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A new strategy for the synthesis of β-benzylmercaptoethylamine derivatives

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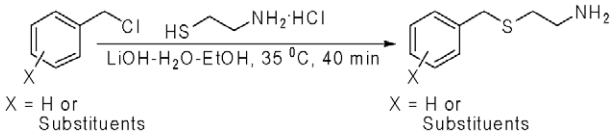
ABSTRACT

Here, we describe a new experimental approach to the synthesis of the β-benzylmercaptoethylamine functionality, and illustrate its synthetic utility in multi-component reactions. Although prevalent in modern organic synthesis, no general methods have been described for this functionality. Using a carefully developed LiOH–water–ethanol reaction mixture, we were able to produce a diverse collection of β-benzylmercaptoethylamines containing a range of sensitive functional groups in excellent yields. To further illustrate their utility in molecular library synthesis, we also report the use of β-benzylmercaptoethylamines in five different multi-component reactions.

The β-benzylmercaptoethylamine functionality and its derivatives are widely utilized with applications in organic,[1] inorganic,[2] medicinal,[3] and cosmetic chemistry.[4] For example, this functionality played a critical role in the synthesis of pantetheine (a cysteamine derivative of pantothenic acid–Vitamin B_5).[3a] Reisner reported the synthesis of D/L-γ-sulfamyl-α-amino acids as potential anti-metabolites utilizing β-benzylmercaptoethylamine as a key intermediate.[3b] When Okarvi et al. were exploring an alternative of 131I-hippuran (a renal radiopharmaceutical), they synthesized



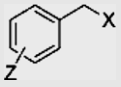
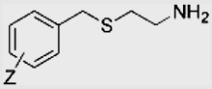
Scheme 1. General synthesis of β-benzylmercaptoethylamine and its derivatives using a combination of LiOH–water–ethanol.

Table 1
A systematic evaluation of solvent systems and bases for the formation of β-benzylmercaptoethylamines

Base used	Solvent used	Yield (%)
LiOH	EtOH	72
LiOH	EtOH–H_2O (3:1)	86
LiOH	H_2O	20
NaOH	EtOH	66
NaOH	EtOH–H_2O (3:1)	78
KOH	EtOH–H_2O (3:1)	75
CsOH	EtOH–H_2O (3:1)	75
K_2CO_3	EtOH	30
K_2CO_3	EtOH–H_2O (3:1)	50
Et_3N	EtOH	25
Et_3N	DCM	5

The reported yields are for reaction 7 from Table 2. All entries reacted for 40 min at 35 °C.

Table 2
Reaction between various benzyl halides and cysteamine hydrochloride using a combination of LiOH–H_2O–EtOH

Entry	Benzyl halide[a]	Product	Yield[b] (%)
			
1	Z = H, X = Br	Z = H	90
2	Z = H	Z = H	90
3	Z = 4-OMe	Z = 4-OMe	94
4	Z = 3-OMe	Z = 3-OMe	85
5	Z = 3-F, X = Br	Z = 3-F	83
6	Z = 3-F	Z = 3-F	82
7	Z = 3-Cl	Z = 3-Cl	86
8	Z = 3-Br	Z = 3-Br	85
9	Z = 3-I	Z = 3-I	85
10	Z = 2-NO_2	Z = 2-NO_2	78
11	Z = 3-NO_2	Z = 3-NO_2	82
12	Z = 4-NO_2, X = Br	Z = 4-NO_2	75
13	Z = 4-NO_2	Z = 4-NO_2	75
14	Z = 3-CO_2Me	Z = 3-CO_2Me	60[c]
15	Z = 3-CN	Z = 3-CN	80[d]
16	Z = 3-Me	Z = 3-Me	82
17	Z = 3-CF_3	Z = 3-CF_3	80
18	Z = 4-*t*-Butyl	Z = 4-*t*-Butyl	82
19	Z = 2,3-Di-OMe	Z = 2,3-Di-OMe	81
20	Z = 2,6-Di-Cl	Z = 2,6-Di-Cl	80
21	Z = 3-Cl-5-OMe	Z = 3-Cl-5-OMe	78
22	Z = 2-CN-3-Cl, X = Br	Z = 2-CN-3-Cl	80

[a] Unless otherwise stated, X = Cl and reaction time is 40 min.
[b] Isolated yield.
[c] Reaction time was 15 min.
[d] Reaction time was 30 min.

