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Chiral *N*-Fmoc-β-Amino Alkyl Isonitriles Derived from Amino Acids: First Synthesis and Application in 1-Substituted Tetrazole Synthesis

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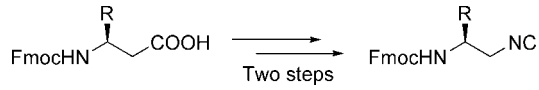

A novel class of optically active *N*-Fmoc-protected amino isonitriles has been described for the first time. Conversion of the carboxyl group of Fmoc-β-amino acids into an isocyano group has resulted in a new class of *N*-urethane-protected amino isonitriles. All the isonitriles have been isolated as stable solids, purified, and completely characterized. A synthetic application of the obtained isonitriles has also been demonstrated through the synthesis of 1-substituted tetrazole analogues of amino acids via a 2 + 3 cycloaddition with trimethylsilyl azide.

Introduction

Organic isonitriles are employed as key intermediates in a wide range of reactions. The broad-spectrum reactivity of isonitriles originates from their ability to react as both electrophiles and nucleophiles as a result of the presence of a formally divalent carbon in the isocyano group. Their important synthetic utilities include conversion into isothiocyanates,[1] formamidino urea derivatives,[2] α-keto and β-keto amides,[3,4] and *N*,*N*′-dialkyl carbodiimides.[5] They are used in addition reactions to benzyne species and pyridinium salts[6] and in nitrile oxide reduction.[7] 1-Substitued tetrazoles and imidazoles are obtained through isonitrile-azide cycloaddition[8] and heterocoupling reaction between two different isonitriles, respectively.[9] Pyrrolles, indoles, oxazoles, and thiazoles are some of the other heterocycles synthesized from isonitriles.[10] *N*-Heterocyclic carbenes are generated through metal-mediated coupling of isonitriles with propargyl amine.[11]

Isonitriles are used in Passerini three-component (Passerini 3CR) and Ugi four-component reactions (Ugi 4CR) to synthesize a wide range of compounds.[12] These include α-acyloxy amides, α-epoxy and α-hydroxy amides, lactones, 2-hydroxy furans, thiophenes and *O*-arylated phenols[13] (via Passerini 3CR), α-acyl amino amides, libraries for combinatorial synthesis, small molecule macroarrays, macrocycles, natural products, [14] heterocycles,[15] and several other classes of compounds[16−18] (via Ugi 4CR). The isocyano group is also present in many natural

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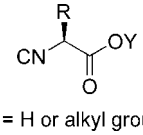

FIGURE 1. α-Isocyano esters/amides.

products and biologically active molecules.[19] The vast literature on the preparation, properties, and reactions of the isonitriles has been reviewed by various workers.[20]

In peptide chemistry, isonitriles of the type α-isocyano ester/amide (Figure 1) that are obtained by converting the amino group of amino acid ester into an isocyano group are well known. Since the discovery of their use in peptide synthesis by Ivar Ugi, these compounds are being explicitly employed in the synthesis of amino acid and peptide derivatives. Peptide synthesis via the Ugi four-component condensation of these isonitriles with cleavable amine or aldehyde components has been well described. Special cleavable isonitriles have also been employed for MCR-based peptide synthesis.[21] They are also used to assemble di- and tripeptides containing tandem α,α-diisopropyl and diphenyl glycyl residues,[22] for macrocyclization of oligopeptides,[23] synthesis of β-lactams and other small and medium ring sized lactams,[24] glycopeptides,[25] depsipeptides,[26] peptide nucleic acids,[27] peptides containing nonproteinogenic amino acids, *N*-hydroxy peptides,[28] selenocystine containing peptide libraries,[29] peptide β-turn mimetics,[30] Weinreb amido peptides,[31] peptide heterocycles and peptide mimics, amino acid derivatives such as α-methylated amino acids,[32] fluorinated amino acids,[33] α-hydroxy β-amino amides,[34] and thiazoles.[35] Polyfunctionalized 1-isocyano-2-methylamino-alkenes derived from simple α-isocyano esters have been used in diversity-oriented organic synthesis.[36] Solid-phase multicomponent reactions using resin-bound isonitriles have also been described.[37]

