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Synthesis of Boc-Amino Tetrazoles Derived from α-Amino Acids

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Synthesis of Boc-Amino Tetrazoles Derived from α-Amino Acids

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Abstract: A simple route for the synthesis of Boc-protected tetrazole analogs of amino acids starting from N^{α}-Boc amino acids has been described. The [2 + 3] cycloaddition of Boc-α-amino nitrile and sodium azide in the presence of a catalytic amount of zinc bromide yielded the desired tetrazoles in good yields and purity. All the compounds obtained have been characterized by ^{1}H and ^{13}C-NMR and mass spectral studies.

Keywords: Boc-Amino acids, [2 + 3], cycloaddition, nitriles, tetrazoles

INTRODUCTION

Tetrazoles are a versatile class of compounds frequently used as metabolically stable surrogates for carboxylic acid group[1] and have shown valuable properties as precursors of a variety of nitrogen-containing heterocycles.[2]

The tetrazolic acid fragment $-CN_4H$ (Fig. 1) has acidity similar to the carboxylic acid group and is isosteric with it. The interest in the ability of tetrazoles to mimic the carboxylic acid group has motivated the incorporation of tetrazoles into biologically active compounds. The tetrazolic ring has also featured in the structure of many efficient drugs.[3] Organocatalysis has experienced a renaissance in asymmetric synthesis. In this context, proline-derived tetrazoles have proved to be versatile

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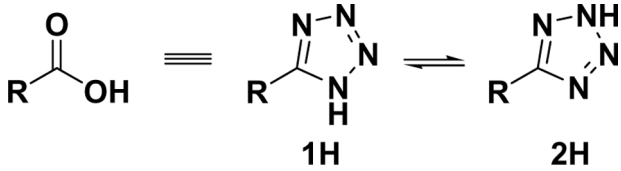

Figure 1. Tetrazolic acids: bioisosters of carboxylic acids.

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catalysts for the asymmetric Mannich, nitro-Micheal, and aldol reactions.[4]

The cycloaddition of an azide and a nitrile has been the conventional route for the synthesis of 5-substituted tetrazoles. However, the azide source, hydrazoic acid (HN_3),[5] was of major concern on account of its high toxicity in solution, explosive nature, and low boiling point (37 °C). Even addition of azide salts to nitriles was a commonly employed method for the synthesis of tetrazoles involving the use of sodium azide in the presence of ammonium chloride or tertiary ammonium chloride.[6] Trimethylsilyl and trialkyl tin azides[7] are also important alternatives but the use of expensive reagents, harsh reaction conditions and difficulty in removal of highly toxic organotin compounds cannot be ignored. Demko and Sharpless have coined the term "click chemistry"[8] for one of the most practical and reliable transformations. His group employed Z-protected amino acids as key synthons for the synthesis of Z-protected amino acid derived tetrazoles.[9] Sureshbabu et al.[10] have reported the synthesis of tetrazoles employing Fmoc-chemistry. Grzonka et al.[11] have reported the synthesis of tetrazole analogs of amino acids using sodium azide and aluminum chloride. There is one report on the synthesis of Boc-Asn and Boc-Gln tetrazoles using n-Bu_3SnN_3 at reflux.[12] As the Boc group is regularly employed in peptide chemistry, we believe Boc-protected tetrazole analoges of amino acids will find utility in solution-phase synthesis, and hence, we describe here the synthesis of these compounds.

RESULTS AND DISCUSSION

The key problem encountered in amide synthesis is the development of an adequate method for carboxyl group activation, which determines the method's efficiency, occurrence of side reactions, and formation of by-products. Z/Boc-amino acid amides are generally prepared using a di-*tert*-butyl pyrocarbonate[13] [$(Boc)_2$]-pyridine system. We chose to synthesize Boc-amino acid amides by an alternate cost-effective procedure involving addition of aq. ammonia to the *in situ* generated mixed

