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A Facile Approach to the Synthesis of Benzothiazoles from *N*-Protected Amino Acids

M. Arfan[a,*], A. Tahira[a], A. Mannan[b], and T. Fatima[c]

[a] *Department of Chemistry, School of Natural Sciences, National University of Sciences and Technology, Islamabad, 44000 Pakistan*
[b] *Department of Pharmacy, COMSATS University, Abbottabad Campus, Abbottabad, 22010 Pakistan*
[c] *Department of Chemistry, COMSATS University, Islamabad Campus, Islamabad, 44000 Pakistan*
**e-mail: marfan@sns.nust.edu.pk*

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Abstract—A simple trituration method for the synthesis of 2-substituted benzothiazoles derived from *N*-protected amino acids and 2-aminothiophenol using molecular iodine as a mild Lewis acid catalyst has been proposed. The reaction occurs in one step for 20–25 min in solve-free conditions and provides the target roducts in excellent yields.

Keywords: benzothiazole, *N*-protected amino acids, Lewis acid catalyst

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Among the known heterocycles benzothiazole is one of the most biologically and chemically active moiety, due to which it has found a large number of pharmaceutical and industrial applications [1–4]. Over the past decade, rapidly increasing application of benzothiazoles in medicinal and pharmaceutical chemistry has been observed, and a large number of methods have been reported for their synthesis. However, the methods available in literature have such limitations as the use of metal catalysts, expensive reagents, and toxic solvents, as well as long reaction times, high temperatures, and low yields [5–11].

In the present study for the synthesis of benzothiazoles we developed a method that overcomes all the above-mentioned limitations. We employed iodine as a catalyst, the reaction was carried out without the use of any solvent, at room temperature, and was complete in 20–25 min. The efficiency of iodine catalysis in benzothiazole synthesis has been repeatedly mentioned in the literature [12–18].

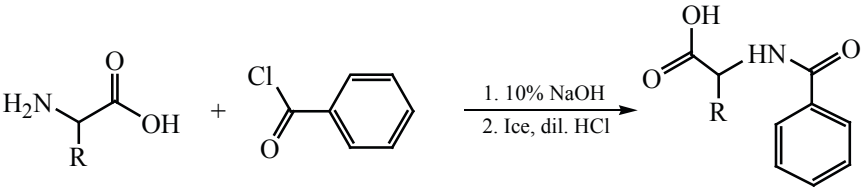
In this work we synthesized 2-substituted benzothiazoles using *N*-protected amino acids as substrates for the first time. For the protection of the amino group, the benzoyl and Boc protecting groups were selected. Amino acids were selected as substrates as they show remarkable metabolic and regulatory versatility. They are known to serve as important starting materials for the synthesis of a variety of molecules, regulate key metabolic pathways and processes, and play a role in the health, growth, homeostasis, and reproduction of living organisms [19].

As part of our studies for the development of new methodology, herein we now describe a new approach for the synthesis of 2-substituted benzothiazoles in a single step, with an excellent yield, a shorter reaction time, without the use of any costly or toxic reagent and using iodine as a Lewis acid catalyst.

The six amino acids used in this study, namely glycine, leucine, proline, tryptophan, valine and phenylalanine, were first benzoyl and Boc-protected following published procedures [20] (Schemes 1 and 2, respectively).

The synthesis of benzothiazoles was carried out by the procedure in [13] by trituration of *N*-protected amino acids with 2-aminothiophenol in the presence of molecular iodine as a catalyst. The reaction is novel in the sense that up to date *N*-protected amino acids have never been involved in such reaction as a reactant for the synthesis of benzothiazoles. In 2013, Panda et al. [21] used *N*-protected aminoacylbenzotriazole or *N*-protected peptidylbenzotriazole for the synthesis of benzothiazoles

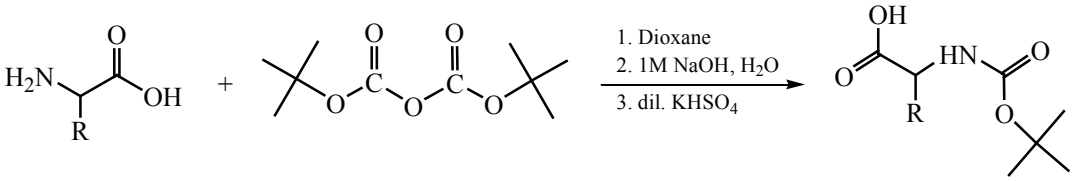
Scheme 1. Synthesis of *N*-benzoyl-protected amino acids **1a–1f**.



