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Synthesis of 2-(methylsulfonyl)-5-(4-(methylsulfonyl) phenyl)-4-phenyl-1H-[5-^{14}C] imidazole, a selective COX-2 inhibitor, via asymmetrical benzoins

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4,5-Diarylimidazoles labeled with carbon-14 in the 5-position of the imidazole ring were prepared as a part of three-step sequence from 2-hydroxy-1-(4-(methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone as a key synthetic intermediate which has been synthesized from potassium [^{14}C]cyanide.

Keywords: 4,5-diarylimidazole; asymmetrical benzoins; selective COX-2 inhibitors; carbon-14

Introduction

Extensive studies have been conducted on selective cyclooxygenase (COX-2) inhibitors in the past 10 years.[1–8] COX inhibitors can reduce pain and inflammatory markers. Aspirin, indomethacin, celecoxib and many other COX inhibitors have been extensively used as anti-inflammation drugs.[9] COX-1 and COX-2 are two types of COX enzymes differing only in the amino acid at position 523. In COX-2, valine has been identified as 523rd amino acid that was substituted by isoleucine in the COX-1 structure. Therefore, the smaller size of valine 523 allows access to the hydrophobic pocket easily for COX-2 selective compounds. Selective COX-2 inhibitors such as celecoxib could be designed based on the consideration of the different active sites of the two subtypes of the COX enzymes.[10] Gastrointestinal side effects were recognized as major side effect of traditional non-steroidal anti-inflammatory drugs such as aspirin, indomethacin, diclofenac and many others that have been categorized as non-selective COX inhibitors (NSAIDs). This important side effect limits the long usage of NSAIDs in chronic inflammation disease.[9]

The overall host–guest interactions of selective inhibitors such as 4,5-diarylimidazoles consist of hydrogen bond formation and van der waals forces.[11] These stereoelectronic interactions can be affected by electron-withdrawing and electron-donating groups.[12] A common base structural motif of the most COX-2 selective inhibitors consists of two aryl groups linked to adjoining atoms of a central ring, which can be homocyclic or heterocyclic.[13–16] One of the aryl groups is substituted in the para position with an aminosulfonyl (SO_2NH_2) or a methylsulfonyl (SO_2CH_3) group. There are also examples of potent COX-2 inhibitors that possess cycloalkyl, alkoxy or phenoxy moieties in the non-sulfonyl containing 'aryl' region. Thiophene, pyrazole, furanone, isoxazole and cyclopentene are commonly used as central rings in this class of molecules which exemplified by celecoxib (Celebrex).[17–19]

The design and synthesis of new cyclooxygenase inhibitors are currently under investigation in order to find safer lead compounds. Unfortunately, these compounds are associated with adverse cardiovascular effects such as myocardial infarction, thrombosis and cardiac dysfunction. The most plausible reason for this effect is the suppression of COX-2 dependent prostacyclin which mediates platelet activation and atherogenesis.[11] Therefore, the search for a novel, structurally different and better pharmacodynamic profile of selective COX-2 inhibitors devoid of the noted side effects is still an ongoing need for anti-inflammatory therapy. Some diaryl-heterocycles bearing a 6-alkylthio substituted lactone (pyrane-2-one) in the central ring have been reported to possess good selectivity toward COX-2[15]. 3-Alkylthio-4,5-diaryl-1,2,4-triazole[14] and some 2-alkylthio substituted 1,5-diaryl-imidazole analogs[13] also represent good COX-2 selectivity and anti-inflammatory effects.

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[§] *This paper is dedicated to memory of Dr. Nader Saemian.*

Some 4,5-diaryl-imidazoles bearing a sulfonyl methyl pharmacophore on one of the adjacent phenyl rings and also containing a 2-alkylthio or 2-sulfonylalkyl on the imidazole ring were synthesized with the aim of investigating the effect of these groups on COX selectivity and potency.[20–22]

To further clarify the mechanism of action and to augment the on-going inhibitor studies, there is growing need to synthesize the corresponding carbon-14 compounds with the label situated in a biologically stable site. In this paper we present a convenient synthetic pathway for the synthesis of a series of 2-alkylthio or 2-sulfonylalkyl substituted aromatics on the imidazole ring labeled with carbon-14 via 2-hydroxy-1-(4-(methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone **1** as a key synthetic intermediate which has been synthesized as part of a 4-step sequence from barium [^{14}C]carbonate (Figure 1).

