Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 2 July 2007, Revised 20 August 2007, Accepted 17 October 2007 Published online 14 January 2008 in Wiley Interscience

(www.interscience.wiley.com) DOI: 10.1002/jlcr.1477

Synthesis of [^{14}C]-, [$^{13}C_4$]-, and [$^{13}C_4$, $^{15}N_2$]-5-amino-4-iodopyrimidine

Bachir Latli,[a]* Paul-James Jones,[b] Dhileepkumar Krishnamurthy,[a] and Chris H. Senanayake[a]

5-Amino-4-iodopyrimidine labeled with either carbon-14 or with the stable isotopes carbon-13 and nitrogen-15 was prepared starting from commercially available labeled diethylmalonate and formamide. This compound is a useful intermediate for carbon–nitrogen and carbon–carbon bond formations.

Keywords: carbon-14; carbon-13; nitrogen-15; radiosynthesis; pyrimidines

Introduction

Pyrimidines are among the most important heterocyclic compounds.[1] They are ubiquitous in nature. The pyrimidine moiety is an important pharmacophore, and interest in pyrimidine derivatives as potential drugs is well documented. These derivatives are used in the treatment of AIDS, as antibiotics, antifungals, anthelmentics, antitubercular drugs, cardiac agents, analgesics and NSAID and as metabolic electrolytes.[2] Substituted pyrimidines are known to posses antimalarial activities. Recently, a substituted pyrimidine was found to be a potent inhibitor of a methionine aminopeptidase enzyme, a novel molecular target for the treatment of malaria.[3] The synthesis of pyrimidine and their derivatives has been extensively reviewed.[4] In general, pyrimidines are usually prepared from formamidines or from amidinium salts. Formamidine is hygroscopic and its salts, either the hydrochloride or the acetate is often used.[5] Formamide, usually used as a solvent in organic syntheses, is a better substitute.[6] We are very surprised to find that this reagent is not used as often in the synthesis of pyrimidines. Here, we describe the synthesis of 5-amino-4-iodopyrimidine labeled either with carbon-14 or with stable isotopes C-13 and N-15, see Scheme 1 Synthesis of substituted pyrimidines: (a) NaOEt, EtOH, 110°C; (b) HNO_3, 0–25°C; (c) $POCl_3$, $C_6H_5N(CH_3)_2$, reflux; (d) $SnCl_2 \cdot 2H_2O$, EtOH, reflux; (e) HI 40 wt% H_2O, NaI, 25°C; (f) *i*-PrMgCl, THF, NH_4Cl, HCl (6N), −50°C to −20°C; and (g) HCO_2NH_4, MeOH, 10% Pd/C. This reagent is useful in introducing radioactive or stable isotopes on drug candidates containing pyrimidines via carbon–nitrogen or carbon–carbon bond forming reactions.

