A Facile Synthetic Approach to Labeled 4-Acetoxy-2-(4-methylphenyl)benzothiazole

Noriyuki HORI,*[a] Norihiko SEKO,[b] Goro TSUKAMOTO,[c] and Kohichiro YOSHINO[a]

Kanebo Institute for Cancer Research,[a] New Drug Research Laboratories,[b] and Pharmaceuticals Research Center,[c] Kanebo, Ltd., 5–90, Tomobuchi-cho 1-chome, Miyakojima-ku, Osaka 534, Japan.

Received November 10, 1995; accepted February 9, 1996

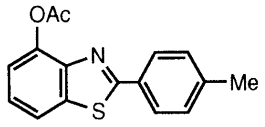
To study the pharmacokinetics and metabolism of 4-acetoxy-2-(4-methylphenyl)benzothiazole (KB-2683), which has potential immunomodulating activity, a practical preparation of labeled KB-2683 was needed. This paper describes an efficient method for the synthesis of ^{14}C-labeled KB-2683 by means of procedures which include a metal-catalyzed cross-coupling reaction.

Key words 4-acetoxy-2-(4-methylphenyl)benzothiazole; cross-coupling reaction; isotopic label; Grignard reagent; zinc chloride

Recently, we found a novel antiarthritic agent, 4-acetoxy-2-(4-methylphenyl)benzothiazole (KB-2683), which was characterized by immunomodulating activity without antiinflammatory activity, being distinct from non-steroidal antiinflammatory drugs (NSAIDs).[1] KB-2683 was selected as a candidate therapeutic agent for rheumatoid arthritis (RA).

Investigation of the pharmacokinetic profile is important for the development of drugs, and is greatly simplified if a suitably labeled derivative is available. In this paper, we describe a method for the preparation of ^{14}C-labeled KB-2683, as well as its application to the synthesis of 4-hydroxy-2-(4-methyl-d_3-phenyl)benzothiazole, the deacetyl derivative of KB-2683.

Selective cross-coupling reactions catalyzed by transition metal complexes are one of most effective methods of carbon–carbon bond formation.[2] We used such a cross-coupling reaction to achieve a practical synthesis of labeled KB-2683, in which a ^{14}C-label can be incorporated in the final step to reduce cost and improve safety. The synthetic strategy is shown in Chart 1. The key precursor **6** for the cross-coupling reaction was prepared as follows. Condensation of *p*-bromobenzoyl chloride, which was prepared from *p*-bromobenzoic acid and excess thionyl chloride in the presence of a catalytic amount of *N*,*N*-dimethylformamide (DMF), with *o*-anisidine in pyridine–tetrahydrofuran (THF) gave the amide **2** in 84% yield. Treatment of **2** with phosphorus pentasulfide in pyridine gave the thioamide **3** in 73% yield. Oxidative cyclization of **3** with $K_3Fe(CN)_6$ in aqueous KOH solution afforded the benzothiazole **4**,[3] which was then demethyl-



