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Fast and efficient synthesis of ^{14}C labelled benzonitriles and their corresponding acids

Søren Christian Schou*

^{14}C-Anthranilic acid has been prepared in a fast and efficient way in a two-step reaction in 82% overall radiochemical yield. Thus, 2-iodoaniline was transformed into 2-amino-[7-^{14}C]-benzonitrile using a palladium catalyzed cyanation with zinc ^{14}C-cyanide. Subsequent basic hydrolysis of the cyano group afforded [7-^{14}C]-anthranilic acid. The method was successfully applied to a benzophenone scaffold, 4-iodophenol and 4-iodobenzoic acid producing the corresponding carboxylic acids in good to excellent radiochemical yields (62–82%) and with high specific activity (1.94–1.98 GBq/mmol).

Keywords: cyanation; carbon-14; potassium cyanide; zinc cyanide; anthranilic acid

Introduction

When synthesis of a ^{14}C labelled compound is required, access to suitable precursors are often limited due to price or availability. Therefore, efficient and high yielding synthetic steps with inexpensive ^{14}C-precursors are preferable. KCN is an inexpensive cyanide precursor, which can be readily incorporated into a variety of organic compounds.[1–8] The cyano group can readily be transformed to a number of different functional groups such as carboxylic acids and pharmacologically important heterocycles.[9–11]

The cyano group has been introduced under a variety of conditions, e.g. diazotation,[12] palladium catalysis[13] or copper catalysis (Rosenmund von Braun reaction).[1,2] Usually more than one equivalent of cyanide is used.

When ^{14}C-labelled cyanide is the precursor, it is preferred not to use an excess of cyanide, to avoid lowering the radiochemical yield and generating unnecessary radioactive waste. Using the classical cyanation procedure with $Cu^{14}CN$, high temperatures (150–250°C) for long reaction times (7 h or more) are often required.[4] This can be a disadvantage if sensitive functional groups are present in the molecule.

Synthesis of ^{14}C labelled anthranilic acid (**3**) has been reported in the literature[1,14,15] but most of the reported methods involve multistep synthesis,[14] $Cu^{14}CN$,[3,4] $Ba^{14}CO_3$[15,16] or $^{14}CO_2$ (g),[1] which requires special equipment for handling. In all reported methods more than one equivalent of ^{14}C precursor was used. In addition, Sunay *et al.* [1] have reported an unsuccessful attempt to synthesize [7-^{14}C]-anthranilic acid based on an ortho-lithiation protocol starting from BOC-protected aniline. The intermediate lithium species was quenched with $^{14}CO_2$ affording BOC-protected anthranilic acid. In the deprotection step difficulties with the stability (decarboxylation) were observed and only aniline was isolated.

We decided to develop a simpler route to ^{14}C labelled anthranilic acid with a high radiochemical yield. Different authors have reported[17–27] a method using $Zn(CN)_2$ as the cyanide source for a palladium catalyzed cyanation. $Zn(CN)_2$ is preferred as the cyanide source due to low solubility, whereby catalyst poisoning is prevented.[17] Therefore, we chose $Zn(^{14}CN)_2$ as the cyanide source and via the cyano species obtained the anthranilic/corresponding acids. To the best of our knowledge, all reported methods use more than 0.5 equivalent $Zn(CN)_2$, which will lower the radiochemical yield.

Here, we report a fast and efficient palladium catalyzed synthesis of ^{14}C labelled benzonitriles and their corresponding acids with $Zn(^{14}CN)_2$ as the cyanide source, using only 0.5 equivalent of $Zn(^{14}CN)_2$.

Results and discussion

^{14}C labelled potassium cyanide was readily transformed into ^{14}C labelled zinc cyanide in a quantitative yield by mixing aqueous solutions of $K^{14}CN$ and zinc chloride. The practically insoluble zinc cyanide precipitates and can be collected by filtration or centrifugation (Scheme 1).