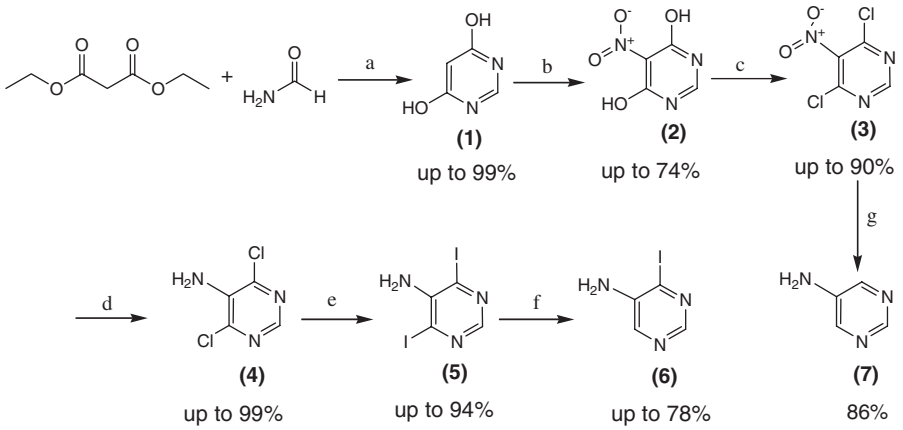
Results and Discussion

Dihydroxypyrimidine is prepared by the condensation of formamidine salts and dialkylmalonate.[5] Labeled formamidine is not available commercially. Literature search showed that dihydroxypyrimidine can be prepared from the condensation of dimethylmalonate and formamide in the presence of suspension of sodium methoxide in methanol. The condensation was run in an autoclave at 95°C with 2.1–2.24 equivalent of formamide and 3.3 equivalent of sodium methoxide. The yields ranged from 84 to 91%.[6] We found that the use of an autoclave is not necessary. This condensation can be achieved at 90–110°C in a sealed tube or in a flask fitted with a condenser. Thus, to prepare 5-amino-4-iodopyrimidine, diethylmalonate was condensed with formamide in a solution of sodium ethoxide in ethanol at 110°C to give 4,6-dihydroxypyrimidine (1) in yields ranging from 82 to 99%. Nitration of this material with 90% nitric acid gave 4,6-dihydroxy-5-nitropyrimidine (2) in up to 74% yield.[7,8] Conversion of 4,6-dihydroxy-5-nitropyrimidine to the dichloro derivative (3) was accomplished by heating it to reflux in phosphorus oxychloride in the presence of *N,N*-dimethylaniline in yields ranging from 82 to 90%.[9,10] Reduction of the nitro group using tin chloride in refluxing ethanol gave 5-amino-4,6-dichloropyrimidine (4) in 83–99% yields.[11] This derivative was either transformed to 5-aminopyrimidine (7) using ammonium formate and 10% palladium on carbon in methanol in 86% yield, or converted to 5-amino-4,6-diiodopyrimidine (5) in an aqueous solution of hydroiodic acid and sodium iodide in 82–94% yields.[12] Removal of one iodine was accomplished using a procedure similar to the one described by Knochel and coworkers.[13] The 5-amino-4-iodopyrimidine (6) was obtained in yields up to 78% when using 2.1 equivalent of isopropyl magnesium chloride in THF. This route was applied to the synthesis of [5-^{14}C]-5-amino-4-iodopyrimidine with a resulting

[a]*Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Research and Development Center, 900 Ridgebury Road, Ridgefield, CT 06877, USA*

[b]*Department of Analytical Sciences, Boehringer Ingelheim Pharmaceuticals, Research and Development Center, 900 Ridgebury Road, Ridgefield, CT 06877, USA*

**Correspondence to: Bachir Latli, Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Research and Development Center, 900 Ridgebury Road, Ridgefield, CT 06877, USA.*
E-mail: blatli@rdg.boehringer-ingelheim.com