KB-2683

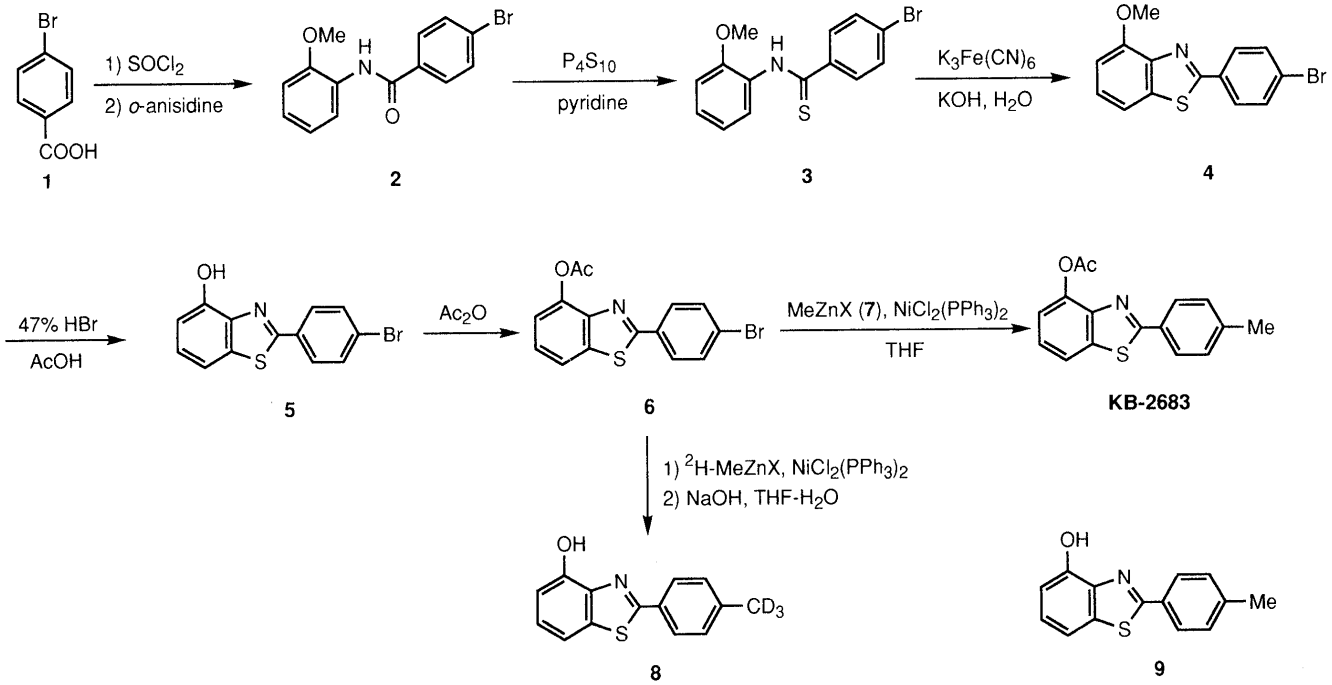


Chart 1

* To whom correspondence should be addressed.

ated with 47% HBr to give the hydroxy compound **5** in good yield (97%).[4] Compound **5** was acetylated by refluxing in Ac_2O to give the acetyl compound **6**. Finally, we examined the cross-coupling reaction of **6** with methyl-zinc reagent (**7**) using non-labeled methyl iodide. When the bromo compound **6** was treated in THF with methyl-zinc salt (**7**), which was prepared by transmetalation of methyl Grignard reagent with zinc chloride in THF, in the presence of 10 mol% of $NiCl_2(PPh_3)_2$, the coupling reaction proceeded at room temperature to give KB-2683 in 17% yield. The reaction produced a mixture of the desired product, the starting compound (**6**), and the deacetylated compounds (**5**, **9**). Purification by recrystallization to remove these minor by-products afforded a low yield of KB-2683.

This cross-coupling reaction was applied to the synthesis of 4-hydroxy-2-(4-methyl-d_3-phenyl)benzothiazole (**8**). The bromide (**6**) was treated with methyl-d_3-zinc reagent according to above method to give D_3-KB-2683. After work-up, the crude coupling product was hydrolyzed with KOH in THF–H_2O to give the desired compound **8** in good yield.

In conclusion, we have developed a practical and inexpensive synthetic method for KB-2683 by the cross-coupling reaction of the bromo compound (**6**) with methyl-zinc reagent in the presence of a Ni(II) catalyst. Use of [^{14}C]methyl iodide in the final step would provide easy access of labeled KB-2683. This method was also applied to the preparation of deacetylated D_3-KB-2683 in excellent yield.

Experimental

Melting points were determined on a Yamato MP-21 melting point apparatus without correction. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were determined on Bruker AM300 spectrometers with tetramethylsilane as an internal standard.

4-Bromo-2′-methoxybenzanilide (2) A catalytic amount of DMF (0.5 ml) was added to a mixture of *p*-bromobenzoic acid (50.5 g, 0.251 mol) and thionyl chloride (80 ml). After refluxing for 3 h, the excess thionyl chloride was removed *in vacuo*. The residue was dissolved in THF (40 ml) and added dropwise to a solution of *o*-anisidine (30.9 g, 0.251 mol) in pyridine (190 ml) at 0—5 °C. After having been stirred at room temperature for 1 h, the reaction mixture was poured into water (2.5 l). The precipitate was collected by filtration, washed with water, dried, and recrystallized from ethanol to give **2** (64.5 g, 84%): mp 138.0—139.5 °C. NMR ($CDCl_3$) δ: 3.93 (3H, s), 6.93 (1H, dd), 7.00—7.15 (2H, m), 7.60—7.65 (2H, m), 7.75—7.80 (2H, m), 8.40—8.60 (2H, m). *Anal.* Calcd for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.58. Found: C, 54.83; H, 4.07; N, 4.55.

