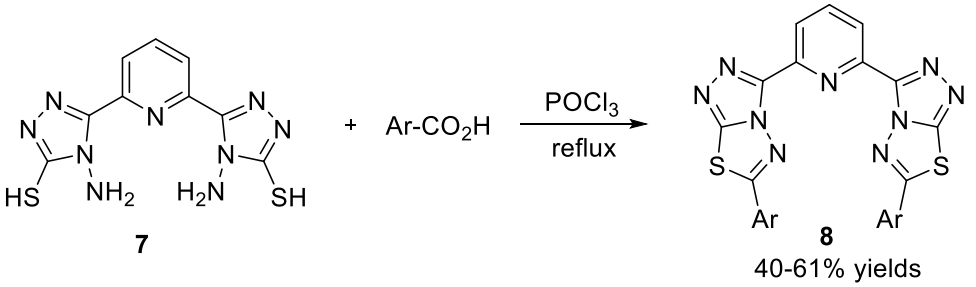
Apart from fatty acids, aromatic acids were demonstrated to be applicable partner, which reacted with 4-amino-1,2,4-triazole-3-thiols to provide 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives.

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.



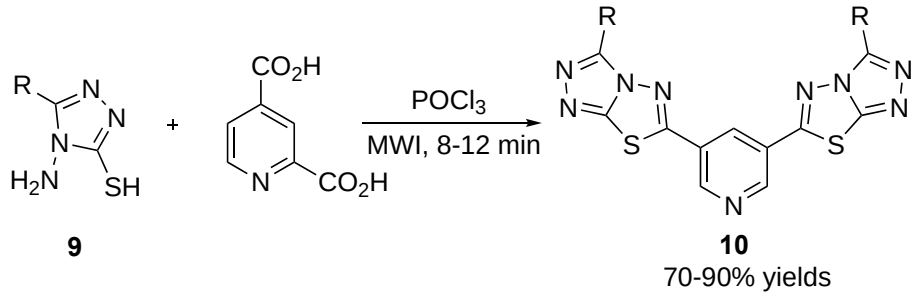
Scheme 4. Synthesis of compounds **6**

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**

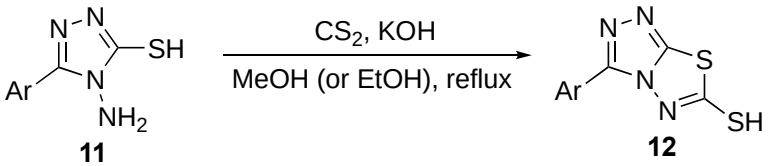
Moreover, 2,4-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]pyridines (**10**) were synthesized in 70-90% yields by reacting of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol (**9**) with 2,4-pyridinedicarboxylic acid under microwave irradiation (Scheme **6**).[29]



Scheme 6. Synthesis of compounds **10**

2-3. Carbon disulfide as an electrophile

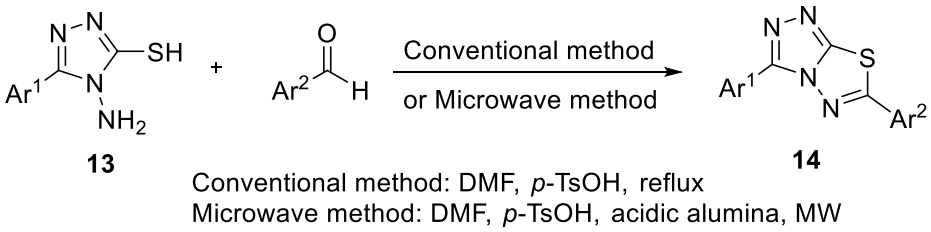
The 3-substituted-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiols (**12**) were achieved by refluxing 4-amino-5-substituted-phenyl-4*H*-1,2,4-triazole-3-thiol (**11**) with carbon disulfide using MeOH and KOH as a catalyst (Scheme **7**).[30-33] Further derivatization of compounds **12** exhibited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



Scheme 7. Synthesis of compounds **12**

2-4. Aromatic aldehydes as electrophiles

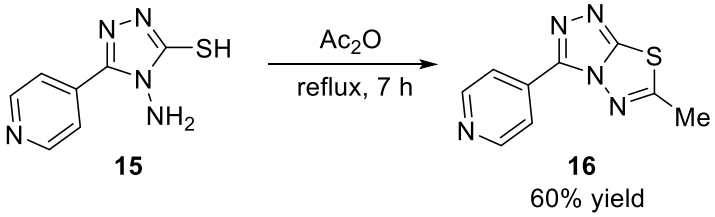
Many 5,6-dihydro-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (**14**) were prepared from 1,2,4-triazoles (**13**) with heteroaromatic aldehydes by microwave-assisted and conventional methods (Scheme **8**).[34-36]