We decided to use the palladium catalyzed cyanation approach using an aryl iodide, $Zn(^{14}CN)_2$ and $Pd(PPh_3)_4$ in dry DMF. Thereby, we were able to convert 2-iodoaniline (**1**) to the corresponding cyano compound **2** in excellent radiochemical yield (89%). The catalytic system is sensitive to air so degassing is recommended to obtain high yields.[28] Compound **2** was subsequently transformed into anthranilic acid (**3**) by basic hydrolysis in excellent yield as well (92%) (Scheme 2).

To investigate the scope of the reaction aryl iodides possessing electron-donating (4-OH) or withdrawing (4-COOH) groups were investigated. 4-Iodo-phenol (**4**) was converted into the benzonitrile **5** in good radiochemical yield and the corresponding benzoic acid **6** was obtained after basic

LEO Pharma, Medicinal Chemistry Research, Industriparken 55, DK-2750 Ballerup, Denmark

**Correspondence to: Søren Christian Schou, LEO Pharma, Medicinal Chemistry Research, Industriparken 55, DK-2750 Ballerup, Denmark.*
E-mail: soeren.schou@leo-pharma.com

hydrolysis in an overall radiochemical yield of 63%. Similarly **9** was prepared from **7** in 69% overall radiochemical yield (Scheme 2).

This protocol was also investigated using a benzophenone scaffold. Compound **11** was prepared in 92% radiochemical yield from the corresponding aryliodide **10**, which was prepared as described in the literature.[29] Compound **11** was subsequently hydrolyzed under basic conditions affording **12** in 89% overall radiochemical yield. Compound **11** was also prepared using a microwave protocol reported by Srivastava *et al.*[30] The palladium source was $Pd(OAc)_2$ and the ligand was solid supported triphenylphosphine (see Scheme 3) and by using this procedure, **11** was synthesized in a moderate radiochemical yield (43%) (Scheme 3).

In conclusion, a simple and practical approach for the high yielding synthesis of ^{14}C labelled aryl nitriles and their corresponding acids, starting from the aryl iodides and $Zn(^{14}CN)_2$ has been developed using palladium catalyzed cyanation as the key step.

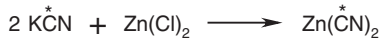
Recently the use of aryl bromides instead of aryl iodides in palladium catalyzed cyanation with $Zn(^{14}CN)_2$ has been published by Ho *et al.*[19] using one equivalent of $Zn(^{14}CN)_2$. An advantage for our method compared to other methods is the use of only 0.5 equivalent of $Zn(^{14}CN)_2$. The scope and limitations of the method are currently being investigated in our laboratories.

Experimental

General

HPLC was performed using a Merck Hitachi apparatus with an L-4250 UV-VIS detector and an L-6000 pump. Columns used were Merck LiChrospher 250–10 containing RP-18 (10 μm). Concentrations and specific activities were determined by HPLC by comparison of peak areas of radio-inactive reference compounds. A Packard Tri-Carb 2900TR Liquid Scintillation Analyzer was used to determine activity in liquid samples using Pico-Fluor™ 40 (Packard) as scintillation cocktail. ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX500 spectrometer. Chemical shifts are reported in ppm with tetramethylsilane (TMS, $\delta = 0.00$) as internal reference.

All air and moisture sensitive reactions were carried out in oven-dried (120°C) glassware under an inert atmosphere of argon. Potassium [^{14}C]-cyanide was purchased from Amersham (GE Healthcare). DMF was dried over molecular sieves (4 Å). All other solvents and reagents were used as received, purchased from Sigma-Aldrich. Column chromatography was performed using silica gel 60 (Merck) (70–230 mesh). Reactions under microwave irradiation were performed in a CEM Discover Microwave oven.



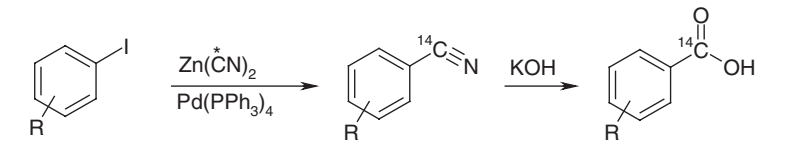
Scheme 1.