4-Bromo-2′-methoxybenzothioanilide (3) A solution of **2** (64.2 g, 0.210 mmol) in pyridine (150 ml) was added to a suspension of phosphorus pentasulfide (18.7 g, 42.1 mmol) in pyridine (100 ml). The resulting mixture was refluxed for 1 h, then cooled to 90 °C, and poured into water (2 l). The suspension was stirred at room temperature for 2 h. The precipitate was collected by filtration, washed with water, dried, and recrystallized from ethanol to give **3** (49.6 g, 73%): mp 121.5—124.5 °C. NMR ($CDCl_3$) δ: 3.92 (3H, s), 6.97 (1H, d), 7.05 (1H, dd), 7.23 (1H, d), 7.56 (2H, d), 7.72 (2H, d), 9.10 (1H, d), 9.59 (1H, br s). *Anal.* Calcd for $C_{14}H_{12}BrNOS$: C, 52.19; H, 3.75; N, 4.35. Found: C, 52.12; H, 3.87; N, 4.29.

4-Methoxy-2-(4-bromophenyl)benzothiazole (4) A solution of KOH (40.2 g, 0.616 mol) in water (100 ml) was added dropwise over 1 h to a suspension of **3** (49.6 g, 0.154 mol) and potassium ferricyanide (102 g, 0.310 mol) in water (800 ml) under reflux. Refluxing was continued for 2 h, then the reaction mixture was cooled to room temperature under stirring. The precipitate was collected by filtration, washed with water, dried, and dissolved in ethyl acetate (1 l). To this solution was added 10% HCl (360 ml), and the mixture was stirred at room temperature for 2 h. The organic layer was separated, washed with aqueous $NaHCO_3$ solution, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was recrystallized from ethanol to give **4** (25.2 g, 51%): mp 125.0—126.5 °C. NMR ($CDCl_3$) δ: 4.08 (3H, s), 6.93 (1H, dd), 7.34 (1H, dd), 7.47 (1H, dd), 7.55—7.65 (2H, m), 7.95—8.05 (2H, m). *Anal.* Calcd for $C_{14}H_{10}BrNOS$: C, 52.51; H, 3.15; N, 4.37. Found : C, 52.50; H, 3.35; N, 4.31.

4-Hydroxy-2-(4-bromophenyl)benzothiazole (5) A solution of **4** (25.2 g, 78.8 mmol) in acetic acid (100 ml) was treated with 47% HBr (300 ml). The mixture was refluxed for 46 h, and cooled to room temperature. The precipitate was collected by filtration, washed with water, dried, and suspended in water (500 ml). The suspension was neutralized with 10% NaOH solution. The precipitate was collected by filtration, washed with water, and dried to give crude **5** (23.5 g, 97%). Recrystallization from acetonitrile produced pure **5**: mp 167.0—168.0 °C. NMR (DMSO-d_6) δ: 6.95 (1H, dd), 7.30 (1H, dd), 7.52 (1H, dd), 7.75—7.85 (2H, m), 7.95—8.05 (2H, m), 10.29 (1H, br s). *Anal.* Calcd for $C_{13}H_8BrNOS$: C, 51.00; H, 2.63; N, 4.57. Found : C, 50.92; H, 2.87; N, 4.55.

