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Authors: Hemalatha Bukya, Kiranmai Nayani, Pavankumar Gangireddy, and Prathama S. Mainkar

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FULL PAPER

Benzoisothiazolone (BIT): A Fast, Efficient and Recyclable Redox Reagent for Solid Phase Peptide Synthesis

Hemalatha Bukya,[a,c] Kiranmai Nayani,[a] Pavankumar Gangireddy*[c,d] and Prathama S. Mainkar*[a,b]

Abstract: Solid-phase peptide synthesis (SPPS), a preferred synthetic procedure, generates by-products and effluents in multiples of equivalents for one equivalent of desired product. Presented here is the use of a fast and efficient coupling protocol for SPPS using a benzoisothiazolone (BIT), which can be fully recycled. The BIT, as redox activator, works under very mild conditions and generates very minimal waste. As a case study, the BIT coupling protocol is applied to the synthesis of side chain of recently discovered antibiotic, teixobactin.

Introduction

In nature, peptide and protein functions are significant in physiological and biological processes, which are mandatory for biological activities in living organisms. Understanding the proteins' mechanism of action in biochemical pathways is one of the most intriguing parts of drug discovery. Consequently, several groups have carried out research to discover novel peptides as pharmacophore for most challenging pathologies such as cancer, diabetes, osteoporosis, bacterial infections and cardiovascular diseases.[1] Approvals for drugs with peptide skeletons are increasing significantly due to their higher safety and efficiency profile. The efficacy of peptide drugs is better than non-peptidic molecules because their therapeutic interventions are very close mimics of natural biochemical pathways.[2]

Peptide research requires the availability of peptides or proteins in sufficient quantities and with high purity. These can be accessed by extraction from cells using a recombinant technology, using a chemical synthesis or a combination of both. The recombinant protein expression is a highly useful tool for the large-scale production of bioactive proteins or longer peptides.[3] However, biochemical engineering methods are often facing difficulties in cracking suitable genes for the production of targeted proteins and unfeasible to access peptides with unnatural amino acids. In contrast, chemical synthesis can offer flexible access to customised peptide sequences. Therefore, peptide synthesis is an important transformation in organic chemistry from the last century.[4] Although the solution phase peptide synthesis assures good yields for shorter peptides, there are limitations while coupling longer peptides due to rigidity and insolubility that can prevent peptide elongation. Longer and complex peptides can be synthesized using solid-phase peptide synthesis (SPPS) in a much simpler way.[5] In due course lot of developments have been made in SPPS.[5-7] Traditional coupling methods, such as diimide-based activation, anhydride-mediated couplings and preactivated esters, which are used in solution phase, have also been successfully applied to SPPS. Coupling reagents such as phosphonium- or uronium/guanidinium (aminium)-based structures (for example BOP, HBTU, TBTU and HATU) are the most widely used in today's SPPS. However, these reagents are required in nearly 4-6 molar equivalents per amidation, which in turn generates the same amount of by-product as a waste. Recently, a case study was described by James Nowick and co-workers where uronium coupling agents (HATU, HBTU, and HCTU) can induce anaphylaxis and had recommended to take extra precautions while using these reagents.[8] The minimization of waste production and improvement of safety profile is an important objective in large-scale peptide synthesis and it demands the development of a new coupling reagent with either a great catalytic turnover capacity or a stoichiometric recycling ability. Recently, Handoko *et al*., building off of earlier results described by Liebeskind and co-workers,[9] developed a urea-based diselenide organocatalyst for solution-phase catalytic peptide synthesis of a range of amino acid substrates.[10] One example of a solid-phase reaction was described. However, in the SPPS example, after the coupling of three amino acid residues two coupling cycles were required for the complete consumption of the free amine. In addition, this protocol requires molecular sieves to trap a water molecule released during oxidation of the selenium catalyst, which presents a significant technical difficulty in SPPS.