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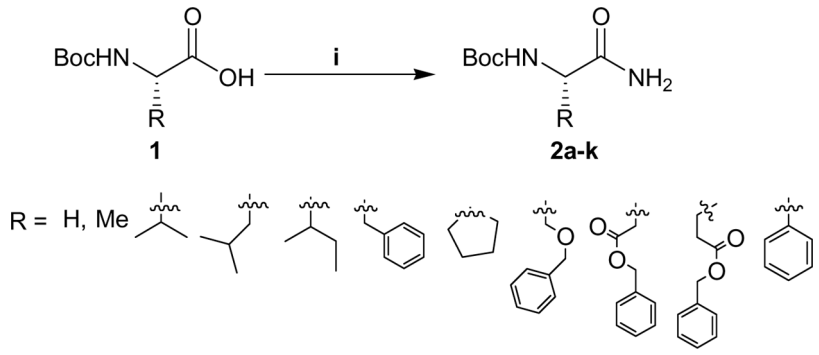
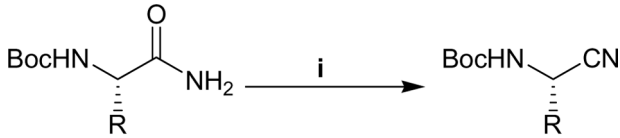
anhydride.[14] Initially, Boc-protected alanine was treated with *N*-methylmorpholine and ethyl chloroformate at −10 °C, resulting in its mixed anhydride generation, to which aqueous ammonia solution was added. The reaction mixture was stirred for 4 h during which the entire starting material was consumed. Boc-Ala-NH_2 was obtained as solid in excellent purity. Similarly, all amides were synthesized and isolated as stable solids in 90–96% yield (Scheme 1).

Nitriles are valuable intermediates in organic synthesis and can be transformed to yield a broad spectrum of functionalities (e.g., tetrazoles, triazoles, thiazoles, and oxazolidones). The conversion of amides to nitriles is brought about by various dehydrating agents such as trifluroacetic anhydride (TFAA), cyanuric chloride, Burgess reagent, and dicyclohexylcarbodiimide (DCC)–pyridine system.[15] Upon careful study of these reagents, TFAA was found to be ideally suited for our protocol as it could be used with milder reaction conditions and it avoids the formation of by-products, thus simplifying the isolation of the product and furnishing better yields. The use of pyridine enhances the rate of reaction and neutralizes the subsequently formed trifluoroacetic acid. In a typical experiment, Boc-Ala-NH_2 was stirred with TFAA in the presence of pyridine in tetrahydrofuran (THF) at 0 °C. The reaction was complete in 2 h (as monitored by thin-layer chromatography, TLC, and infrared, IR). Further, the conversion of amide to nitrile was confirmed by a characteristic peak around 2240 cm^{-1} in the IR spectrum. After evaporating the solvent and a simple workup, Boc-protected alanine nitrile was obtained as a pure solid in 90% yield. Employing TFAA and pyridine system, the Boc-amino acid amides **2a–k** were converted into the corresponding nitriles **3a–k** with excellent yields (Scheme 2).

The methodology introduced by Sharpless et al., which involves simple heating of the N-protected α-amino nitrile in water/2-propanol



Scheme 1. Synthesis of Boc-amino acid amides: (i) NMM, ECF, aq. NH_3, −10 °C, 4 h.

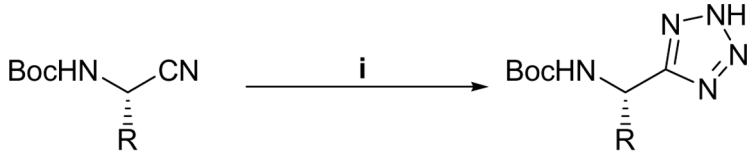


2a-k 3a-k

Sl. No.	Amino acid	Yield (%)	Sl. No.	Amino acid	Yield (%)
3a	Gly	91	3g	Pro	82
3b	Ala	93	3h	Ser(OBzl)	80
3c	Val	86	3i	Asp(OBzl)	89
3d	Leu	80	3j	Glu(OBzl)	84
3e	Ile	85	3k	L-Phg	86
3f	Phe	92			

Scheme 2. Synthesis of Boc-amino nitriles: (i) TFAA, pyridine, THF, 0 °C, 2 h.

mixture at reflux (80 °C) in the presence of sodium azide and zinc bromide for the synthesis of 5-substituted tetrazoles was found to be applicable in the case of Boc-α-amino nitriles also. In a typical experiment, Boc-Ala-CN was dissolved in a water/2-propanol (2:1) mixture to which sodium azide and a stoichiometric amount of zinc bromide were added and refluxed for nearly 16 h. When the nitrile was completely consumed, the reaction mixture was acidified with citric acid and the product was extracted into ethyl acetate. A simple work-up followed by recrystallization using ethyl acetate–hexane (2:8) yielded Boc-AlaT as pure solid in 80% yield. The procedure was applied to other Boc-α-amino nitriles and all the Boc-amino tetrazoles were obtained as obtained as solids in good yields (Scheme 3, Table 1). The compounds were characterized by ^{1}H and ^{13}C NMR and mass spectral data. The reaction sequence was found to be free from racemization as determined by chiral high-performance liquid



3a-k 4a-k

Scheme 3. Synthesis of Boc-protected tetrazole analogs of amino acids: (i) NaN_3, $ZnBr_2$, water/2-propanol, 80 °C, 16 h.

