Research article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 17 March 2015, Revised 29 June 2015, Accepted 29 July 2015 Published online 28 August 2015 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jlcr.3330

Palladium-catalyzed decarboxylative cyanation of aromatic carboxylic acids using [^{13}C] and [^{14}C]-KCN

Olivier Loreau, Dominique Georgin, Frédéric Taran, and Davide Audisio*

The development of robust and straightforward methods to efficiently label aromatic moieties starting from simple and convenient radio-synthetic sources still represents a considerable challenge. In this report, a new palladium-catalyzed decarboxylative cyanation protocol has been described. This procedure utilizes [^{14}C]-labeled potassium cyanide, one of the simplest and commercially available sources of carbon-14. Under the optimized reaction conditions, a series of [^{13}C] and [^{14}C]-aromatic nitriles were easily prepared (12–74% yield starting from potassium cyanide). The usefulness of this methodology is highlighted by a rare example of a formal two-step [^{12}C]–[^{14}C] carbon isotope exchange. The current synthetic approach may represent a promising alternative to traditional preparations of relevant building blocks such as labeled aromatic nitriles.

Keywords: isotopic labeling; carbon; cyanide; cyanation; palladium catalyzed; carbon isotope exchange

Introduction

Aromatic nitriles are highly important intermediates in organic synthesis as well as relevant building blocks frequently encountered in pharmaceutical and agrochemical industrial compounds.[1] As a direct consequence, the preparation of carbon-14-labeled aryl nitriles has drawn much attention over the years.[2] To date, several methods exist to prepare aryl nitriles, the most conventional being the Sandmeyer and the Rosenmund-von Braun reactions.[3] More recently, transition metal-catalyzed cyanation of aryl halides has become a valuable alternative to traditional methods, allowing the use of milder reaction conditions and a broader functional group tolerance.[4]

In 2010, our group published a palladium-catalyzed decarboxylative cyanation of aromatic carboxylic acids.[5,6] This methodology was successfully applied to the synthesis of [^{13}C] and [^{14}C]-arene nitriles. Although the protocol proved satisfactory, the use of [^{14}C]-cyclohexanone cyanohydrin[7] as cyanide source was necessary for the success of the reaction. Although the preparation of [^{14}C]-cyanohydrins from [^{14}C]-KCN is straightforward, the storage and manipulation of [^{14}C]-cyanohydrins is not easy that is a clear limitation to our previously described procedure.

Looking for a more direct [^{14}C]-cyanation protocol, we decided to further investigate this transformation. In this communication, we disclose a straightforward decarboxylative cyanation of aromatic carboxylic acids using commercially available K^{14}CN, which is a rare example of a formal two-step carbon isotope exchange involving [^{12}C]–[^{12}C] bond breaking and [^{14}C]–[^{12}C] bond formation in the same synthetic process.

Experimental

Unlabeled starting materials and chemical reagents were purchased from Aldrich (Saint Quentin Fallavier, France). Solvents were from Carlo Erba Reagents (Val de Reuil, France) or VWR Chemicals (Fontenay-sous-Bois, France). Silica gel 60 (40–63 μm) for column chromatography was from Merck (Darmstadt, Germany). Potassium [^{13}C]cyanide (99% isotopic enrichment) and NMR solvents were from Euriso-Top (Saint Aubin, France). Potassium [^{14}C]cyanide with low specific activity was prepared from unlabeled KCN, and potassium [^{14}C]cyanide (specific activity: 31.6 MBq mg^{-1}) from Quotient Bioresearch (Cardiff, UK). NMR spectra were measured on a Bruker Avance 400 spectrometer (Bruker Wissembourg, France), and chemical shifts (δ) are given in parts per million. Mass spectra were obtained by gas chromatography/mass spectrometry analyses on an HP 6890 Series gas chromatograph system (Hewlett-Packard, Les Ulis, France) coupled to an HP 5973 mass selective detector. Liquid scintillation analysis was performed on a Wallac 1409 counter using Ultima Gold cocktail from Perkin-Elmer (Waltham, MA).

General procedure for the synthesis of labeled aryl nitriles (method A)

Labeled potassium cyanide (0.5 mmol, 1 eq), arene carboxylic acid (1 mmol, 2 eq), Ag_2CO_3 (3 mmol, 6 eq), and $Pd(OCOCF_3)_2$ (0.2 mmol, 40 mol%) were suspended in DMF-DMSO (95:5, 10 mL) under air. The flask was connected to a reflux condenser, and the reaction mixture was heated to 120 °C for 3 h. After cooling, the reaction mixture was poured into AcOEt and filtered. The filtrate was sequentially washed with an aqueous $NaHCO_3$ solution (1 M) and H_2O then dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (heptane : AcOEt – 80:20) giving the desired labeled aryl nitrile.

