SYNLETT
Spotlight 295

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

1,3-Disubstituted Thioureas: Versatile Building Blocks for the Construction of Heterocycles

Compiled by Harisadhan Ghosh

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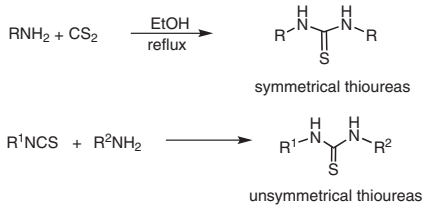
Dedicated to my mentor, Professor Bhisma K. Patel for his constant encouragement.

Introduction

Derivatives of thioureas, also known as thiocarbanilides, are versatile intermediates for the synthesis of flame retardants, vulcanization accelerators, plant protection agents, pesticides, fungicides, peptizing agents, corrosion inhibitors, and thiazole drugs. 1,3-Disubstituted thioureas are the main precursors for the synthesis of disubstituted carbodiimides[1a] and trisubstituted guanidines.[1b] The use of substituted thiourea as organocatalyst is common.[1c]

Preparation:

Symmetrical 1,3-disubstituted thioureas can be easily prepared from amines and carbon disulfide in ethanol under reflux.[2] Whereas the unsymmetrical thioureas can be obtained by reacting an amine with an isothiocyanate of another amine (Scheme 1).[3]

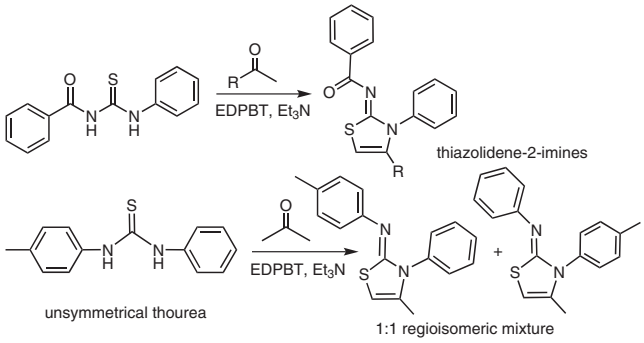


Scheme 1 Synthesis of symmetrical and unsymmetrical thioureas

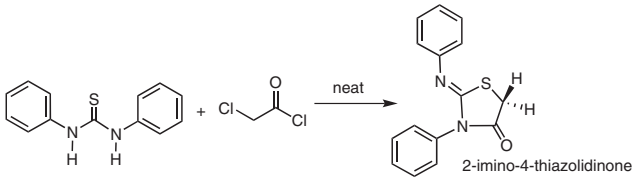
Most of the 1,3-disubstituted thioureas are stable solids, which makes them convenient for storage and transportation. The presence of both nitrogen and sulfur in thioureas, which are common heteroatoms in bioactive heterocycles, makes them important precursors for the construction of heterocycles.

Abstracts

(A) *Synthesis of Thiazolidene-2-imines:* 1,3-Disubstituted thioureas react with an enolizable ketone and 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) in the presence of triethylamine to give thiazolidene-2-imine derivatives.[4] The unsymmetrical thiourea gives a regioisomeric mixture of products and the regioselectivity is dependent on the p*Ka* values of the corresponding amines attached to the thiourea moiety.[5]



(B) *Synthesis of 2-Imino-4-thiazolidinones:* A facile, general and high-yielding protocol for the synthesis of novel 2-imino-4-thiazolidinone has been described utilizing 1,3-disubstituted thiourea and chloroacetylchloride in solvent-free conditions at room temperature.[6]