The isocyano compounds (Figure 1) have played a vital role in developing new MCR-based routes for peptide and peptide derivatives. Their numerous synthetic applications in peptide as well as peptidomimetic chemistry have been reported. They have been synthesized through different methods and isolated mostly as liquids or low melting solids. On the other hand, contrary to α-isocyano esters/amides, insertion of the isocyano group in place of the carboxylic group of amino acids can also be accomplished to generate a new class of *N*-protected amino isonitriles. With the expanding area of peptidomimetics and increasing interest in new classes of molecules for combinatorial synthesis, these novel isonitriles may form a useful set of monomers to carry out several reactions leading to synthesis of novel amino acid/peptide derivatives, construction of libraries of new compounds, and obtaining MCR adducts with modified structures. However, the synthesis of such type of *N*-protected amino alkyl isonitriles starting from amino acids and their synthetic applications still have to be demonstrated. In view of this, we herein report the synthesis of optically active isonitriles derived from *N*-Fmoc amino acids (Figure 2), which to the best of our knowledge are hitherto unreported, and demonstrate one

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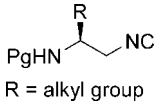


FIGURE 2. *N*-Protected amino isonitriles from amino acids.

TABLE 1. List of Isonitriles and 1-Sustituted Tetrazoles Prepared through Schemes 1 and 2, Respectively

R^1	compound	yield[a] (%)	compound	yield[a] (%)
H	**3a**	80	**6a**	90
CH_3	**3b**	78	**6b**	88
$CH(CH_3)_2$	**3c**	75	**6c**	87
$CH_2C_6H_5$	**3d**	81	**6d**	90
$CH_2CH(CH_2)_3$	**3e**	73	**6e**	88
$CH(CH_3)CH_2CH_3$	**3f**	75	**6f**	86
C_6H_5 (D-amino acid)	**3g**	80	**6g**	89
C_6H_5	**3h**	83	**6h**	90
$-(CH_2)_3-$ (amino acid is proline)	**3i**	70	**6i**	86
$(CH_2)_2SCH_3$	**3j**	80	**6j**	86
$CH_2COOCH_2C_6H_5$	**3k**	75	**6k**	88
$(CH_2)_2COOCH_2C_6H_5$	**3l**	73	**6l**	84
$CH_2SCH_2C_6H_5$	**3m**	76	**6m**	87
$(CH_2)_4NH$-Z	**3n**	72	**6n**	85

[a] Yield after purification by chromatography.

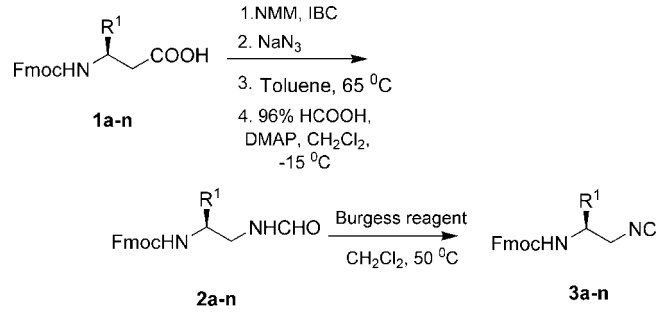
of their synthetic applications through the synthesis of novel class of 1-substitued tetrazole analogues of Fmoc-amino acids.

Results and Discussion

Isonitriles are commonly prepared by dehydration of the formamides. Accordingly, the synthesis of *N*-Fmoc alkyl formamides as precursors of the title isonitriles was undertaken.[38] Formamides **2** can be synthesized by formylation of the mono-*N*-Fmoc-protected alkyl vicinal diamines, which in turn have to be prepared through a multistep protocol from Fmoc-amino acids. Instead, we chose a more concise and efficient route from using Fmoc β-amino acids as starting materials and directly converted the -COOH group into formyl amino group. Our group has reported for the first time a reaction of this sort for the synthesis of *N*-Fmoc/Z,*N*′-formyl alkyl gem diamines from amino acids via the Goldsmith−Wick coupling of isocyanates derived from *N*-Fmoc/Z-amino acids with formic acid.[39] Adhering to this strategy, Fmoc β-amino acids **1** were converted into acyl azides using the mixed anhydride method. Heating the toluene solution of these azides for about 30 min yielded the isocyanates, which were directly reacted without isolation with 96% formic acid in presence of catalytic amount of DMAP in dry CH_2Cl_2 solvent to obtain the desired formamides. The crude products that precipitated out as solids from the reaction mixture were isolated and purified through recrystallization in about 80% yields. All of the formamides **2a**−**n** were characterized (see Supporting Information).