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Table 1. Boc-protected tetrazole analogs of amino acids

Sl. no.	Amino acid	Yield (%)	Mp (°C)	Mass (obs./calc.)[a]
4a	Gly	72	112–114	184.3/184.0
4b	Ala	75	135–137	198.3/198.1
4c	Val	75	104–106	226.4/226.1
4d	Leu	71	96–98	240.3/240.1
4e	Ile	78	119–121	240.2/240.1
4f	Phe	80	142–144	274.5/274.1
4g	Pro	65	81–83	239.3/239.0
4h	Ser(OBzl)	70	126–128	304.5/304.1
4i	Asp(OBzl)	68	133–135	332.4/332.2
4j	Glu(OBzl)	69	142–144	346.2/346.1
4k	L-Phg	74	145–147	260.4/260.2

[a]ES-MS.

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chromatography (HPLC) of the methylated derivatives of the corresponding tetrazoles. An attempt to prepare side chain–derived tetrazoles in the case of Boc-Asn and Gln was made using a similar protocol but was not satisfactory even after extended hours of reflux.

CONCLUSION

1,3-Dipolar nitrile-azide cycloaddition reaction has been used successfully to obtain the tetrazole analogs of Boc-amino acids. The Boc-α-amino nitrile reactants have been prepared *via* an efficient TFAA-mediated dehydration of the corresponding amide. Treatment of the nitriles with NaN_3 in the presence of $ZnBr_2$ has resulted in tetrazoles, which have been isolated as stable solids and fully characterized.

EXPERIMENTAL

All solvents were freshly distilled before use. Amino acids were used as received from Sigma-Aldrich Company. Melting points were determined on a Buchi model 150-melting point apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Nicolet model impact 400D FT-IR spectrometer (KBr pellets, $3\,cm^{-1}$ resolution). ^1H NMR spectra were recorded on a Bruker AMX 400-MHz spectrometer. Mass spectra were recorded on Maldi-TOF (Kratos) mass spectrometer. Unless otherwise mentioned, all amino acids used have an L-configuration. TLC analysis was carried out using the precoated silica-gel G_{254} plates.

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General Procedure for the Synthesis of Boc-Amino Acid Amides, 2

A solution of Boc-protected amino acid (1 mmol), *N*-methylmorpholine (1.1 mmol), and ethyl chloroformate (1.1 mmol) in THF (5 mL) was cooled to $-10\,^{\circ}C$ (ice/salt bath). After stirring for 20 min at the same temperature, NH_3 solution (0.4 mL) was added, and stirring was continued for another 4 h. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N $KHSO_4$, water, and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was recrystallized from ethyl acetate–hexane (3:8). The amide was obtained as pure solid.

General Procedure for the Synthesis of Boc-Amino Nitriles, 3

TFAA (1.5 mmol) and pyridine (3 mmol) were added to an ice-cold solution of N^{α}-Boc-amino amide (1 mmol) in dry THF (5 mL) at $-10\,^{\circ}C$. The resulting reaction mixture was stirred for 2 h. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N $KHSO_4$, water, and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was recrystallized using ethyl acetate–hexane (2:8). The resulting nitrile was obtained as a solid.

General Procedure for the Synthesis of Boc-Amino Tetrazoles, 4

N^{α}-Boc-amino nitrile (1 mmol), sodium azide (2 mmol), and zinc bromide (0.5 mmol) were dissolved in a mixture of 2-propanol (15 mL) and water (30 mL) and stirred at reflux for 16 h. After completion of the reaction [as monitored by TLC, using chloroform–methanol (9:1) as eluant], 5 mL of 10% citric acid and 30 mL of ethyl acetate were added and stirring was continued until no solid remained. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was recrystallized from EtOAc–hexane (1:4).

Data

N-tert-Butyloxycarbonyl Glycine Nitrile, **3a**

IR (KBr) 2243, 1705, 1532 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40 (m, 9H), 4.08 (d, 2H), 4.60 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 28.5, 32.6, 80.2, 118.3, 154.5.

