Tetrahedron Letters 52 (2011) 6865–6868

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Synthesis of isotopomers of *N*-(*tert*-butoxycarbonyl)-4-cyano-L-phenylalanine methyl ester: choice of cyanation solvent

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ARTICLE INFO

*Article history:*
Received 21 July 2011
Revised 5 October 2011
Accepted 10 October 2011
Available online 17 October 2011

*Keywords:*
4-Cyano-L-phenylalanine
Infrared spectroscopy
Isotope editing
Vibrational reporters

ABSTRACT

*N*-(*tert*-butoxycarbonyl)-4-cyano-L-phenylalanine methyl ester and three isotopomers ($C^{15}N$, $^{13}CN$, and $^{13}C^{15}N$) were successfully synthesized in two steps to expand the utility of the nitrile symmetric stretch vibration of this modified amino acid as a vibrational reporter of local environments. The choice of cyanation solvent directly impacted the level of isotopic enrichment of the isotopomers. The commonly used solvent acetonitrile resulted in an isotopic enrichment of only ~80% with a cyanation reaction time of 4.5 h, however, the cyanation solvent *N*,*N*-dimethylformamide afforded the isotopomers with >98% isotopic enrichment.



The nitrile group has shown great promise as a sensitive, site-specific vibrational reporter of local environments in a number of biological systems.[1–16] This vibrational probe is attractive due to the position of the nitrile symmetric stretching frequency, which is in a relatively clear region of the IR spectrum, and the sensitivity of the nitrile IR absorbance band (peak position and/or fwhm) to the local environment.[2,8,11,17] Additionally, the small size (two-atom) and intermediate polarity of this group allow addition of this probe at various positions of proteins to be well tolerated.[18–20]

The nitrile-modified amino acid, 4-cyano-L-phenylalanine (PheCN), has been especially utilized as a vibrational probe of peptide and protein structure and dynamics.[2,3,9,11,12,21] This unnatural amino acid (UAA) has been incorporated into peptides by solid-phase peptide synthesis[2,9,11,12,21] and into larger proteins utilizing an engineered, orthogonal aminoacyl-tRNA synthetase.[3,9,20] This nitrile-modified amino acid has provided an insight into the local environments in proteins through vibrational spectroscopy, including both infrared and Raman spectroscopy.[2,21] PheCN has also been coupled with fluorescence spectroscopy to yield distance information between PheCN and the natural amino acid, tryptophan, since PheCN and tryptophan form a FRET pair with a Förster distance of 16.0 ± 0.5 Å.[22]

Recent efforts in our lab with biomolecular vibrational reporters have necessitated the ability to selectively isotopically label the nitrile group of 4-cyano-L-phenylalanine (PheCN). Specifically $C^{15}N$, $^{13}CN$, and $^{13}C^{15}N$ labeled versions of PheCN are of interest to enhance and expand the utility of this vibrational reporter. These isotopomers could be used for accurate identification[5,23] of nitrile IR absorbance bands based upon known isotopic shifts of the nitrile symmetric stretch vibration. Additionally, multiple isotopomers could be used in concert to probe multiple local protein environments simultaneously. Also, the isotopomers could potentially be used as vibrational distance probes due to vibrational coupling between nitrile groups as observed with $C^{14}N$ and $C^{15}N$ variants of 5-cyano-2′-deoxyuridine in DNA oligomers.[7]

Here we discuss the synthesis of three isotopomers of a fully protected version of PheCN, *N*-(*tert*-butoxycarbonyl)-4-cyano-L-phenylalanine methyl ester (Boc-PheCN-OMe, **3**). These protected isotopomers can be subsequently de-protected in a straightforward manner[20] to generate isotopically labeled PheCN. The choice of solvent in the nickel-catalyzed cyanation step was found to be especially important to obtain isotopically pure (>98% isotopic enrichment) isotopomers of **3**. The impact of the isotopic labels on the position and line shape of the nitrile IR absorbance band for each isotopomer is discussed. The experimentally measured isotopic shifts of the nitrile symmetric stretch vibration are compared with density functional theory (DFT) calculated isotopic shifts.