Our group has been working in the area of peptides and peptidomimetics with a special interest to antimicrobial peptides.[11] Recently, we have initiated the synthesis of teixobactin, an antibiotic peptide and achieved side chain fragment synthesis in solution phase.[12] Our continued interest in peptide synthesis prompted us to explore possibilities of a recyclable and milder acid activator for SPPS. Preferred features of such reagent would be to carry out coupling reactions avoiding epimerization and minimizing the generation of waste. With these goals in mind, we explored the feasibility of BIT-derived thioesters in SPPS. Earlier, Liebeskind *et al*. demonstrated benzoisothiazolones (BITs) as organocatalytic oxidants in an oxidation-reduction condensation reaction, to generate peptides,[13] and subsequent mechanistic investigations[14] revealed that thioesters derived from benzoisothiazolone (BIT) **1**,

[a] *Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India. E-mail: prathama@iict.res.in, https://www.iictindia.org/People/view?id=410*
[b] *Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, 201002, India*
[c] *National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad 500037, India*
[d] *NSJ Prayog Life Sciences, Hyderabad 500007, India. E-mail: grpavan@gmail.com*
Supporting information for this article is given via a link at the end of the document.

H. Bukya and K. Nayani contributed equally to this work.

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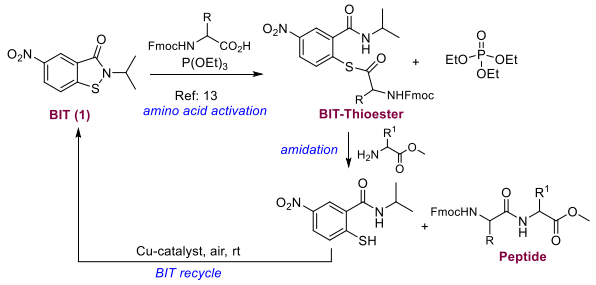
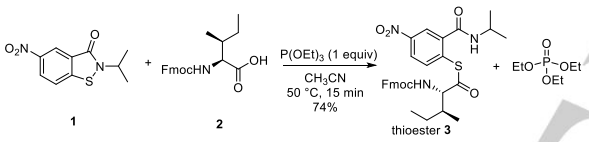
carboxylic acid **2**, and triethyl phosphite were excellent electrophile reacting with amines to generate the corresponding amide and *o*-mercaptobenzamide. The *o*-mercaptobenzamide was easily re-oxidized to the BIT (**1**) under Cu-catalyzed aerobic conditions (Scheme 1).



Scheme 1. BIT mediated peptide synthesis and recycle of BIT.

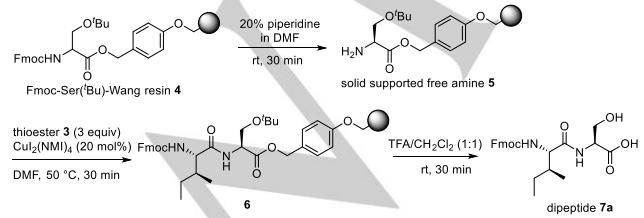
Results and Discussion

Our study began with the synthesis of thioester **3** from BIT **1** and Fmoc-Ile-OH **2**. BIT **1** was prepared from 2-chloro 5-nitrobenzoic acid according to a literature procedure.[13,15] The BIT was treated with Fmoc-Ile-OH **2** in the presence of triethyl phosphite in acetonitrile at 50 °C for 15 min to generate BIT-derived thioester **3** in 74% yield (Scheme 2).



Scheme 2. Synthesis of BIT-derived thioester **3**.

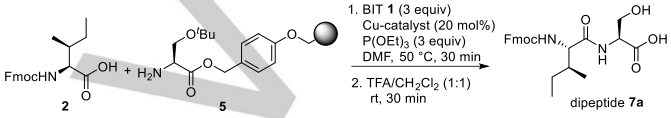
The amine coupling partner was prepared by Fmoc-deprotection of Fmoc-Ser(ᵗBu)-Wang resin **4** using 20% piperidine in DMF. The solid supported free amine **5** was reacted with thioester **3** (3 equiv) in the presence of 20 mol% $CuI_2(NMI)_4$ catalyst in DMF at 50 °C for 30 min to generate amide **6**. After 30 min, reaction mixture was filtered and the resin beads were washed with CH_2Cl_2. Complete consumption of free amine was confirmed by the Kaiser test. Finally, the resin was cleaved with trifluoroacetic acid in CH_2Cl_2 at room temperature to provide dipeptide **7a**. A simple trituration of this crude dipeptide with diethyl ether and hexane provided Fmoc-Ile-Ser-OH **7a** in 87% yield over three steps (Scheme 3).