N-tert-Butyloxycarbonyl Alanine Nitrile, **3b**

IR (KBr) 2241, 1705, 1532 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.39 (m, 9H), 1.65 (d, $J = 5.9$ Hz, 3H), 4.72 (d, 1H), 4.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2, 28.2, 42.0, 80.6, 118.5, 155.2.

N-tert-Butyloxycarbonyl Valine Nitrile, **3c**

IR (KBr) 2240, 1706, 1534 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.96 (d, $J = 5.2$ Hz, 6H), 1.40 (s, 9H), 1.90 (m, 1H), 4.58 (br, 1H), 4.82 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.8, 28.1, 28.5, 46.6, 81.2, 118.8, 155.6.

N-tert-Butyloxycarbonyl Leucine Nitrile, **3d**

IR (KBr) 2242, 1705, 1532 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.98 (d, 6H), 1.47 (s, 9H), 1.56–1.85 (m, br., 3H), 4.60 (m, 1H), 4.74 (d, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.8, 22.1, 24.7, 28.2, 40.9, 41.8, 42.0, 81.0, 119.0, 154.1.

N-tert-Butyloxycarbonyl Isoleucine Nitrile, **3e**

IR (KBr) 2240, 1705, 1534 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.83 (d, $J = 4.8$ Hz, 3H), 0.93 (d, $J = 5.9$ Hz, 3H), 1.41 (s, 9H), 1.60 (m, 2H), 1.92 (m, 1H), 4.31 (t, $J = 5.9$ Hz, 1H), 5.3 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.2, 21.5, 26.4, 28.3, 32.8, 57.9, 80.8, 119.2, 155.1.

N-tert-Butyloxycarbonyl Phenylalanine Nitrile, **3f**

IR (KBr) 2240, 1705, 1534 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.44 (s, 9H), 3.12 (m, 2H), 4.84 (m, 1H), 4.94 (d, $J = 8.1$ Hz, 1H), 7.25–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.1, 39.3, 43.2, 81.0, 118.5, 127.7, 128.9, 129.3, 134.0.

N-tert-Butyloxycarbonyl Proline Nitrile, **3g**

IR (KBr) 2243, 1704, 1532 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40 (s, 9H), 1.80–1.94 (m, 4H), 3.42–3.55 (m, 2H), 4.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.3, 28.1, 30.1, 46.8, 52.0, 80.7, 118.3, 155.2.

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N-tert-Butyloxycarbonyl-*O*-Benzyl Serine Nitrile, **3h**

IR (KBr) 2240, 1705, 1534 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.45 (s, 9H), 3.60–3.76 (m, br., 2H), 4.62 (s, 2H), 4.73 (m, 1H), 5.35 (d, br., 1H), 7.25–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.2, 42.3, 68.9, 73.6, 80.9, 117.7, 127.8, 128.2, 136.7, 154.2.

N-tert-Butyloxycarbonyl-*O*-Benzoyl Aspartic Nitrile, **3i**

IR (KBr) 2243, 1704, 1532 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40 (s, 9H), 2.80 (m, 2H), 4.52 (m, 1H), 5.34 (s, 2H), 5.51 (t, $J = 5.9$ Hz, 1H), 7.15–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.3, 39.9, 48.3, 68.5, 79.5, 118.0, 127.2, 127.7, 129.0, 141.2, 156.0, 171.8.

N-tert-Butyloxycarbonyl-*O*-Benzoyl Glutamic Nitrile, **3j**

IR (KBr) 2240, 1705, 1534 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.39 (s, 9H), 1.8–2.35 (m, 4H), 4.91 (s, 1H), 5.34 (s, 2H), 7.12–7.24 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.3, 28.4, 30.6, 50.2, 68.2, 79.8, 118.4, 127.2, 127.8, 129.1, 141.1, 156.5, 172.3.

N-tert-Butyloxycarbonyl Phenylglycine Tetrazole, **3k**

IR (KBr) 2240, 1704, 1532 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40 (s, 9H), 6.18 (d, $J = 7.9$ Hz, 1H), 7.22–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.5, 50.32, 80.1, 118.2, 126.8, 127.0, 128.6, 142.2, 156.3.