CEA, iBiTecS, Service de Chimie Bioorganique et de Marquage, Gif sur Yvette F-91191, France

**Correspondence to: Davide Audisio, CEA, iBiTecS, Service de Chimie Bioorganique et de Marquage, Gif sur Yvette, F-91191, France.*
E-mail: davide.audisio@cea.fr

General procedure for the synthesis of labeled aryl nitriles (method B)

Labeled potassium cyanide (0.25 mmol, 1 eq), arene carboxylic acid (1 mmol, 4 eq), Ag_2CO_3 (3 mmol, 12 eq), and $Pd(OCOCF_3)_2$ (0.2 mmol, 0.8 eq) were suspended in DMF-DMSO (95:5, 10 mL) under air. The flask was connected to a reflux condenser, and the reaction mixture was heated to 120 °C for 3 h. After cooling, the reaction mixture was treated and purified as described earlier.

*[^{13}C-Cyano]-2,4-dimethoxybenzonitrile ([**^{13}C**]-**2a**)*

Method A: white solid; 56 mg; 68% yield from $K^{13}CN$, isotopic enrichment: 98.3% (based on MS-EI$^+$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3H), 3.92 (s, 3H), 6.46 (s, 1H), 6.52 (dd, *J* = 2.1, 8.6 Hz, 1H), 7.48 (dd, *J* = 5.6, 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.91 (^{13}C-enriched). MS (EI): *m/z* = 164 (100, [M]$^+$).

*[^{14}C-Cyano]-2,4-dimethoxybenzonitrile ([**^{14}C**]-**2a**)*

Method A: white solid; 110.3 MBq; 74% yield from $K^{14}CN$ (307.1 MBq mmol^{-1} based on [**^{14}C**]-**3a**, 4.4 MBq mg^{-1}, 34 mg, 149.6 MBq).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H), 3.90 (s, 3H), 6.46 (d, *J* = 2.2 Hz, 1H), 6.52 (dd, *J* = 2.4, 8.6 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H). MS (EI): *m/z* = 163 (100, [M]$^+$).

*[^{13}C-Cyano]-2,6-dimethoxybenzonitrile ([**^{13}C**]-**2b**)*

Method A: white solid; 61 mg; 74% yield from $K^{13}CN$, isotopic enrichment: 99% (based on $K^{13}CN$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 6H), 6.55 (dd, *J* = 1.4, 8.5 Hz, 2H), 7.44 (t, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.03 (^{13}C-enriched). MS (EI): *m/z* = 164 (100, [M]$^+$).

*[^{13}C-Cyano]-2,6-dimethoxynicotinonitrile ([**^{13}C**]-**2c**)*

Method A: white solid; 31 mg; 37% yield from $K^{13}CN$, isotopic enrichment: 99% (based on $K^{13}CN$).

Method B: white solid; 21 mg; 51% yield from $K^{13}CN$.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.97 (s, 3H), 4.04 (s, 3H), 6.36 (d, *J* = 8.3 Hz, 1H), 7.69 (dd, *J* = 5.2, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.05 (^{13}C-enriched). MS (EI): *m/z* = 165 (100, [M]$^+$).

*[^{13}C-Cyano]-anthracene-9-carbonitrile ([**^{13}C**]-**2d**)*

Method A: yellow solid; 19 mg; 19% yield from $K^{13}CN$, isotopic enrichment: 99% (based on $K^{13}CN$).

Method B: yellow solid; 34 mg; 67% yield from $K^{13}CN$, isotopic enrichment: 99% (based on $K^{13}CN$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (t, *J* = 7.4 Hz, 2H), 7.73 (t, *J* = 7.4 Hz, 2H), 8.09 (d, *J* = 8.6 Hz, 2H), 8.43 (d, *J* = 8.6 Hz, 2H), 8.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.18 (^{13}C-enriched). MS (EI): *m/z* = 204 (100, [M]$^+$).

