Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **43**, 1075-1085 (2000)

Palladium-Catalyzed Aryl Cyanations with [^{14}C]KCN: Synthesis of ^{14}C-Labelled Fadrozole, a Potent Aromatase Inhibitor

Alban J. Allentoff*, Bohdan Markus, Timothy Duelfer, Amy Wu, Lawrence Jones, Grazyna Ciszewska and Tapan Ray

Isotope Laboratory, Novartis Pharmaceutical Corporation, Department of Drug Metabolism and Pharmacokinetics, 59 Route 10, East Hanover, New Jersey 07936, USA

SUMMARY

The potent aromatase inhibitor [^{14}C]Fadrozole (**1**), was prepared in a single radiosynthetic step via a palladium(0)-catalyzed cyanation of the imidazole-containing aryl iodide **2b** with [^{14}C]KCN. Attempted preparation of **2b** by metal-halogen interchange of the corresponding aryl bromide **2a** with *tert*-butyl lithium followed by quenching with iodine afforded only the imidazole iodide **5** via disproportionation of the intermediate anion. The desired precursor was finally synthesized through a three-step sequence beginning with the alkylation of known imidazole derivative **8** with 4-iodobenzylbromide. This alkylation product was treated with thionyl chloride to convert a side chain hydroxyl to its corresponding primary chloride **10**. Cyclization of chloride **10** using LDA/TMEDA gave the desired aryl iodide **2b**. While initial attempts at the palladium(0)-catalyzed cyanation of **2b** with unlabelled KCN in THF at reflux gave modest yields of Fadrozole, the reaction with [^{14}C]KCN afforded only trace amounts of [^{14}C]Fadrozole. By including Copper(I) iodide as a co-catalyst and using deoxygenated THF, the palladium(0)-catalyzed cyanation of **2b** gave [^{14}C]Fadrozole in 39% radiochemical yield with >99% radiochemical purity.

Keywords: Cyanation reactions, Palladium-catalyzed, Fadrozole, Copper iodide, [^{14}C]Potassium cyanide

INTRODUCTION

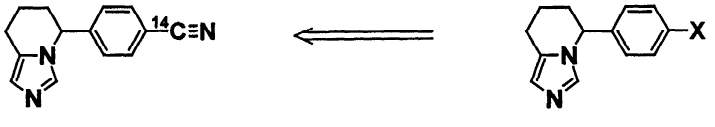
The introduction of carbon-14 labelled cyano groups into molecules is one of the most widely used methods to incorporate carbon-14 into medicinal compounds required for metabolism and pharmacokinetic studies [1]. We [2] and others [3, 4,

Received 8 March 2000
Revised 30 May 2000
Accepted 30 May 2000

5] have recently explored the use of tetrakis(triphenyl-phosphine)palladium(0)-catalyzed cyanation reactions as a convenient and versatile method for the direct cyanation of aryl halides with labelled cyanide salts or metal cyanides. While this reaction has been well known since its discovery in the seventies [6], until recently, little work has gone into exploring its application to the synthesis of radiolabelled pharmaceuticals.

We now report on the use of this reaction as a key step in a synthesis of radiolabelled Fadrozole (**1**), a potent aromatase inhibitor, presently marketed in Japan for treatment of estrogen-dependent breast cancer [7]. In our previously reported synthesis of [^{14}C]Fadrozole [8], the ^{14}C-label was introduced at the beginning of the synthesis via a Rosenmund reaction of an aryl bromide with [^{14}C]copper(I) cyanide, and was carried through seven steps, affording Fadrozole hydrochloride in an overall radiochemical yield of 1%. We envisioned that this radiosynthesis could be shortened considerably via a direct palladium-catalyzed cyanation of a halogenated analog of Fadrozole as displayed in Scheme 1. This approach seemed reasonable based on literature precedent showing that palladium-catalyzed cyanations of 4-alkyl-substituted aryl iodides proceed in high yield [9]. Also supporting this approach were results recently reported from our laboratory [2] suggesting that tetrakis(triphenyl-phosphine)palladium(0)-catalyzed cyanations tolerate the presence of dinitrogen-containing heterocycles in the substrate although lower yields of product are sometimes obtained. The following results detail the synthesis of the appropriate halogenated Fadrozole analog and describe the conditions required for the successful palladium-catalyzed cyanation of this analog with labelled potassium cyanide affording [^{14}C]Fadrozole in one radiosynthetic step.

