**SYNLETT Spotlight 425**

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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**N,O-Bis(trimethylsilyl)acetamide**

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**Introduction**

*N,O*-Bis(trimethylsilyl)acetamide (BSA) is a colorless liquid with a boiling point of 71–73 °C/35 mmHg. It is extremely moisture sensitive and can also be rapidly contaminated with trimethylsilylacetamide and acetamide. The reagent is commercially available and can be prepared from acetamide with an excess of triethylamine and chlorotrimethylsilane (Scheme 1). Since the early use of BSA in chromatographic analysis for the preparation of volatile trimethylsilyl derivatives, it has also proved to be useful in many synthetic applications. At first, BSA has been used as a powerful silylating agent for the protection of amines, amides, carboxylic acids, alcohols, enols and phenols. In these cases, BSA is an attractive alternative to other silylating agents, such as trimethylsilyl chloride. Indeed, the reaction conditions are generally mild and neutral, and the byproducts are sufficiently volatile to be easily removed from the reaction mixture by evaporation under reduced pressure. It has also been used as a Brønsted base precursor in Tsuji–Trost reactions. More recently, it has been used to activate various functional groups during the formation of nucleosides, peptides and heterocycles to name but a few.

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**Abstracts**

(A) **BSA as N-Silylating Agent: Activation of Nucleobases**

The Vöhringen reaction is useful for the preparation of nucleobases. Generally, the nucleobase is pre-activated by silylation with BSA and reacts with the sugar in the presence of a Lewis acid, such as trimethylsilyl trifluoromethanesulfonate. Bookser et al. have reported a one-step microwave-assisted Vöhringen glycosylation followed by neutralization of the resulting trifluoromethanesulfonic acid with triethanolamine (TEOA) and subsequent automated medium-pressure liquid chromatography (MPLC). A large panel of nitrogen-containing heteroaromatic bases is tolerated, allowing access to a structurally diverse library of nucleosides with satisfactory yields of up to 51%.

(B) **BSA as S-Silylating Agent: Activation of Thiol Acids**

At the same time, thiol acids have been shown to react with primary and secondary amines at room temperature in the presence of BSA to form amides and peptides. O-Silylthionoester, generated in situ from thiol acid and BSA via a sequence of S-silylation and spontaneous S-to-O silatropy, reacts with the amine to afford a tetrahedral intermediate. Subsequent tautomer migration of silicon from oxygen to sulfur, via pentavalent silicon intermediate A, allows amide bond formation without racemization after elimination of trimethylsilanethiol.

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**Scheme 1** Synthesis of *N,O*-Bis(trimethylsilyl)acetamide
(C) BSA as N-Silylating Agent: Activation of Amines
A metal-free direct amidation of peptidyl thiol esters with α-amino esters without racemization mediated by BSA has been described. få From a mechanistic viewpoint, in situ generation of N-silylamines from amines and BSA facilitates amide bond formation.

(D) BSA as Lewis Acid: Activation of Nitro Groups
Some pyrrolo[3,2-b]quinoline derivatives have been prepared by intermolecular cyclization of nitroarenes possessing an unsaturated side chain in the ortho position by means of BSA and DBU. få The latter combination promotes the cyclization of the benzyl-type anion with silylation of the nitro oxygen followed by elimination of silanol anion to produce the corresponding N-oxide heterocycle. A spontaneous deoxygenation–aromatization provides the targeted product.

(E) BSA as Bronsted Base Precursor
Craig et al. have demonstrated that exposure of allylic tosylacetates to BSA and a sub-stoichiometric quantity of potassium acetate triggers in situ silyl ketene acetal formation followed by [3,3]-sigmatropic rearrangement–decarboxylation sequence, allowing access to vinylcyclopropylsulfones and vinylcyclobutylsulfones, respectively, with moderate to excellent diastereoselectivity. få

(F) BSA-Induced C–F Bond Cleavage
Shibata et al. have reported the synthesis of a series of 3,5-diaryl-2-fluoromethyl-oxazolidin-2-ones through desymmetrization of aryl-fluoromethylcarbamates using BSA and a catalytic amount of CsF. få The BSA–CsF combination first generates cesium amide B, a Bronsted base able to deprotonate the carbamate. Intramolecular cyclization of C through C–F bond cleavage is accelerated by interaction with the silicon atom of BSA (transition state model D). This affords the desired oxazolidinone, releases TMSF and regenerates the catalytic active species B.

References