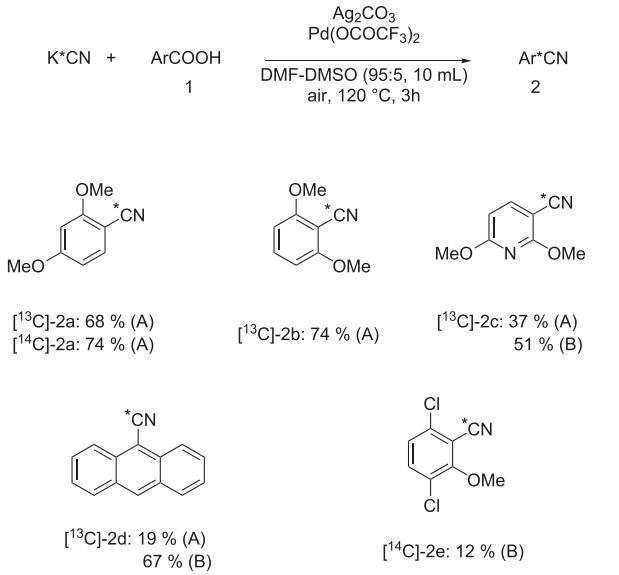
*[^{14}C-Cyano]-3,6-dichloro-2-methoxybenzonitrile ([**^{14}C**]-**2e**)*

Method B: white solid; 14 MBq; 12% yield from $K^{14}CN$ (462.2 MBq mmol^{-1} based on $K^{14}CN$, 7.1 MBq mg^{-1}, 17 mg, 120.7 MBq).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.09 (s, 3H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H). MS (EI): *m/z* = 201 (100, [M]$^+$).

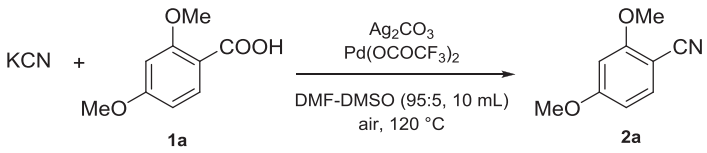
Procedure for the synthesis of labeled 2,4-dimethoxybenzoic acid

Labeled 2,4-dimethoxybenzonitrile (41.5 mg of [**^{13}C**]-**2a** or 110.3 MBq of [**^{14}C**]-**2a**) was reacted overnight at 80 °C with an aqueous KOH solution



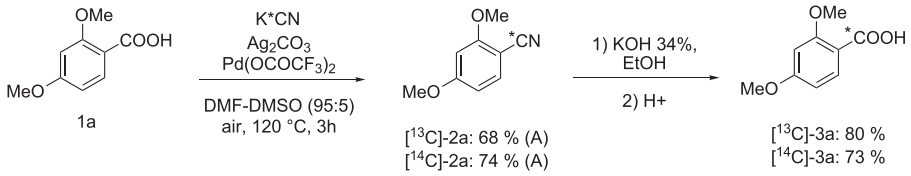
Scheme 1. Synthesis of labeled aryl nitriles (isolated yields from K*CN); * labeling (^{13}C or ^{14}C). Method A: K*CN (0.5 mmol), ArCOOH (1 mmol), Ag_2CO_3 (3 mmol), $Pd(OCOCF_3)_2$ (0.2 mmol). Method B: K*CN (0.25 mmol), ArCOOH (1 mmol), Ag_2CO_3 (3 mmol), $Pd(OCOCF_3)_2$ (0.2 mmol).

Table 1. Optimization of the model reaction



Entry	KCN (mmol)	**1a** (mmol)	Ag_2CO_3 (mmol)	$Pd(OCOCF_3)_2$ (mmol)	Time (h)	Yield (**2a**)[a,b] (%)
1	1	1 (1 eq)	3 (3 eq)	0.2 (0.2 eq)	3	38
2	1	1 (1 eq)	3 (3 eq)	0.5 (0.5 eq)	3	45
3	**0.5**	**1 (2 eq)**	**3 (6 eq)**	**0.2 (0.4 eq)**	**3**	**79**
4	0.5	1 (2 eq)	3 (6 eq)	0.2 (0.4 eq)	1	61
5	0.25	1 (4 eq)	3 (12 eq)	0.2 (0.8 eq)	3	78

[a]Isolated yield from KCN.
[b]This optimization was performed using [^{12}C]KCN.



Scheme 2. Carbon exchange procedure; * labeling (^{13}C or ^{14}C). Method A: K*CN (0.5 mmol), 2,4-dimethoxybenzoic acid **1a** (1 mmol), Ag_2CO_3 (3 mmol), $Pd(OCOCF_3)_2$ (0.2 mmol).

(34%, 2 mL) and EtOH (2 mL). After cooling, the reaction mixture was diluted with water and extracted with diethyl ether. The aqueous fraction was acidified to pH 2 with a 6N HCl solution and then extracted twice with diethyl ether. The combined organic layers were washed with water until washes were of neutral pH, dried over Na_2SO_4, filtered, and concentrated to give labeled 2,4-dimethoxybenzoic acid.