1a–1f

R = H (**a**), –$CH_2CH(CH_3)_2$ (**b**), (**c**), (**d**), $CH(CH_3)_2$ (**e**), (**f**).

Scheme 2. Synthesis of *N*-Boc-protected amino acids **2a–2f**.



2a–2f

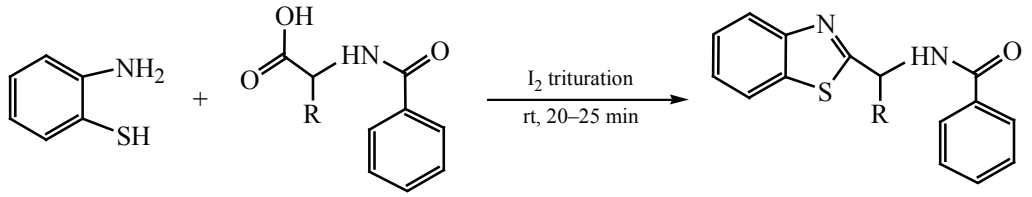
R = H (**a**), –$CH_2CH(CH_3)_2$ (**b**), (**c**), (**d**), $CH(CH_3)_2$ (**e**), (**f**).

in noncatalytic conditions under microwave irradiation, and the maximum yield of the target products was 89%. However, by our procedure we obtained yields of up to 98% not using microwave irradiation and in half the reaction time in [21]. Furthermore, we used *N*-protected amino acids rather than *N*-protected benzotriazoles.

The reaction of *N*-benzoyl-protected amino acids **1a–1f** with 2-aminothiophenol gave the corresponding 2-substituted benzothiazoles **3a–3f** (Scheme 3). The synthesized compounds were characterized by FTIR spectroscopy and mass spectrometry. The FTIR spectra of all the products showed a characteristic benzothiazole C=N absorption band in the region of 1600 cm^{-1} [22, 23]. The absence of a broad OH stretching band at 3200–3400 cm^{-1} was considered as further evidence for the formation of the target products.

Scheme 4 shows the mass spectral fragmentation pathway of compound **3a** (as a representative of the series), which is confirmative of the structure of the product.

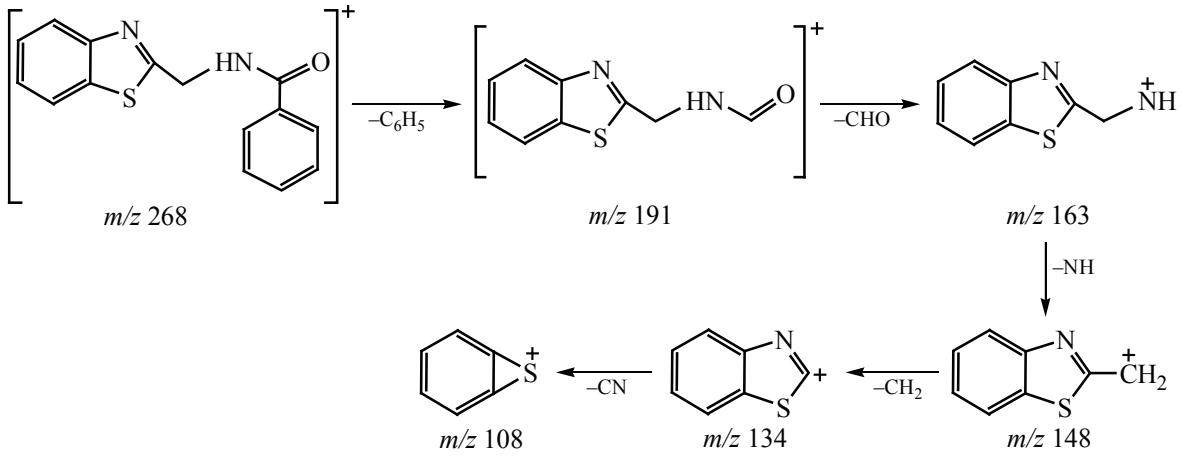
Scheme 3. Synthesis of benzothiazoles **3a–3f** from *N*-benzoyl-protected amino acids **1a–1f**.



1a–1f **3a–3f**

R = H (**a**), –$CH_2CH(CH_3)_2$ (**b**), (**c**), (**d**), $CH(CH_3)_2$ (**e**), (**f**).

