Sulfur-Mediated Multicomponent Reactions in the Synthesis of Thioamides

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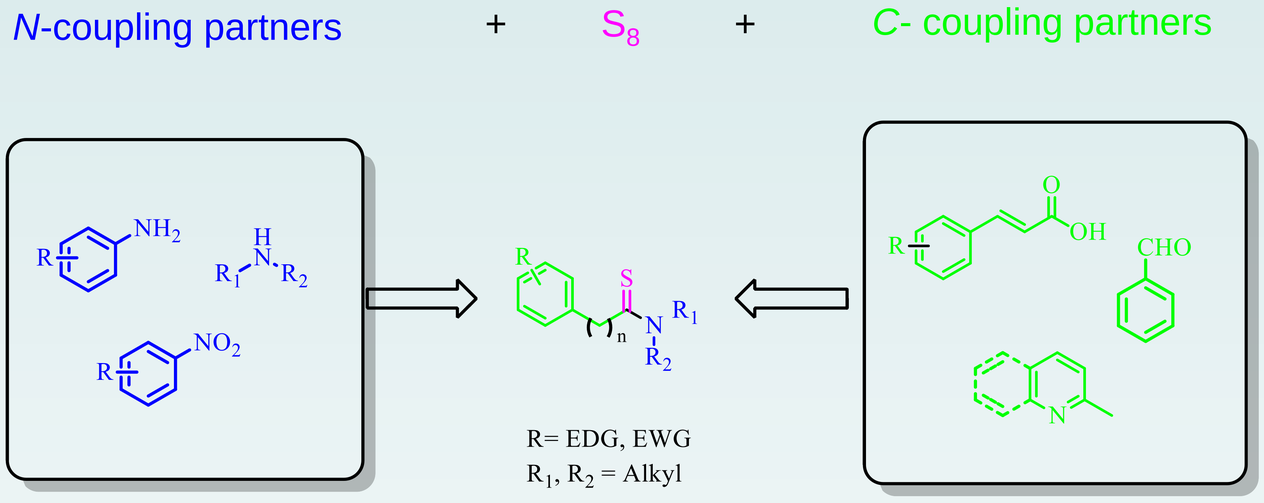
Introduction

A multicomponent reaction (MCR) is one in which three or more reactants are combined in a single reaction vessel, and each are incorporated into the final product. MCRs are thus an efficient tool for the synthetic chemist in achieving good atom economy and waste minimization. MCRs have an added benefit of having good compatibility with a wide substrate scope, greener materials and benign solvents.[1]

MCRS in Thioamide Synthesis

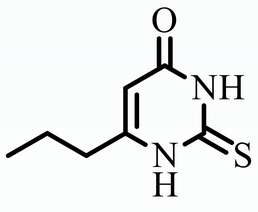
Elemental sulfur is an abundant and benign material, that can be suitably applied to MCRs. Recently advances in sulfur-mediated MCR protocols have been explored towards more efficient syntheses of thioamide compounds. These protocols utilize elemental sulfur and an array of basic conditions to access thioamides from the coupling reaction between *N*-donors such as nitroarenes and aliphatic or aromatic amines and *C*-coupling partners such as aldehydes, cinnamic acids and active methylenes.[2]

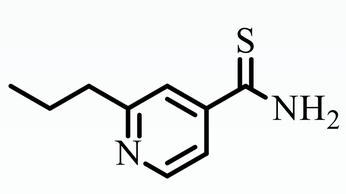


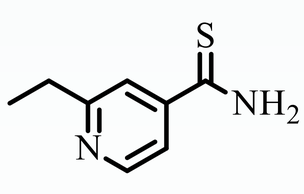
Advantages of MCRs

- Wide substrate scope
- Benign materials
- Good atom economy
- Waste minimization
- Energy efficiency
- Cost-effective

The synthesis of thioamides remain of note, because they may exhibit a range of biological activity including anti-microbial, antioxidant and anti-thyroidism. They are therefore employed in commercially available drugs such as propylthiouracil, used in the treatment of various disorders such as Graves' disease and goitres. Some biologically active thioamides are listed below.