Result and discussion

The route to [^{14}C] **12** is shown in scheme 1. Barium [^{14}C]carbonate **2** was converted to potassium [^{14}C]cyanide **3** under standard conditions. Benzyl [cyano-^{14}C] cyanide **5** was derived from reaction of benzyl chloride **4** and potassium [^{14}C]cyanide **3** in dry acetone and sodium iodide in good yield.[24–26] The product **5** was hydrolyzed under acidic conditions to 2-phenyl[1-^{14}C] acetic acid **6**.[27–30] By reaction between methyl phenyl sulfide **7** and **6** in the presence of phosphoric acid and trifluoroacetic anhydride produced compound 1-(4-(methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone **8**.[20,21,31–33] Compound **8** was treated with bromine in acetic acid as solvent to give 2-bromo-1-(4-(methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone **9**.[34–40] Then 2-hydroxy-1-(4-(methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone **1** was produced via the reaction between **9** and sodium methoxide in methanol.[21,41–45] Conversion of **1** to 4-(4-(methylthio)phenyl)-5-phenyl-1,3-dihydro-2H-[4-^{14}C]imidazole-2-thione **10** was accomplished in the presence of excess ammonium thiocyanate in *n*-butanol as a solvent.[22] 2-(Methylthio)-5-(4-(methylthio)phenyl)-4-phenyl-1H-[5-^{14}C]imidazole **11** was produced via the reaction between **10** and methyl iodide in the presence of triethylamine and methanol under refluxing conditions. The last compound, 2-(methylsulfonyl)-5-(4-(methylsulfonyl)phenyl)-4-phenyl-1H-[5-^{14}C]imidazole **12**, was synthesized by oxidation of **11** with oxone in methanol and THF at 0 °C.[15]

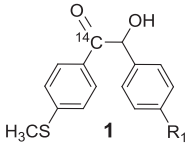


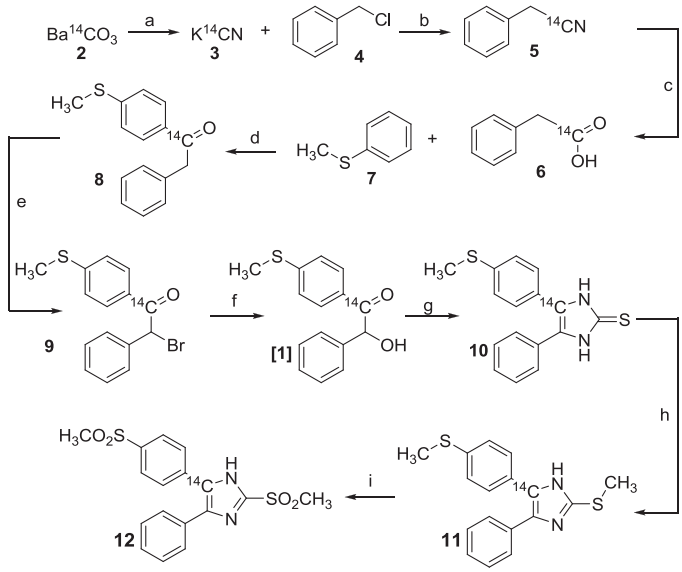
Figure 1. The key synthetic intermediate 1 for ^{14}C-labeling of adjacent aryl groups on imidazole ring.

Experimental

Barium [^{14}C]carbonate (235.9 MBq/mmol) was converted to potassium [^{14}C]cyanide according to the standard procedure.[23] ^{1}H-NMR spectra were recorded on Bruker AVANCE 500 spectrometer. The IR spectra were taken using Nicolet FT-IR Magna 550 spectrographs (KBr disks).

2-Phenyl[1-^{14}C]acetic acid 6

In a 10-mL round-bottomed flask, fitted with a reflux condenser capped by a drying tube, were placed dried benzyl chloride (1 g, 7.94 mmol), potassium [^{14}C]cyanide (318 MBq, 228 mg, 3.4 mmol), sodium iodide (74.4 mg) and dry acetone (4 mL). The mixture was heated at reflux temperature for 20 h. After cooling to room temperature, the reaction mixture was filtered and the filter cake washed with acetone. Then the filtered mixture was evaporated, and oily residue was dissolved in 50-mL ethyl acetate and the later solution was washed twice with 30 mL water. The solution was dried over anhydrous sodium sulfate and dried *in vacuo*. The crude benzyl cyanide, which was prepared from last step, was added to a solution of concentrated sulfuric acid (0.3 mL), glacial acetic acid (0.3 mL) and H_2O (0.3 mL). The mixture was refluxed for 45 min, then water was added to the mixture. Ethyl acetate was added to the mixture and the organic layer was separated, dried over sodium sulfate and the residue was purified by silica gel chromatography using ethyl acetate: hexane (50%) as eluent to give the title compound **6** (199 mg, 135 MBq) in 42% radiochemical yield. ^{1}H-NMR ($CDCl_3$, TMS) δ(ppm): 7.23–7.38 (m, 5H, ArH); 3.64 (s, 2H).



