

SYNLETT Spotlight 325

Thiophenol-Mediated Radical Cyclizations

Compiled by Shovan Mondal



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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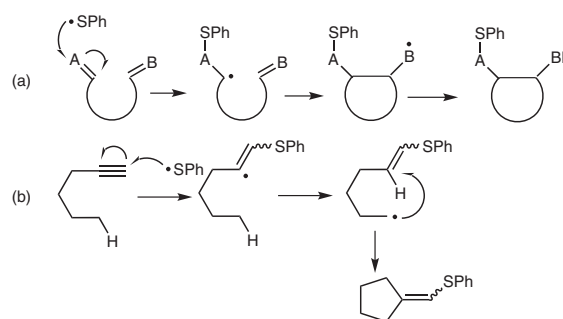
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Dedicated to my supervisor, Professor K. C. Majumdar, for his constant inspiration

Introduction

Thiophenol (PhSH, CAS: 108-98-5-Y) is a commercially available organosulfur compound. Recently thiophenol-mediated radical cyclizations become highlighted for the construction of heterocycles due to the cost-effective, tin-free methodology. These radical reactions proceed via the formation of a carbon-centered radical species generated by the addition of a sulfanyl radical to an unsaturated bond and a subsequent intramolecular addition of the resulting carbon-centered radical to another multiple bond, followed by the abstraction of hydrogen from thiophenol to afford the product (Scheme 1a). Otherwise, the sulfanyl radical, generated from thiophenol and radical initiator, adds to the terminus of the triple bond to generate an alkenyl radical, which undergoes a 1,5-hydrogen atom

transfer (HAT). After translocation, the new radical species can cyclize intramolecularly to give a cyclopentane derivative (Scheme 1b).

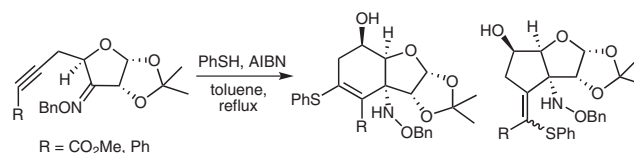


Scheme 1

Abstracts

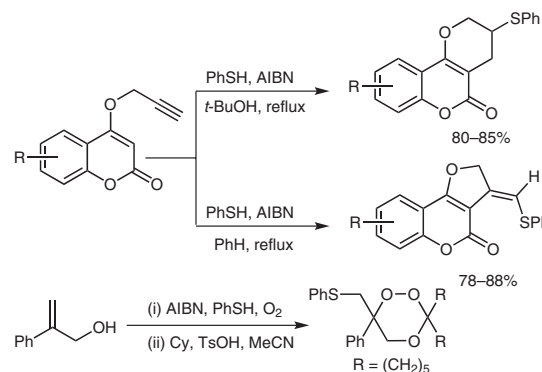
(A) Synthesis of Carbocycles:

Alonoso and Fernandez¹ carried out thiophenol-mediated tandem radical addition and cyclization of ϵ -substituted δ -yne ketimines to obtain cyclized allylamine derivatives. The terminal alkyne substituted with a CO₂Me group afforded a mixture of the 5-*exo* and 6-*exo* products, whereas the terminal alkyne substituted with a phenyl group gave exclusively the 6-*exo* products.



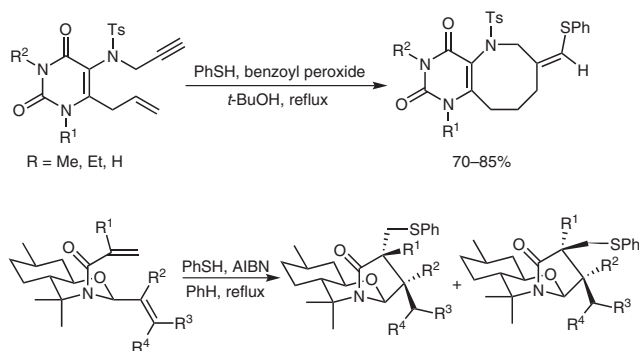
(B) Synthesis of O-Heterocycles:

Majumdar et al. described the regioselective synthesis of dihydrofurano- and dihydropyranocoumarins by thiol-mediated radical cyclizations.² Recently, O'Neill et al.³ have observed that thiol-olefin co-oxygenation (TOCO) of substituted allylic alcohols generates α -hydroxyperoxides that can be condensed in situ with various ketones in the presence of a catalytic amount of tosic acid to afford a series of functionalized 1,2,4-trioxanes, which is an important functional group in medicinal chemistry.

