Synthesis of Thioureido-Linked Peptidomimetics, Glycosylated Amino Acids, and Neoglycoconjugates Using Bis(benzotriazolyl)methanethione as Thioacylating Agent

Vommina V. Sureshbabu,* Gundala Chennakrishnareddy, Hosahalli P. Hemantha

Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Dr. B. R. Ambedkar Veedhi, Bangalore University, Bangalore 560001, India
E-mail: sureshbabuvommina@rediffmail.com; E-mail: hariccb@hotmail.com; E-mail: hariccb@gmail.com

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Abstract: A practical synthesis of thiourea-linked peptidomimetics, glycosylated amino acids, and neoglycoconjugates is described employing bis(benzotriazolyl)methanethione as thiocarbonylating reagent. The entire protocol is mild, efficient, high-yielding, and free from hazardous reagents. All the intermediates and products have been isolated and fully characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

Key words: peptidomimetics, isothiocyanates, thioureidopeptides, pseudoglycoconjugates

Peptidomimetics and glycomics are known to exhibit improved therapeutical and biological properties.[1] Their ability to sustain enzymatic hydrolysis due to the presence of unnatural linkages provides them with a longer shelf life while the better solubility in the biological system helps to deliver the desired drug action effectively. Among various backbone modifications used, several classes of pseudopeptides and neoglycoconjugates have been reported by inserting urea,[2] sulfonamide,[3] phosporamide,[4] carbamate[5] functionalities and also several heterocycles as native bond surrogates.[6] Among them, the ureidopeptides and oligoureas have received special interest due to their significance in medicinal chemistry.[7] Similarly, the thioureido linkage has also received attention because of its interesting biological as well as structural aspects. The ability to provide hydrogen-bond donor and acceptor points makes it an efficient anion receptor[8] and it serves as a building block in the construction of supramolecular structures.[9] A number of thioureido derivatives has been reported to exhibit marked antiarrhythmic,[10] antiviral,[11] and anticancer[12] activities. Their utility as non-nucleoside inhibitors of HIV-1, HIV-2 RT,[13] antagonists for the human NK1 tachykinin receptor,[14] influenza virus, and potential anti-TB therapeutic agents[15] has also been documented. The –NHCSNH– moiety has been widely employed to bridge carbohydrates and related glycoconjugates,[16] which are used in tailoring oligonucleoside analogues. The thiourea moiety is the key structural element in many organic catalysts being exploited in the asymmetric synthesis in a wide variety of reactions.[17] Furthermore, thiourea-linked glycooligomers have been employed as phosphate binders in water[18] and in the design of mimics of natural oligosaccharides.[19]

Among several strategies available for the synthesis of thioureas, coupling of isothiocyanates with amines is the most widely employed.[20] Though the nucleophilic displacement of a substituted halide with isothiocyanate ion is another option, this suffers from the ambidentate nature of the ion itself.[21] Other methods such as the reaction of CS_2 with amines,[22] H_2S with substituted guanidines,[23] treatment of an amine with triphenylphosphine thiocyanogen,[24] and catalyst-driven decomposition of dithicarbamic salts have also been reported.[25] Many of them involve the use of the toxic reagents, generate unstable intermediates, and result in isolation and handling problems. On the other hand the use of several thiocarbonyl transfer reagents such as 1-(methyldithiocarbonyl)imidazole,[26] di-2-pyridyl thionocarbonate (DTP),[27] 1,1′-(thiocarbonyldioxy)dibenzotriazole,[28] 1,1′-thiocarbonyldi-2,2′-pyridone,[29] 1,1′-thiocarbonyldiimidazole[30] are known. Among them, bis(benzotriazolyl)methanethione (Bt-CS-Bt, **1**) stands out as the preferred reagent due to its ease of preparation, stability, and efficient reaction with the nucleophiles.[31] Katritzky and co-workers have demonstrated its applications in the preparation of diverse array of alkyl and aryl thiocarbonyl benzotriazoles.[31] These intermediates have been employed as isothiocyanate equivalents in organic synthesis. However, to the best of our knowledge, the application of this reagent in peptide and glycochemistry for the synthesis of thioureido derivatives has yet to be demonstrated. In this letter, we report a simple and convenient protocol for the synthesis of thioureidopeptides, thiourea-tethered glycosylated amino acids and neoglycoconjugates. The protocol employs a stepwise replacement of each benzotriazolyl unit of **1** with a suitably protected amino acid or carbohydrate derived amine.

