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A stepwise one-pot synthesis of aliphatic thiols and their derivatives from acrylamides and sulfur†

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Elemental sulfur enables the convenient formation of C–S bonds and the direct incorporation of S–S bonds. The reactivity of easily accessible electron deficient alkenes towards sulfur, however, is barely disclosed. Herein, we investigated the reactivity of acrylamides with sulfur and eventually developed a new pseudo-multicomponent reaction for the preparation of polysulfides. Sequential one-pot reduction led to diversely substituted thiols. Additional third stage one-pot modifications provided thioethers, unsymmetric disulfide and thioester.

Introduction

C–S and S–S bonds appear in important natural products, pharmaceuticals and functional materials.^{1,2} In particular, organic di-, tri and tetrasulfides (–S_x–) are considered potent sources of H₂S, being an important gasotransmitter.^{3–5} Di- and trisulfide bridges provide higher stability and potency to peptide based therapeutics, while tetrasulfides find application in rechargeable lithium–sulfur batteries.^{6,7} Therapeutic applications of sulfides are also significant. A number of di- and trisulfides are high potency antitumor agents. In fact, calicheamicin and shishijimicin A derivatives are used as payloads of ADCs.^{8–10} In addition, polysulfides might act as precursors to thiols, which are biologically and synthetically important compounds. Mucolytic *N*-acetylcysteine and carbocysteine are used to loosen thick mucus in bronchitis or COPD.^{11,12} Mycothiol serves as an intracellular detoxification agent, similar to GSH in functionality, scavenging reactive oxygen and nitrogen species (Fig. 1).¹³ Captopril, derived from L-proline is a potent ACE inhibitor prescribed for hypertension and to treat heart failure.¹⁴

Due to their nucleophilicity thiols are often applied in late-stage appendage reactions for the formation of C–S bonds. For example, the last steps in the synthesis of antifungal butoconazole

and immunosuppressive azathioprine are *S*-alkylation and nucleophilic aromatic substitution (S_NAr) reactions, respectively.^{15,16} Michael addition or thiol–ene click reaction is popularly applied in the preparation of linear, cross-linked polymers and dendrimers or in medicinal chemistry and chemical biology settings for protein labelling. One might mention covalent drugs having an acrylamide function for labelling cysteine residues (e.g. ibrutinib or osimertinib) and the synthesis of the highly potential antibody–drug conjugate Kadcyla from the cytotoxic payload mertansine and the antibody trastuzumab both used in oncology indications.^{17–20}

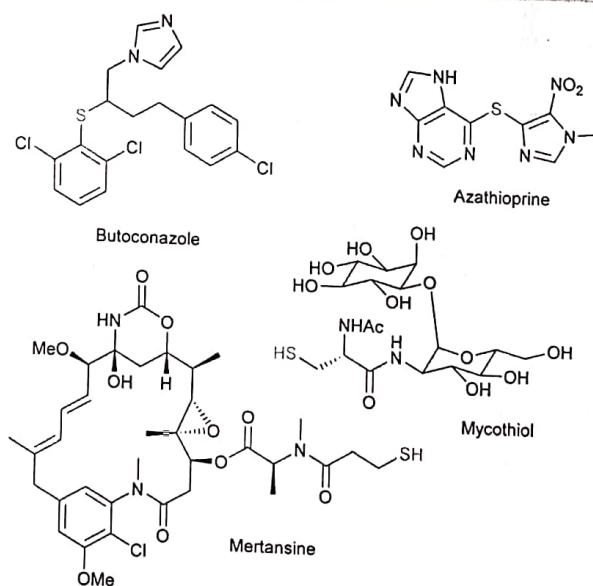


Fig. 1 Selected examples of biologically active thiols and thioethers.

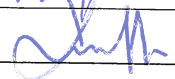
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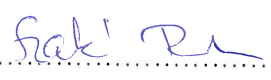


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⁴ Témavezető igazolja, aláírásával hitelesíti.