Scheme 1



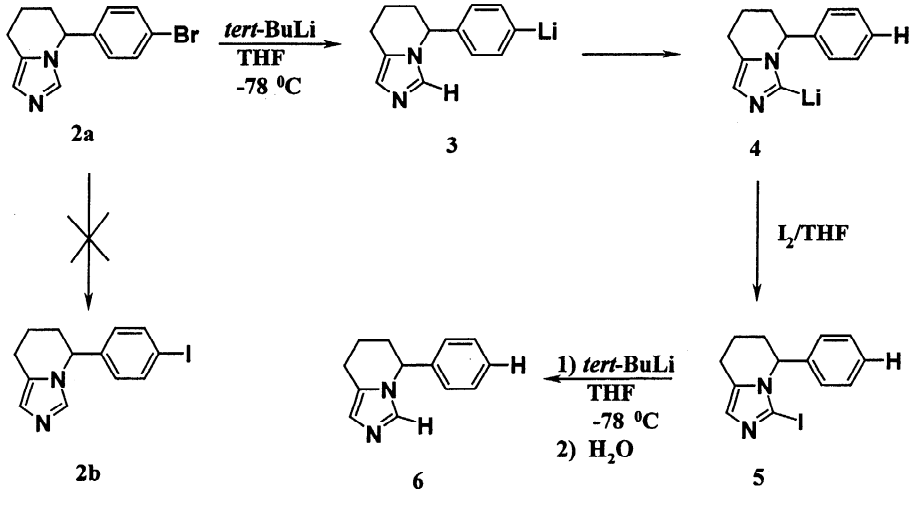
1
[^{14}C]Fadrozole

2a, X = Br
b, X = I

RESULTS AND DISCUSSION

Initially, since we had considerable amounts of the known aryl bromide **2a** [10] in hand from previous work, we attempted the direct cyanation of bromide **2a** to [^{14}C]Fadrozole. Treatment of **2a** with copper(I) cyanide in DMF at high temperature [8] or with potassium cyanide with tetrakis(triphenylphosphine)palladium(0) in THF at reflux, afforded no observable amounts of cyanated product. Therefore, we considered preparing the aryl iodide **2b** which was potentially more reactive towards palladium-catalyzed cyanation [9]. Attempted direct conversion of bromide **2a** to iodide **2b** via metal-halogen interchange followed by quenching with iodine (Scheme 2) gave none of the desired aryl iodide **2b**. Instead, treatment of **2a** with *tert*-butyllithium in THF at -78 ^{0}C formed aryl anion **3**, which disproportionated to the imidazole anion **4**. Quenching anion **4** with iodine in THF yielded imidazole iodide **5**. The position of the iodide on the carbon between the imidazole nitrogens in **5** was established by ^{1}H- and ^{13}C-NMR analysis and was confirmed by HMBC analysis which showed a clear interaction between the iodide-substituted carbon (88.2 ppm) and the imidazole proton (6.98 ppm). Further confirmation of the structure of **5** came from metal-halogen interchange with *tert*-butyl lithium followed by rapid