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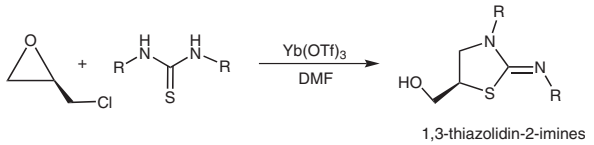
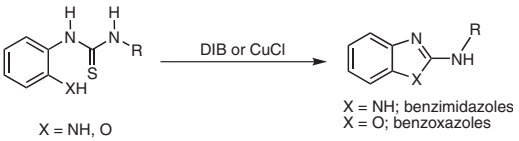
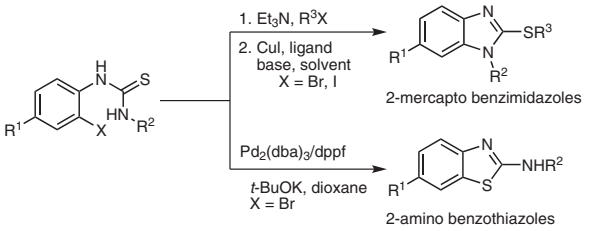
(C) *Synthesis of 1,3-Thiazolidin-2-imines:* The reaction of 1,3-disubstituted thiourea with epichlorohydrin in DMF gives 2-arylimino-3-aryl-1,3-thiazolidine.[7] In this reaction, $Yb(OTf)_3$ has been used as the catalyst and inversion of configuration was observed at the chiral center of the epoxide.



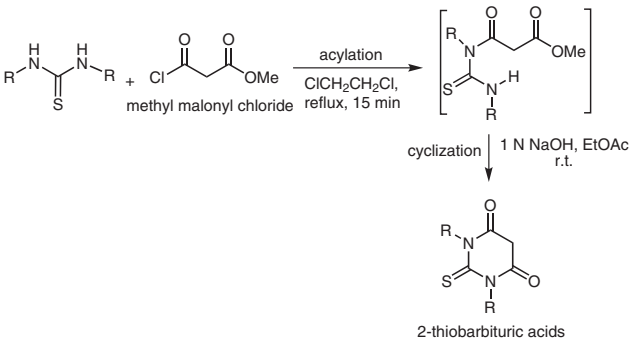
(D) *Synthesis of N-Substituted 2-Amino Benzimidazoles and Benzoxazoles:* N-substituted 2-amino benzimidazoles and benzoxazoles have been prepared using suitable desulfurizing agent, such as CuCl or diacetoxyiodobenzene (DIB), starting from in situ generated *N*-(2-amino/hydroxy aryl)thioureas.[8,9]



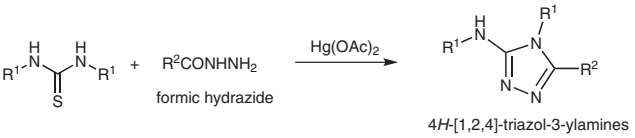
(E) *Synthesis of Substituted 2-Mercapto Benzimidazoles and 2-Amino Benzothiazoles by Catalytic Approaches:* Substituted 2-mercapto benzimidazoles have been synthesized from their corresponding 1,3-disubstituted thioureas through S-alkylation followed by copper-catalyzed intramolecular N-arylation.[10] In a similar strategy Castillon and co-workers have reported the synthesis of 2-amino benzothiazoles by a palladium-catalyzed cyclization of *o*-bromophenylthioureas.[11] These types of heterocycles have immense importance in medicinal chemistry.



(F) *Synthesis of N,N′-Disubstituted Thiobarbituric Acids:* 1,3-Disubstituted 2-thiobarbituric acids have been prepared in excellent yield from 1,3-disubstituted thioureas, via an acylation–cyclization strategy.[12] These heterocycles have pharmaceutical importance as anticonvulsants, immunotropic, anti-inflammatory, and antineoplastic agents as well as in the synthesis of other biologically active compounds.



(G) *Synthesis of Triazoles:* Chorev and co-workers have reported a thiophile-promoted synthesis of disubstituted 4*H*-[1,2,4]-triazol-3-ylamines.[13] When 1,3-disubstituted thiourea was reacted with formic hydrazide and mercury(II) acetate as thiophile, the reaction mixture produced acyl hydrazide adduct, which was cyclized to the corresponding [1,2,4]triazole under acidic conditions.



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