The reagent **1** (Figure 1) was prepared by the reaction of trimethylsilyl benzotriazole with thiophosgene employing the reported procedure.[30] The required trimethylsilyl de-

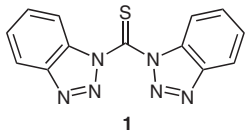

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Figure 1 Bt-CS-Bt

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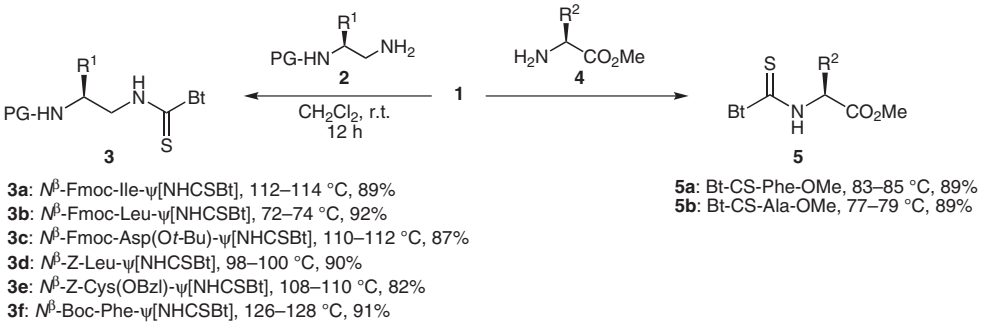


Scheme 1 Preparation of monosubstituted thiocarbonyl benzotrazoles

rivative was synthesized according to the Birkofer procedure.[32] We initiated our studies on the synthesis of dipeptidomimetics **6** possessing both N- and C-terminals as such peptidomimetics with N- and C-termini, similar to the natural peptides, will enable further chain extensions/modifications. For such molecular assembly, one of the contributing amines has to be derived from an N-protected amino acid through suitable carboxyl modification, and the amino acid ester is an obvious choice as another partner. Initially, for the synthesis of the required N^{β}-protected alkyl amine **2**, the N^{α}-Fmoc-amino acid was converted to the corresponding alcohol by reduction of its mixed anhydride using $NaBH_4$.[33] The hydroxyl group was transferred to azide moiety via the iodo intermediate under Mitsunobu conditions employing Ph_3P, imidazole, and I_2.[34] On subjecting the N^{β}-Fmoc-alkyl azide to catalytic hydrogenation employing Pd/C, the corresponding amine **2** was obtained in good yield and purity.[35] In the case of *Z*-chemistry, N^{β}-*Z*-protected amino acid derived alkyl azides were reduced using Ph_3P in refluxing THF.[36] In a different approach, the Boc counterparts were prepared by reducing the N^{α}-Boc-amino nitriles using $LiAlH_4$.[37]

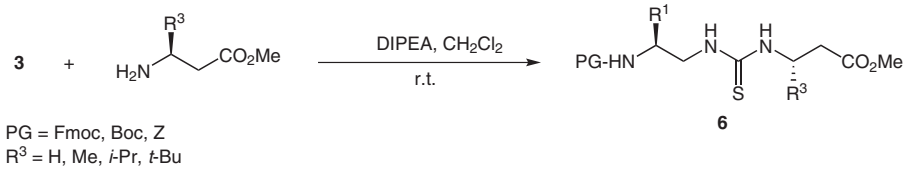
In the following step towards **6**, we undertook tandem nucleophillic replacement of the Bt groups of **1** with the amines in hand. Thus, a reaction of N^{β}-Fmoc/Boc/Z-amino alkyl amine **2** with Bt-CS-Bt at room temperature yielded the corresponding monosubstituted thiocarbonyl benzotriazoles **3** in yields greater than 80% (Scheme 1).