Scheme 3. Thioester-mediated amidation on solid support

After successfully utilizing the BIT-derived thioester in SPPS, we have concentrated on optimization of the reaction conditions.

To avoid the separate preparation and purification of the BIT-derived thioester **3**, a one pot reaction was conducted with BIT **1**, Fmoc-protected amino acid and the solid supported free amine **5** using triethyl phosphite and copper catalyst in DMF at 50 °C for 30 min. After coupling, the resin was cleaved. To our delight the dipeptide **7a** was obtained in 88% yield. It is thus established that thioester **3** can be generated *in-situ* and reacted with amine in a SPPS reaction. Direct activation of the carboxylic acid with the BIT in presence of the amine made the strategy more straightforward, simple and efficient. The by-products such as triethyl phosphate and *o*-mercaptobenzamides obtained in the reaction were easily removed by CH_2Cl_2 washings. Later, from this filtrate BIT **1** was recycled under aerobic conditions at ambient temperature (See Supporting Information). The resin cleavage provided peptide **7a** (>95% pure by HPLC) (Scheme 4).

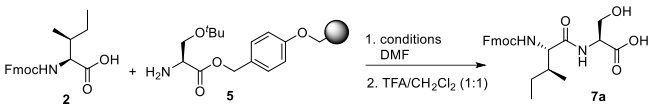


Scheme 4. BIT-mediated amidation in SPPS

The reaction was also performed at room temperature with BIT, Fmoc-protected amino acid and solid-supported free amine in DMF. The room temperature reaction delivered dipeptide **7a** in 89% yield, which is equally good as compared to the 50 °C reaction. To optimize equivalents of BIT **1** and amino acid, several control experiments were carried out where 1.1 equivalents of amino acid and 3 equivalents of BIT **1** also provided **7a** in 91% yield with 98% HPLC purity (see Supporting Information).

After optimization of the BIT mediated amide formation, a comparative study was performed with different standard coupling reagents that are typically used in SPPS reactions (Table 1). To realize the potential of BIT **1** in SPPS, the coupling reaction was performed using BIT **1**, HATU and EDC.HCl/HOBt. BIT reagent **1** proved to be equally good as other coupling reagents in terms of yield and purity as judged by HPLC. In addition, the amidation was completed in shorter time (30 min) when compared to other coupling reagents (1-2 h) (see Supporting Information for details).

Table 1. Comparison of coupling reagents in SPPS.[a,d]



Entry	Conditions	Temp/Time	Yield[b] (%)
1	HATU (1.5 equiv), DIPEA (3 equiv)	rt, 1 h	92
2	EDC.HCl (3 equiv), HOBt (2 equiv), DIPEA (6 equiv)	rt, 2 h	88
3[c]	BIT **1** (3 equiv), $P(OEt)_3$ (3 equiv), Cu-catalyst (20 mol%)	rt, 30 min	91

[a] Reactions were performed using free amine **5** (obtained from 300 mg resin, 0.6 mmol of Fmoc-amino acid/gram), acid partner **2** (2 equiv) at 25 °C in DMF solvent. [b] Yield corresponds to isolated dipeptide after resin cleavage without chromatographic purification. [c] 1.1 equiv of **2** was used. [d] No epimerization was observed in the above experiments, confirmed by HPLC.