Zinc [^{14}C]-cyanide

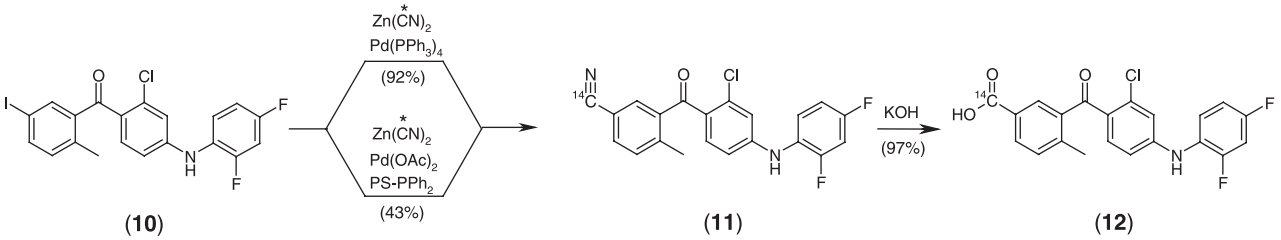
To a solution of zinc chloride (1.29 mmol, 176 mg) in H_2O (500 μL) was added dropwise an aqueous solution of potassium [^{14}C]-cyanide (1.72 mmol, 3.7 GBq, 2.10 GBq/mmol, 1000 μL) at rt. Precipitation of the white zinc ^{14}C-cyanide started immediately. The reaction mixture was stirred at rt for 5 min and then centrifuged (3000*g* for 5 min). The supernatant was removed and remaining solid was washed with H_2O (4 × 500 μL) and Et_2O (2 × 500 μL). The obtained white crystals were dried overnight using high vacuum affording the desired product in quantitative yield (0.86 mmol, 104 mg).

*2-Amino-benzonitrile-[cyano-^{14}C] (**2**)*

Zinc [^{14}C]-cyanide (47 mg, 0.39 mmol, 1.52 GBq), 2-iodoaniline (**1**) (0.78 mmol, 171 mg) and $Pd(PPh_3)_4$ (0.07 mmol, 45 mg) were weighed in a dry flask charged with argon. Freshly degassed, dry DMF (2.5 mL) was added, and the flask was gently degassed (vacuum) and charged with argon, repeated two times. The



Scheme 2.



Scheme 3.

reaction mixture was stirred under an argon atmosphere at 80°C for 1 h, cooled to rt, added sat. $NaHCO_3$ (20 mL) and extracted with ethyl acetate (4 × 10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* affording 594 mg of brown oil. The oil was purified by silica gel chromatography (5 g SiO_2) using a gradient of heptane:ethyl acetate [100:0→75:25] affording the desired product as pale yellow crystals in 89% yield (83 mg, 0.69 mmol, 1.36 GBq). ^{1}H NMR (d_6-DMSO) δ = 7.37 (d, *J* = 7.8, 1H), 7.29 (t, *J* = 7.8, 1H), 6.78 (d, *J* = 8.4, 1H), 6.59 (t, *J* = 7.5, 1H), 5.99 (s, 2H). ^{13}C NMR (d_6-DMSO) δ = 151.96, 134.32, 132.79, 116.28, 115.56, 93.79.

*2-Amino-benzoic acid-[carboxyl-^{14}C] (**3**)*

2-Amino-benzonitrile-[cyano-^{14}C] (**2**) (78 mg, 0.65 mmol, 1.29 GBq) and KOH (1.8 g, 32.5 mmol, 50 eq) were weighed in a 100 mL round bottom flask. H_2O was added in the flask (30 mL) and stirred at reflux (115°C) for 5 h affording a clear brown solution. The reaction mixture was cooled to rt and pH was adjusted to pH = 3–4 using conc. HCl, whereby precipitation occurred. The reaction mixture was extracted with ethyl acetate (5 × 15 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* affording the desired product as beige/light brown crystals in 96% yield (87 mg, 0.64 mmol, 1.23 GBq, SA: 1.97 GBq/mmol)).