Scheme 2

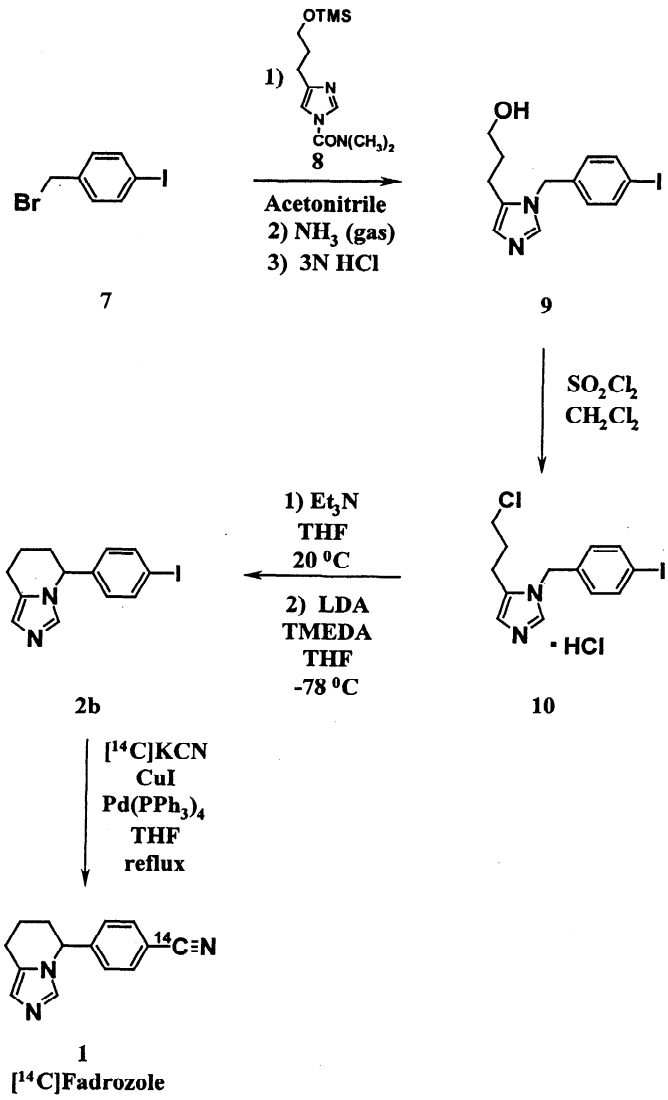


quenching of the resulting anion with water affording the dehalogenated compound **6**. ^{1}H NMR analysis of **6** clearly showed the expected second imidazole proton resonance at 7.14 ppm which was not present in the corresponding iodide **5**. Other attempts at directly converting bromide **2a** to the aryl iodide utilizing nickel metal with potassium iodide [11] were also unsuccessful yielding only unreacted starting material.

Iodide **2b** was finally prepared through a three-step route starting with commercially available 4-iodobenzylbromide (**7**) as displayed in Scheme 3. Bromide **7** was used to alkylate the known imidazole **8** (prepared from 4-imidazole acrylic acid [10]), and the resulting product was deprotected to alcohol **9** by successive treatment with anhydrous ammonia and 3N hydrochloric acid. Chlorination of **9** by treatment with thionyl chloride in methylene chloride gave primary chloride **10** which was cyclized to the desired iodo-substituted Fadrozole precursor **2b**. The cyclization of the 4-iodobenzene **10** required a strong base (LDA with TMEDA) compared to the previously reported cyclization of the corresponding 4-cyano-substituted aromatic system (in which *tert*-butoxide was used [8]) probably due to the weaker electron withdrawing ability of an iodide compared to a nitrile group in stabilizing a benzylic anion.

Initial trial cyanations of iodide **2b** with 1.3 equivalents of unlabelled potassium cyanide using standard Sekiya-Ishikawa conditions [6] (tetrakis(triphenyl-phosphine)palladium(0) in THF at reflux for 18 h) gave unlabeled Fadrozole in 35% isolated yield (based on iodide **2b**) with unreacted starting iodide remaining. However, when the same reaction was performed using [^{14}C]KCN, labeled Fadrozole (**1**) was obtained in only 2.5% radiochemical yield also with mostly unreacted starting material remaining in the reaction mixture. Low yields in a tetrakis(triphenylphosphine)palladium(0)-catalyzed cyanation of a tetrazole-containing aryl iodide with unlabeled KCN using similar conditions were also recently reported [5]. We therefore investigated possible modifications of the reaction conditions to increase the reactivity of iodide **2b** to cyanation with [^{14}C]KCN. Recently, Anderson and co-workers observed enhancement of tetrakis(triphenylphosphine)palladium(0)-catalyzed cyanations of aryl iodides with