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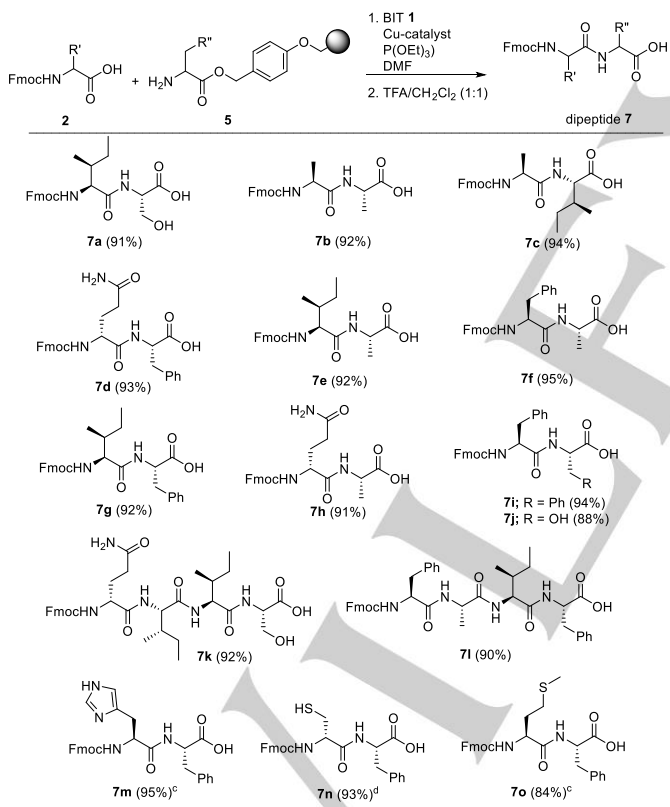
To check the synthetic utility of this reaction, a variety of dipeptides (**7a-7j**), and tetrapeptides (**7k** and **7l**) were prepared (Table 2). All amidations were completed within 30 min (confirmed by Kaiser test) under optimized conditions and provided corresponding peptides ranging from 88 to 95% yields after trituration with diethyl ether and hexanes. The obtained peptides showed 95-99% HPLC purity. In the case of coupling of Fmoc-L-His(Trt)-OH with NH_2-L-Phe-wang resin, after 30 min the free amine was not consumed completely which is confirmed by the Kaiser test. It took 6 h for the complete conversion of free amine to get Fmoc-L-His-L-Phe-OH **7m** in 95% yield. Epimerization (*dr* 96.5:3.5) was observed. When sulfur-containing amino acid such as Fmoc-L-Cys(Trt)-OH was coupled with NH_2-L-Phe-wang resin, a mixture of products was obtained. The LC-MS analysis showed 57.7% of required dipeptide, Fmoc-L-Cys-L-Phe-OH **7n** and 27.6% of dimerized product of dipeptide through S-S bond formation (see Supporting Information). Another sulfur-containing amino acid Fmoc-L-Met-OH was successfully utilized in BIT-mediated SPPS to get Fmoc-L-Met-L-Phe-OH **7o** in 84% yield (*dr* 98:2) without any oxidation to methionine sulfur.

Table 2. BIT-mediated synthesis of peptides in SPPS[a,b]



[a] Reaction conditions: Step-1: **2** (1.1 equiv), **5** (0.086-0.2 mmol, 1 equiv), BIT **1** (3 equiv), Cu-catalyst (20 mol%), $P(OEt)_3$ (3 equiv), DMF (2-4 mL), rt for 30 min-1 h. Step-2: TFA/DCM (2-3 mL, 1:1), rt, 30 min. [b] Yields of isolated products without chromatographic purification. [c] step-2: rt, 6 h (amidation) and epimerization observed (see Supporting Information). [d] dimerized dipeptide was formed along with dipeptide **7n**.

As a part of our research on the synthesis of antimicrobial peptides, we have initiated the synthesis of teixobactin **8**. Teixobactin is a promising lead compound having antibiotic activity with a novel mechanism of action against a range of Gram-positive bacteria including virulent strain of *Micobacterium tuberculosis (Mtb),* methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and penicillin-resistant *Staphylococcus pneumonia* (PRSP) (Figure 1).[16] Most of the synthetic reports of teixobactin used SPPS protocols where stoichiometric amounts of coupling reagents were used.[17]