Scheme 1

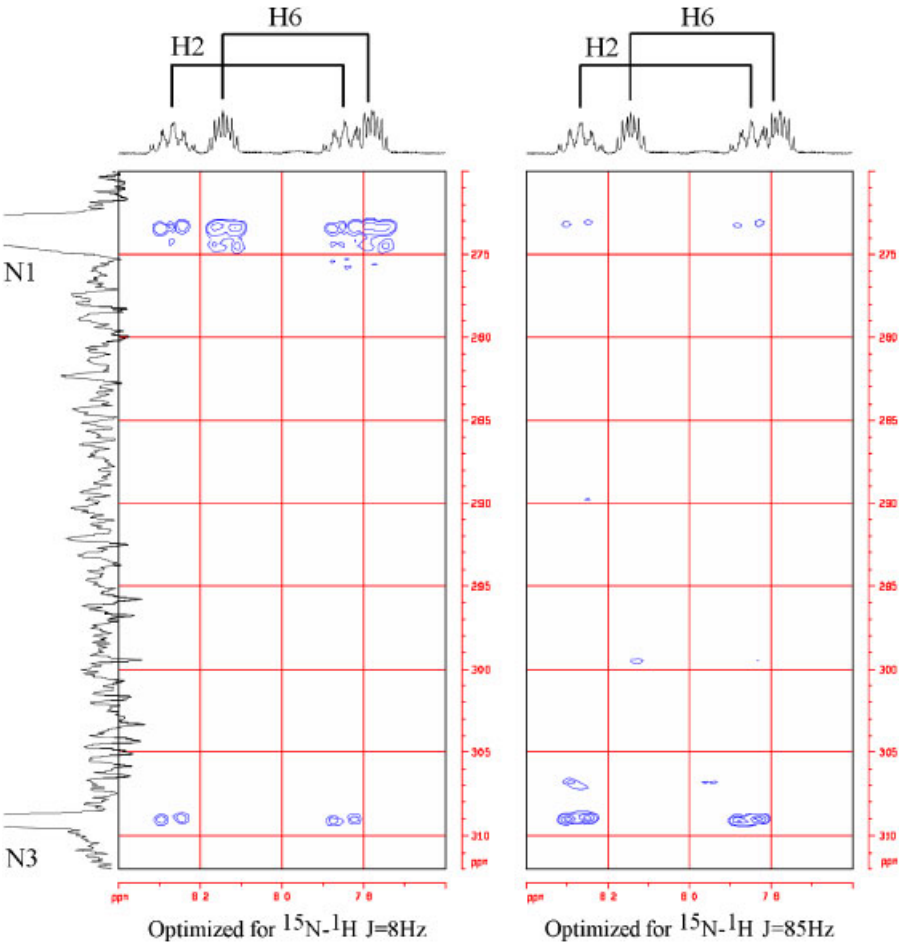


Figure 1. ^{15}N-^{1}H HMQC data from [$^{13}C_4$, $^{15}N_2$]-5-amino-4-iodopyrimidine, optimized for two different ^{15}N–^{1}H coupling constants. These data were used to assign the ^{15}N signals and to estimate the relative magnitudes of the ^{1}J ^{15}N–^{1}H couplings for [$^{13}C_4$, $^{15}N_2$]-(6); these couplings could not be observed directly because of broad signals in the directly detected 1D-^{15}N spectra, and complex multiplet patterns in the directly detected 1D-^{1}H spectra. From the HMQC data, we determine that ^{1}J ^{15}N(3)-^{1}H(2) >> ^{1}J ^{15}N(1)-^{1}H(2) > ^{1}J ^{15}N(1)–^{1}H(6). This figure is available in color online at www.interscience.wiley.com/journal/jlcr.

specific activity of 48.54 mCi/mmol (1.8 GBq/mmol), and in 21% radiochemical yield over a six-step synthesis starting from diethyl-[2-^{14}C]-malonate. The preparation [$^{13}C_4$]-5-amino-4-iodopyrimidine and [$^{13}C_4$, $^{15}N_2$]-5-amino-4-iodopyrimidine was also accomplished using diethylmalonate (1,2,3-$^{13}C_3$, min 99 atom% ^{13}C) and formamide (^{13}C, min 99 atom% ^{13}C) or formamide (^{13}C, ^{15}N, min 99 atom% ^{13}C, min 99 atom% ^{15}N), respectively. See Figure 1 for ^{15}N-^{1}H HMQC data from [$^{13}C_4$, $^{15}N_2$]-(6).

Experimental Procedures

Materials and Methods

Liquid scintillation counting was accomplished using a Beckman LS5000TA and ready safe™ cocktail (Beckman, Fullerton, CA). Mass spectra for non-radioactive compounds were acquired by a Hewlett-Packard auto sampler Series 1100, connected to a

Micromass Platform LCZ in the electron spray positive ion mode using 95–5% water/acetonitrile gradient (0.1% formic acid) for 3 min, and a SunFire™ C_{18}, 3.5 mm (4.6 × 30 μm) column. NMR spectra were recorded with a Bruker-Biospin DPX-400 spectrometer operating at 400.13 MHz ^{1}H frequency and at 100.66 MHz for ^{13}C using deuterated chloroform as a solvent and tetramethyl silane as the internal standard unless stated otherwise. Pre-coated TLC sheets (silica gel 60 F_{254}) were obtained from EM Science (Gibbstown, NJ) Purification was carried out using Combi-Flash Companion (Isco, Inc. Lincoln, NE) and RediSep™ (Isco, Inc. Lincoln, NE). Formamide (^{13}C, min 99 atom% ^{13}C), formamide (^{13}C, ^{15}N, min 99 atom% ^{13}C, min 99 atom% ^{15}N) and diethylmalonate ((1,2,3-$^{13}C_3$, 99 atom% ^{13}C) were purchased from *ISOTEC* (St. Louis, MO). Diethyl[2-^{14}C]malonate (specific activity of 54 mCi/mmol) was purchased from ViTrax (Placentia, CA). The rest of the reagents were purchased from Aldrich Chemical Company.

Synthesis

Synthesis of 5-Amino-4-Iodopyrimidine

4,6-Dihydroxypyrimidine (1): To a mixture of formamide (0.5 mL, 11.25 mmol) and a solution of sodium ethoxide in ethanol (21 wt%, 6.2 mL, 16.5 mmol) was added diethylmalonate (0.76 mL, 5 mmol) in a 1 h period at 65–70°C. After the addition was complete, the mixture was heated to 110°C and stirred for 48 h. After cooling to room temperature, most of the ethanol was removed under reduced pressure and the residue was treated with concentrated aqueous HCl (1.16 mL) and water (1.8 mL) at 0°C. The resulting precipitate was filtered, washed with cold water and dried under reduced pressure to give 460 mg of an off-white solid in 82% yield. ^{1}H NMR (d_6-DMSO) δ: 8.01(s, 1H), 5.22(s, 1H). ^{13}C NMR (d_6-DMSO) δ: 166.20, 149.95, 90.01. LC-MS: $MH^+ = 117.32$ runs with the solvent front.