## Cyanation solvent: acetonitrile (MeCN)

Scheme 1 illustrates the general procedure utilized in the synthesis of Boc-PheCN-OMe (**3**). Initially, *N*-(*tert*-butoxycarbonyl)-4-((trifluoromethyl)sulfonyl)-L-phenylalanine methyl ester (**2**) was produced by the reaction of *N*-(*tert*-butoxycarbonyl)-L-tyrosine methyl ester (**1**) with trifluoromethanesulfonic anhydride.[24,25] The second step involved the nickel-catalyzed cyanation[25–27] of **2**

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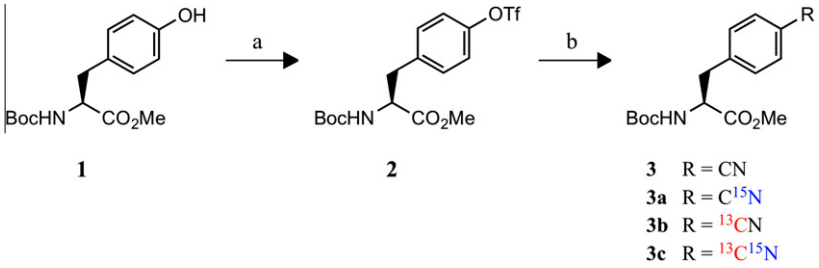
doi:10.1016/j.tetlet.2011.10.050




**Scheme 1.** Reagents and conditions: (a) $C_5H_5N$, $(CF_3SO_2)_2O$, $CH_2Cl_2$, 0 °C, 91%; (b) $Ni(PPh_3)_2Br_2$, $PPh_3$, Zn, (KCN, $KC^{15}N$, $K^{13}CN$, or $K^{13}C^{15}N$), (MeCN or DMF), 60 °C.

with bis(triphenylphosphine)nickel (II) bromide ($Ni(PPh_3)_2Br_2$, 10 mol %), triphenylphosphine ($PPh_3$, 20 mol %), zinc (Zn) powder (60 mol %), and 1.1 equiv of potassium cyanide (KCN) in acetonitrile (MeCN) at 60 °C for 4.5 h to afford **3** with a yield of 58% (see Supplementary data for complete synthetic details and NMR characterization). Figure 1A shows the resulting FTIR absorbance spectrum of **3** dissolved in tetrahydrofuran (THF) in the nitrile symmetric stretching region. This spectrum shows the nitrile IR absorbance band at 2229.2 $cm^{-1}$ as a single band, as expected based upon previous studies with Fmoc-PheCN in THF and PheCN in water.[2] The choice of the commonly used solvent acetonitrile was based upon the previous literature procedures involving the nickel-catalyzed cyanation of aryl triflates.[25–27]

Due to the success of Scheme 1 in generating **3**, the $^{15}N$ isotopomer **3a** was subsequently synthesized based upon this procedure using $^{15}N$ labeled potassium cyanide ($KC^{15}N$) instead of KCN. The resulting FTIR absorbance spectra of the purified cyanation product(s) dissolved in THF is shown in Figure 1B. This spectrum shows two absorbance bands in the nitrile symmetric stretching region at 2229.2 and 2202.1 $cm^{-1}$. DFT calculations at the B3PW91/6-31++G(d,p) level predict that the $^{15}N$ isotope label should result in a 29 $cm^{-1}$ red shift in the nitrile symmetric stretch vibration relative to **3**. Based upon this calculation and the position of the nitrile IR absorbance band of **3** (Fig. 1A), the absorbance bands at 2229.2 and 2202.1 $cm^{-1}$ are assigned to the nitrile symmetric stretch vibration of **3** and **3a**, respectively. Thus the experimental $^{15}N$ isotopic shift is 27 $cm^{-1}$. The DFT calculated isotopic shift is in qualitative but not quantitative agreement with the experimental isotopic shift since the calculation was performed in the gas phase and excluded anharmonic effects.[28] The integrated area of the two nitrile IR absorbance bands in Figure 1B shows that the product from this reaction is a mixture of **3** (23%) and **3a** (77%) despite $KC^{15}N$ being 98+% $^{15}N$ enriched. Therefore, the observed percentage of **3** in the product mixture is not a result of incomplete enrichment (98+%) of the $^{15}N$ labeled potassium cyanide employed as starting material.