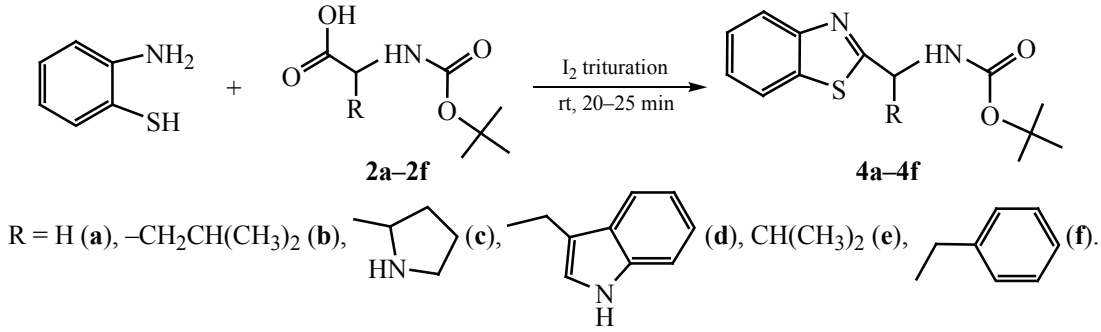
Scheme 4. Mass spectral fragmentation pattern of compound **3a**.



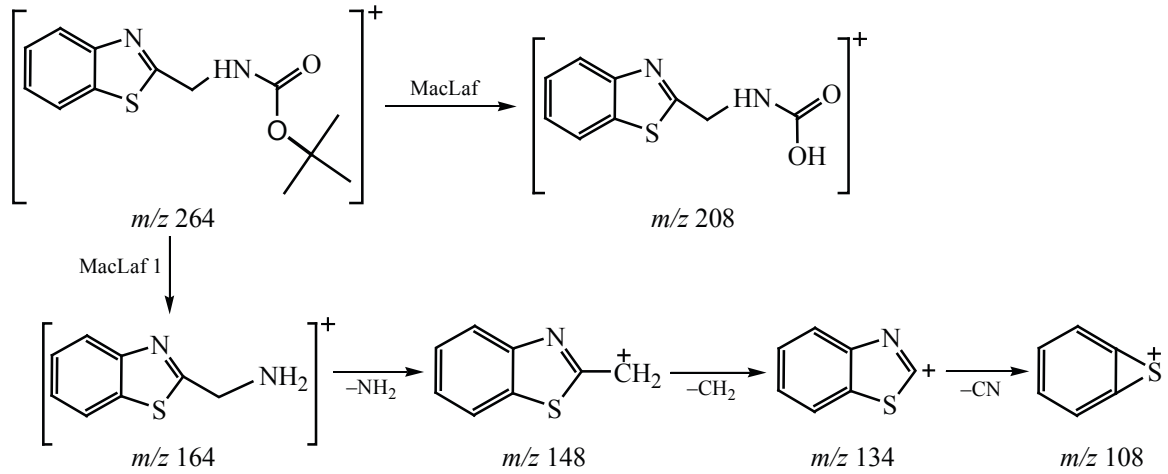
The reaction of *N*-Boc-protected amino acids **2a–2f** with 2-aminothiophenol resulted in the synthesis of the corresponding 2-substituted benzothiazoles **4a–4f** (Scheme 5). The FTIR spectra of the products and the mass spectrum of compound **4a** as a representative of the series (Scheme 6) confirm the formation of the target products.

The study resulted in the successful development of a facile synthesis of 2-substituted benzothiazoles from *N*-benzoyl- and *N*-Boc-protected amino acids, using molecular iodine as a catalyst. Twelve previously unknown benzothiazoles were synthesized, and their structures were confirmed by FTIR spectroscopy and GCMS analysis.

Scheme 5. Synthesis of benzothiazoles **4a–4f** from *N*-BOC-protected amino acids **2a–2f**.



Scheme 6. Mass spectral fragmentation pattern of compound **4a**.



EXPERIMENTAL

All chemicals of analytical grade were purchased from Sigma–Aldrich and used without further purification. The melting points were determined on an SMP10 melting point apparatus and are uncorrected. The reaction progress was monitored by TLC on plates (eluent), spots visualization under UV light. The FTIR spectra were recorded on a Bruker ATR FTIR spectrophotometer in the range 4000–500 cm^{-1}. Recrystallized samples were analyzed by GCMS on a Perkin Elmer Clarus 600 GC coupled with 600c MS Quadrupole EI (dimensions Elite-5 column, carrier gas He, 1 mL/min).

***N*-Benzoyl-protected amino acids 1a–1f** (*general procedure*). A solution of 0.5g (6.66 mmol) of amino acid in 0.4 mL of 10% aqueous NaOH was stirred for 30 min, after which 0.68 mL of benzoyl chloride was added dropwise in five portions, and stirring was continued for an additional 30 min. The progress of the reaction was monitored by TLC. After the reaction had been complete, ice was added, and the pH of the mixture was adjusted to 2–3 by carefully adding dilute HCl. The crystals that formed were filtered off, washed with cold water, dried, boiled in CCl_4 for 5 min to remove excess benzoic acid, washed with water, and recrystallized from methanol.

