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[5-^{14}C]-4-methyltriazolepyridines via facile preparation of methyl-[^{14}C]-isothiocyanate

Peter Ström* and Jonas Malmquist

A fast and convenient microwave assisted one-pot synthesis of methyl-[^{14}C]-isothiocyanate 4 was shown. The continued one-pot synthesis with 4 to a highly refined material like [5-^{14}C]-dimethylsulfanyltriazolepyridines 8 and 13 without any intermediate purification, six steps in the same pot from [^{14}C]KCN. Oxidation of the sulfur provided access to triazole-ethers upon reaction with alcohols. The triazole-ethers, 15, were obtained at fair to good yields and specific activities above 2 GBq/mmol.

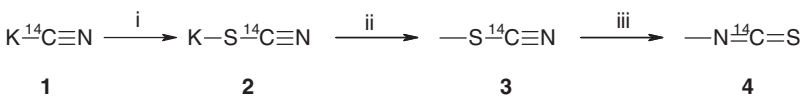
Keywords: [^{14}C]potassium thiocyanate; methyl-[^{14}C]-thiocyanate; methyl-[^{14}C]-isothiocyanate; [^{14}C]triazole; carbon-14

Introduction

With the objective to label a triazole-ring in a couple of triazolepyridine containing drug candidates, we started the labeling in the 2-position of the triazole. Labeling the carbonyl carbon of nicotinic acid or isonicotinic acid provided the right position. Starting from bromopyridine and [^{14}C]carbondioxide via nicotinic acid and niazide, proved to be tedious and time consuming. We repeated the labeling of the isomer in the 5-position. A key intermediate is methyl-[^{14}C]-isothiocyanate, 4. The use of 4 in radiolabeling synthesis is rather scarce according to the literature. The reagent is very powerful because the label will be obtained in the core of a heterocycle when it is applied appropriately in radiosynthesis. Anjanevulu *et al.* [1] and Maller *et al.* [2] prepared 4 in a rather tedious manner. A related reagent, *p*-chlorobenzyl-[^{14}C]isothiocyanate, was prepared and used by Esses-Reiter *et al.* [3] in labeling of a thiourea containing substance. They carefully adjusted the conditions for optimal isomerization. In this work we show a fast and convenient microwave assisted one-pot synthesis of 4. The continued one-pot synthesis with 4 to a highly refined materials like [5-^{14}C]-dimethylsulfanyltriazolepyridines 8 and 13 without any intermediate purification, i.e. six steps in the same pot from [^{14}C]potassium cyanide. Oxidation of the sulfur provided access to triazole-ethers upon reaction with alcohols. The final products were obtained at fair to good yields and high specific activities.

Results and discussions

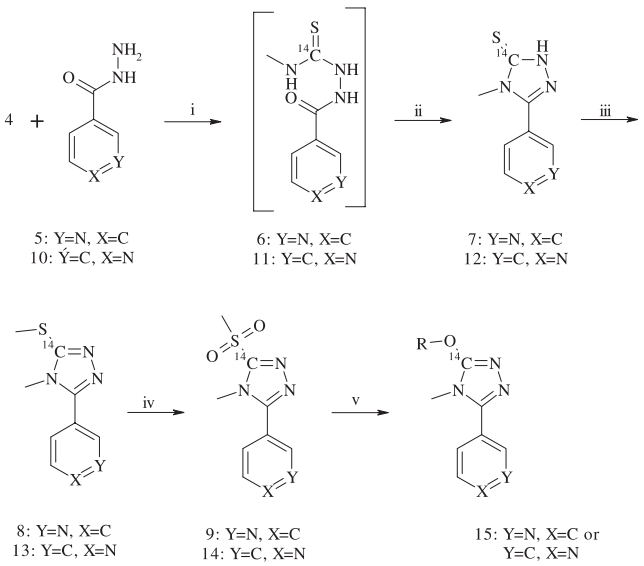
[^{14}C]Potassium cyanide 1 (Scheme 1) was mixed with one equivalent sulfur and heated at 110°C for 10 min in a microwave reactor. The mixture was concentrated in a stream of nitrogen. The crude [^{14}C]potassium thiocyanate 2 was methylated with iodomethane in dimethylformamide at 60°C for 10 min in a microwave reactor to obtain methyl-[^{14}C]thiocyanate 3. The reaction mixture of 3 was heated at 180°C for 10 min to rearrange 3 to methyl-[^{14}C]isothiocyanate 4. Nicotinohydrazide 5 (Scheme 2) was added and the mixture was again heated in a microwave reactor for 10 min at 100°C to obtain 6. To this mixture, sodium hydroxide was added and was then heated to 120°C for 10 min in a microwave reactor to obtain [3-^{14}C]triazole-pyridine 7. Iodomethane was added in order to methylate the sulfur. The mixture was heated for 10 min at 60°C in a microwave reactor, and after work-up, the methylated sulfanyltriazolepyridine 8 was isolated as a purple solid crystalline material. Oxidation of 8 with potassium permanganate in 50% acetic acid at room temperature for 1 h yielded sulfonyltriazolepyridine 9 in 76% from 1.