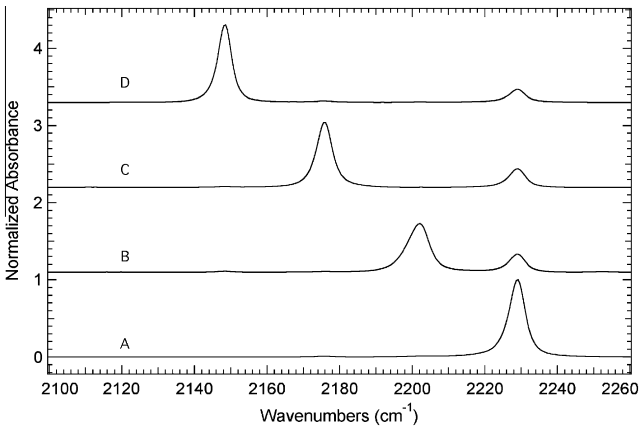



**Figure 1.** FTIR absorbance spectra of isotopomers of *N*-(*tert*-butoxycarbonyl)-4-cyano-L-phenylalanine methyl ester (**3**) in the nitrile symmetric stretching region recorded at 298 K in THF. The isotopomers were synthesized based upon Scheme 1 with MeCN and either KCN (A), $KC^{15}N$ (B), $K^{13}CN$ (C), or $K^{13}C^{15}N$ (D) in the cyanation step. The spectra have been area normalized and offset for comparison.

A possible explanation for this mixture of **3** and **3a** is that MeCN is serving as both the solvent and the unlabeled nitrile (CN) source, while $KC^{15}N$ is serving as the $^{15}N$ labeled nitrile ($C^{15}N$) source. A previous study has demonstrated the nickel-catalyzed cyanation of the aryl chloride, *o*-chlorotoluene, in acetonitrile in the absence of another cyanide source, such as potassium cyanide, where the nitrile group of MeCN was transferred to the aryl chloride.[29] However, this reaction required 4 equiv of Zn, a reaction time of 24 h, and a reaction temperature of 90 °C.[29] Here, less than a stoichiometric amount of Zn was used with a shorter reaction time (4.5 h) and a lower reaction temperature (60 °C). Under these conditions, attempts to generate **3** from **2** in the absence of KCN have been unsuccessful, which suggest that these milder conditions do not readily promote nitrile group transfer from MeCN to **2**. An alternative to a nitrile group transfer from MeCN to **2** could be that the nitrile group of acetonitrile is exchanging with the $^{15}N$ labeled cyanide anion from the $^{15}N$ labeled potassium cyanide generating an unlabeled cyanide anion. The extent of this exchange would thus modulate the percentage of **3** and **3a** obtained. There is debate in the literature as to whether the cyanide anion can exchange with the nitrile group of acetonitrile.[30–35] This debate is due in part to the relatively low solubility of potassium cyanide in acetonitrile, which severely limits the ability to determine if this exchange does occur. Here, FTIR spectroscopy was not able to observe the presence of $^{15}N$ labeled MeCN due to cyanide exchange between $C^{15}N^-$ and MeCN after the 4.5 h cyanation reaction used to generate **3a**.

The percentage of **3** in this mixture of **3** and **3a** was also found to be dependent upon the length of the cyanation reaction increasing to 43% after 24.5 h at 60 °C based upon the FTIR absorbance spectrum of the isolated cyanation product(s) (see Supplementary data Fig. S1). However, the overall yield of the reaction was not improved with this longer reaction time. One possible explanation for these results is that the cyanation step is reversible. The percentage of nonisotopically labeled cyanide anion in the reaction mixture should increase with time if $^{15}N$ labeled cyanide anion can exchange with MeCN. A reversible cyanation would allow for the incorporation of unlabeled cyanide formed from this exchange thereby increasing the percentage of **3** in the final reaction mixture. Additionally, the concentration of $^{15}N$ labeled cyanide in the reaction mixture could be decreasing with time due to the formation of volatile $^{15}N$ labeled hydrogen cyanide resulting from the presence of trace amounts of water.[36] Thus, if the nitrile group of acetonitrile can be transferred (through a nickel-mediated process)[29] to the aryl triflate **2**, less competition from $C^{15}N^-$ in the reaction mixture could result in a larger percentage of **3** over time. A second related possibility is that the nitrile group of **3a** could exchange (likely through a nickel-mediated process)[37–39] with

the nitrile group of cyanide or acetonitrile in the reaction mixture without reforming **2**. This possibility was tested by substituting **2** for **3b** (>98% $^{13}C$ enrichment, synthesis described below) in the cyanation reaction step, while keeping the reaction time, temperature, and amounts of all other reagents ($Ni(PPh_3)_2Br_2$, $PPh_3$, Zn, $KC^{15}N$, and MeCN) unchanged. After 4.5 h, FTIR spectroscopy revealed the presence of **3b** (92%), **3a** (6%), and **3** (2%) in the reaction mixture (see Supplementary data Fig. S2). Thus nitrile exchange between **3b** and $C^{15}N^-$ from $KC^{15}N$ can occur to generate **3a** in the presence of the cyanation reagents, while the amount of **3** present can be explained based upon the original isotopic enrichment of **3b** and the isotopic enrichment of $KC^{15}N$.

