Cyanogen Bromide as Dehydrosulfurizing Agent for the Synthesis of N^{β}-Fmoc-Amino Alkyl Isonitriles from N^{β}-Fmoc-Amino Alkyl Thioformamides

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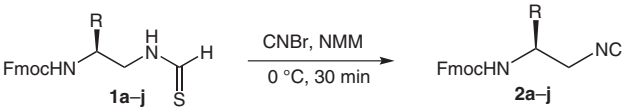
Abstract: Synthetically useful N^{β}-Fmoc amino alkyl isonitriles are prepared conveniently from N^{β}-Fmoc amino alkyl thioformamides via a cyanogen bromide mediated dehydrosulfurization. The reaction is fast, clean, and yields are good.

Key words: N^{β}-Fmoc-amino alkyl thioformamides, isonitriles, dehydrosulfurization, cyanogen bromide

In recent years, the synthetic utility of isonitriles[1] in organic reactions has been exploited. Compounds containing an isocyano group find use as antibiotics,[2] antineoplastics,[3] and antianaesthetics.[4] The synthetic utility of isonitriles arises from their divergent character[5] and this functionality has wide utility, such as in the preparation of isothiocyanates,[6] *N*,*N*-dialkylcarbodiimides,[7] 1-substituted tetrazoles,[8] pyrazoles,[9] oxazoles,[10] and thiazoles.[11] The use of isonitriles in multicomponent reactions such as the Passerini[12] and Ugi[13] reactions for generating a wide variety of biologically important derivatives of peptides,[14] glycopeptides,[15] and other peptidic molecules[16–20] has been well demonstrated.

In peptide chemistry, the application of isonitrile derivatives of amino acids has led to a variety of peptidomimetics[21] and other useful products such as β-lactams,[22] glycopeptides,[23] depsipeptides,[24] peptide nucleic acids,[25] and *N*-hydroxy peptides.[26] Amino acid ester derived isonitriles are the known entities, which are prepared from corresponding formyl amino acid esters.[27] A recent entry into this new class of amino acid derived isonitriles has been described by our group wherein N^{β}-Fmoc amino alkyl isonitriles were obtained through carboxyl group modification.[28]

Of the many methods available for the preparation of isonitriles, dehydration of formamides is the widely followed route in amino acid chemistry, showing general applicability and reproducibility.[29] Reaction of alkyl halides with heavy metal cyanide salts,[30] addition of dichlorocarbene to amines,[31] reduction of isocyanates and isothiocyanates[32] are other available routes. Dehydration of formamides has been carried out by using tosyl chloride, phosphorus oxychloride ($POCl_3$) in the presence of a base, cyanuric chloride, triphenyl phosphine–CCl_4, phosgene, diphosgene, and triphosgene.[33] The method employing $POCl_3$ being quite harsh is found to cause racemization and therefore is not applicable in peptide chemistry, and isolation of enantiomerically pure isonitriles is always challenging and demanding. Danishefsky and co-workers have isolated enantiomerically pure α-isocyanoesters[34] derived from formyl amino acid esters, employing triphosgene/*N*-methylmorpholine (NMM) at –78 °C. Nenajdenko's group has synthesized the amino acid derived nonracemic isonitriles employing the less commonly used 4-methyl-2,6,7-trioxabicyclo[2.2.2] octyl-protected formyl amino ester.[35] Sureshbabu et al. reported the synthesis and isolation of enantiomerically pure *N*-Fmoc-amino alkyl isonitriles by the dehydration of the corresponding N^{β}-Fmoc amino alkyl formamides under neutral conditions employing Burgess' reagent.[28] In a continuation of our current studies on isonitriles, we sought a simple and economically viable route involving dehydrosulfurization of N^{β}-Fmoc amino alkyl thioformamides using cyanogen bromide (CNBr, Scheme 1).



