Tetrahedron 65 (2009) 10515–10534

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 894

# The syntheses and applications of β-benzylmercaptoethylamine derivatives

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ARTICLE INFO

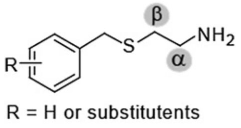
*Article history:*
Received 8 September 2009
Available online 14 October 2009

**Contents**

## 1. Introduction

The β-benzylmercaptoethylamine (β-BMEA) functionality and its derivatives are the most widely used synthons for the incorporation of the cysteamine moiety into many natural and non-natural products. The utility of this functionality arises from distinct advantages, including: ease of preparation, stability, compatibility with diverse reaction conditions, commercial availability, and scope of functional group manipulation through the reactive amine terminal, thioether linkage, or substituents in the aryl ring.

The general structure of these functionalities is represented below (Fig. 1). In accordance with IUPAC nomenclature, the $NH_2$ group receives priority over thioether, and therefore its attached carbon atom is denoted α. Occasionally this functionality has been referred to in the literature as 2-(benzylthio)ethylamine.



**1**

**Figure 1.** General structure of β-BMEA derivatives.

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*Abbreviations:* β-BMEA, β-benzylmercaptoethylamine; TFA, trifluoroacetic acid; DCM, dichloromethane; TBAB, tetrabutylammonium bromide; DMF, *N*,*N*-dimethylformamide; CIP, 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate; DIEA, *N*,*N*-diisopropylethylamine; DIPC, *N*,*N*′-diisopropylcarbodiimide; DMAP, 4-dimethylaminopyridine; TEA, triethylamine; THF, tetrahydrofuran; LDA, lithium diisopropylamide; LAH, lithium aluminum hydride; TMSI, trimethylsilyl iodide; DCC, *N*,*N*′-dicyclohexylcarbodiimide; BOP, benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate; *m*-CPBA, *meta*-chloroperoxybenzoic acid; HOBt, 1-hydroxybenzotriazole; HBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOAt, 1-hydroxy-7-aza-benzotriazole; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; MW, microwave; rt, room temperature.

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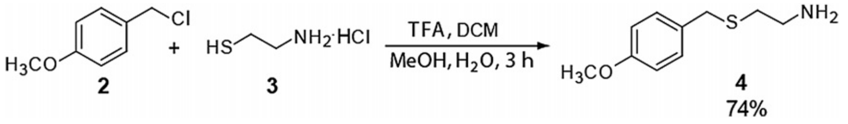
doi:10.1016/j.tet.2009.10.041

The range of utility of the β-BMEA has spanned from the synthesis of natural products and respective analogs to critical building blocks for the synthesis of heterocycles. Due to the presence of the highly reactive terminal amine, the primary route of synthetic utility stems from a reaction with an amine coupling partner. Apart from their wide ranging applications in organic synthesis, this functionality has been further utilized in a range of applications that span from materials to cosmetics. This functionality has gained traction especially in polydentate metal complexation, due to the presence of both the thioether linkage and amine functionality.[1,2] Recently in our own work, the β-BMEA proved a critical component in the synthesis of a panel of molecules that modulate α-secretase activity.[3] This review is responsive to our observation that despite the utility of the β-BMEA, no comprehensive reviews had been compiled to date. This review will provide a complete overview of currently developed methods for the preparation of β-BMEA derivatives and the wide ranging research of the application of these functionalities in the diverse fields of chemistry.

## 2. Survey of synthetic procedures

### 2.1. Acid mediated synthesis

The availability of acid mediated syntheses of β-BMEA has been limited. This is surprising given our own work showing that the reaction pathway likely proceeds via a borderline/$S_N1$-type reaction.[3] Regardless, Bierbach group reported the acid catalyzed synthesis of β-BMEA derivatives using a strategy entailing the dropwise addition of a solution of 4-methoxybenzyl chloride **2** in dichloromethane to a mixture of 2-aminoethanethiol hydrochloride **3** and trifluoroacetic acid in dichloromethane at 0 °C (Scheme 1). Extraction with a mixture of water and methanol followed by crystallization was the only purification necessary to afford pure β-BMEAs.[4]