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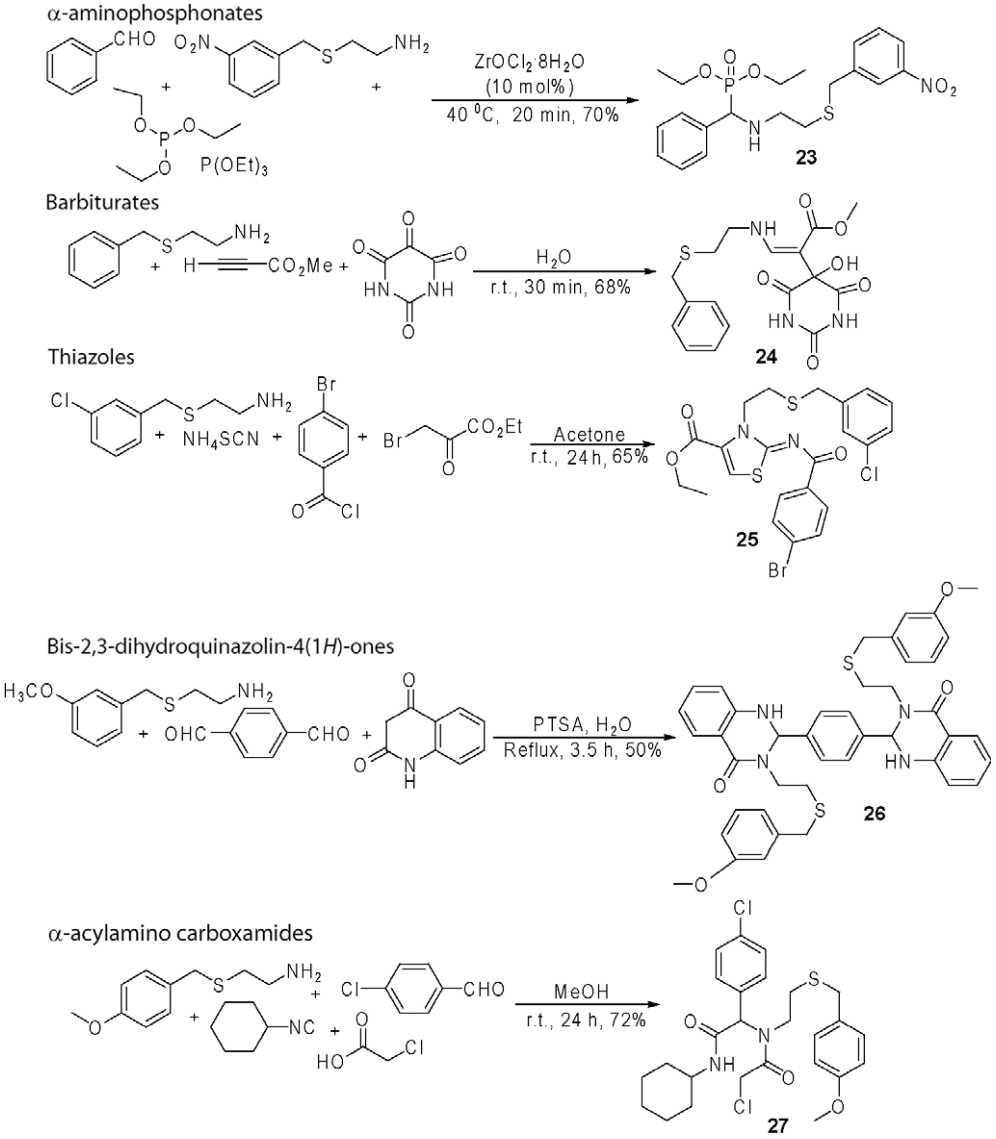
a number of S-protected derivatives of MAG3 (mercaptoacetyltriglycine), and discovered that the *p*-methoxy derivative of β-benzylmercaptoethylamine was a key starting material.[3l] Finally, in order to prove the necessity of the disulfide unit present in a series of psammaplin A type anti-bacterial agents (prepared by a novel combinatorial disulfide exchange strategy), Nicolaou et al. used β-benzylmercaptoethylamine as a thioether containing primary amine coupling partner.[3k]