Scheme 1

There has been a surge in the synthesis of thio analogues of peptides and related intermediates, the replacement of O with S yielding novel unnatural amino acids and peptidomimetics such as thiopeptides,[36] thioureas, and isothiocyanates[37] possessing therapeutic importance. Sulfur-containing compounds such as thioamides and thioesters have been found to be better reactants in the preparation of several heterocycle-tethered peptidomimetics and other related compounds compared to their oxygenated analogues.[38,39] Furthermore, some thioformamides show antifungal[40] and antibacterial activity,[41] and they have been employed in the synthesis of thiazoles via the Hantzsch protocol.[42] We envisaged the use of *N*-urethane-protected amino alkyl thioformamides for the synthesis of the corresponding isonitriles through a dehydrosulfurization reaction. In a patent, Ugi had demonstrated the conversion of thioformamides into their respective isonitriles using CNBr.[43] However, this protocol has yet to be exploited to its full advantage although the method shows promise.[44,45] Thus, in the present communication,

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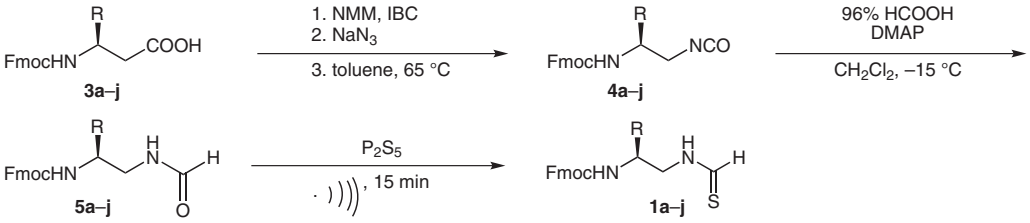


Scheme 2

we describe the synthesis of N^{β}-Fmoc amino alkyl thioformamides and their conversion to isonitriles employing cyanogen bromide as the dehydrosulfurization reagent.

In the first part of this study, we undertook the preparation of N^{β}-Fmoc amino alkyl thioformamides, a hitherto unreported class of molecules, by the thionation of the corresponding formamides. Starting with a N^{β}-Fmoc amino acid, the carboxyl group was converted to its formamide under Gold–Schmidt–Wick formolysis of the corresponding isocyanate using formic acid/DMAP.[46] On treating a solution of *N*-Fmoc-Ala-Ψ[CH_2NHCHO] **5b** in THF with an equimolar quantity of P_2S_5 at room temperature, the respective thioformamide was obtained within an hour in satisfactory yield and purity after a flash chromatography. By way of optimization, a suspension of *N*-Fmoc-Ala-Ψ[CH_2NHCHO] **5b** (1 mmol) and P_2S_5 (0.7 mmol) in THF was subjected to ultrasonication at 25 °C. To our satisfaction, the reaction was complete in 15 minutes as judged by TLC, and the product was isolated after flash chromatography in excellent yield (Scheme 2) and enantiomeric purity.[47] The protocol was then successfully extended to other amino acids as well to prepare a series of N^{β}-Fmoc-amino alkyl thioformamides **1a**–**j**,[49,50] and the products were isolated as stable solids after purification in 92–96% yield and adequately characterized (Table 1).

In the next step, conversion of the thioformamides into isonitriles was undertaken.[48] Accordingly, a reaction of thioformamide **1** with CNBr (1.5 mmol) in the presence of NMM in dry CH_2Cl_2 at 0 °C afforded the corresponding isonitrile **2**[51,52] within 30 minutes (Scheme 1). The reaction was rapid and complete, and the product was isolated after chromatography in excellent yield as a stable solid. When the reaction was carried out at room temperature, a considerable drop in the yield of isonitrile **1** (up to 20%) was incurred. Reproduceable results were obtained when the protocol was employed for dehydrosulfurization of several other N^{β}-Fmoc amino alkyl thioformamides. All the compounds were isolated as stable solids (Table 1) whose physical properties matched those previously reported by us[28] and were also further characterized spectroscopically. Thus dehydrosulfurization of thioformamides is more efficient when compared to the dehydration of formamides for the synthesis of isonitriles.