To further explore the potential of this synthetic route to generate isotopomers of **3**, $K^{13}CN$ or $K^{13}C^{15}N$ was utilized in the nickel-catalyzed cyanation of **2** to generate **3b** and **3c**, respectively. The resulting FTIR absorbance spectra are shown in Figures 1C and D, respectively. Figure 1C shows two nitrile IR absorbance bands at 2229.2 and 2176.1 $cm^{-1}$. Based upon the position of the nitrile IR absorbance spectrum of **3** and the DFT predicted isotopic shift, the bands at 2229.2 and 2176.1 $cm^{-1}$ are attributed to the nitrile symmetric stretch vibrations of **3** and **3b**, respectively. Similarly, the two bands at 2229.2 and 2148.6 $cm^{-1}$ in Figure 1D are assigned to the nitrile symmetric stretch vibrations of **3** and **3c**, respectively. The relative integrated areas of the nitrile IR absorbance bands in Figures 1C and D show the presence of 17% and 21% of **3**, respectively, in addition to the desired isotopomers (**3b** and **3c**, respectively). As expected based upon the change in the reduced mass of the nitrile oscillator and DFT calculations, the magnitude of the isotopic shift is the largest for **3c** (relative to **3**) followed by **3b** and **3a**. The magnitude of the isotopic shift results in the nitrile IR absorbance bands of **3**, **3a**, **3b**, and **3c** being well resolved from each other. Therefore, the synthetic procedure outlined in Scheme 1 using MeCN as the solvent in the second step successfully generated the desired isotopomers of **3**. The incorporation of isotopically enriched cyanide was only ~80%.

### Cyanation solvent: *N*,*N*-dimethylformamide (DMF)

In order to increase the isotopic enrichment of the isotopomers of **3**, the effect of solvent in the nickel-catalyzed cyanation of **2** was investigated. Specifically, acetonitrile was replaced with *N*,*N*-dimethylformamide (DMF) in the cyanation step. The replacement of MeCN with DMF as the cyanation solvent did not significantly alter the yield of **3** (see Supplementary data for complete synthetic details and NMR characterization). The resulting FTIR absorbance spectra of the purified cyanation product, obtained using $KC^{15}N$, $K^{13}CN$, or $K^{13}C^{15}N$, in the nitrile symmetric stretching frequency region are shown in Figure 2. As illustrated in Figure 2, the FTIR absorbance spectra of each isotopomer dissolved in THF show a single nitrile IR absorbance band corresponding to **3** (Boc-PheCN-OMe), **3a** (Boc-Phe$C^{15}$N-OMe), **3b** (Boc-Phe$^{13}$CN-OMe), or **3c** (Boc-Phe$^{13}C^{15}$N-OMe). Each of the isotopomers showed an isotopic enrichment >98%, limited by the isotopic enrichment of the potassium cyanide isotopomer used. The nitrile IR absorbance bands for **3**, **3a**, **3b**, and **3c** appeared at 2229.2, 2202.1, 2176.1, and 2148.6 $cm^{-1}$, respectively, which are identical with the band positions of the cyanation products generated using MeCN as the cyanation solvent.

Each of the nitrile IR absorbance bands could be fit to a single line shape composed of a linear combination of a Gaussian and Lorentzian function having the same central frequency (see Supplementary data) except **3a**. The nitrile IR absorbance band of **3a** was slightly asymmetric and required two line shapes to sufficiently model the experimental absorbance band. The position of the smaller component is 2202.7 $cm^{-1}$ while the larger component has a central frequency of 2200.9 $cm^{-1}$. These two components