Scheme 3



excess potassium cyanide using copper(I) iodide as a co-catalyst in deoxygenated THF [12]. Such catalytic properties of Copper(I) iodide have also been widely used in Stille coupling reactions [13]. Using the reported conditions, treatment of iodide **2b** with two equivalents of [^{14}C]KCN including 10 molar % of copper(I) iodide and 5 molar % of tetrakis(triphenyl-phosphine)palladium(0) in

deoxygenated THF at reflux for 18 hours gave 80% conversion of iodide **2b** to [^{14}C]Fadrozole (**1**). Longer reaction times did not lead to further conversion of iodide **2b** to nitrile **1**. Purification by flash chromatography afforded a 39% isolated radiochemical yield (based on [^{14}C]KCN, 77% chemical yield from iodide **2b**) of the desired product with >99% radiochemical purity. We are presently investigating the potential optimization of these reaction conditions, and their generality in enhancing the tetrakis(triphenylphosphine)palladium(0)-catalyzed cyanation of aromatic iodides with [^{14}C]KCN.

CONCLUSION

In conclusion, using a palladium(0)-catalyzed cyanation reaction co-catalyzed with copper(I) iodide, we have prepared [^{14}C]Fadrozole in 39% radiochemical yield in one step from [^{14}C]KCN. This synthetic pathway offers an approximate 39-fold increase in radiochemical efficiency when compared to a previously reported preparation of the compound. It demonstrates that on choosing correct reaction conditions, the Pd(0)-catalyzed cyanation reaction with [^{14}C]KCN offers a versatile and efficient route towards incorporating carbon-14 into nitrogen-containing heterocyclic compounds

EXPERIMENTAL

Potassium-[^{14}C]-cyanide (specific activity = 57.1 mCi/mmol) was purchased from American Radiolabelled Chemicals Incorporated of St. Louis, MO. Unlabelled reagents were purchased from Aldrich Chemical Company of Milwaukee, WI; 4-iodobenzylbromide (**7**) was purchased from Alfa Aesar Organics of Ward Hill MA. All thin layer chromatography (TLC) was performed on EM Silica-Gel 60 F254 plates, 0.250 mm thickness. Radiochemical purity was determined by scanning the TLC plates with a Bioscan System 200 imaging scanner. All NMR spectra were recorded on a Brucker DPX 300 spectrometer with chemical shifts reported in δ and coupling constants reported in Hz. Electrospray mass spectra were obtained on a Finnigan LCQ ion trap spectrometer by direct infusion in water/acetonitrile.

(5,6,7,8-Tetrahydro-8-iodoimidazo[1,5-a]pyridin-5-yl)benzene (5).

To a solution of bromide **2a** (0.45 g, 1.6 mmol) in THF (10 mL) at –78 °C under nitrogen was added dropwise, a solution of *tert*-butyllithium (2.1 mL, 2.7 M in pentane, 5.6 mmol) and the resulting yellow solution was stirred at –78 °C for 1 h. A solution of I_2 (1.26 g, 5.0 mmol) in 2.3 mL of THF was then added in one part and the solution was stirred at –78 °C for 1.5 h. It was then allowed to warm to ambient temp over 6 h and was stirred at ambient temp for an additional 10 h. The reaction was quenched by addition of water. TLC analysis (95:5 CH_2Cl_2:methanol) showed quite clean formation of the less polar iodide product (Rf = 0.69). After extracting the solution twice into CH_2Cl_2 the organic layer was washed with aqueous sodium bisulfite solution, dried over $MgSO_4$, and the solvent was removed to afford the crude product. Purification by flash chromatography on silica gel (95:5 CH_2Cl_2:methanol) yielded 0.21 g (41% yield) of pure **5** as a yellow crystalline solid: ^1H NMR ($CDCl_3$) δ 1.63 (m, 1 H), 1.72 (m, 1 H), 2.15 (br d, 1 H, J = 12), 2.30 (m, 1 H), 2.76 (m, 1 H), 3.00 (br d, 1 H, J = 12), 5.38 (t, 1 H, J = 2.5), 6.79 (d, 2 H, J = 9.3), 6.98 (s, 1 H), 7.31 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_2), 21.2 (CH_2), 31.7 (CH_2), 58.6 (CH), 88.2 (C-I), 126.1 (2 C, phenyl CH), 127.3 (CH), 128.0 (CH), 128.5 (2 C, phenyl CH), 133.0 (imidazole C), 141.4 (phenyl C); HMBC experiments showed an interaction between the imidazole proton (δ 6.98) and the iodo-substituted carbon (δ 88.2) confirming the presence of an iodide substituent between the imidazole nitrogens; MS (electrospray positive ion) $[M+H]^+ = 325$.