Table 1 List of Thioformamides **1** and Isonitriles **2**

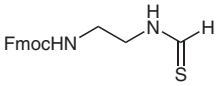
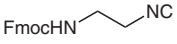
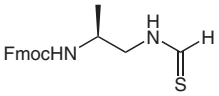
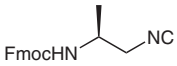
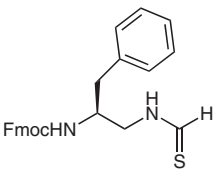
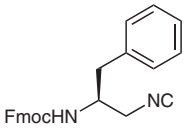
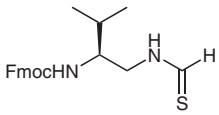
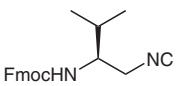
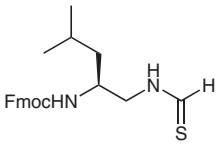
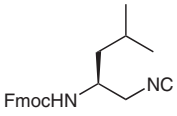
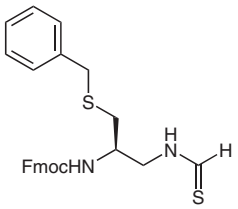
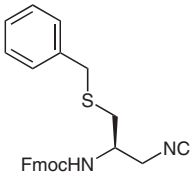
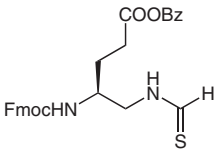
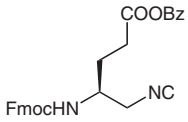
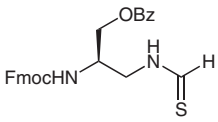
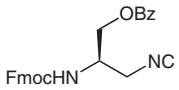
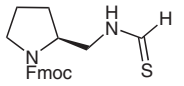
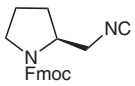
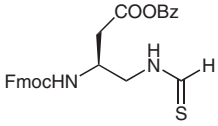
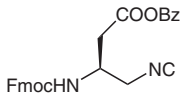
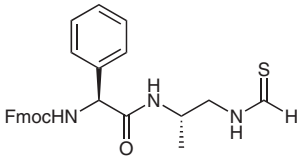
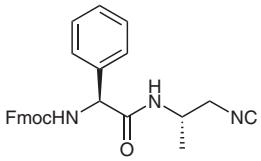
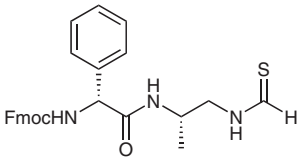
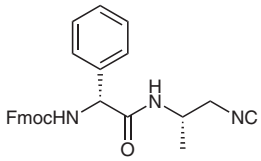
Compd	Thioformamide **1**	Mp (°C)	HRMS [M + Na]$^+$ (found/calcd)	Isonitrile **2**	Mp (°C)	HRMS [M + H]$^+$ (found/ calcd)
a		141	349.0978/ 349.0987		165	293.1031/ 293.1200
b		105	363.1132/ 363.1143		112	307.1346/ 307.1368
c		118	439.1443/ 439.1456		128	383.1672/ 383.1681
d		126	391.1438/ 391.1456		101	335.1672/ 335.1681
e		117	405.1603/ 405.1613		109	349.1816/ 349.1838

Table 1 List of Thioformamides **1** and Isonitriles **2** (continued)

Compd	Thioformamide **1**	Mp (°C)	HRMS [M + Na]$^+$ (found/calcd)	Isonitrile **2**	Mp (°C)	HRMS [M + H]$^+$ (found/ calcd)
f		129	485.1319/ 485.1333		115	429.1536/ 429.1558
g		97	511.1658/ 511.1667		56	455.1865/ 455.1893
h		103	469.1549/ 469.1562		76	413.1767/ 413.1787
i		124	389.1289/ 389.1300		104	333.1518/ 333.1525
j		107	497.1500/ 497.1511		80	441.1718/ 441.1736
k		167	459.1609/ 459.1617		160	440.1887/ 440.1896
l		165	459.1607/ 459.1617		160	440.1865/ 440.1896