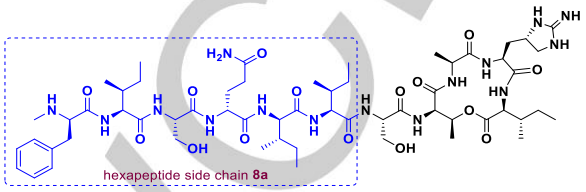
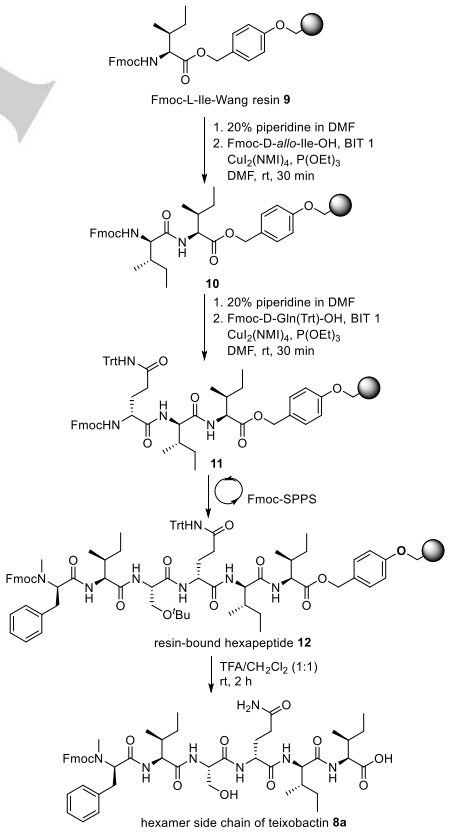


Figure 1. Structure of teixobactin **8**

To show the potential application of the present amidation protocol, we attempted SPPS for teixobactin side chain **8a** using BIT **1** as recyclable acid activator, to avoid expensive, conventional acid activators. The synthesis started with Fmoc-deprotection of Fmoc-L-Ile-Wang resin **9** using 20% piperidine in DMF to deliver the resin-bounded free amine (Scheme 5). The

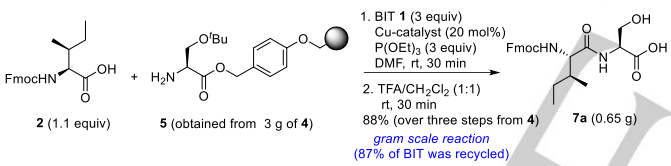


Scheme 5. Synthesis of teixobactin side chain **8a** using BIT in SPPS

free amine was subjected to coupling with Fmoc-D-*allo*-Ile-OH (1.1 equiv) using BIT **1** (3 equiv), 20 mol% $CuI_2(NMI)_4$ catalyst, and triethyl phosphite (3 equiv) in DMF at room temperature for

30 min to generate Fmoc-D-*allo*-Ile-L-Ile-Wang resin **10**. After coupling, the reaction was filtered and the resin beads washed with CH_2Cl_2 to remove reagents and by-products. The Fmoc-dipeptide **10** was treated with 20% piperidine in DMF to generate the free amine which was coupled with Fmoc-D-Gln(Trt)-OH under the standard conditions to construct solid-supported tripeptide **11**. Having successfully obtained the tripeptide chain, the remaining linear portion of the target hexapeptide was extended using the same protocol, including incorporation of L-Ser and L-Ile, consecutively, and finally the *N*-terminal *N*-methyl-Fmoc-D-Phe-OH to afford the resin-bound hexapeptide **12**. With successful assembly of the hexapeptide **12**, the resin, trityl group and *tert*-butyl protecting groups were all removed with TFA/CH_2Cl_2 (2:1) in one step and the target *N*-Fmoc protected hexapeptide **8a** was obtained in 44% yield over all steps[12,18] with 90% purity by LC-MS without any chromatographic purification. Generally, the synthesis of peptides *via* Fmoc/t-Bu chemistry suffers from base mediated epimerization resulting in a complex product profile.[19] In our protocol, during hexapeptide synthesis using BIT, no epimerization was observed (confirmed by LC-MS analysis; see Supporting Information for details).