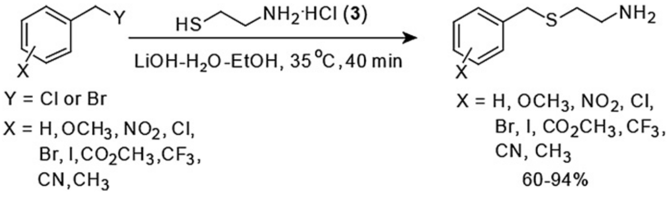


**Scheme 1.** Synthesis of β-(4-methoxybenzylmercapto)ethylamine **4**.

### 2.2. Base mediated synthesis

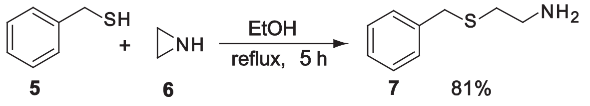
Among all of the synthetic strategies developed so far for the preparation of β-BMEA derivatives, base mediated syntheses dominate the literature. Generally, benzyl halides react with 2-aminoethanethiol hydrochloride in the presence of an alkali metal base in alcoholic solution to furnish the corresponding β-BMEA derivatives. This generalized scheme takes advantage of the enhanced nucleophilicity of the thiol as compared to the amine. Alkali metal bases such as NaOH,[5] NaOMe,[6] NaOEt,[7] Na/liq. $NH_3$,[8] TBAB–NaOET,[9] and $K_2CO_3$[10] are typically employed as the base.

Very recently our research group developed a synthetic methodology for the preparation of β-BMEA derivatives employing LiOH as an alkali metal base (Scheme 2).[3] We hypothesized that the general reaction could possibly be proceeding via a borderline/$S_N1$-type reaction mechanism, in contrast to the prototypical $S_N2$-type pathway we had originally hypothesized at the outset of the work. Lending support to this hypothesis, we were able to identify high dielectric mixtures of water and ethanol as ideal for smooth conversions. In this strategy, benzyl chlorides/bromides react with cysteamine hydrochloride **3** in the presence of a solution of LiOH in $H_2O$/EtOH (1:3) mixture at 35 °C in 40 min. After carrying out a number of experiments, we concluded that the varying amounts of water played an important role in both reaction time and yield and the 1:3 ratio of water/ethanol provided a balance between solvent dielectric and substrate solubility for the reaction pathway.



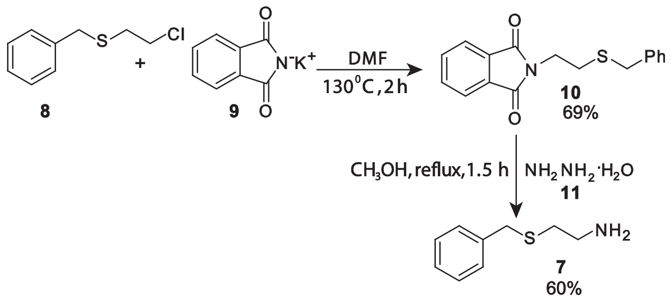
**Scheme 2.** LiOH mediated synthesis of β-BMEA derivatives.

During the synthesis of β-BMEA **7**, Chu et al. used ethyleneimine **6** as an alternative strategy that opened the aziridine in the process of forming the β-BMEA. In this approach, the ethyleneimine acted as both reagent and catalyst. The reaction between α-toluenethiol **5** and ethyleneimine **6** in absolute ethanol under refluxing condition furnished β-BMEA **7** in 81% yield (Scheme 3).[11]



**Scheme 3.** Ethyleneimine mediated synthesis of β-BMEA.

Reisner et al. reported another base mediated synthetic strategy utilizing a combination of *N*-(β-benzylmercapto)-ethylphthalimide **10** and hydrazine hydrate **11** under refluxing conditions in methanol (Scheme 4).[12] This was a two-step procedure that first involved conversion of the β-benzylmercaptoethyl chloride **8** to the *N*-(β-benzylmercapto)-ethylphthalimide **10** using potassium phthalimide **9** as a reagent, which was followed by reaction with hydrazine hydrate **11** to produce β-BMEA **7**.



**Scheme 4.** Synthesis of β-BMEA from β-benzylmercaptoethyl chloride.

Thiourea has also been used as an efficient reagent for the synthesis of alkoxy functionalized β-BMEA derivatives **15** in a two-step procedure.[13] First, thiourea **12** is reacted with 4-alkoxybenzyl chlorides to form the corresponding *S*-(4-alkoxybenzyl)isothiourea **13**, which upon treatment with 2-chloroethylamine hydrochloride **14** in the presence of NaOH produced the corresponding β-(4-alkoxybenzylmercapto)ethylamines **15** in good yields (Scheme 5).