The conditions employed in the synthesis of isonitriles were scrutinized to check for the possibility of racemization during the reaction. Two dipeptide thioformamides **1k**,**l**, prepared by the reaction of alanyl alkyl isonitrile with Fmoc-D/L-Phg-OH, were converted into their respective dipeptidyl isonitriles **2k**,**l** following the protocol described above. The ^{1}H NMR spectra possessed methyl doublets of the Ala residue of **2k** and **2l** at δ = 1.16, 1.18 ppm and at δ = 1.23, 1.24 ppm, respectively, indicating the presence of a single epimer in each sample, a conclusion which was also supported by HPLC data. Furthermore, the *N*-Fmoc-peptidyl isonitrile obtained by the reaction of an equimolar mixture of Fmoc-L/D-Phg-OH with alanyl alkyl thioformamide followed by dehydrosulfurization showed two separate doublets for the alanyl methyl group in the ^{1}H NMR spectrum, once again demonstrating the absence of epimerization.

In summary, we have described an efficient synthesis of N^{β}-Fmoc-amino alkyl isonitriles by the dehydrosulfurization of corresponding thioformamides employing CNBr. This protocol provides an alternative efficient method for the preparation of the title compounds in high yields.

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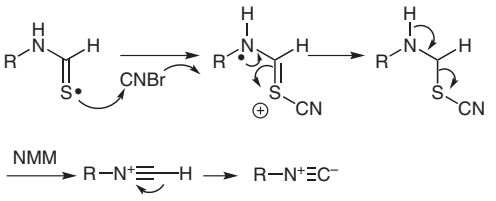
(47) The two dipeptide thioformamides were synthesized in to verify the optical purity of N^{β}-Fmoc-amino alkyl thiofor mamides **1**. For this, **1b** was treated with 20% Et_2NH in CH_2Cl_2 to deprotect the Fmoc group. The resulting amino-free N^{β}-(1-amino alanine)-thioformamide was coupled both D and L isomers of Fmoc-Phg-OH using EDC/separately to obtain **1k** and **1l**. The ^1H NMR spectra of both Fmoc-L-Phg-Ala-Ψ[CH_2NHCHS] and Fmoc-D-Phg-Ala-Ψ[CH_2NHCHS] showed distinct methyl group doublets at δ = 1.13, 1.14 ppm and δ = 1.21, 1.23, respectively. However, the mixture of epimers prepared by coupling amino-free N^{β}-(1-amino alanine)-thioformamide with epimeric mixture of Fmoc (L/D)-Phg-OH had two separate doublets corresponding to each diastereomer. This clearly confirmed the optical purity of thioformamides.
(48) The mechanism of the dehydrosulforization of thioformamides using CNBr is given in Scheme 3.



Scheme 3

(49) **Typical Experimental Procedure for 1a–j**
To a stirred solution of N^{β}-Fmoc amino alkyl formamide **5** (1 mmol) in THF (5 mL), P_2S_5 (0.7 mmol) was added. The reaction mixture was subjected to ultrasonication for 15 min. After the completion of reaction (TLC), the solvent was evaporated in vacuo, and the crude was purified by a flash chromatography to obtain the thioformamides as solids.
(50) **Selected Spectroscopic Data.**
Compound **1b**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, 3 H, *J* = 6.53 Hz), 2.65 (d, 2 H), 3.90 (m, 1 H), 4.20 (t, 1 H, *J* = 13.04 Hz), 4.41 (d, 2 H, *J* = 6.62 Hz), 5.01 (br, 1 H), 7.31 (t, 2 H, *J* = 14.79 Hz), 7.39 (t, 2 H, *J* = 14.69 Hz), 7.57 (d, 2 H, *J* = 7.21 Hz), 7.76 (d, 2 H, *J* = 7.48 Hz), 8.20 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.44, 46.83, 47.18, 56.18, 66.83, 122.24, 124.93, 127.08, 128.17, 141.34, 143.66, 155.77, 139.31.
Compound **1j**: ^1H NMR (400 MHz, $CDCl_3$): δ = 2.39–2.65 (m, 2 H), 3.12–3.51 (m, 2 H), 3.1 (m, 1 H), 4.10 (t, 1 H, *J* = 6.90 Hz), 4.12 (d, 2 H, *J* = 7.2 Hz), 4.74 (s, 2 H), 5.56 (br, 1 H), 7.15–7.80 (m, 13 H), 8.25 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$; CCl_4): δ = 36.91, 43.06, 46.82, 51.89, 65.83, 69.82, 119.15, 124.90, 126.25, 127.53, 128.12, 128.24, 141.67, 143.53, 143.81, 156.38, 139.22, 171.58.
Compound **1k**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, 3