*[^{13}C-Carboxyl]-2,4-dimethoxybenzoic acid ([**^{13}C**]-**3a**)*

White solid; 37 mg; 80% yield from [**^{13}C**]-**2a**, isotopic enrichment: 99% (based on K^{13}CN).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.89$ (s, 3H), 4.05 (s, 3H), 6.54 (s, 1H), 6.65 (dd, $J = 2.2$, 8.8 Hz, 1H), 8.14 (dd, $J = 4.5$, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.66$ (^{13}C-enriched). MS (EI): $m/z = 183$ (100, $[M]^+$).

*[^{14}C-Carboxyl]-2,4-dimethoxybenzoic acid ([**^{14}C**]-**3a**)*

White solid; 80.6 MBq; 73% yield from [**^{14}C**]-**2a**, specific activity: 307.1 MBq mmol^{-1} (based on MS EI$^+$).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.89$ (s, 3H), 4.05 (s, 3H), 6.54 (d, $J = 2.2$ Hz, 1H), 6.66 (dd, $J = 2.2$, 8.8 Hz, 1H), 8.14 (d, $J = 8.8$ Hz, 1H). MS (EI): $m/z = 182$ (100, $[M]^+$).

Results and discussion

In order to improve the applicability of our previously developed palladium-catalyzed decarboxylative cyanation, we decided to use [^{14}C]-KCN as isotopic cyanide source on the model substrate **1a**. Potassium cyanide is one of the simplest [^{14}C]-labeled starting materials, commercially available, and a very convenient source for radio-synthesis.

An initial attempt using 1 mmol of KCN, 1 mmol of 2,4-dimethoxybenzoic acid **1a**, 3 mmol of silver carbonate, and 20 mol% of palladium(II) trifluoroacetate in 10 mL of DMF-DMSO (95/5) allowed the isolation of 2,4-dimethoxybenzonitrile **2a** with a moderate yield of 38% (Table 1, entry 1). Taking into consideration the poisoning effect of cyanide on the palladium catalysts, we decided to increase the amount of $Pd(OCOCF_3)_2$. Carrying out the reaction with 50 mol% of the palladium catalyst only slightly ameliorated the yield of the transformation, and **2a** was isolated in 45% yield (Table 1, entry 2). The reaction was successfully improved by increasing the amount of the carboxylic acid substrate in the reaction mixture. With 2 eq of **1a** (Table 1, entry 3) and 40% of catalyst loading, the corresponding aryl nitrile **2a** was isolated in satisfying 79% yield. A shorter reaction time (Table 1, entry 4) led to a reduced yield (61%). A final attempt with 4 eq of **1a** and 80% of $Pd(OCOCF_3)_2$ did not result in a significant improvement of the yield (78%; Table 1, entry 5).

With an optimized set of conditions in our hands, we decided to study the scope of this transformation. A series of aromatic carboxylic acids were successfully labeled to the corresponding [^{13}C] and [^{14}C] nitriles in moderate to good yields. In analogy with literature precedents and our previous observations, the presence of an *ortho*-substituent to the reacting carboxylic functionality was necessary;[5] nevertheless, electron-rich carboxylic acids as well as heteroaromatic acids were well tolerated in the transformation, and also halogens provided the desired product, albeit in rather low yields (2e, Scheme 1).

In contrast to hydrogen isotope exchange techniques,[8] [^{12}C]–[^{14}C] replacement strategies are more challenging and were only sporadically described.[2a,9] We sought to take advantage of our protocol to develop a formal two-step carbon isotope exchange. The first step involves the Pd-catalyzed decarboxylative cyanation reaction, and the second step the hydrolysis of the corresponding labeled nitrile to reconstruct the carboxylic acid starting material. To validate this strategy, 2,4-dimethoxybenzoic acid **1a** was used as model substrate. As anticipated, the formal carbon isotopic exchange was successfully performed with an overall 54% yield for both carbon-13 and −14 isotopes (Scheme 2).

Conclusions

We have developed a palladium-catalyzed decarboxylative cyanation of aromatic carboxylic acids that allows the synthesis of [^{13}C] and [^{14}C]-labeled nitrile derivatives. This protocol utilizes [^{14}C]-labeled potassium cyanide, one of the simplest commercially available sources for radio-synthesis. The usefulness of this methodology was showcased by a successful example of carbon isotope exchange in two steps with 54% overall yield.

Acknowledgements

The authors thank Céline Puente and David-Alexandre Buisson (CEA, iBiTecS, Service de Chimie Bioorganique et de Marquage) for liquid scintillation measurements.

Conflict of interest

The authors did not report any conflict of interest.

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