(5,6,7,8-Tetrahydroimidazo[1,5-a]pyridin-5-yl)benzene (6).

To a solution of iodide **5** (0.015g, 0.046 mmol) in THF (2 mL) at –78 °C was added *tert*-butyllithium (0.067 mL, 2.7 M in pentane, 0.18 mmol) and the resulting bright-orange solution was stirred at –78 °C for 2.5 h. Addition of water gave a clear, colorless solution which was warmed to ambient temp and stirred for an additional 2 h. The solution was then extracted twice into CH_2Cl_2, the organic layer was dried over $MgSO_4$, and the solvent was removed affording 8.9 mg of **6** as

a white crystalline solid: ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 1 H), 1.91-1.98 (m, 2 H), 2.26 (m, 1 H), 2.84-2.99 (m, 2 H), 5.17 (t, 1 H, J = 5), 6.83 (s, 1 H), 7.07 (d, 2 H, J = 8.8), 7.14 (s, 1 H), 7.30-7.42 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 18.9 (CH_2), 21.0 (CH_2), 33.1 (CH_2), 58.2 (CH), 112.6 (C), 124.3 (CH), 126.5 (2 C, CH), 128.0 (CH), 128.7 (2 C, CH), 135.9 (CH), 141.9 (C).

4-[5-(3-Hydroxypropyl)-1H-imidazol-1-yl)methyl]-1-iodobenzene (9).

To a solution of the protected imidazole **8** (prepared *in situ* from 1H-imidazole-4-propanol (2.0 g, 15.8 mmol)) [10], in 50 mL of acetonitrile, was added 4-iodobenzyl bromide (**7**, 4.7 g, 15.8 mmol) and the resulting mixture was heated at reflux for 10 h. After cooling the solution to 0 °C with an ice bath, anhydrous ammonia gas was gently bubbled through the solution at 0 °C for 4 h. The solution was then stirred at ambient temp for 2 h and then evaporated to dryness *in vacuo*. Aqueous 3N HCl (40 mL) was added to the residue and the resulting mixture was stirred for 18 h at ambient temp. After washing with toluene, the aqueous layer was basified with NaOH solution to pH 9 and extracted twice with ethyl acetate. The organic layer was dried over $MgSO_4$ and the solvent removed to afford 5.7 g of crude **9** as a gummy brownish solid. TLC analysis (9:1 CH_2Cl_2:methanol) showed considerable product formation (Rf = 0.32). Acetronitrile (50 mL) was added to the crude product with heating, followed by enough methanol to dissolve the solid, and the heating continued to evaporate the solvent until cloudiness was observed. On cooling at -20 °C for 18 h, a white solid formed which was filtered and washed with cold ethyl acetate. Drying under vacuum at ambient temp for 2 h yielded 1.95 g (5.7 mmol, 36%) of **9** as a white crystalline solid: ^{1}H NMR ($CDCl_3$) δ 1.80 (p, 2 H, J = 7.5), 2.50 (t, 2 H, J = 7.5), 3.65 (t, 2H, J = 7.5), 5.03 (s, 2 H), 6.77 (d, 2 H, J = 8.2), 6.83 (s, 1 H), 7.47 (s, 1 H), 7.65 (d, 2 H, J = 8.2); MS (electrospray positive ion) $[M+H]^+$ = 343.

4-[5-(3-Chloropropyl)-1H-imidazol-1-yl)methyl]-1-iodobenzene monohydrochloride (10).