Employing a similar approach, an amino acid ester **4** was reacted with **1** to afford monosubstituted thiocarbonyl benzotriazoles **5**. Isolating monosubstituted compounds **3** and **5**, which can be further utilized in the synthesis of unsymmetrical thioureas, is possible because replacement of the first Bt moiety by a nucleophile takes place readily at room temperature whereas the second Bt group gets replaced by another nucleophile only in the presence of a base. All derivatives **3** and **5** were isolated as crystalline solids and were fully characterized. They were found to be stable and storable at ambient temperature for long periods with out any decomposition.

In the next stage, isothiocyanate equivalents **3a–f** and **5a**,**b** were further substituted; accordingly, reaction of **3a** with β-alanine methyl ester in the presence of diisopropylethyl amine (DIPEA) afforded the desired thiouredo dipeptidomimetic **6a** (Scheme 2). The *N*-Fmoc thioureido peptides **6a–c** were obtained as low melting solids; whereas the Boc- and Z-protected thioureoido peptides **6d–f** were gummy compounds; all were fully characterized spectroscopically.

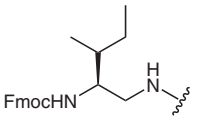
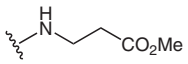
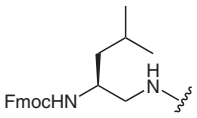
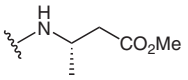
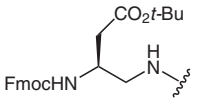
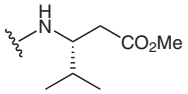
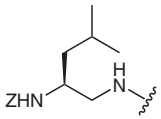
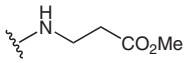
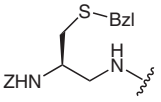
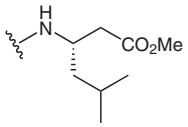
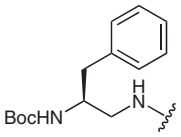
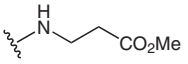
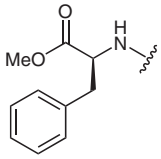
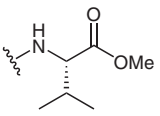
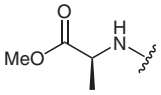
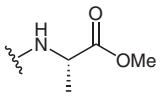
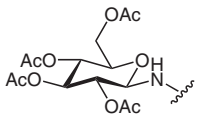
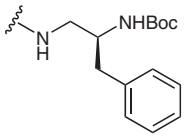
In the same manner, the reaction of valine methyl ester with **5a** and alanine methyl ester with **5b** in the presence of DIPEA afforded unsymmetrical and symmetrical thioureidopeptides **6g** and **6h**, respectively; while reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl-1-amine with N^{β}-Boc-Phe-ψ[NH-CS-Bt] (**3f**) yielded thiourea-linked glycosylated amino acid **6i** in good yield and purity (Table 1). Importantly, the above protocol was found to cause no racemization as confirmed through NMR studies.[38]

Sugar isothiocyanates constitute an important class of intermediates but the synthetic difficulties involved in the preparation of glycosyl isothiocyanates are a major concern in assembling a diverse array of thiourea-linked carbohydrate derivatives.[39] Hence, we prepared sugar isothiocyanate equivalent **8** by replacing one Bt group of **1** with amino sugar **7** (Scheme 3). O-Protected sugar-1-amines **7** were prepared from glucose, galactose, and lactose through established protocols using acetyl or benzoyl groups for hydroxyl protection.[40] The masked sugar isothiocyanates **8a–d** from both monosaccharides and disaccharides were isolated in good yield after a simple workup and were characterized spectroscopically (Scheme 3). Subsequent reaction of these derivatives **8** with amino sugars in the presence of DIPEA yielded symmetrical and unsymmetrical thioureido neoglycoconju-