4,6-Dihydroxy-5-nitropyrimidine (2): The above compound (0.561 g, 5 mmol) was added in small portions to a solution of nitric acid (90%, 2 mL) at 0°C in a 1 h period. Stirring was continued for 90 min at 0°C, followed by warming to room temperature and stirring for 2 h. The resulting mixture was poured into crushed ice (100 mL) and the solid was filtered and washed with water. The solid was further dried under reduced pressure at 40°C to give 580 mg of a pink solid in 74% yield. ^{1}H NMR (d_6-DMSO) δ: 8.75(s, 1H), 3.55(brs, 2H). ^{13}C NMR (d_6-DMSO) δ: 155.05, 150.46, 119.50. The spectra were identical to an Aldrich sample.

4,6-Dichloro-5-nitropyrimidine (3): To a solution of $POCl_3$ (5 mL) was added the above material (785.45 mg, 5 mmol) in one portion, followed by *N,N*-dimethylaniline (1 mL). The resulting mixture was heated to reflux for 2 h. After cooling to room temperature, the dark mixture was concentrated under reduced pressure and then poured into water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to a dark viscous oil. Purification by flash chromatography using methylene chloride as eluent gave 0.8 g of a pale yellow solid in 82% yield. $R_f = 0.6$ in 100% CH_2Cl_2. ^{1}H NMR ($CDCl_3$) δ: 8.91(s, 1H). ^{13}C NMR ($CDCl_3$) δ: 157.73, 152.95, 143.01.

5-Amino-4,6-dichloropyrimidine (4): A mixture of the above compound (1.0 g, 5.15 mmol) and tin chloride dihydrate (5.64 g, 25 mmol) in ethanol (10 mL) was refluxed for 1 h. The resulting yellow solution was cooled to room temperature and then poured into crushed ice (35 g). Solid sodium bicarbonate was added slowly until pH = 8 and the mixture was extracted with ethyl acetate (3 × 200 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 0.86 g of a white solid in 99% yield. ^{1}H NMR ($CDCl_3$) δ: 8.21(s, 1H), 4.50(brs, 2H). ^{13}C NMR ($CDCl_3$) δ: 143.59, 141.79, 133.45.

5-Amino-4,6-diiodopyrimidine (5): The above compound (656 mg, 4 mmol) was added in one portion to solution of HI in water (40%, 19 mL), followed by NaI (3 g, 20 mmol). The mixture was stirred for 48 h then poured into water and extracted with methylene chloride (200 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (2 × 150 mL), a saturated solution of $Na_2S_2O_3$ (100 mL), brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on RediSep™ column (40 g) and using 1–5% MeOH/CH_2Cl_2 gave 1.31 g of a cream-colored solid in 94% yield. ^{1}H NMR ($CDCl_3$) δ: 7.90(s, 1H), 4.62(brs, 2H). ^{13}C NMR ($CDCl_3$) δ: 147.97, 144.96, 113.22. LC-MS-ES$^+$: $R_t = 1.04$, $MH^+ = 349.99$ (100%).

5-Amino-4-iodopyrimidine (6): To a solution of the above material (347 mg, 1 mmol) in dry THF (2 mL) was added a solution of isopropyl magnesium chloride (2.0 M in THF, 1.1 mL) dropwise at −30°C under nitrogen in a 5 min period. The resulting dark mixture was stirred at −25 to −20°C for 45 mins before the reaction was quenched with a saturated solution of NH_4Cl, followed by aqueous HCl (6 N, 1 mL). The solution was treated with a saturated solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 250 mg of an orange solid. Purification by Combi-Falsh chromatography using 40 g RediSep™ and 5–50% EtOAc/CH_2Cl_2 to elute the product, 150 mg, $R_f = 0.44$ in 10% MeOH/CH_2Cl_2 and 100 mg of starting material ^{1}H NMR ($CDCl_3$) δ: 8.27(s, 1H), 7.99(s, 1H), 4.15(brs, 2H). ^{13}C NMR ($CDCl_3$) δ: 148.71, 143.05, 139.92, 123.97. LC-MS-ES$^+$: $R_t = 0.46$ min, $MH^+ = 222.15$ (100%).

5-Aminopyrimidine (7): To a mixture of 5-amino-4,6-dichloropyrimidine (10 g, 61 mmol), ammonium formate (20 g, 317 mmol) in methanol (110 mL) was added Pd/C (10%, 1.22 g) (the mixture becomes exothermic). An ice-bath was used to cool the reaction. After stirring at 0°C for 30 min, the ice-bath was removed and the mixture was stirred at room temperature for 14 h. The mixture was filtered through a short pad of Celite® 545 and concentrated under reduced pressure. The residue was dissolved in water (200 mL) and extracted with ethyl acetate (3 × 100 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The pure product was isolated by crystallization from methanol/ethyl acetate to give 5.0 g of a white solid in 86% yield. ^{1}H NMR ($CDCl_3$) δ: 8.44(s, 1H), 8.09(s, 2H), 3.82(brs, 2H). ^{13}C NMR ($CDCl_3$) δ: 147.94, 142.42, 141.66. LC-MS-ES$^+$: $R_t = 0.22$ min, $MH^+ = 96.42$ (100%).