Scheme 8. Synthesis of compounds **14**

2-5. Acetic anhydride as an electrophile

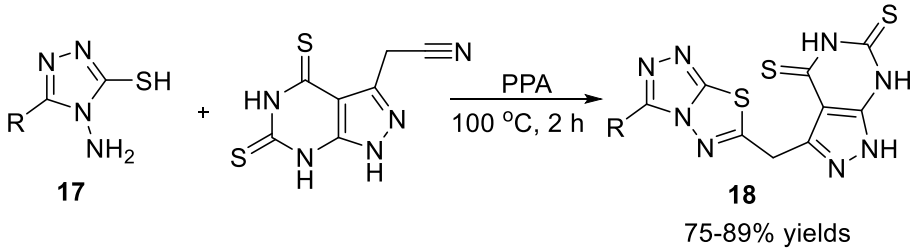
A mixture of 4-amino-5-pyridin-4-yl-4*H*-1,2,4-triazole-3-thiol (**15**) and acetic anhydride was heated under reflux for 7 h to produce novel compound 6-methyl-3-(pyridin-4-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole (**16**) with anticancer activity (Scheme **9**).[37]



Scheme 9. Synthesis of compound **16**

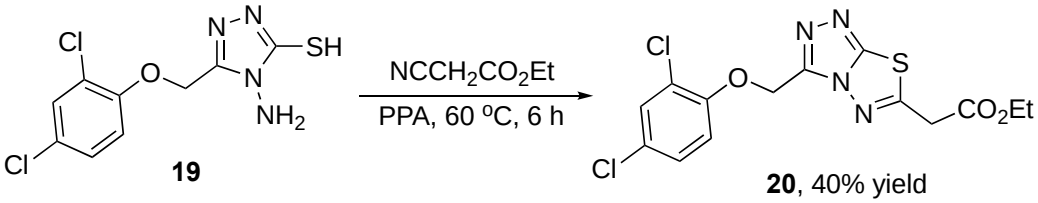
2-6. Cyanide as electrophiles

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**

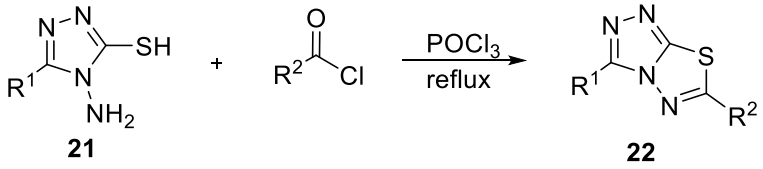
The reaction of 4-amino-5-((2,4-dichlorophenoxy)methyl)-4*H*-1,2,4-triazole-3-thiol (**19**) with ethyl cyanoacetate in PPA at 60 °C for 6 h afforded ethyl-2-(3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)acetate (**20**) in 40% yield (Scheme **11**).[39]



Scheme 11. Synthesis of compound **20**

2-7. Acyl chlorides as electrophiles

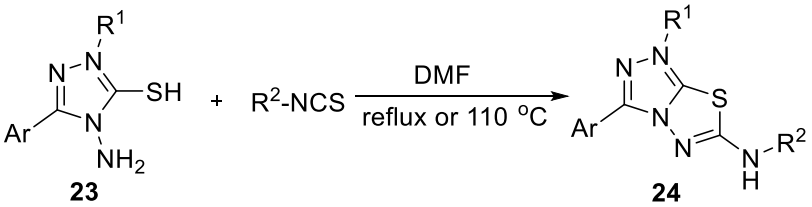
An efficient synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds (**22**) was developed by the cyclo-condensation of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol (**21**) with acyl chloride in refluxing $POCl_3$ (Scheme **12**).[40-43]



Scheme 12. Synthesis of compounds **22**

2-8. Isothiocyanates as electrophiles

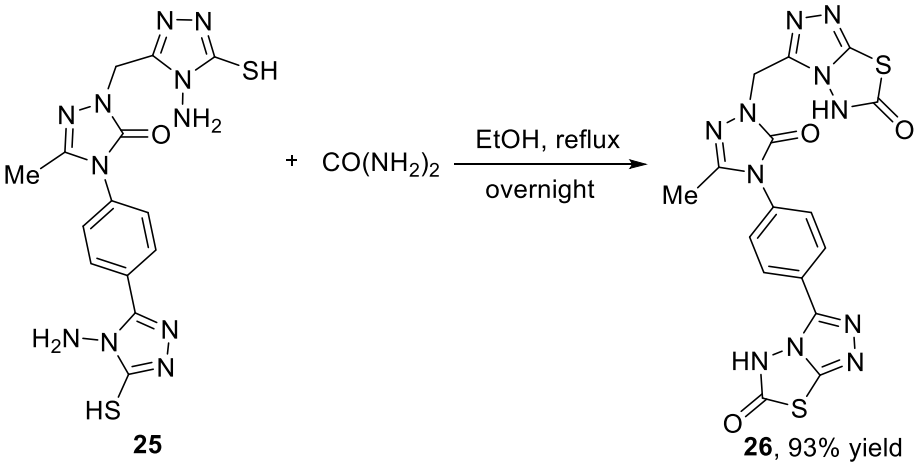
A range of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives (**24**) were prepared by the reaction of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol (**23**) with various isothiocyanates in the presence of DMF (Scheme **13**).[44-48] It was worth noting that aliphatic, aryl, and glycosyl isothiocyanates 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