***N*-Boc-protected amino acids 2a–2f** (*general procedure*). Amino acid (4.3 g, 37.4 mmol) was dissolved in dioxane (75 mL) and after 30 min 1 M NaOH (38 mL) and H_2O (38 mL) were added followed by $(Boc)_2O$ (9 g, 41.4 mmol). The reaction mixture was stirred for 1 h and concentrated under reduced pressure to about 30–40 mL, after which ice and a little of ethyl acetate. A dilute $KHSO_4$ solution was then added very carefully to the reaction mixture to adjust its pH to 2–3. The solution was then washed with brine and the product was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was evaporated under reduced pressure.

Benzothiazoles 3a–3f and 4a–4f from *N*-protected amino acids (*general procedure*). The reaction between protected amino acid (500 mg, 2.7 mmol) and 2-aminothiophenol (0.67 mL, 5.3 mmol) in the presence of iodine (223 mg, 1.8 mmol) as a catalyst was carried out following the procedure described in [14]. The reaction was complete (TLC monitoring) in 20 min. The product was washed with aqueous $Na_2S_2O_3$ to remove unreacted iodine and purified by recrystallization from a 70 : 30 ethanol–water mixture.

***N*-(1,3-Benzothiazol-2-ylmethyl)benzamide (3a)** was prepared by the general procedure using amino acid **1a**. Yield 76%, mp 110–111°C, R_f. IR spectrum, ν, cm^{-1}: 1613 (C=O), 1600 (C=N), 1582 (C=C), 700 (C–S). Mass spectrum, *m/z* (I_{rel}, %): 268 $[M]^+$, 191 $[M - C_6H_5]^+$, 163 $[M - C_6H_5CO]^+$, 148 $[M - C_6H_5CONH]^+$, 134 $[C_7H_4NS]$, 108 $[C_6H_4S]$.

***N*-[1-(1,3-Benzothiazol-2-yl)-3-methylbutyl]-benzamide (3b)** was prepared by the general procedure using amino acid **1b**. Yield 86%, mp 118–119°C, R_f 0.63. IR spectrum, ν, cm^{-1}: 1703 (C=O), 1603 (C=N), 1578 (C=C), 710 (C–S). Mass spectrum, *m/z*: 324 $[M]^+$, 247 $[M - C_6H_5]^+$, 219 $[M - C_6H_5CO]^+$, 204 $[M - C_6H_5CONH_2]^+$, Second Route: 281 $[M - CH_3CH_2CH_3]^+$, 176 [281 – C_6H_5CO], 134 $[C_7H_4NS]$, 108 $[C_6H_4S]$.

[2-(1,3-Benzothiazol-2-yl)pyrrolidin-1-yl]-(phenyl)methanone (3c) was prepared by the general procedure using amino acid **1c**. Yield 91%, mp 101–102°C, R_f 0.59. IR spectrum, ν, cm^{-1}: 1680(C=O), 1600 (C=N), 1575 (C=C), 712 (C–S). Mass spectrum, *m/z*: 308 $[M]^+$, 231 $[M - C_6H_5]^+$, 203 $[M - C_6H_5CO]^+$, 175 $[C_{10}H_{10}NS]$, 134 $[C_7H_4NS]$, 108 $[C_6H_4S]$.

***N*-[1-(1,3-Benzothiazol-2-yl)-2-(1*H*-indol-3-yl)-ethyl]benzamide (3d)** was prepared by the general procedure using amino acid **1d**. Yield 82%, mp 122–125°C, R_f 0.70. IR spectrum, ν, cm^{-1}: 1713 (C=O), 1614 (C=N), 1539 (C=C), 710 (C–S). Mass spectrum, *m/z*: 397 $[M]^+$, 320 $[M - C_6H_5]^+$, 292 $[M - C_6H_5CO]^+$, 277 $[M - C_6H_5CONH]^+$, 281 $[M - C_8H_6N]^+$, 267 $[M - C_8H_6NCH_2]^+$, 34 $[C_7H_4NS]$.

***N*-[1-(1,3-Benzothiazol-2-yl)-2-methylpropyl]-benzamide (3e)** was prepared by the general procedure using amino acid **1e**. Yield 97%, mp 92–94°C, R_f 0.77. IR spectrum, ν, cm^{-1}: 1678 (C=O), 1603 (C=N), 1565 (C=C), 700 (C–S). Mass spectrum, *m/z*: 310 $[M]^+$, 190 $[M - C_6H_5CO]^+$, 134 $[C_7H_4NS]$, 108 $[C_6H_4S]$.