In order to demonstrate gram-scale feasibility and BIT recovery of this amidation protocol, a reaction was performed between **2** and **5** under the optimized reaction conditions (Scheme 6) to produce **7a** in 88% yield (93% purity by HPLC) with 87% of BIT recovery (see Supporting Information).



Scheme 6 Gram scale synthesis of **7a** and BIT recovery in SPPS

Conclusions

In conclusion, BIT-mediated SPPS successfully produces a series of peptides in a short time (30 min for each coupling) with good yields under mild conditions without noticeable epimerization. Also, BIT (**1**) recycle was demonstrated for gram scale reaction in 87% BIT recovery and amino acid consumption minimized (1.1 equiv) irrespective of peptide length. This fast and efficient method applied for the production of teixobactin side chain that provides the targeted peptide **8a** within 2 days with 90% purity. We have replaced the conventional coupling reagents in SPPS with recyclable BIT, improving on the economical, environmental, and health factors of the amidation process. The synthesis of other commercial antibiotic peptides is underway presently in our laboratory.

Experimental Section

General Information: All chemicals have been purchased from commercial sources and were used without further purification unless otherwise noted. All solvents are reagent grade or HPLC grade. Anhydrous acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2) and *N,N*-dimethylformamide (DMF) were obtained from a dry solvent system. Dichloromethane was freshly distilled from CaH_2. Yields refer to spectroscopically pure compounds after isolation. ^1H and ^{13}C NMR spectra were recorded in DMSO-d6 using 400 or 500 MHz (^1H) and 100 or 125 MHz (^{13}C). Chemical shifts (δ-values) are reported in ppm, spectra were calibrated related to solvents' residual proton chemical shifts (DMSO-d_6, δ = 2.5) and solvents' residual carbon chemical shifts (DMSO-d_6, δ = 49.0), multiplicity is reported as follows: s = singlet, brs = d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet or unresolved and coupling constant *J* in Hz. Melting points (mp) were determined in open capillaries and are uncorrected. Infrared spectra (IR) were recorded on a 0.1 mm KBr demountable cell. Optical rotations $[\alpha]_D^T$ were measured in $CHCl_3$ with a digital polarimeter in a 1 mL cell of 1 dm path length at 20 °C. High-resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) using a Q-TOF-Waters mass spectrometer (Xevo GS-XS model) in positive ion mode (M + H or M + Na) as indicated. LC-MS analysis was performed using Xevo-TQS Micro (Waters Make) and LC-MS-8040 (Shimadzu make) mass spectrometer. HPLC analyses were performed on Agilent 1200 series with appropriate columns and elution conditions.

Supporting Information (see footnote on the first page of this article): Further detailed experimental procedures and copies of ^1H and ^{13}C NMR spectra as well as other chromatograms disseminated are available as supporting information.

Conflict of Interest
The authors declare no conflict of interest.
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Keywords: Benzoisothiazolone • Solid phase peptide synthesis • Antimicrobial peptides • Amidation • Teixobactin

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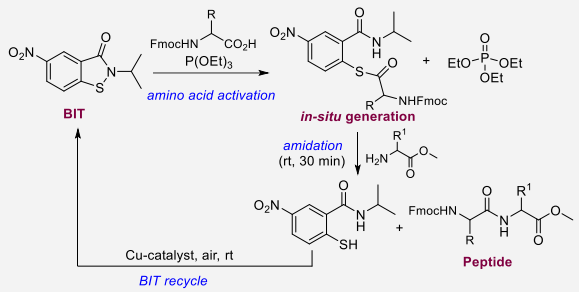

Hemalatha Bukya, Kiranmai Nayani, Pavankumar Gangireddy* and Prathama S. Mainkar*

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Benzoisothiazolone (BIT): A Fast, Efficient and Recyclable Redox Reagent for Solid Phase Peptide Synthesis

A fast and efficient coupling protocol for SPPS using a benzoisothiazolone (BIT) under mild conditions with minimal waste has been developed. BIT recycle is demonstrated for gram scale reaction and amino acid consumption has been minimized irrespective of the peptide length. This coupling protocol has been sucessfully applied for the synthesis of side chain of recently discovered antibiotic, teixobactin.