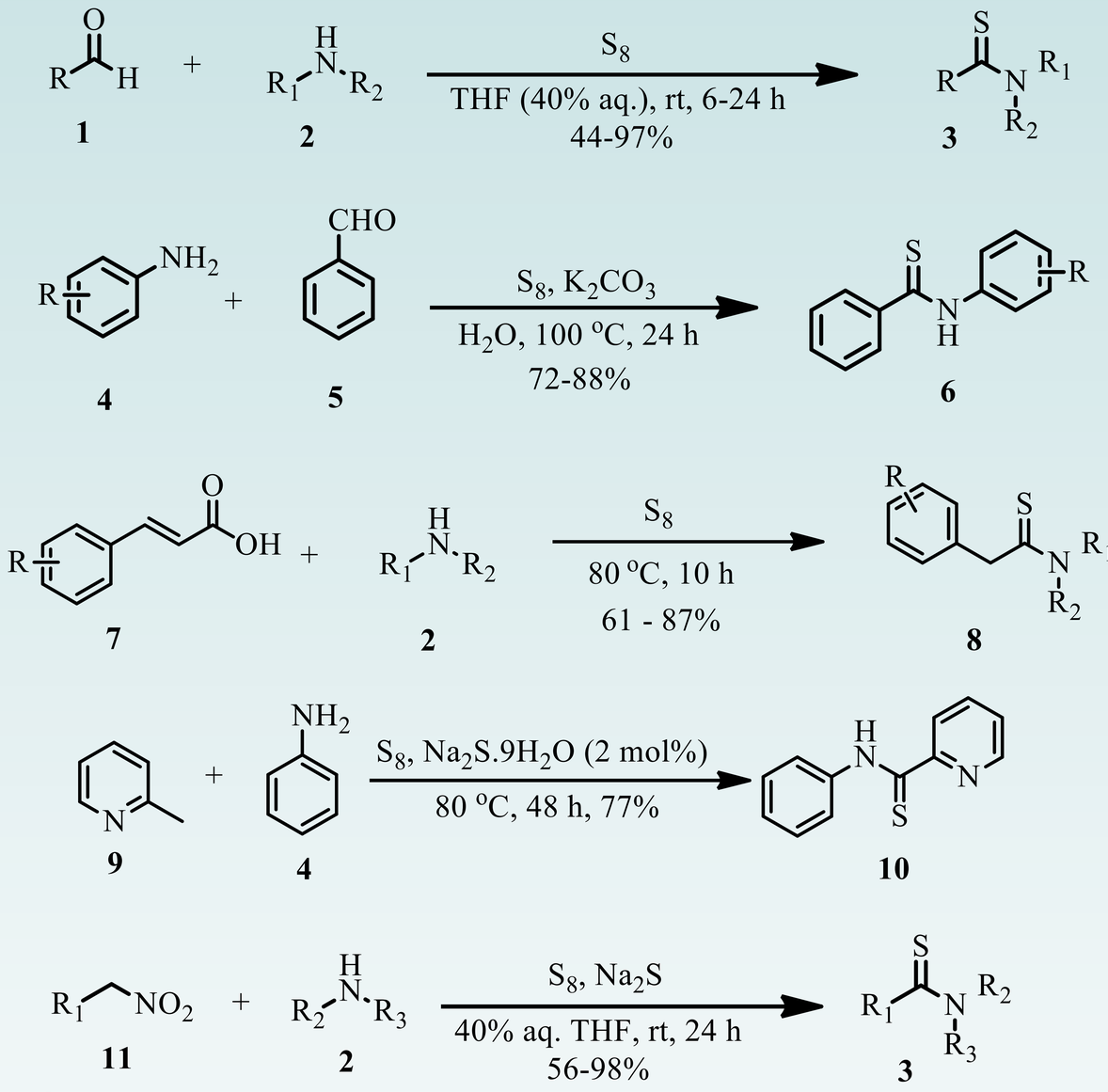

propylthiouracil


propthionamide


ethionamide

Sulfur-Mediated MCRs in Thioamide Synthesis

Thioamides are traditionally accessed by thionation of their corresponding amide precursor. These include the use of thionating agents such as phosphorus pentasulfide and Lawesson's reagent. These methods typically employ the use of harsh reaction conditions, toxic reagents, multiple steps and lengthy reaction times. Another limitation of these reactions is the use of toxic solvents and the production of harmful waste materials. Modern synthetic approaches which utilize MCR protocols overcome these limitations, with retention or improvement of the yields of traditional protocols. Selected examples of sulfur-mediated MCRs for the synthesis of thioamides are demonstrated below (Scheme 1).[3-7]



Scheme 1

Conclusion

MCRs are a sustainable alternative to access thioamides in good yields. This approach is beneficial in avoiding limitations to traditional synthetic methods such as long reaction times, high temperatures and poor atom economy.

Acknowledgements

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References

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