Synthesis of [5-^{14}C]-5-Amino-4-Iodopyrimidine

4,6-Dihydroxy[5-^{14}C]pyrimidine ([^{14}C]-(1)): To a mixture of formamide (1 mL, 25 mmol) and a solution of sodium ethoxide in ethanol (21 wt%, 12 mL, 40.17 mmol) was added diethyl[2-^{14}C]malonate (500 mCi, SA = 54 mCi/mmol, 9.25 mmol) in a 1 h period at 65–70°C. After the addition was complete, the mixture was heated to 110°C and stirred for 14 h. Work up as seen before and drying under reduced pressure at 40°C gave 1.45 g of an orange solid. Total activity was 496 mCi or 99.34%

radiochemical yield. The product was used as it is in the next step.

4,6-Dihydroxy-5-nitro[5-^{14}C]pyrimidine ([^{14}C]-(2)): Prepared from the above compound (1.45 g, 496 mCi) and nitric acid (90%, 5 mL) to obtain 646 mg of an off-white solid in 39% yield. Total activity was 193 mCi. The product was used as it is in the next step.

4,6-Dichloro-5-nitro[5-^{14}C]pyrimidine ([^{14}C]-(3)): Obtained as described before from $POCl_3$ (3.77 mL) and the above material (592 mg, 3.77 mmol) to give after purification by Combi-Flash Companion using 40 g RediSep^{TM} column and methylene chloride as eluent, 611 mg of a pale yellow solid in 86% radiochemical yield (151.43 mCi). The product was used as it is in the next step.

5-Amino-4,6-dichloro[5-^{14}C]pyrimidine ([^{14}C]-(4)): Prepared from the above compound (151.43 mCi) and tin(II) chloride dihydrate (3.48 g, 15.42 mmol) in ethanol (20 mL). The product was isolated in 99% radiochemical yield, or 518 mg of a white solid, 149.70 mCi. The product was used as it is in the next step.

5-Amino-4,6-diiodo[5-^{14}C]pyrimidine ([^{14}C]-(5)): The above compound (500 mg, 3.04 mmol), HI in water (40%, 17 mL) and NaI (2.3 g, 15.33 mmol) were reacted as described before. The usual work up and purification by Combi-Flash chromatography on RediSep^{TM} column (40 g) and using 1–5% MeOH/CH_2Cl_2 gave 867 mg of a cream-colored solid (121.726 mCi) in 82% radiochemical yield. The product was used as it is in the next step.

5-Amino-4-iodo[5-^{14}C]pyrimidine ([^{14}C]-(6)): To solution of the above material (0.86 g, 2.48 mmol, 121.7 mCi) in dry THF (5 mL) was added a solution of isopropyl magnesium chloride (2.0 M in THF, 2.5 mL) as described before. After the work up, the ethyl acetate extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 0.528 g of an orange solid. Purification by Combi-Falsh chromatography using 40 g RediSep^{TM} and 0–50% EtOAc/CH_2Cl_2 gave 435 mg of the desired product with more than 95% radiopurity. A total of 95.15 mCi of material was obtained in 78% radiochemical yield. 5.6 mCi of 5-amino[5-^{14}C]-pyrimidine was also isolated as a by-product.

Synthesis of [$^{13}C_4$]-5-Aminopyrimidine

[$^{13}C_4$]-4,6-Dihydroxypyrimidine ([$^{13}C_4$]-(1)): To a mixture of formamide (^{13}C, 99 atom% ^{13}C, 0.6 mL, 16.27 mmol) and a solution of sodium ethoxide in ethanol (21wt%, 12 mL, 32.14 mmol) was added diethylmalonate (1,2,3-$^{13}C_3$, 99 atom% ^{13}C, 1 mL, 5.81 mmol) in a 1 h period at 65–70°C. After the addition was complete, the mixture was heated to 110°C and stirred for 48 h. After the work up and treatment with concentrated aqueous HCl (2.5 mL) at 0°C, the resulting precipitate was filtered and dried under reduced pressure to give 675 mg of an off-white solid. ^{1}H NMR (d_6-DMSO) δ: 12.92(brs, 2H), 8.01(dt, $J_{^{13}C-^1H}$ = 203.45, 9.67 Hz, 1H), 5.22(d, $J_{^{13}C-^1H}$ = 165.94 Hz, 1H). ^{13}C NMR (d_6-DMSO) δ: 166.17(d, J = 71.79 Hz), 149.96, 89.99 (t, J = 71.79 Hz). LC-MS-ES$^+$: MH^+ = 117.32 runs with the solvent front.