H, *J* = 5.0 Hz), 2.65–3.16 (m, 2 H), 4.05–4.20 (m, 3 H), 4.22 (d, 2 H, *J* = 8.0 Hz), 6.65 (br, 1 H), 6.88 (br, 1 H), 7.28–7.48 (m, 8 H), 7.56 (d, 2 H, *J* = 4.0 Hz), 7.74 (d, 2 H, *J* = 8.0 Hz), 8.16 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.12, 43.09, 45.86, 53.69, 58.29, 67.18, 125.34, 126.22, 127.09,127.77, 128.01, 128.40, 128.63, 135.54, 141.30, 143.75, 159.14, 156.29, 138.9.

(51) **Typical Experimental Procedure for 2a–j**

A solution of N^{β}-Fmoc amino alkyl thioformamide **1** (1 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C, NMM (2 mmol) and CNBr (1.5 mmol) were added, and the reaction mixture was stirred at this temperature for 30 min. After completion of reaction, it was diluted with CH_2Cl_2 (10 mL) and was washed with H_2O, brine, and dried over anhyd Na_2SO_4. The solvent was evaporated under reduced pressure followed by chromatographic purification (silica gel, 100–200 mesh, 20% EtOAc in hexane) to afford the desired isonitriles **2** in excellent yield and purity as stable solids.

(52) **Selected Spectroscopic Data**

Compound **2c**: IR (KBr): ν_{max} = 1715, 2149 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.81 (br, 2 H), 3.12–3.65 (m, 2 H), 3.95 (br, 1 H), 4.12 (br, 1 H), 4.29 (d, 2 H, *J* = 4.0 Hz), 5.15 (br, 1 H), 7.17 (m, 9 H), 7.44 (d, 2 H, *J* = 8.0 Hz), 7.69 (d, 2 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.30, 44.39, 47.19, 50.79, 66.99, 120.10, 125.04, 127.15, 127.35, 127.84, 129.03, 129.10, 135.98, 141.38, 143.65, 155.55, 158.45.

Compound **2f**: IR (KBr) ν_{max} = 1710, 2151 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20–2.71 (m, 2 H), 3.00–3.59 (m, 4 H), 4.00 (br, 1 H), 4.12 (d, 1 H, *J* = 7.8 Hz), 4.41 (br, 2 H), 6.02 (s,1 H), 7.00–7.74 (m, 13 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.10, 36.21, 44.00, 46.85, 49.12, 53.34,66.88, 119.90, 124.82, 126.95, 127.08, 127.83, 128.15, 136.77, 141.00, 143.13, 155.11, 158.10.

Compound **2l**: IR (film/pellet) ν_{max} = 1715, 2151 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, 3 H, *J* = 4.0 Hz), 3.12–3.79 (m, 2 H), 3.87–4.10 (m, 3 H), 4.11 (d, 2 H, *J* = 8.0 Hz), 5.09 (br, 1 H), 5.89 (br, 1 H), 7.28–7.48 (m, 8 H), 7.56 (d, 2 H, *J* = 4.0 Hz), 7.74 (d, 2 H, *J* = 8.0 Hz), 8.18 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.00, 43.69, 46.42, 54.10, 57.95, 67.10, 119.77, 125.45, 127.22, 127.75, 128.53, 128.40, 128.63, 135.09, 141.30, 143.75, 154.94, 156.49, 170.97.