N-tert-Butyloxycarbonyl Glycine Tetrazole, **4a**

IR (KBr) 1705, 1532, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.39 (s, 9H), 4.12 (t, $J = 6.6$ Hz, 2H), 5.40 (br d, $J = 5.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.3, 43.2, 78.2, 154.5, 158.3.

N-tert-Butyloxyarbonyl Alanine Tetrazole, **4b**

IR (KBr) 1707, 1530, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40 (s, 9H), 1.49 (d, $J = 6.1$ Hz, 3H), 4.15 (m, 1H), 5.42 (br d, $J = 5.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 28.3, 46.6, 78.2, 151.3, 155.0.

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N-tert-Butyloxycarbonyl Valine Tetrazole, **4c**

IR (KBr) 1705, 1532, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.96 (d, $J = 4.4$ Hz , 6H), 1.39 (s, 9H), 1.90 (m, 1H), 4.21 (br, 1H), 5.31 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.0, 28.2, 31.7, 61.6, 78.3, 153.4, 155.1.

N-tert-Butyloxycarbonyl Leucine Tetrazole, **4d**

IR (KBr) 1707, 1530, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87–0.91 (m, 6H), 1.39 (s, 9H), 1.56–1.65 (m, 1H), 1.70–1.87 (m, 2H), 4.15 (t, $J = 6.6$ Hz, 1H), 5.05 (m, 3H), 5.37 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 22.6, 24.1, 28.1, 41.8, 44.4, 65.6, 78.3, 154.2, 155.3.

N-tert-Butyloxycarbonyl Isoleucine Tetrazole, **4e**

IR (KBr) 1705, 1532, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.82 (d, $J = 4.4$ Hz, 3H), 0.91 (d, $J = 5.8$ Hz, 3H), 1.40 (s, 9H), 1.62 (m, 2H), 1.91 (m, 1H), 4.32 (t, $J = 5.9$ Hz 1H), 5.4 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.1, 21.6, 26.3, 28.2, 32.6, 57.7, 78.2, 153.5, 154.9.

N-tert-Butyloxycarbonyl Phenylalanine Tetrazole, **4f**

IR (KBr) 1706, 1531, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40 (s, 9H), 3.20 (t, $J = 5.9$ Hz, 2H), 5.21 (m, 1H), 7.02–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.2, 38.2, 65.5, 78.2, 126.6, 127.5, 128.3, 129.1, 129.8, 136.6, 154.2, 155.7.

N-tert-Butyloxycarbonyl Proline Tetrazole, **4g**

IR (KBr) 1705, 1530, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.42 (s, 9H), 1.80–1.96 (m, 4H), 3.42–3.55 (m, 2H), 4.94 (t, $J = 12.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.1, 28.2, 30.1, 46.8, 52.0, 79.1, 136.7, 155.2.

N-tert-Butyloxycarbonyl-*O*-benzyl Serine Tetrazole, **4h**

IR (KBr) 1705, 1532, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40 (s, 9H), 3.80–3.92 (m, 2H), 4.48 (m, 1H), 4.52 (s, 2H), 5.25 (br, 1H), 7.12–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.1, 46.7, 69.6, 72.3, 79.3, 127.4, 127.5, 127.8, 127.9, 128.2, 137.8, 153.9, 155.1.

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N-tert-Butyloxycarbonyl-*O*-benzoyl Aspartic Tetrazole, **4i**

IR (KBr) 1705, 1530, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40 (s, 9H), 2.80 (m, 2H), 4.1 (t, 1H), 5.34 (s, 2H), 5.51 (t, $J = 5.9$ Hz), 7.15–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.3, 39.9, 48.3, 68.5, 79.5, 127.2, 127.7, 129.0, 141.2, 156.0, 158.2, 171.8.

N-tert-Butyloxycarbonyl-*O*-benzoyl Glutamic Tetrazole, **4j**

IR (KBr) 1704, 1534, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.39 (s, 9H), 1.8–2.35 (m, 4H), 5.15 (s, 1H), 5.34 (s, 2H), 7.12–7.24 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.3, 28.4, 30.6, 50.2, 68.2, 79.8, 127.2, 127.8, 129.1, 141.1, 156.5, 157.5, 172.3.

N-tert-Butyloxycarbonyl Phenylglycine Tetrazole, **4k**

IR (KBr) 1705, 1532, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.39 (s, 9H), 6.16 (d, $J = 7.9$ Hz, 1H), 7.24–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.5, 50.32, 80.1, 126.8, 127.0, 128.6, 142.2, 156.3, 158.1.

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