Scheme 2 N^{β}-Fmoc/Boc/Z-protected thioureido peptides

Table 1 Characteristic Data for Thiourea-Linked Peptidomimetics

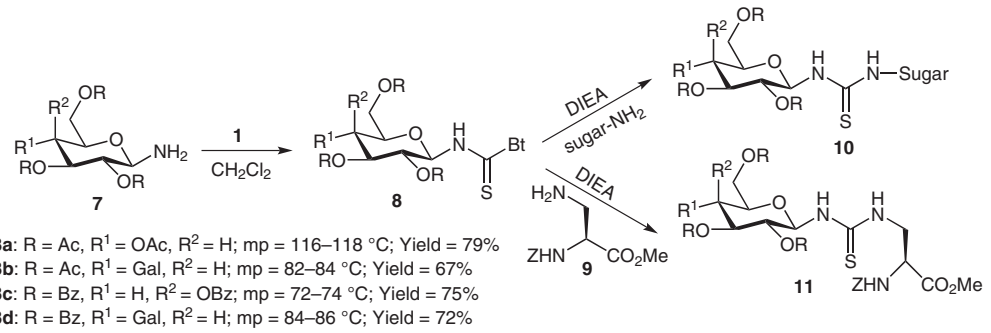
Compd **6**	X	Y	Mass (Calcd, Found)[a]	Yield (%)
6a			506.2089, 506.2079	87
6b			520.2246, 520.2241	92
6c			606.2614, 606.2618	85
6d			418.1776, 418.1781	90
6e			554.2123, 554.2119	86
6f			418.1776, 418.1776	85
6g			375.1354, 375.1351	83
6h			271.0728, 271.0720	87
6i			662.2359, 662.2355	79

[a] Mass = HRMS.

gates **10a–c**, which were isolated and recrystallized using CH_2Cl_2–hexane before being fully characterized (Table 2).

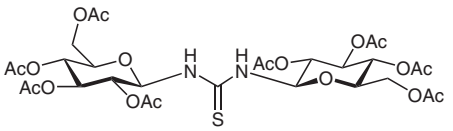
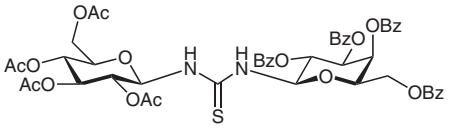
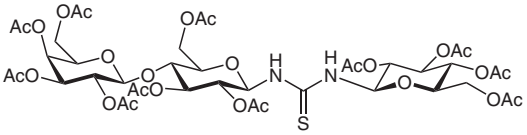
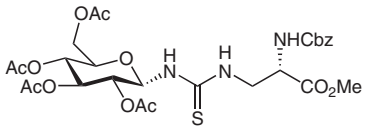
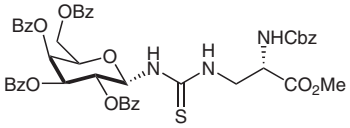
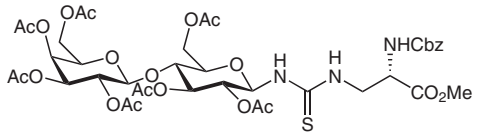
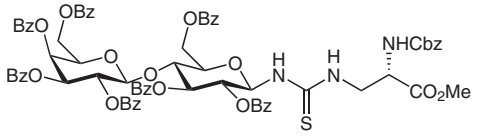
It is known from the literature that the molecules bearing β-amino-L-alanine unit have acquired profound biological and synthetic interest and are present in several natural products of therapeutic significance.[41] N^{α}-Cbz-β-amino-L-alanine methyl ester (**9**) was synthesized through Hoffmann rearrangement of L-Asn using iodosobenzene diacetate (PIDA) as reported by Zhang et al.[42] The resulting free γ-amine was reacted with various O-protected glycosylamino thiocarbonyl benzotriazoles **8** to afford the corresponding thiourea-tethered glycosylated amino acid conjugates **11a–d** as solids in 85–90% yields (Scheme 3, Table 2).[43]