[$^{13}C_4$]-4,6-Dihydroxy-5-nitropyrimidine ([$^{13}C_4$]-(2)): Nitration of the above compound (0.7 g, 6.03 mmol) was accomplished with a solution of nitric acid (90%, 2.4 mL) at 0°C in a 1 h period. The product 686 mg was isolated as a pink solid in 70% yield. ^{1}H NMR (d_6-DMSO) δ: 8.75(dt, $J_{^{13}C-^1H}$ = 206.53, 7.99 Hz, 1H), 4.02(brs, 2H). ^{13}C NMR (d_6-DMSO) δ: 155.04(d, J = 84.73 Hz), 150.46, 119.45(t, J = 84.73 Hz). LC-MS-ES$^+$: R_t = 0.19, MH^+ = 162.32 (100).

[$^{13}C_4$]-4,6-Dichloro-5-nitropyrimidine ([$^{13}C_4$]-(3)): $POCl_3$ (3.1 mL) was added to the above material (0.5 g, 3.1 mmol) in one portion, followed by *N,N*-dimethylaniline (0.62 mL). The usual work up and purification by flash chromatography using methylene chloride as eluent gave 0.55 g of a pale yellow solid in 90% yield. R_f = 0.6 in 100% CH_2Cl_2. ^{1}H NMR ($CDCl_3$) δ: 8.85(dt, $J_{^{13}C-^1H}$ = 215.70, 13.22 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 152.72, 153.02(d, J = 79.16 Hz), 143.02(t, J = 79.16 Hz). LC-MS-ES$^+$: R_t = 1.32, MH^+ = 199.31 (100%).

[$^{13}C_4$]-5-Amino-4,6-dichloropyrimidine ([$^{13}C_4$]-(4)): Obtained as before from the above compound (1.0 g, 5.05 mmol) and tin chloride dihydrate (5.7 g, 25.0 mmol) in ethanol (20 mL). The usual work up gave 880 mg of a white solid. ^{1}H NMR ($CDCl_3$) δ: 8.14(dt, $J_{^{13}C-^1H}$ = 213.27, 13.22 Hz, 1H), 4.45(brs, 2H). ^{13}C NMR ($CDCl_3$) δ: 146.03(m), 144.24(d, J = 70.65 Hz), 135.84(t, J = 70.65 Hz). LC-MS-ES$^+$: R_t = 0.65, MH^+ = 168.18 (100%).

[$^{13}C_4$]-5-Amino-4,6-diiodopyrimidine ([$^{13}C_4$]-(5)): Prepared from the above compound (0.85 g, 5.05 mmol), HI in water (40%, 15 mL) and NaI (3.7 g, 10.5 mmol). The usual work up and purification of the residue by flash chromatography on RediSep^{TM} column (40 g) and using 1–5% MeOH/CH_2Cl_2 gave 1.6 g of a cream-colored solid in 90% yield. ^{1}H NMR ($CDCl_3$) δ: 7.29(dt, $J_{^{13}C-^1H}$ = 213.47, 12.88 Hz, 1H), 4.55(brs, 2H). ^{13}C NMR ($CDCl_3$) δ: 147.02(dt, J = 14.02, 8.98 Hz), 144.94(td, J = 14.02, 63.10 Hz), 113.25(dd, J = 8.98, 63.10 Hz). LC-MS-ES$^+$: R_t = 1.02, MH^+ = 352.09 (100%).

[$^{13}C_4$]-5-Amino-4-iodopyrimidine ([$^{13}C_4$]-(6)): Prepared from the above material (0.565 g, 1.61 mmol) in dry THF (5 mL) and isopropyl magnesium chloride (2.0 M in THF, 2 mL). The usual work up gave 0.4 g of an orange solid. Purification by Combi-Falsh chromatography using 40 g RediSep^{TM} and 5–50% EtOAc/CH_2Cl_2 to elute the product, 168 mg or 46%, R_f = 0.4 in 10% MeOH/CH_2Cl_2. The by-product 5-aminopyrimidine (7) was eluted using 10–20% MeOH/CH_2Cl_2 to give 60 mg of a yellow solid in 38% yield, R_f = 0.15 in 10% MeOH/CH_2Cl_2. LC-MS-ES$^+$: MH^+ = 225.99 (for the desired product) and 99.10 for (7). ^{1}H NMR ($CDCl_3$) δ: 8.19(ddd, $J_{^{13}C-^1H}$ = 209.52, 12.01, 10.21 Hz, 1H), 7.91(ddt, $J_{^{13}C-^1H}$ = 180.10, 11.80, 6.57 Hz, 1H), 4.14(brs, 2H). ^{13}C NMR ($CDCl_3$) δ: 148.63(quintet, J = 7.95 Hz), 143.50(ddd, J = 15.76, 58.26, 63.87 Hz), 139.91(dd, J = 7.27, 58.26 Hz), 118.50(dd, J = 8.22, 63.87 Hz). LC-MS-ES$^+$: R_t = 4.92, MH^+ = 225.99 (100%).