Despite the wide ranging implications of this functionality, the disparate methods for producing it have afforded varying yields, and a systematic synthetic study is lacking. Some conditions that have been utilized with varying degrees of success include NaOMe–methanol,[3a] hydrazine hydrate–methanol,[3b] thiourea–NaOH–ethanol,[1e] ethyleneimine–ethanol,[1b] K_2CO_3–ethanol,[1c,3k] NaOEt–ethanol,[1d] Na/liq. NH_3,[1h] NaI–NaOEt,[2c] TFA–CH_2Cl_2,[2f] and NaOH–ethanol.[3i] These methods suffer from various disadvantages such as long reaction times,[1b,2f,3i,k] refluxing conditions,[1b,3a,b] the use of moisture-sensitive solvents and reagents,[1h] extensive work-up procedures,[2f] and a two-step reaction procedure.[1e]

During the course of synthesizing a small library of molecules to modulate the secretion of the Aβ peptide by a neuronal cell line, we became interested in a specific molecule that contained the β-benzylmercaptoethylamine functionality. It was during these studies that we identified the need to develop the method described here.

In our initial consideration of this reaction, and after a careful evaluation of previously reported reaction conditions, we hypothesized that the general reaction (depicted in Scheme 1) could possibly be proceeding via a borderline/S_N1-type reaction mechanism, in contrast to the prototypical S_N2-type pathway. Thus, we envisioned that a careful optimization of both the solvent conditions and the base used would be critical for developing a superior method. Toward the first point, and lending support to our borderline mechanism hypothesis, we were able to identify mixtures of water and ethanol as ideal for smooth conversions. Further lending support to our hypothesis, we found that simple ionic bases further facilitated smooth conversions (Scheme 1).

Here, we report a LiOH–water–ethanol reaction system that with the corresponding benzyl chlorides/bromides and cysteamine hydrochloride affords excellent yields, rapid reaction times, and a facile workup.[5] We have subsequently tested this methodology utilizing a wide range of substrates, and we illustrate the utility of these β-benzylmercaptoethylamines in combinatorial chemistry



Scheme 2. The use of β-benzylmercaptoethylamine and its derivatives in various multi-component reactions.

and diversity-oriented synthesis through five separate multi-component reactions (MCRs).

Table 1 illustrates a sampling of the reaction conditions we studied. Our initial exploration focused primarily on alcoholic solvents; however, we quickly determined that varying amounts of water played an important role in both reaction time and yield. It is likely that the 3:1 ratio of ethanol/water provided a balance between solvent dielectric for the reaction pathway while still allowing the reagents to be soluble in the media. Keeping the ethanol/water ratio fixed, we subsequently screened the effect of various alkali metal and organic bases to find LiOH the most effective.

Using this approach, not only were our yields superior to those previously reported, but we were also able to accomplish the conversions in a minimal amount of time (approximately 40 min) and at low temperatures (35 °C). For the reactions listed in Table 1, we utilized 3-chlorobenzyl chloride as the representative benzyl halide mainly due to its importance in the molecules we were synthesizing to modulate Aβ secretion.