Scheme 1. a) According to the standard procedure[23]; b) NaI, acetone; c) H_2SO_4, reflux; d) H_3PO_4, $(CF_3CO)_2O$, 25 °C; e) Br_2, acetic acid; f) CH_3ONa, CH_3OH, reflux; g) NH_4SCN, *n*-Butanol, reflux; h) CH_3I, Et_3N, CH_3OH, reflux; i) Oxone (potassium peroxymonosulfate), $CH_3OH/THF/H_2O$, 0 °C.

1-(4-(Methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone 8

Trifluoroacetic anhydride (5.62 mmol, 0.8 mL) was added to the mixture of phenyl acetic acid (192 mg, 130 MBq), methyl phenyl sulfide (1.68 mmol, 0.2 mL) and orthophosphoric acid (1.68 mmol, 0.8 mL) rapidly with vigorous stirring at room temperature, and the mixture was stirred for one extra minute and poured into 10-mL ice-cold water with stirring. Then it was washed with cold hexane(2 × 2 mL) to obtain title compound **8** as solid. The radiochemical yield (204 mg, 78 MBq) was 60%. ^{1}H NMR ($CDCl_3$) δ(ppm): 7.84(d, J = 9 Hz, 2H,ArH),7.274–7.150(m, 7H, ArH), 4.164 (s, 2H, CH_2), 2.434 (s, 3H, SCH_3).

2-Bromo-1-(4-(methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone 9

1-(4-(Methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone **8** (157 mg, 60 MBq) and unlabeled 8 (553 mg) were mixed carefully and added to acetic acid (3.31 mL) in a round bottom flask fitted with a reflux condenser. Bromine (0.13 mL) was added to acetic acid (1.1 mL), and this solution was added gradually to flask within 1 h. The mixture was stirred at room temperature for 24 h, and the title compound was purified by silica gel column chromatography and ethyl acetate: *n*-hexane (20:80) as eluent. Radiochemical yield (750 mg, 48 MBq) was 80% (20.6 MBq/mmol); ^{1}HNMR ($CDCl_3$) δ(ppm): 7.833–7.816 (two, dd, 2H, J_1 = 8Hz, J_2 = 1Hz, ArH); 7.458–7.442 (two, dd, 2H, J_1 = 8Hz, J_2 = 1Hz, ArH); 7.319–7.149 (m, 5H, ArH); 6.265 (s, 1H, CHBr); 2.432 (s, 3H, SCH_3).

4-(4-(Methylthio)phenyl)-5-phenyl-1,3-dihydro-2H-[4-^{14}C] imidazole-2-thione-10

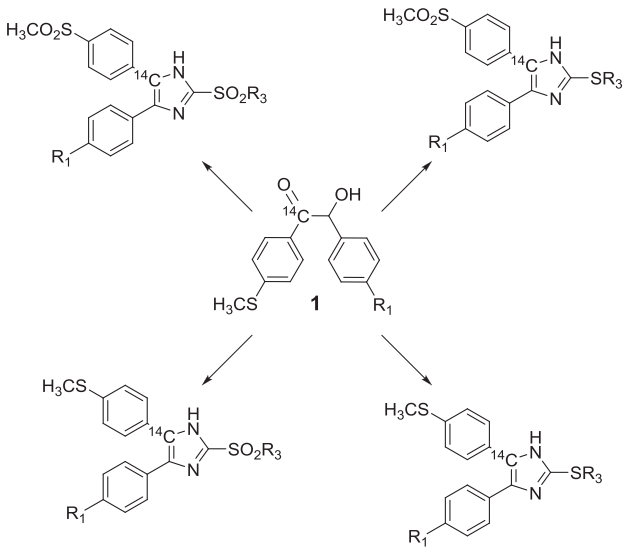
Sodium (117 mg) was added to dry methanol (2.1 mL) and mixed until solid particles had dissolved. 2-Bromo-1-(4-(methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone **9** (548 mg, 35 MBq) was poured into the sodium methoxide solution, and 4 mL of dry methanol was added to the mixture. The mixture was stirred under reflux for 2 h. Then the mixture was poured into water and neutralized with cold 5% hydrochloric acid. Organic compounds were extracted with ethyl acetate and dried over sodium sulfate. The ethyl acetate was evaporated under reduced pressure. The oily residue, which contained 2-hydroxy-1-(4-(methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone **1**, was used for the next reaction directly. The mixture of crude product **1** and NH_4SCN (1.289 g) and *n*-butanol (4.5 mL) was refluxed for 2 h. Then water was added to the mixture, and crude title compound **10** was extracted with ethyl acetate. The extracted crude product was purified with silica gel column chromatography and ethyl acetate:*n*-hexane (20:80) as eluent. Overall radiochemical yields (233 mg, 16 MBq) of two steps were 46%. ^{1}HNMR ($CDCl_3$) δ(ppm): 2.526 (s, 3H, SCH_3); 7.28(d, 2H, J = 8Hz, 3,5-methyl sulfide phenyl); 7.3 (m, 3H, 3,4,5-phenyl); 7.41(d, 2H, J = 8Hz, 2,6-methyl sulfide phenyl); 7.539 (b, 2H, 2,6-phenyl).