Synthesis of [$^{13}C_4$, $^{15}N_2$]-5-Amino-4-Iodopyrimidine

[$^{13}C_4$, $^{15}N_2$]-4,6-Dihydroxypyrimidine ([$^{13}C_4$, $^{15}N_2$]-(1)): Formamide (^{13}C, ^{15}N, min 99 atom% ^{13}C, min 99 atom% ^{15}N, 1.058 g, 22.51 mmol), a solution of sodium ethoxide in ethanol (21wt%, 12.4 mL, 33.21 mmol), and diethylmalonate ((1,2,3-$^{13}C_3$, 99 atom% ^{13}C, 1.76 mL, 10.0 mmol) gave 842 mg of an off-white solid in 71.35% yield. ^{1}H NMR (d_6-DMSO) δ: 12.01(brs, 2H), 8.01(dquintet, $J_{^{13}C-^1H}$ = 203.30, 9.50 Hz, 1H), 5.23(d, $J_{^{13}C-^1H}$ = 165.89 Hz, 1H). ^{13}C NMR (d_6-DMSO) δ: 166.5(m), 150.08, 90.8(m). LC-MS-ES$^+$: R_t = 0.21 min, MH^+ = 119.72 (100%)

[$^{13}C_4$, $^{15}N_2$]-4,6-Dihydroxy-5-nitropyrimidine ([$^{13}C_4$, $^{15}N_2$]-(2)): The above compound (0.84 g, 7.11 mmol) and a solution of nitric acid (90%, 3 mL) gave 550 mg of a pink solid in 47.4% yield. ^{1}H NMR (d_6-DMSO) δ: 13.28(brs, 2H), 8.76(m, $J_{^{13}C-^1H}$ = 206.47, 4.02 Hz, 1H). ^{13}C NMR (d_6-DMSO) δ: 155.64(dd, J = 86.62, 9.01 Hz), 150.80(t, J = 14.06 Hz), 119.85(m). LC-MS-ES$^+$: R_t = 0.36 min, MH^+ = 164.50 (100%).

[$^{13}C_4$, $^{15}N_2$]-4,6-Dichloro-5-nitropyrimidine ([$^{13}C_4$, $^{15}N_2$]-(3)): $POCl_3$ (3.31 mL), the above material (0.54 g, 3.31 mmol) and

N,N-dimethylaniline (0.66 mL) gave 560 mg of a pale yellow solid in 83% yield after flash chromatography, $R_f = 0.6$ in 100% CH_2Cl_2. ^1H NMR ($CDCl_3$) δ: 8.92(m, $J_{^{13}C-^1H} = 215.66$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 157.5–157.9(m), 153.01(m), 143.03(m). LC-MS-ES$^+$: $R_t = 1.43$, $MH^+ = 201.33$ (100%).

[$^{13}C_4$, $^{15}N_2$]-5-Amino-4,6-dichloropyrimidine ([$^{13}C_4$, $^{15}N_2$]-(4)): The above compound (0.56 g, 2.74 mmol) and tin chloride dihydrate (3.1 g, 13.72 mmol) in ethanol (20 mL) gave 492 mg of an off-white solid. ^1H NMR ($CDCl_3$) δ: 8.20(m, $J_{^{13}C-^1H} = 213.40$ Hz, 1H), 4.55(brs, 2H). ^{13}C NMR ($CDCl_3$) δ: 145.27(m), 144.04(m), 135.89(m). LC-MS-ES$^+$: $R_t = 0.83$, $MH^+ = 170.40$ (100%).

[$^{13}C_4$, $^{15}N_2$]-5-Amino-4,6-diiodopyrimidine ([$^{13}C_4$, $^{15}N_2$]-(5)): The above compound (0.466 g, 2.74 mmol), a solution of HI in water (47%, 14 mL) and NaI (2.05 g, 13.66 mmol) gave 0.8 g of an off-white solid in 83% yield. After purification by flash chromatography on RediSep^{TM} column (40 g) and using 5–10% EtOAc/CH_2Cl_2 ^1H NMR ($CDCl_3$) δ: 7.89(m, $J_{^{13}C-^1H} = 213.40$ Hz, 1H), 4.62(brs, 2H). ^{13}C NMR ($CDCl_3$) δ: 147.21–148.10(m), 144.38–145.63(m), 112.83–113.58(m). LC-MS-ES$^+$: $R_t = 1.15$ min, $MH^+ = 355.80$ (100%).