A solution of alcohol **9** (1.8 g, 5.3 mmol) in 50 mL of CH_2Cl_2 was treated with thionyl chloride (0.93 g, 7.8 mmol) dropwise at ambient temp. Immediately after

this addition, the mixture became cloudy, but reverted back to a clear solution within a few minutes with stirring at ambient temp. The solution was heated at reflux under nitrogen for 1.5 h, then cooled and the solvent removed to afford the crude product as a white solid. TLC analysis (9:1 CH_2Cl_2:methanol) showed clean conversion to product (Rf = 0.57). The crude product was suspended in CH_2Cl_2, and filtered, washed with CH_2Cl_2, and dried under vacuum at ambient temp for 3 h yielding 1.91 g of chloride **10** as a white crystalline solid: ^{1}H NMR (CD_3OD) δ 2.03 (tt, 2 H, J = 7.7, 6.2), 2.77 (t, 2 H, J = 7.7), 3.61 (t, 2H, J = 6.2), 5.43 (s, 2 H), 7.08 (d, 2 H, J = 9.8), 7.45 (s, 1 H), 7.80 (d, 2 H, J = 9.8), 8.94 (s, 1 H); ^{13}C NMR (CD_3OD) δ 21.8 (CH_2), 31.3 (CH_2), 44.4 (CH_2), 50.8 (CH_2), 95.4 (C-Cl), 118.6 (CH), 130.6 (2 C, CH), 134.9 (C), 135.8 (C), 136.9, (CH), 139.7 (2 C, CH); MS (electrospray positive ion) $[M+H]^+$ = 361, 363 (fragment pattern consistent with the presence of a single chlorine substituent).

4-(5,6,7,8-Tetrahydroimidazo[1,5-a]pyridin-5-yl)-1-iodobenzene (2b).

Triethylamine (0.32 mL, 2.3 mmol) was added to a suspension of **10** (0.65 g, 1.6 mmol) in THF (25 mL) at 20 °C and the resulting mixture was stirred at 20 °C for 1 h. The mixture was filtered and the filter cake washed with THF. After removing the solvent from the combined filtrate, the resulting white powder was dried for 18 h *in vacuo* at ambient temp affording 0.56 g of the free base of **10** as a white powder. To a solution of the free base of chloride **10** (0.56 g, 1.55 mmol) and TMEDA (0.39 g, 0.50 mL, 3.3 mmol) in THF (16 mL) at -78 °C was added Lithium diisopropylamide (1.65 mL of a 2.0 M solution in heptane/THF/ethylbenzene, 3.3 mmol) and the reaction was stirred at -78 °C for 6 h. MS analysis (electrospray positive ion, direct infusion) of a concentrated aliquote of the solution showed only the presence of product **2b** $(M+H)^+$ = 325 with none of chloride **10** remaining. The reaction was quenched at -78 °C by addition of 10 mL of saturated aqueous ammonium chloride solution and the volatile components were removed *in vacuo*. The resulting aqueous residue was extracted three times with CH_2Cl_2 and the combined organic layers dried over Na_2SO_4. Removal of the solvent afforded 0.562 g of crude **2b** as a yellow solid.

Purification of the crude product by flash chromatography on silica gel (95:5 CH_2Cl_2:methanol) yielded 0.466 g (1.44 mmol, 92%) of pure **2b** as a yellowish crystalline solid: ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 1 H), 1.94 (m, 2 H), 2.28 (m, 1 H), 2.85 (m, 2 H), 5.16 (dd, 1 H, J = 5, 5), 6.82 (d, 2 H, J = 8.4), 6.84 (s, 1 H), 7.14 (s, 1 H), 7.68 (d, 2 H, J = 8.4); ^{13}C NMR ($CDCl_3$) δ 18.7, 20.9, 33.0, 57.6, 93.4, 124.5, 128.2, 128.3 (2 C), 135.7, 137.9 (2 C), 141.7; MS (electrospray positive ion) $[M+H]^+$ = 325; IR (KBr) 3439, 2941, 2917, 2854, 1635, 1485, 1224, 1011, 813, 663 cm^{-1}.