After our careful optimization, we applied this methodology to a wide range of substrates summarized in Table 2 using a uniform set of reaction conditions.[5] Interestingly, we obtained comparatively lower yields for the nitro derivatives. Among all other nitro derivatives, *p*-nitro (Table 2, entries **12** and **13**) gave the lowest yield, further substantiating a borderline/S_N1-type mechanism, where at least a partial charge builds at the benzylic position. Further, the best yields were obtained for the substrates containing an electron-donating functional group such as $-OCH_3$ (Table 2, entry **3**). It is worth pointing out that the reaction was highly compatible with a number of functional groups including $-OCH_3$, $-NO_2$, halogens, –CN, $-CO_2CH_3$, $-CH_3$, and $-CF_3$. Benzyl chlorides and bromides gave similar yields (Table 2, compare entry **1** and entry **2**, entry **5** and entry **6**, entry **12** and entry **13**).

In conjunction with our efforts to synthesize small libraries that modulate Aβ-peptide excretion, we became further interested in exploiting β-benzylmercaptoethylamines in MCRs, as they create significant possibilities for molecular diversity in one step, affording more economical synthetic approaches as compared to linear syntheses.[6] We explored five separate MCRs with aims of generating a broad swath of diverse small molecules quickly (Scheme 2). We first explored α-aminophosphonates due, in large part, to their well-documented, diverse biological activities.[7] As a first trial, we synthesized the novel α-aminophosphonate **23** by following a literature procedure utilizing 2-(3-nitrobenzylsulfanyl)-ethylamine as the amine component. The reaction proceeded smoothly, affording a similar yield (70%) to those previously reported utilizing the Zr(IV) catalyst.[8] Because of the well-known therapeutic value of barbiturates,[9] next we turned our attention toward the synthesis of **24** via a three-component reaction using 2-benzylsulfanyl-ethylamine. Our 68% yield is in line with the 72–90% yields previously reported in the water-based solvent system.[10] Due to the prevalence of the thiazoles across diverse pharmaceutical targets,[11] we utilized the methodology of Yavari et al.[12] to synthesize **25** via a four-component reaction with 2-(3-chlorobenzylsulfanyl)-ethylamine.[12] The reaction proceeded with reasonable yield (65%) after 24 h. We further explored the synthesis of novel bis-2,3-dihydroquinazolin-4(1*H*)-one derivatives **26** utilizing a three-component reaction following a literature procedure.[13] As compared to precedent, our substrate proved to be effective as a reagent in the *p*-toluenesulfonic acid-catalyzed reaction affording **26** in 50% yield. Finally, since its discovery, the 'Ugi four-component reaction' is one of the best known and most popular multi-component reactions. In this reaction, an aldehyde/ketone, an amine, a carboxylic acid, and an isocyanide form an α-acylamino carboxamide through a one-pot condensation.[14] The final application is illustrated by the formation of **27**, derived from 2-(4-methoxybenzylsulfanyl)-ethylamine, in 72% yeild.[14c]

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Supplementary data

Supplementary data (experimental procedure, NMR spectra, high resolution mass spectra and compound characterization data are available) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.133.

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5. *Typical reaction procedure*: LiOH (0.245 g, 10.2 mmol) was dissolved in 5 mL of water, and 15 mL of ethanol was added. The resulting solution was added to a flask containing cysteamine hydrochloride (0.568 g, 5 mmol), followed by the dropwise addition of benzyl halides (5 mmol) with continuous stirring. The reaction mixture was stirred for 40 min at 35 °C, and ethanol was removed in vacuo. Twenty millilitres of water were subsequently added, and the mixture was extracted with dichloromethane (3×30 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified via column chromatography over silica gel (60 Å, 230–400 mesh, SiliCycle) using a mobile phase consisting of a suitable mixture of dichloromethane–methanol (gradient from 2% v/v methanol/dichloromethane to 20% v/v methanol/dichloromethane) to afford the chromatographically pure desired β-benzylmercaptoethylamine derivatives.
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