[$^{13}C_4$, $^{15}N_2$]-5-Amino-4-iodopyrimidine ([$^{13}C_4$, $^{15}N_2$]-(6)): To a solution of the above material (0.456 g, 1.28 mmol) in dry THF (5 mL) and a solution of isopropyl magnesium chloride (2.0 M in THF, 1.3 mL, 2.26 mmol) gave 0.35 g of an orange solid. Purification by Combi-Falsh chromatography using 40 g RediSep^{TM} and 5–50% EtOAc/CH_2Cl_2 gave 205 mg of an orange solid in 70% yield. ^1H NMR ($CDCl_3$) δ: 8.26(m, $J_{^{13}C-^1H} = 209.58$ Hz, 1H), 7.99($J_{^{13}C-^1H} = 180.53$ Hz, 1H), 4.54(brs, 2H). ^{13}C NMR ($CDCl_3$) δ: 148.64–148.80(m), 142.77–144.15(m), 139.56–140.24(m), 118.13–118.89(m). ^{15}N NMR (Bruker-Biospin DRX500; [500.13 MHz ^1H frequency] in methanol-d_4) δ: 309.1 (brd), 273.6 (brs); ^{15}N shifts referenced via lock frequency, see Figure 1. LC-MS-ES$^+$: $R_t = 0.89$, $MH^+ = 228.12$ (100%).

Conclusion

5-Amino-4-iodopyrimidine-labeled pyrimidine is a useful reagent in carbon–nitrogen and carbon–carbon bond formation. It was prepared starting from the commercially available carbon-13- and nitrogen-15-labeled formaldehyde and carbon-13- or carbon-14-labeled diethylmalonate. The syntheses were straightforward and enabled us to introduce the pyrimidine moiety in several drug candidates needed for drug metabolism and pharmacokinetic studies.

Acknowledgement

We thank our colleague Zhulin Tan for sharing details on the transformation of 5-amino-4,6-diiodopyrimidine to 5-amino-4-iodopyrimidine.

References

[1] I. M. Lagoja, *Chem. Biodiversity.* **2005**, *2*, 1–50.
[2] K. S. Jain, T. S. Chitre, P. B. Miniyar, M. K. Kathiravan, V. S. Bendre, V. S. Veer, S. R. Shahane, C. J. Shishoo, *Curr. Sci.* **2006**, *90*, 793–803.
[3] X. Chen, C. R. Chong, L. Shi, T. Yoshimoto, D. J. Sullivan Jr, J. O. Liu, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 14548–14553.
[4] D. J. Brow, R. F. Evans, W. B. Cowden, M. D. Fenn, in *Chemistry of Heterocyclic Compounds*, Vol. 52, Wiley, New York, **1994**.
[5] G. W. Kenner, B. Lythgoe, A. R. Todd, A. Topham, *J. Chem. Soc.* **1943**, 388–390.
[6] A. Hunds, German Patent DE 19640756 A1, **1998**.
[7] N. Baindur, N. Chadha, M. R. Player, *Comb. Chem.* **2003**, *5*, 653–659.
[8] C. Parkanyi, H. L. Yuan, M-K. M. Tsai, *J. Heterocyclic Chem.* **1991**, *28*, 465–467
[9] W. R. Boon, W. G. M. Jones, G. R. Ramage, *J. Chem. Soc.* **1951**, 96–102.
[10] G. S. Hanan, U. S. Schubert, D. Volkmer, E. Riviere, J-M. Lehn, N. Kyritsakas, J. Fischer, *Can. J. Chem.* **1997**, *75*, 169–182.
[11] J. Béres, G. Sági, E. Baitz-Gács, I. Töemöesköezi, L. Öetvöes, *Tetrahedron* **1998**, *44*, 6207–6216.
[12] A. Gomtsyan, S. Didomenico, C-H. Lee, M. A. Matulenko, K. Kim, E. A. Kowaluk, C. T. Wismer, J. Mikusa, H. Yu, K. Kohlhaas, M. F. Jarvis, S. S. Bhagwat, *J. Med. Chem.* **2002**, *45*, 3639–3648.
[13] G. Varchi, C. Kofink, D. M. Lindsay, A. Ricci, P. Knochel, *Chem. Commun.* **2003**, *3*, 396–397.