In summary, we report the synthesis of thioureido-linked peptidomimetics, neoglycosylated amino acids, and pseudoglycoconjugates by employing bis(benzotriazole)methanethione as the thiocarbonyl transfer reagent. The stepwise replacement of each Bt group of the reagent **1** with an appropriate amine has resulted in thiourea-linked products. The method obviates the use of hazardous reagents and handling problems. All the monosubstituted thiocarbonyl benzotriazoles and thioureas have been



Scheme 3 Preparation of pseudoglycoconjugates and neoglycosylated amino acids

Table 2 Characterization Data of Pseudoglycoconjugates and Neoglycosylated Amino Acids

Compd **10** and **11**	Pseudoglycoconjugates/neoglycosylated amino acids	Mp (°C)	Mass (Calcd, Found)[a]	Yield (%)
10a		113	759.1895, 759.1891	81
10b		115	1007.2521, 1007.2518	89
10c		116	1047.2740, 1047.2735	80
11a		68	664.1788, 664.1785	88
11b		96	912.2414, 912.2409	79
11c		90	952.2633, 952.2638	81
11d		94	1386.3729, 1386.3719	76

[a] Mass = HRMS.

isolated and well characterized. The protocol is simple and efficient giving quantitative yields in all the steps.

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(43) **General Procedure for the Preparation of 3, 5, or 8**
To a solution N^{β}-Fmoc/Boc/Z-amino alkyl amine **2** (1.0 mmol), amino acid ester **4**, and O-protected β-glycosyl amine **7** (1.0 mmol) in CH_2Cl_2 (10 mL), Bt-CS-Bt **1** (1.0 mmol) was added at r.t., and the reaction mixture was stirred overnight. After the completion of reaction (as monitored by TLC), it was diluted with CH_2Cl_2, the organic layer was washed with 10% $NaHCO_3$ (to remove benzotriazole byproduct), brine, and dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure to afford **3**, **5**, or **8** which were recrystallized from CH_2Cl_2–*n*-hexane.
General Procedure for the Preparation of 6a–i, 10a–c, and 11a–d
To a stirring solution of **3**, **5**, or **8** (1.0 mmol) in CH_2Cl_2 (10 mL) was added amino-free amino acid ester (1.0 mmol), or O-protected β-glycosyl amine (1.0 mmol), or N^{α}-Cbz-β-amino-L-alanine methyl ester (1.0 mmol) followed by the addition of DIPEA (1.0 mmol) at r.t. The mixtrue was stirred for about 5–6 h until completion (TLC analysis). The solvent was removed in vacuo, and the residue was taken into EtOAc. The organic layer was washed with 10% citric acid solution, $NaHCO_3$ (10%) solution, brine, and dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure and the residue recrystallized from CH_2Cl_2–*n*-hexane to afford the title compounds.
Fmoc-*β*-Ile-*ψ*[NH-CS-NH]-*β*-Ala-OMe (6a)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.96 (m, 6 H), 1.25

(m, 2 H), 2.00 (m, 2 H), 2.35 (t, *J* = 8.0 Hz, 2 H), 3.37 (t, *J* = 8.0 Hz, 2 H), 3.56 (s, 3 H), 3.67 (m, 2 H), 3.81 (m, 1 H), 4.18 (m, 1 H), 4.37 (m, 2 H), 5.35 (br, 1 H), 6.84 (br, 1 H), 7.31–7.76 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 15.9, 25.8, 30.9, 33.9, 37.8, 40.1, 47.6, 52.3, 56.4, 67.5, 125.6, 125.7, 127.6, 128.2, 141.7, 144.2, 158.0, 173.5, 183.1 HRMS: *m/z* calcd for $C_{26}H_{33}N_3O_4S$: 506.2089 [M + Na]; found: 506.2079 [M + Na].