*4-Hydroxy-benzonitrile-[cyano-^{14}C] (**5**)*

4-Hydroxyiodobenzene (**4**) (33 mg, 0.149 mmol) was dissolved in dry DMF (1 mL) in a dry flask charged with argon. The solution was degassed (vacuum) and flushed with argon. $Zn(CN)_2$ (8.8 mg, 0.073 mmol, 289 MBq) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) were added and the solution was degassed and flushed with argon again. The reaction mixture was stirred at 80°C for 1 h, then cooled to rt, added H_2O (5 mL) and extracted with ethyl acetate (3 × 5 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (2 g SiO_2) using a gradient of heptane:ethyl acetate [100:0→75:25] as eluent affording the desired product as off-white crystals in 63% yield (11 mg, 0.09 mmol, 183 MBq). ^{1}H NMR (d_6-DMSO) δ = 7.62 (d, *J* = 8.7, 2H), 6.89 (d, *J* = 8.7, 2H). ^{13}C NMR (d_6-DMSO) δ = 161.99, 134.23, 116.50, 100.65.

*4-Hydroxy-benzoic acid-[carbonyl-^{14}C] (**6**)*

4-Hydroxy-benzonitrile-[cyano-^{14}C] (**5**) (9.5 mg, 0.078 mmol, 155 MBq) was dissolved/suspended in H_2O (10 mL) in a round bottom flask. KOH (224 mg, 4 mmol) was added and the reaction mixture was stirred at reflux (115°C) for 5 h affording a brown solution. The reaction mixture was cooled to rt and pH was adjusted to pH = 3–4 using conc. HCl, whereby precipitation occurred. The reaction mixture was extracted with ethyl acetate (4 × 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* affording the desired product as off-white crystals in 98% yield (11 mg, 0.077 mmol, 153 MBq, SA: 1.94 GBq/mmol).

*Cyano-benzoic acid-[cyano-^{14}C] (**8**)*

4-Iodobenzoic acid (**7**) (37 mg, 0.149 mmol) was dissolved in dry DMF (500 μL) in a dry flask charged with argon. The solution was degassed (vacuum) and flushed with argon. $Zn(^{14}CN)_2$ (8 mg, 0.067 mmol, 263 MBq) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) were added and the solution was degassed and flushed with argon again. The reaction mixture was stirred at 80°C for 1 h affording a yellow solution. The reaction mixture was cooled to rt, added H_2O (5 mL) and extracted with ethyl acetate (3 × 5 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (2 g SiO_2) using a gradient of heptane:ethyl acetate:acetic acid [100:0:0→67:33:1] as eluent affording the desired product as off-white crystals in 77% yield (16 mg, 0.11 mmol, 203 MBq). ^{1}H NMR (d_6-DMSO) δ = 8.09 (d, *J* = 8.2, 1H), 7.98 (d, *J* = 8.2, 1H). ^{13}C NMR (d_6-DMSO) δ = 166.07, 132.67, 131.44, 129.92, 115.01.

*Terephthalic acid-[monocarbonyl-^{14}C] (**9**)*

Cyano-benzoic acid-[cyano-^{14}C] (**8**) (11 mg, 0.078 mmol, 154 MBq) was dissolved/suspended in H_2O (10 mL) in a round bottom flask. KOH (215 mg, 3.85 mmol) was added and the reaction mixture was stirred at reflux (115°C) for 5 h affording a brown solution. The reaction mixture was cooled to rt and pH was adjusted to pH = 3–4 using conc. HCl, whereby precipitation occurred. The reaction mixture was extracted with ethyl acetate (4 × 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* affording the desired product as off-white crystals in 89% yield (11.6 mg, 0.069 mmol, 137 MBq, SA: 1.98 GBq/mmol).