Scheme 1. (i) S_8, acetone, μ, 110°C, (ii) MeI, DMF, μ, 60°C, (iii) μ, 180°C.

AstraZeneca R&D Södertälje, Medicinal Chemistry, S-151 85 Södertälje, Sweden

**Correspondence to: Peter Ström, AstraZeneca R&D Södertälje, Medicinal Chemistry, S-151 85 Södertälje, Sweden.*
E-mail: peter.strom@astrazeneca.com



Scheme 2. (i) μ, 100°C, (ii) NaoH, μ, 130°C, (iii) MeI, μ, 60°C, (iv) $KMnO_4$, 50% AcOH, rt, (v) R—OH, Cs_2CO_3, DMF, 60°C.

Upon addition of iso-nicotinohydrazide 10 (Scheme 2) to a reaction mixture of 4 and heating the mixture to 100°C for 10 min in a microwave reactor, 11 was formed. To this mixture, sodium hydroxide was added and it was then heated to 120°C for 10 min in a microwave reactor to obtain [3-^{14}C]triazolepyridine 12. Iodomethane was added in order to methylate the sulfur. The mixture was heated for 10 min at 60°C in a microwave reactor, and after work-up the methylated sulfanyltriazolepyridine 13 was isolated as a purple solid crystalline material. Oxidation of 13 with potassium permanganate in 50% acetic acid at room temperature for 1 h yielded sulfonyltriazolepyridine 14 in 32% from 1.

Three different alcohols were alkylated with 9 or 14 in DMF at 60 °C using cesium carbonate as a base and conventional heating in an oil-bath. Microwaves did not improve the final alkylation step in this sequence. The final products, 15, were obtained in 5–20% overall yield from [^{14}C]potassium cyanide, with a specific activity above 2 GBq/mmol.

Experimental

General methods

All solvents used were analytical grade and commercially available. Anhydrous solvents were routinely used for reactions. Reactions were typically run under an inert atmosphere of nitrogen or argon.

Microwave reactions were performed in a Biotage Initiator Eight.

Mass spectra were recorded on a Waters LCMS consisting of an Alliance 2795 (LC), Waters PDA 2996, and ELS detector (Sedex 75) and a ZMD single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ES) operated in a positive or negative ion mode. The capillary voltage was 3 kV and cone voltage was 30 V. The mass spectrometer was scanned between *m/z* 100–600 with a scan time of 0.7 s. The column temperature was set to 40°C. The diode array detector was scanned from 200–400 nm. The temperature of the ELS detector was adjusted to 40°C and the pressure was set to 1.9 bar. For LC separation a linear gradient was applied starting at 100% A (A: 10 mM NH_4OAc in 5% MeCN) and ending at 100% B (B: MeCN) after 4 min. The column used was a X-Terra MS C8, 3.0 × 50; 3.5 μm (Waters) run at 1.0 mL/min.

HPLC analyses were performed on an Agilent HP1100 system consisting of a G1379A micro vacuum degasser, a G1312A Binary Pump, a G1367A well plate auto-sampler, a G1316A thermostatted column compartment and a G1315B diode array detector. The column used was a X-Terra MS, Waters (3.0 × 100 mm, 3.5 μm). The column temperature was set to 40°C and the flow rate to 1.0 mL/min. The diode array detector was scanned from 210–300 nm, step and peak width were set to 2 nm and 0.05 min, respectively. A linear gradient was applied, starting at 100% A (A: 10 mM NH_4OAc in 5% MeCN) and ending at 100% B (B: MeCN), in 6 min. Alternatively HPLC analyses were performed on a Agilent 1100, HPLC-system with a binary pump, auto-injector, DAD and column oven, coupled in series with a Packard Radiomatic Flow Scintillator 525TR, equipped with a solid scintillator (SolarScint) cell with a volume of 33 μL. The column used was a Xterra MS Waters(C8, 3 × 100 mm, 3 μm). The column temperature was set to 40°C and the flow rate to 0.5 mL/min. A linear gradient was applied, starting at 100% A (A: 0.1% TFA) and ending at 95% B (B: MeCN), in 12 min.

Liquid scintillation analysis was performed on a PACKARD TRI-CARB 2900TR. Thin layer chromatography (TLC) was performed on Merck TLC-plates (Silica gel 60 F254) and UV-light (254 nm) visualized the spots. Flash column chromatography was performed on Silica gel 60. Typical solvents used for flash column chromatography were mixture of dichloromethane, methanol, and ammonia.