Synthesis of Isonitriles. Fmoc-Aaa-ψ[CH_2NC]. Synthesis of the isonitriles from the formamides **2** was pursued using compound **2d** as specimen. Different dehydrating reagents such as phosgene, di- and triphosgene, $POCl_3$, PPh_3/CCl_4, PCl_5, P_2O_5,

SCHEME 1. Synthesis of *N*-Fmoc-Protected Amino Alkyl Isonitriles



$SOCl_2$, and chlorothionoformates have been reported for conversion of the formamides into isonitriles.[40] Among them, Burgess reagent[41] displayed several advantageous features such as mild and neutral reaction conditions, chemoselective dehydration, and impressive yields that were ideally suited to carry out the reactions of amino acid and peptide substrates without loss of optical purity, cleavage of protecting groups, or modification of the side chain functional groups. Burgess reagent has been used for the conversion of a variety of formamides including an *N*-formyl dipeptide ester, For-Val-Gly-OEt, into isonitriles.[42]

In a typical experiment, the mixture of compound **2d** and Burgess reagent in dry CH_2Cl_2 was refluxed, and the reaction was monitored through TLC and IR. Formation of isonitriles could be easily detected by appearance of a strong stretching frequency at 2158 cm^{-1} in the IR spectrum. Upon completion of the reaction (which took 30 min), the desired isonitrile **3d** was isolated in 81% yield after purification through column chromatography. Structure of **3d** was confirmed by spectroscopic techniques. Other dehydrating agents were also screened with the same substrate **2d**. Phosgene and its surrogates diphosgene and triphosgene were avoided because of their toxicity. With $POCl_3$ and pyridine the reaction was slower at room temperature, and heating the reaction mixture resulted in the cleavage of the Fmoc group. The isonitrile so formed was also partially hydrolyzed to its formamide when the reaction mixture was treated with aqueous Na_2CO_3 (required to remove unreacted $POCl_3$). Sluggishness in the reaction was noticed with PPh_3/CCl_4 also. Thus, it was decided that Burgess reagent would be preferred for further studies.

Employing Burgess reagent and maintaining the same conditions, *N*-Fmoc-amino alkyl isonitriles **3a**−**i** containing alkyl and

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aryl side chains were synthesized from the formamides **2a**−**i** in excellent yields. The procedure was repeated for five examples of the formamides obtained from bifunctional amino acids, Fmoc-Met-OH, Fmoc-Cys(Bzl)-OH, Fmoc-Asp(OBzl)-OH, Fmoc-Glu(OBzl)-OH, and Fmoc-Lys(Z)-OH. In all cases, the corresponding multifunctional isonitriles **3j**−**n** were obtained in good yields without the side chain protections being affected (Scheme 1). The isocyano group was inserted into the side chains of aspartic acid and glutamic acid also. Fmoc-Asp and Fmoc-Glu were converted into 5-oxazolidinones and the free β/γ-COOH of the latter was converted into the formyl-amino group via the reported protocol.[39] The resulting formamides were then treated with Burgess reagent to yield the isonitriles **4a** and **4b** (Figure 3) in 68% and 65% yields, respectively.

4a: n=1; **4b**: n=2 **7a**: n=1; **7b**: n=2

FIGURE 3

Interestingly, unlike most of the organic isonitriles, including α-isocyano esters, which are largely liquids or low melting solids, isonitriles **3a**−**n** were solids with high melting points. They could be stored as stable solids at room temperature for a long duration under anhydrous conditions. They were also completely stable toward column chromatographic separation. However their HPLC profiles contained the corresponding formamide peaks to an extent of 15−20%, though the TLC of the injected samples had a single peak. Appearance of the formamide peak in HPLC could be due to partial hydrolysis of the isonitriles during the analysis by standard 0.1% TFA water−acetonitrile gradient.

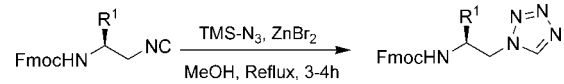
5a **5b**

Two examples of Fmoc-peptide isonitriles were also synthesized and used as models to study the possibility of racemization during the reaction. The dipeptide acids Fmoc-L-Phg-β-Ala-OH and Fmoc-D-Phg-β-Ala-OH were converted into isonitriles **5a** and **5b** following the similar protocol outlined in the Scheme 1. Their ^{1}H NMR spectra contained the methyl group resonances at δ 1.25 and 1.24 (for **5a**) and at δ 1.18 and 1.17 (for **5b**). The appearance of a single doublet (corresponding to methyl group) for each epimer sample revealed that the samples of **5a** and **5b** were optically pure without a mixture of epimers. Also the HPLC profiles of the samples of **5a** and **5b** had a single peak corresponding to isonitrile at distinct t_R values of 30.785 and 28.009 min, respectively, indicating the presence of only one epimer in each sample. These studies confirmed the absence of racemization during synthesis of the isonitriles.