4-(5,6,7,8-Tetrahydroimidazo[1,5-a]pyridin-5-yl)benzonitrile-[^{14}C]-cyano (1) ([^{14}C]Fadrozole free base). A mixture of iodide **2b** (0.050 g, 0.15 mmol), [^{14}C]KCN (0.015 g, 0.223 mmol, 12.7 mCi), KCN (0.005 g, 0.077 mmol), CuI (2.9 mg, 0.015 mmol), and $Pd(PPh_3)_4$ (8.7 mg, 0.0075 mmol) was placed under vacuum for 1 h. Anhydrous THF (5 mL) was degassed by gently bubbling nitrogen gas through the solvent for 15 min, and was then added to the mixture. The resulting mixture was heated at reflux under nitrogen for 18 h during which time a yellow precipitate formed. TLC analysis (5:5:90 NH_4OH:methanol:EtOAc) with UV and iodine visualization, showed good conversion of iodide **2b** (Rf = 0.43) to cyano substituted **1** (Rf = 0.32). The reaction mixture was cooled and filtered through a fritted funnel. Removal of the solvent gave 0.13 g of crude product. ^{1}H NMR analysis of the product mixture showed approximately 70-80% conversion of iodide **2b** to the cyanated product. Purification by flash chromatography on silica gel (5:5:90 NH_4OH:methanol:EtOAc) afforded 26.2 mg (4.94 mCi, 0.116 mmol, 39% radiochemical yield from [^{14}C]KCN, 77% chemical yield from iodide **2b**) of **1** with specific activity = 42.6 mCi/mmol. TLC analysis (as above) showed only one peak identical with with that of authentic Fadrozole free base. The same analysis with radioactivity detection showed radiochemical purity >99%: ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 1 H), 1.80 (m, 1 H), 1.95 (m, 1 H), 2.33 (m, 1 H), 2.88 (dd, 2 H, J = 6, 6), 5.25 (dd, 1 H, J = 7.1, 5.4), 6.75 (s, 1 H), 7.08 (d, 2 H, J = 8.3), 7.10 (s, 1 H), 7.58 (d, 2 H, J = 8.3) the spectral data was in agreement with those previously reported [10]; MS (electrospray positive ion) $[M+H]^+$ = 224, 226 with fragment intensities corresponding to the measured specific activity.

REFERENCES

1. Ellis G., Romney-Alexander T.M. *Chem. Rev., 87*: 779-794 (1987).
2. Allentoff A., Ciszewska G., Markus B., Pfefferkorn H., Ray T., Jones L., Duelfer T. *Synthesis and Applications of isotopically Labelled Compounds 1998*, John Wiley & Sons Ltd, 1999: 185-187.
3. Allen J., Parent, G., Rivron, L. *Synthesis and Applications of isotopically Labelled Compounds 1991*, John Wiley & Sons Ltd, 1992: 202-206.
4. Tschaen D.M., Desmond R., King A.O., Fortin M.C., Pipkin B., King S., Verhoeven T.R. *Synthetic Communications, 24*: 887-890 (1994).
5. Cable K.M., Wells, G.N., Sutherland D.R., *Journal of Labelled Compounds and Radiopharmaceuticals, 43* : 29-45 (2000)
6. Sekiya A., Ishikawa N. *Chemistry Letters*: 277-278 (1975).
7. SCRIP Database-AN: S00451342 950711
8. Markus B., Allentoff A.J., Desai M., Chaudhuri N.K., Duelfer T., *Journal of Labelled Compounds and Radiopharmaceuticals, 39* : 885-890 (1997).
9. Takagi K., Okamoto T., Sakakibara Y., Ohno A., Oka S., Hayama N., *Bulletin of the Chemical Society of Japan, 48*: 3298-3301 (1975).
10. Browne L.J., Gude C., Steele R.E., *J. Med. Chem. 34*: 725-736 (1991).
11. Yang S.H., Li C.S., Cheng C.H., *J. Org. Chem. 52*: 691-694 (1987).
12. Anderson B.A., Becke L.M., Booher R.N., Flaugh M.E., Harn N.K., Kress T.J., Varie D.L., Wepsiec J.P., *J. Org. Chem. 62*: 8634-8639 (1997).
13. Farina V., Kapadia S., Krishnan B., Wang C., Liebeskind L.S., *J. Org. Chem.59*: 5905-5911 (1994).