4-Acetoxy-2-(4-bromophenyl)benzothiazole (6) A mixture of **5** (21.4 g, 69.9 mmol) and acetic anhydride (60 ml) was refluxed for 1.7 h. The reaction mixture was evaporated *in vacuo*. The residue was taken up in cyclohexane (100 ml), and the suspension was stirred at room temperature for 30 min. The precipitate was collected by filtration, washed with cyclohexane, dried, and recrystallized from ethyl acetate to give **6** (19.9 g, 82%): mp 117.5—118.5 °C. NMR ($CDCl_3$) δ: 2.48 (3H, s), 7.21 (1H, dd), 7.38 (1H, dd), 7.55—7.65 (2H, m), 7.74 (1H, dd), 7.85—7.95 (2H, m). *Anal.* Calcd for $C_{15}H_{10}BrNO_2S$: C, 51.73; H, 2.89; N, 4.02. Found: C, 51.62; H, 3.11; N, 3.98.

4-Acetoxy-2-(4-methylphenyl)benzothiazole (KB-2683) A solution of methylmagnesium iodide in dry diethyl ether, which was prepared from methyl iodide (0.39 ml, 6.31 mmol) with Mg (153 mg), was added to a mixture of dry zinc chloride (1.17 g, 8.61 mmol), which had been dried by fusion *in vacuo*, and dry THF (4 ml) in an ice bath under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h, then a solution of **6** (1.0 g, 2.87 mmol) in dry THF (3 ml) was added and the whole was cooled in an ice bath. $NiCl_2(PPh_3)_2$[5] (188 mg, 0.287 mmol) was added and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with diethyl ether (60 ml) and water (60 ml). The aqueous layer was extracted with diethyl ether. The combined ether fractions were dried over magnesium sulfate and evaporated *in vacuo*. The residue was recrystallized from ethyl acetate to give 4-acetoxy-2-(4-methylphenyl)benzothiazole (134 mg, 17%): mp 110.0—113.0 °C. NMR ($CDCl_3$) δ: 2.42 (3H, s), 2.48 (3H, s), 7.20 (1H, dd), 7.28 (2H, d), 7.36 (1H, dd), 7.76 (1H, dd), 7.96 (2H, d).

4-Hydroxy-2-(4-methyl-d_3-phenyl)benzothiazole (8) A solution of methyl-d_3-magnesium chloride in dry diethyl ether, which was prepared from magnesium (461 mg) and methyl iodide-d_3 (1.2 ml, 19.0 mmol) was added to a solution of 1 M zinc chloride solution (25.9 ml) (Aldrich) and dry THF (9 ml) in an ice bath under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h, then a solution of **6** (3.0 g, 8.62 mmol) in dry THF (18 ml) was added, followed by addition of $NiCl_2(PPh_3)_2$ in an ice bath. The resulting mixture was stirred at room temperature for 38 h. Then water (200 ml) was added to it in an ice bath and the whole was extracted with ethyl acetate (×3). The extract was dried over magnesium sulfate and evaporated *in vacuo*. The residue was dissolved in THF (10 ml), and a solution of NaOH (3.4 g, 86.2 mmol) in water (30 ml) was added. The resulting mixture was refluxed for 1.5 h, then diluted with water, and washed once with diethyl ether. The aqueous layer was separated and acidified with concentrated HCl. The precipitate was collected by filtration, washed with water, and dried to give a crude product. This was purified by chromatography on silica gel ($CHCl_3$) and recrystallization from benzene to give **8** (1.4 g, 67%): mp 162.0—165.0 °C. NMR ($CDCl_3$) δ: 6.8—7.4 (1H br), 6.97 (1H, dd), 7.15-7.30 (3H, m), 7.37 (1H, dd), 7.90 (2H, d). *Anal.* Calcd for $C_{14}H_8D_3NOS$: C, 69.25; H, 4.59; N, 5.77. Found: C, 69.15; H, 4.68; N, 5.69.

References

1) Hori N., Tsukamoto G., Imamura A., Ohashi M., Saito T., Yoshino K., *Chem. Pharm. Bull.*, **40**, 2387 (1992).
2) Tamao K., "Comprehensive Organic Synthesis," Vol. 3, ed. by Trost B. M., Fleming I., Pergamon Press, Oxford, 1991, pp. 435—480.
3) Hurd R. N., DeLaMater G., *Chem. Rev.*, **61**, 45 (1961).
4) Bhatt M. V., Kulkarni S. U., *Synthesis*, **1983**, 249.
5) Cotton F. A., Faut O. D., Goodgame D. M. L., *J. Am. Chem. Soc.*, **83**, 344 (1961).