***N*-[1-(1,3-Benzothiazol-2-yl)-2-phenylethyl]benzamide (3f)** was prepared by the general procedure using amino acid **1f**. Yield 66%, mp 144–146°C, R_f 0.66. IR spectrum, ν, cm^{-1}: 1700 (C=O), 1608 (C=N), 1573 (C=C), 715 (C–S). Mass spectrum, *m/z*: 358 $[M]^+$, 281 $[M - C_6H_5]^+$, 253 $[M - C_6H_5CO]^+$, 267 $[M - CH_2C_6H_5]^+$, 134 $[C_7H_4NS]$.

***tert*-Butyl (1,3-benzothiazol-2-ylmethyl)carbamate (4a)** was prepared by the general procedure using amino acid **2a**. Yield 78%, mp 139–141°C, R_f

0.75. IR spectrum, ν, cm^{-1}: 1600 (C=O), 1582 (C=N), 1570 (C=C), 1308 [$C(CH_3)_3$], 1300 (C–O), 712 (C–S). Mass spectrum, *m/z*: 264 $[M]^+$, 208 [MacLafferty], 164 [MacLafferty 1], 148 [C_8H_6NS], 134 [C_7H_4NS], 108 [C_6H_4S].

***tert*-Butyl [1-(1,3-benzothiazol-2-yl)-3-methylbutyl]carbamate (4b)** was prepared by the general procedure using amino acid **2b**. Yield 96%, mp 89–91°C, R_f 0.84. IR spectrum, ν, cm^{-1}: 1735 (C=O), 1605 (C=N), 1600 (C=C), 1298 [$C(CH_3)_3$], 1300 (C–O), 710 (C–S). Mass spectrum, *m/z*: 320 $[M]^+$, 277 $[M - CH(CH_3)_2]^+$, 263 $[M - CH_2CH(CH_3)_2]$. Second Route: 264 [MacLafferty], 220 [MacLafferty 1], 204 [$C_{12}H_{15}NS$], 134 [C_7H_4NS].

***tert*-Butyl 2-(1,3-benzothiazol-2-ylmethyl)pyrrolidine-1-carboxylate (4c).** Yield 98%, mp 95–99°C, R_f 0.81. IR spectrum, ν, cm^{-1}: 1717 (C=O), 1600 (C=C), 1614 (C=N), 1280 [$C(CH_3)_3$], 1100 (C–O), 710 (C–S). Mass spectrum, *m/z*: 304 $[M]^+$, 248 [MacLafferty], 204 [$C_{11}H_{12}N_2S$], 190 [$C_{10}H_{10}N_2S$], 134 [C_7H_4NS].

***tert*-Butyl [1-(1,3-benzothiazol-2-yl)-2-(4-hydroxyphenyl)ethyl]carbamate (4d).** Yield 92%, mp 135–137°C, R_f 0.76. IR spectrum, ν, cm^{-1}: 1680 (C=O), 1603 (C=N), 1582 (C=C), 1305 (C–O), 714 (C–S). Mass spectrum, *m/z*: 393 $[M]^+$, 263 $[M - C_8H_6N]^+$, 337 [MacLafferty 1], 293 [MacLafferty], 134 [C_7H_4NS].

***tert*-Butyl [1-(1,3-benzothiazol-2-yl)-2-methylpropyl]carbamate (4e).** Yield 54%, mp 138–140°C, R_f 0.70. IR spectrum, ν, cm^{-1}: 1735 (C=O), 1604 (C=N), 1578 (C=C), 1299 [$C(CH_3)_3$], 1241 (C–O), 700 (C–S). Mass spectrum, *m/z*: 306 $[M]^+$, 250 [MacLafferty 1], 206 [MacLafferty], 190 [$C_9H_6NS(CH_3)_3$], 134 [C_7H_4NS], 108 [C_6H_4S].

***tert*-Butyl [1-(1,3-benzothiazol-2-yl)-2-phenylethyl]carbamate (4f).** Yield 90%, mp 80–84°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 1693 (C=O), 1607 (C=N), 1506 (C=C), 1366 [$C(CH_3)_3$], 1156 (C–O), 715 (C–S). Mass spectrum, *m/z*: 354 $[M]^+$, 298 (MacLafferty), 238 [$C_7H_4NSC_8H_8$], 134 [C_7H_4NS], 254 [MacLafferty 2], 207 $[M - C(CH_3)_3CH_2C_6H_5]^+$.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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