*3-[2-Chloro-4-(2,4-difluoro-phenylamino)-benzoyl]-4-methyl-benzonitrile-[cyano-^{14}C] (**11**)*

Method A: [2-Chloro-4-(2,4-difluoro-phenylamino)-phenyl]-(5-iodo-2-methyl-phenyl)-methanone (**10**) (72 mg, 0.149 mmol) was dissolved in dry DMF (500 μL) in a dry flask charged with argon. The solution was degassed (vacuum) and flushed with argon. $Zn(^{14}CN)_2$ (9 mg, 0.074 mmol, 293 MBq) and $Pd(PPh_3)_4$ (8 mg, 0.074 mmol) were added and the solution was degassed and flushed with argon again. The red-brown solution was stirred at 80°C for 1 h. The reaction mixture was cooled to rt, added H_2O (10 mL) and extracted with ethyl acetate (4 × 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (5 g SiO_2) using a gradient of heptane:ethyl acetate [100:0→50:50] as eluent affording the desired product as off-white crystals in 92% yield (52 mg, 0.135 mmol, 269 MBq)). ^{1}H NMR (d_6-DMSO) δ = 8.85 (s, 1H), 7.88 (dd, *J* = 1.5, 7.9, 1H), 7.73 (s, 1H), 7.55 (d, *J* = 8.0, 1H), 7.48–7.38 (m, 3H), 7.13 (t, *J* = 7.6, 1H), 6.82 (d, *J* = 1.5, 1H), 6.78 (dd, *J* = 1.7, 8.7, 1H), 2.34 (s, 3H). ^{13}C NMR (d_6-DMSO) δ = 193.44, 159.38 (dd, *J* = 11.4, 244.2), 156.29 (dd, *J* = 12.7, 248.8), 150.43, 142.25, 141.20, 134.78, 134.60, 134.07, 132.53, 131.94, 127.15 (d, *J* = 9.6), 125.66, 124.38 (dd, *J* = 3.3, 12.1), 115.35, 112.44 (dd, *J* = 3.4, 22.2), 112.28, 109.21, 105.50 (dd, *J* = 24.5, 26.5), 20.16.

Method B: $Pd(OAc)_2$ (7 mg, 0.064 mmol, 0.07eq) and solid supported PPh_3 (23 mg, 0.137 mmol, 0.15 eq, 3 mmol/g) were weighed in a dry microwave tube charged with argon and dissolved in dry DMF (2 mL). The solution was stirred at rt for 2 h affording an orange mixture. [2-Chloro-4-(2,4-difluoro-phenylamino)-phenyl]-(5-iodo-2-methyl-phenyl)-methanone (**10**) (440 mg, 0.91 mmol) and $Zn(^{14}CN)_2$ (108 mg, 0.91 mmol, 3.7 GBq) were added, the microwave tube was sealed and exposed to microwaves, 140°C for 50 min. The reaction mixture was cooled to rt, added H_2O (50 mL) and extracted with ethyl acetate (4 × 25 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* affording the desired product as light

brown oil in 86% yield (301 mg, 0.78 mmol, 1.59 GBq) and was used without further purification.

3-[2-Chloro-4-(2,4-difluoro-phenylamino)-benzoyl]-4-methyl-benzoic acid-[carbonyl-^{14}C] (**12**)

3-[2-Chloro-4-(2,4-difluoro-phenylamino)-benzoyl]-4-methyl-benzonitrile-[cyano-^{14}C] (**11**) (37 mg, 0.097 mmol, 192 MBq) was dissolved/suspended in H_2O (10 mL) in a round bottom flask. KOH (271 mg, 4.85 mmol) was added and the reaction mixture stirred at reflux (115°C) for 5 h, affording a brown solution. The reaction mixture was cooled to rt and pH was adjusted to pH = 3–4 using conc. HCl, whereby precipitation occurred. The reaction mixture was extracted with ethyl acetate (4 × 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* affording the desired product as light yellow/orange crystals in 97% yield (38 mg, 0.094 mmol, 186 MBq, SA: 1.97 GBq/mmol).

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