Synthesis of 1-Substiututed Tetrazoles. As an example to demonstrate the reactions of the isocyano group in case of the newly prepared isonitriles, we proceeded with synthesis of the 1-substitued tetrazoles from compound **3**. Amino acid derived tetrazoles are being used as carboxylic acid isosteres, catalysts in asymmetric organic synthesis, pharmaceutical compounds, and stabilizers of metallopeptides.[43] 5-Substituted tetrazoles have been synthesized from 2 + 3 dipolar cycloaddition of azide with nitriles obtained from *N*-urethane-protected amino acids,[44] but the isomeric 1-substituted tetrazole analogues of *N*-protected amino acids are yet to be described. This class of tetrazoles is accessed by the dipolar cycloaddition of azide with isonitriles. These 1-substiutued tetrazoles are hydrophobic, with their lipophilicity being comparable to aromatic heterocycles such as pyrazoles, imidazoles, and even nitriles.[45] *N*-Substituted tetrazole moiety has been incorporated as pharmacophore en route to development of potent bioactive compounds such as apoptosis potentiator dimeric Smac peptide mimetics containing a proline-derived tetrazole subunit, immunosuppressant clotrimazole analogue,[45] and serotonin agonists.[46] Synthesis of 1-substituted tetrazole derivatives of small organic molecules and carbohydrates has also been reported.[47]

Isonitriles **3** were refluxed with trimethylsilyl azide in presence of $ZnBr_2$ as a catalyst in dry MeOH solvent for about 6 h, and the resulting tetrazoles were obtained in ∼90% yields. The crude products were purified through column and were completely characterized. Isonitriles **4a** and **4b** were also treated with TMS azide under the same conditions to obtain new class of unnatural amino acids **7a** and **7b** containing 1-substitued tetrazoles in the side chains in nearly 80% yields. During the reaction it was observed that the isonitriles were partially hydrolyzed to formamides in the presence of a trace amount of moisture in the reaction medium, resulting in decreased yields of the tetrazoles. Hence, carrying out the reaction in completely dry conditions and under nitrogen atmosphere significantly improves the yield by minimizing hydrolysis.

SCHEME 2. Synthesis of *N*-Fmoc Amino Acid Derived 1-Substiututed Tetrazoles



3a-n **6a-n**

Conclusion

A new class of optically pure *N*-Fmoc-protected isonitriles has been efficiently synthesized. The synthesis has involved direct conversion of the carboxyl group of several Fmoc-β-amino acids containing alkyl, aryl, and functionalized side chains

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into a formyl amino group and dehydration of the formamide with Burgess reagent under mild and neutral conditions. All of the isonitriles have been isolated as solids, purified, and well characterized. One application of the new isonitriles in organic reactions has been demonstrated by their conversion into 5-substituted tetrazoles via cycloaddition with trimethylsilyl azide. Further utility of these isonitriles in organic synthesis including MCRs is anticipated.

Experimental Section

General Procedure for the Synthesis of *N*-Fmoc-*β*-Amino Alkyl Isonitriles 3. Burgess reagent (3.58 g, 15.0 mmol) was added to a solution of *N*-Fmoc-*β*-amino formamide (10.0 mmol) in dry CH_2Cl_2 (20 mL), and the resulting mixture was refluxed at 50 °C till completion of the reaction (TLC). The reaction mixture was then rapidly washed with water (2 × 10 mL), dried immediately over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to obtain the crude product, which was purified by column chromatography (20% EtOAc in hexane; 100−200 mesh size, MERCK column chromatography silica gel) to yield the isonitrile as a white solid. Alternatively, the reaction mixture was concentrated under reduced pressure and the crude compound was directly column chromatographed to obtain pure isonitrile.

General Procedure for the Synthesis of 1-Substituted Tetrazoles 6. To 10.0 mmol of the isonitrile **3** in 20.0 mL of dry methanol were added 1.31 mL (12.0 mmol) of trimethylsilyl azide and 450.0 mg (2.0 mmol) of $ZnBr_2$, and the mixture was refluxed with stirring until completion of the reaction as evident by TLC and disappearance of the isonitrile peak at 2158 cm^{-1} in the IR spectrum. Methanol was then evaporated under reduced pressure, and the residue was dissolved in 30 mL of ethyl acetate. The organic layer was washed with water (2 × 15 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to obtain the crude product, which was purified over silica gel column (100−200 mesh size, MERCK column chromatoraphy silica gel; 50% EtOAc in hexane) to yield the pure tetrazole as white solid.