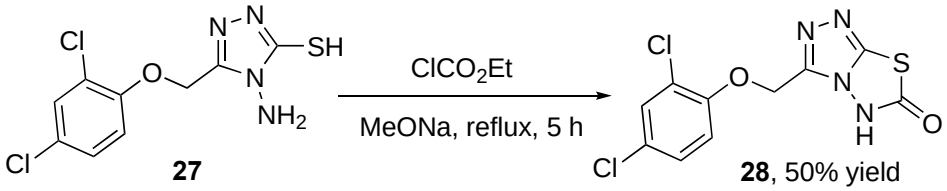
The cyclization of compound (**25**) with urea in EtOH under reflux gave a new compound 3-(4-{3-methyl-5-oxo-1-[(6-oxo-5,6-dihydro-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)methyl]-1,5-dihydro-4*H*-1,2,4-triazol-4-yl}phenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-6(5*H*)-one (**26**) (Scheme **14**).[49]



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]



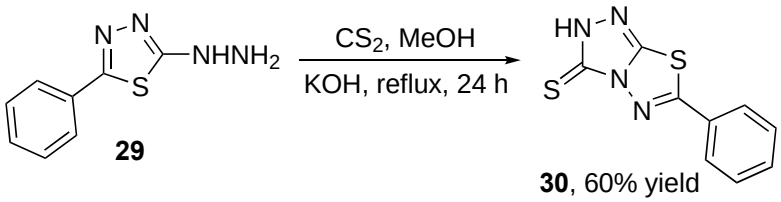
Scheme 15. Synthesis of compound **28**

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

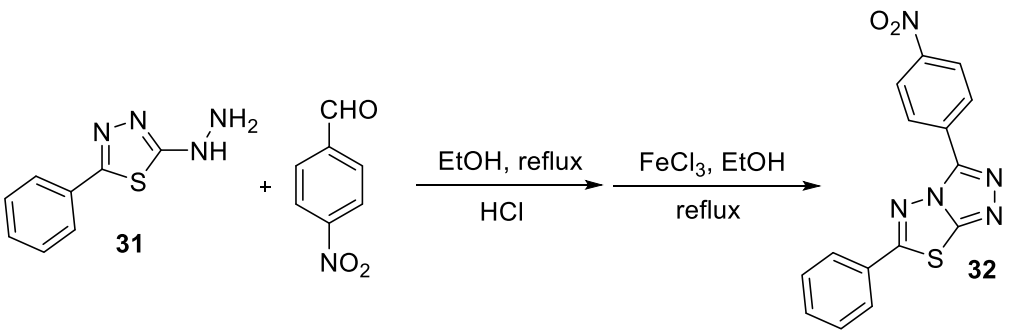
There are several reports on the preparation of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole compounds from (1,3,4-thiadiazol-2-yl)hydrazine. (5-Phenyl-1,3,4-thiadiazol-2-yl)hydrazine (**29**) was treated with carbon disulfide in xylene under reflux to give 3,5-diphenyl-1,2,4-triazolo[3,4-*b*][l,3,4]thiadiazole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

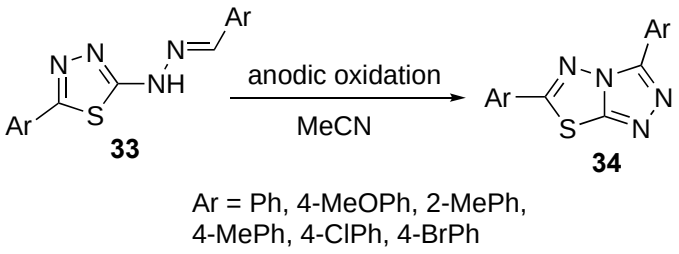
The synthesis of 3,6-bisubstituted phenyl-bi-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives (**37**) was described. The treatment of 2,5-bihydrazino-1,3,4-thiadiazole (**35**) with benzoyl chloride provided 2,5-biacylhydrazino-1,3,4-thiadiazole (**36**), which was further ring-closed by $POCl_3$ as the cyclization agent to produce compounds (**37**) (Scheme **19**).[53]



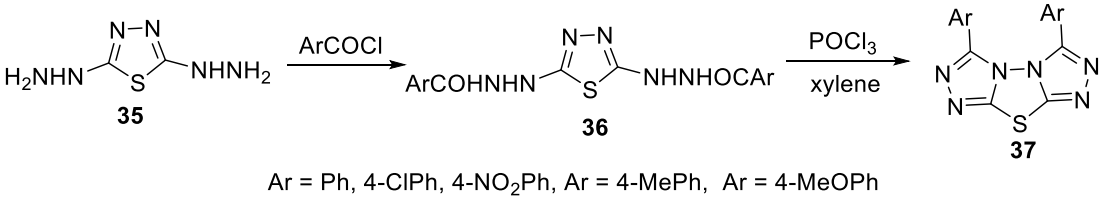
Scheme 16. Synthesis of compound **30**



Scheme 17. Synthesis of compound **32**



Scheme 18. Synthesis of compounds **34**



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

We thank the Young Talents Program of Jiangxi Normal University for financial support.

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