***Z*-β-Cys(*BzI*)-ψ[NH-CS-NH]-β-Leu-OMe (6e)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.8 Hz, 6 H), 1.23 (m, 2 H), 1.76 (m, 1 H), 2.40 (m, 2 H), 2.53–2.67 (m, 2 H), 3.35 (m, 1 H), 3.47 (m, 1 H), 3.77 (m, 3 H), 3.89–3.99 (m, 4 H), 5.04 (s, 2 H), 5.04 (s, 2 H), 5.30 (br, 1 H), 7.23–7.33 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 22.6, 23.0, 25.2, 34.1, 36.9, 44.5, 44.6, 49.6, 55.4, 55.6, 67.3, 127.7, 128.4, 128.6, 128.9, 129.6, 136.9, 137.1, 138.1, 156.7, 175.1, 183.8: HRMS: *m/z* calcd for $C_{27}H_{37}N_3O_4S_2Na$: 554.2123 [M + Na]; found: 554.2119 [M + Na]

OMe-Phe-[NH-CS-NH]-Val-OMe (6g)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 7.6 Hz, 6 H), 2.23 (m, 1 H), 3.12 (m, 2 H), 3.34 (m, 1 H), 3.67 (s, 3 H), 3.76 (s, 3 H), 3.83 (m, 1 H), 6.80 (br, 1 H), 7.10–7.32 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 18.5, 30.5, 37.1, 52.2, 52.6, 60.1, 64.2, 126.8, 127.5, 129.4, 136.3, 168.8, 173.1, 183.4. HRMS: *m/z* calcd for $C_{17}H_{24}N_2O_4S$: 375.1354 [M + Na]; found: 375.1351 [M + Na].

Compound (11b)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05 (br, 1 H), 3.64 (s, 3 H), 3.93 (m, 1 H), 4.18 (m, 1 H), 4.41 (m, 2 H), 4.51 (m, 2 H), 5.06 (m, 3 H), 5.64 (s, 2 H), 5.96 (br, 1 H), 7.14–8.01 (m, 25 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.6, 53.8, 62.7, 68.0, 69.7, 69.9, 71.9, 72.3, 77.8, 83.3, 128.2, 128.8, 128.9, 129.0, 129.2, 129.4, 130.4, 130.5, 131.1, 133.6, 133.9, 134.2, 134.4, 136.1, 157.2, 165.9, 166.5, 168.2, 168.9. 171.2, 183.2. HRMS: *m/z* calcd for $C_{47}H_{43}N_3O_{13}S$: 912.2414 [M + Na]; found: 912.2409 [M + Na].

Compound (11d)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (br, 1 H), 3.64 (s, 3 H), 3.87 (m, 1 H), 4.42–4.49 (m, 3 H), 4.62–4.66 (m, 5 H), 4.82 (m, 1 H), 5.00–5.04 (m, 3 H), 5.17 (m, 1 H), 5.41 (m, 3 H), 5.61 (m, 1 H), 5.70 (m, 1 H), 5.93–5.98 (m, 2 H), 7.20–8.08 (m, 40 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.1, 53.5, 56.1, 63.2, 67.8, 68.5, 69.9, 70.5, 71.5, 71.9, 72.1, 73.0, 73.1, 75.2, 82.6, 102.1, 119.0, 119.1, 119.6, 120.1, 120.4, 120.7, 121.1, 121.4, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 128.8, 129.1, 129.5, 130.3, 130.4, 130.5, 131.1, 131.3, 132.0, 132.3, 133.9, 134.4, 136.5, 137.1, 137.2: 157.6, 170.1, 170.2, 170.4, 170.9, 171.0, 171.3, 171.7, 171.9, 183.1. HRMS: *m/z* calcd for $C_{74}H_{65}N_3O_{21}S$: 1386.3729 [M + Na]; found: 1386.3719 [M + Na].