Spectral Characterization Data of Representative Compounds. (*S*)-(9*H*-Fluoren-9-yl)methyl 1-Formamidopropan-2-yl Carbamate, Fmoc-Ala-*ψ*[CH_2-NHCHO], 2b. Yield 92%; R_f 0.21 (*n*-hexane/AcOEt 5:5); mp = 134−136 °C; IR (KBr) υ_{max} = 1712, 1662 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 1.09 (d, 3H, J = 6.8 Hz), 3.24 (br, 2H), 3.74 (m, 1H), 4.10 (t, 1H, J = 5.6 Hz), 4.34 (d, 2H, J = 6.0), 5.05 (s, 1H), 6.25 (s, 1H), 7.18−7.78 (m, 8H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$, δ) 17.95, 39.62, 42.76, 46.76, 65.72, 119.45, 124.67, 126.60, 127.21, 140.73, 143.48, 155.98, 161.69; HRMS calcd for $C_{19}H_{20}N_2O_3$ *m*/*z* 347.1372 (M^+ + Na), found 347.1381.

(*S*)-(9*H*-Fluoren-9-yl)methyl 1-Isocyano-6-(benzyl carbamate)hexan-2-yl Carbamate, Fmoc-Lys(Cbz)-*ψ*[CH_2-NC], 3n. Yield 70%; R_f 0.40 (*n*-hexane/AcOEt 8:2); $[\alpha]^{23}_D$ = −21.2 (*c* 1.0, $CHCl_3$); mp = 120−122 °C; IR (KBr) υ_{max} = 1705, 2158 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 1.50 (m, 4H), 2.41 (m, 2H), 3.10 (m, 2H), 3.40 (m, 2H), 3.80 (br, 1H), 4.20 (t, 1H, J = 8.0 Hz), 4.40 (d, 2H, J = 8.0 Hz), 4.97 (s, 2H), 5.02 (br, 1H), 7.20−7.8 (m, 13H); ^{13}C NMR ($CDCl_3$, δ) 23.03, 30.04, 30.20, 46.22, 47.69, 49.94, 53.97, 54.81, 59.24, 67.24, 120.54, 125.49, 127.59, 128.28, 128.60, 129.02, 136.97, 141.82, 144.22, 156.36, 157.19, 158.65; HRMS calcd for $C_{30}H_{31}N_3O_4$ *m*/*z* 520.2212 (M^+ + Na), found 520.2216.

(*S*)-(9*H*-Fluoren-9-yl)methyl 3-Phenyl-1-(1*H*-tetrazol-1-yl)-propan-2-yl Carbamate, Fmoc-Phe-*ψ*[CH_2-CN_4], 6d. Yield 90%; R_f 0.37 (*n*-hexane/AcOEt 5:5); mp = 170−172 °C; ^1H NMR ($CDCl_3$, δ) 2.91 (m, 2H), 4.0−4.20 (m, 2H), 4.40−4.56 (m, 4H), 5.01 (br, 1H), 7.23−7.77 (m, 13H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$, δ) 37.50, 47.25, 49.59, 52.43, 66.44, 120.07, 124.81, 127.17, 127.31, 127.87, 128.98, 129.10, 135.87, 141.37, 143.35, 143.60, 158.46; HRMS calcd for $C_{25}H_{23}N_5O_2$ *m*/*z* 448.1749 (M^+ + Na), found 448.1746.

(*S*)-(9*H*-Fluoren-9-yl)methyl 4-(2-(1*H*-Tetrazol-1-yl)ethyl)-5-oxazolidine-3-carboxylate, 7b. Yield 75%; R_f 0.40 (*n*-hexane/AcOEt 5:5); mp = 56−58 °C; $[\alpha]^{23}_D$ = −3.2 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, δ) 2.71−3.69 (br, 2H), 4.18 (t, 2H, J = 7.5 Hz), 4.67 (br, 2H), 4.98 (br, 1H), 5.20 (s, 2H), 7.18−7.79 (m, 8H), 8.82 (s, 1H), ^{13}C NMR ($CDCl_3$, δ) 29.69, 47.19, 52.04, 55.38, 67.21, 70.33, 120.20, 124.43, 127.40, 128.10, 141.38, 143.08, 143.15, 152.74, 170.82; HRMS calcd for $C_{21}H_{19}N_5O_4$ *m*/*z* 428.1335 (M^+ + Na), found 428.1345.

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Supporting Information Available: General experimental procedures for formamides **2** and product characterization data of all the compounds discussed along with copies of ^1H NMR, ^{13}C NMR, and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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