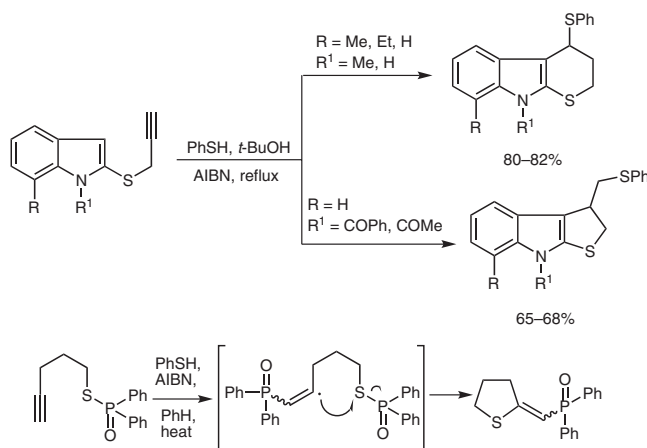


(C) *Synthesis of N-Heterocycles:*

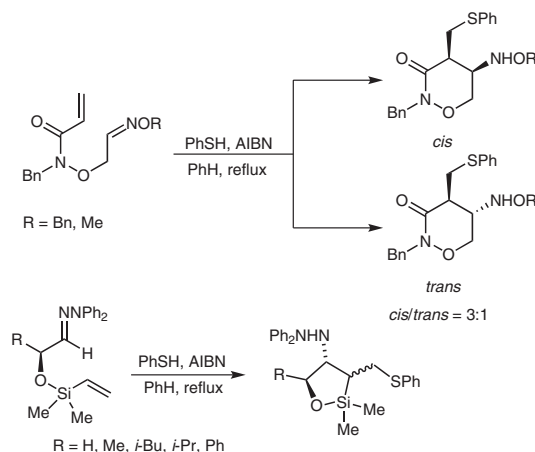
Majumdar et al. reported the concise synthesis of pyrimidine-fused azocine derivatives by thiophenol-mediated radical cyclization via an 8-*endo*-trig mode. They have used benzoyl peroxide as radical initiator instead of AIBN to avoid the difficulty in purification.⁴ Pedrosa et al. reported the thiophenol-mediated radical addition–cyclizations of 2-allyl-3-acyloyl-substituted perhydro-1,3-benzoxazines to give the 3,4-disubstituted pyrrolidinone derivatives with high regioselectivity and good diastereoselectivity.⁵

(D) *Synthesis of S-Heterocycles:*

Recently Majumdar et al.⁶ also described the regioselective synthesis of indole-annulated sulfur heterocycles by tandem cyclization mediated by thiophenol. They observed that the lone pair of electrons present on the nitrogen atom of the indole moiety may facilitate enamine addition, which leads to the formation of six-membered thiopyrano products. However, in the presence of electron-withdrawing groups on the nitrogen of the indole moiety, 5-*endo*-trig radical cyclization is favored. Carta et al. have studied the synthesis of thiophene derivatives from thiophosphine oxide by thiophenol-mediated radical cyclization.⁷ The reaction might have proceeded through an intermediate which was formed by the attack of a phosphinoyl radical at the terminal of the triple bond. The radical was formed by the reaction of thiophosphine oxide and a thiyl radical at the initiation process.

(E) *Miscellaneous Reactions:*

Naito and co-workers⁸ have developed a thiophenol-mediated radical addition–cyclization of α,β -unsaturated hydroxamates containing an oxime ether for the synthesis of amino-1,2-oxazinones. Friestad and Massari reported the oxasilacyclopentane derivatives by application of the thiophenol-mediated tandem addition–cyclization strategy.⁹ They observed that when silylether-linked vinylsilanes are treated with thiophenol and AIBN in cyclohexane, they underwent a 5-*exo* cyclization readily to give the oxasilacyclopentane product.



References

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