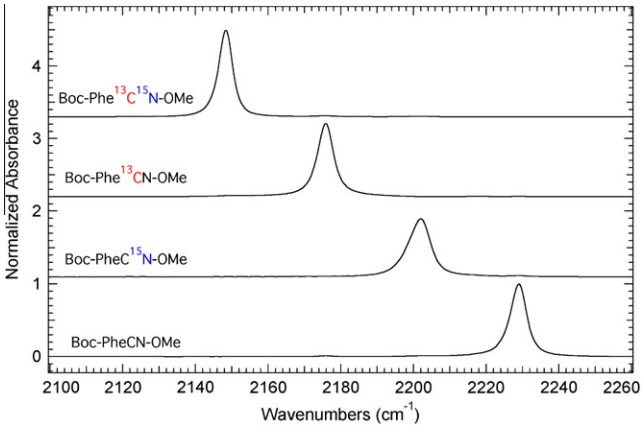



**Figure 2.** FTIR absorbance spectra of isotopomers of *N*-(*tert*-butoxycarbonyl)-4-cyano-L-phenylalanine methyl ester (Boc-PheCN-OMe, **3**) in the nitrile symmetric stretching region recorded at 298 K in THF. The isotopomers were synthesized based upon Scheme 1 with DMF and either KCN (Boc-PheCN-OMe, **3**), $KC^{15}N$ (Boc-Phe$C^{15}$N-OMe, **3a**), $K^{13}CN$ (Boc-Phe$^{13}$CN-OMe, **3b**), or $K^{13}C^{15}N$ (Boc-Phe$^{13}C^{15}$N-OMe, **3c**) in the cyanation step. The spectra have been area normalized and offset for comparison.

could be due to different conformations of the molecule, different solute–solvent interactions, or accidental Fermi resonance between the fundamental nitrile symmetric stretch vibration and a near-resonant overtone or combination band. The first two possibilities are unlikely since the other isotopomers of **3** show essentially a symmetric nitrile IR absorbance band that can be reasonably modeled with a single line shape. The third possibility is most likely. For instance, DFT calculations of **3a** reveal 33 combination bands within 10 $cm^{-1}$ of the fundamental nitrile symmetric stretch vibration. The energy difference between the fundamental nitrile symmetric stretch vibration and the near-resonant combination bands will be modulated upon isotopic labeling of the nitrile group of **3**, which could modulate the accidental Fermi resonance likely present in the nitrile symmetric stretching region of **3a**. Previous work with 3-azidopyridine and phenyl cyanate has demonstrated the ability to modulate accidental Fermi resonance through isotopic editing.[40] The assignment of accidental Fermi resonance in **3a** would explain the nearly symmetric line shapes measured for the nitrile IR absorbance bands in **3**, **3b**, and **3c**. However, 2D IR experiments[41–43] would be required for a definitive assignment of accidental Fermi resonance in **3a**.

The results utilizing DMF as the cyanation solvent further implicate acetonitrile as the source of unlabeled nitrile resulting in only ~80% isotopic enrichment of **3a**, **3b**, and **3c** when using MeCN as the cyanation solvent and a reaction time of 4.5 h. However, it is unclear whether the nitrile group of acetonitrile is transferred to the aryl triflate **2** through a nickel-catalyzed process or whether the nitrile group of MeCN first exchanges with the labeled cyanide anion in the reaction mixture forming unlabeled $CN^-$, which then participates in the nickel-catalyzed cyanation of **2**.

### Conclusions

Three isotopomers ($C^{15}N$, $^{13}CN$ and $^{13}C^{15}N$) of **3** were successfully generated in two steps with an isotopic enrichment >98%. Solvent choice for the nickel-catalyzed cyanation of **2** was found to be critical for achieving isotopically pure (>98% isotopic enrichment) material. The commonly used cyanation solvent, MeCN[25–27] was found to generate the desired isotopomers, but with a ~20% contamination of **3** with a cyanation reaction time of 4.5 h. However, the use of DMF as the cyanation solvent yielded isotopically pure **3a**, **3b**, or **3c** with isotopic enrichment limited by the enrichment

of the corresponding potassium cyanide isotopomer used. The subsequent straightforward deprotection[20] of these isotopomers will result in the isotopically labeled variants of the biomolecular vibrational probe, PheCN. The utilization of these isotopomers to enhance the ability to probe local biomolecular environments is currently underway.

## Acknowledgments

We gratefully acknowledge Kristopher Kolonko for helpful discussions; Lisa Mertzman for obtaining materials and supplies; Beth Buckwalter for acquiring NMR spectra; and Carol Strausser for assistance in editing of the manuscript. This work was supported by F&M Hackman funds and NSF (CHE-1053946) to SHB.

## Supplementary data

Supplementary data (synthetic methods and characterization of **3**, **3a**, **3b**, and **3c**; FTIR experimental methods; line shape analysis of nitrile IR absorbance band of **3**, **3a**, **3b**, and **3c**; and DFT computational details) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.050.

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