2-(Methylthio)-5-(4-(methylthio)phenyl)-4-phenyl-1H-[5-^{14}C] imidazole 11

Compound **10** (144 mg, 0.484 mmol, 10 MBq), methyl iodide (138 mg, 0.968 mmol), methanol (23.3 mL) and triethyl amine (100 μL) were mixed and refluxed for 1 h. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography by using ethylacetate:hexane (20:80) as eluent to give the title compound **11** (113 mg, 7.5 MBq) in 75% yield. ^{1}HNMR ($CDCl_3$) δ(ppm): 2.503 (s, 3H, SCH_3, 4-(methylthio)phenyl); 2.720 (s, 3H, SCH_3, 2-methylthio); 7.226–7.258 (m, 4H, ArH); 7.308–7.368 (m, 3H, ArH); 7.539–7.585 (m, 2H, ArH).

2-(Methylsulfonyl)-5-(4-(methylsulfonyl)phenyl)-4-phenyl-1H-[5-^{14}C]imidazole 12

To a stirred solution of Oxone (0.5 g) in water (10 mL), a solution of compound 11 (60 mg, 4 MBq) in methanol (1.2 mL) and THF (0.6 mL) was slowly added. The mixture was refluxed overnight, and the residue was concentrated under reduced pressure and extracted with ethyl acetate. Further purification was carried out by silica gel column chromatography using ethyl acetate:hexane (80:20) as eluent. The radiochemical yield of title compound **12** was 89% (65 mg, 3.56 MBq), and the overall radiochemical yield from K^{14}CN was 6.3%. ^{1}HNMR ($CDCl_3$) δ(ppm): 3.095 (s, 3H, SO_2CH_3, 4-(methylsulfonyl)phenyl); 3.442 (s, 3H, SO_2CH_3, 2-methylsulfonyl); 7.460–7.521 (m, 3H, ArH); 7.624–7.641 (m, 2H, ArH); 7.84(d, 2H, J = 8Hz, 3,5-(methylsulfonyl)phenyl); 7.96 (d, 2H, J = 8Hz, 2,6-(methylsulfonyl)phenyl).



Scheme 2. Convenient synthetic pathway for labeling of a series of 4,5-diarylimidazole with carbon-14.

Conclusion

In this paper, we have presented a convenient synthetic pathway for labeling of a series of 4,5-diarylimidazole with carbon-14 in the 5-position of imidazole moiety by using 2-hydroxy-1-(4-(methylthio)phenyl)-2-phenyl[1-^{14}C]ethanone **1,** an asymmetrical benzoin as a key synthetic intermediate as shown in Scheme 2.

This article is dedicated to the memory of Dr. Nader Saemian

The late doctor NADER SAEMIAN supervisor of the project passed away before this plan was completed. We would like to express our deep condolence over shocking news of his death as he was one of the best friends of ours during all these years. We will all miss him because of his great supports given to current project and also for very good moments we had together during research activities. We still cannot believe that he is not among us anymore.

He was the greatest encouragement and a supportive mentor whom we had ever seen in our entire life. His friendship, kindness and knowledge are the main reasons which made us to stand at this point. We will cherish all the happy memories we had with him and hope his soul may rest in peace.

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