*[^{14}C]potassium thiocyanate (**2**)*

[^{14}C]potassium cyanide (1, 50 mCi, 56.5 mCi/mmol, 59.1 mg, 0.88 mmol) and sulfur (30 mg, 0.94 mmol), in acetone (2 mL), were mixed in a microwave-vial (2–5 mL) and heated to 110°C for 10 min in a microwave reactor. The reaction was concentrated to dryness. The crude material was used in the next step as is.

*[^{14}C]methylthiocyanate (**3**)*

[^{14}C]potassium thiocyanate (2, 87 mg, 0.88 mmol) was mixed with iodomethane (0.065 mL, 1.04 mmol) in DMF (0.5 mL) in a microwave-vial (2–5 mL) and heated to 60°C in a microwave reactor for 10 min. The crude mixture was used in the next step as is.

*[^{14}C]methylisothiocyanate (**4**)*

[^{14}C]methylthiocyanate (3, 65.8 mg, 0.88 mmol) in DMF (0.5 mL) (reaction mixture from previous synthesis in a microwave-vial (2–5 mL)) was heated to 180°C in a microwave reactor for 10 min. The crude mixture was used in the next step as is.

*[3-^{14}C]-4-methyl-5-pyridin-3-yl-2,4-dihydro-[1,2,4]triazole-3-thione (**7**)*

Nicotinohydrazide (5, 120 mg, 0.88 mmol) was added to [^{14}C]methyl-iso-thiocyanate (4, 65.8 mg, 0.88 mmol) in DMF (0.5 mL) (reaction mixture from previous synthesis in a microwave-vial (2–5 mL)) and heated in a microwave reactor to 100°C for 10 min. Sodium hydroxide (500 μL, 1.00 mmol) was added

and the mixture was heated to 120°C in a microwave reactor for 10 min. The crude mixture of 7 was used in the next step as is. Unlabelled 7 was reported earlier by Singh *et al.* [4]

*[5-^{14}C]-3-(4-methyl-5-methylsulfanyl-4H-[1,2,4]triazol-3-yl)pyridine (**8**)*

Iodomethane (0.060 mL, 0.96 mmol) was added to [3-^{14}C]-4-methyl-5-pyridin-3-yl-2,4-dihydro-[1,2,4]triazole-3-thione (7, 170 mg, 0.88 mmol) in DMF (0.5 mL) and water (0.500 mL) (reaction mixture from previous synthesis in a microwave-vial (2–5 mL)) and heated to 60°C in a microwave reactor for 10 min. Water (3 mL) was added and the mixture was extracted with $CHCl_3$ (3 × 3 mL), dried over Na_2SO_4, filtered and concentrated to isolate 8 (101 mg, 0.48 mmol, 55.4%) as purple solid. Unlabelled 8 was reported earlier by Uda *et al.*[5]

*[5-^{14}C]-3-(5-methanesulfonyl-4-methyl-4H-[1,2,4]triazol-3-yl)pyridine (**9**)*

[5-^{14}C]-3-(4-methyl-5-methylsulfanyl-4H-[1,2,4]triazol-3-yl)pyridine (8, 101 mg, 0.48 mmol) was dissolved in acetic acid (1 mL) and water (1 mL). $KMnO_4$ (135 mg, 0.85 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated to 1/2 volume, NaOH (20% aq, 5 mL) was added and the mixture was extracted with $CHCl_3$ (3 × 3 mL), dried over Na_2SO_4, filtered and concentrated to isolate 9 (89 mg, 0.37 mmol, 76 %) as a pale yellow oil. LC/MS *m/z* 241 ($[M+1]^+$).

*[3-14C]-4-methyl-5-pyridin-4-yl-2,4-dihydro-[1,2,4]triazole-3-thione (**12**)*

Isonicotinohydrazide (10, 137 mg, 1.00 mmol) was reacted with [^{14}C]methylisothiocyanate (4, 75 mg, 1.00 mmol) as for the synthesis of 7. Unlabelled 12 was reported earlier by Brown *et al.*[6]

*[5-^{14}C]-3-(4-methyl-5-methylsulfanyl-4H-[1,2,4]triazol-4-yl)-pyridine (**13**)*

[3-^{14}C]-4-methyl-5-pyridin-4-yl-2,4-dihydro-[1,2,4]triazole-3-thione (12, 55 mg) was treated as for the synthesis of 8 to give 13 (96 mg). Unlabelled 13 was reported earlier by Kubota *et al.*[7]

*[5-^{14}C]-3-(5-methanesulfonyl-4-methyl-4H-[1,2,4]triazol-4-yl)-pyridine (**14**)*

[5-^{14}C]-3-(4-methyl-5-methylsulfanyl-4H-[1,2,4]triazol-4-yl)-pyridine (13, 96 mg, 0.46 mmol) was treated as for the synthesis of 9 to give 14 (77 mg, 0.32 mmol, 70 %). LC/MS *m/z* 241 ($[M+1]^+$).

Conclusions

Six consecutive microwave-assisted synthesis steps with no intermediate purification were shown to be an efficient method for the preparation and labeling of highly refined triazoles.

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