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Improved Synthesis of 2,2′-Bipyrimidine

Gábor Vlád and István T. Horváth*

Department of Chemical Technology and Environmental Chemistry, Eötvös University, Pázmány Péter sétány 1/A, H-1117 Budapest, Hungary

istvan.t.horvath@hit-team.net

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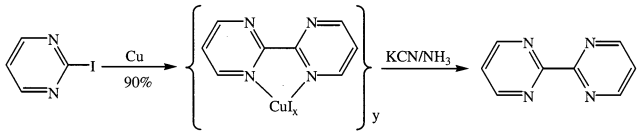
Abstract: A high-yield synthesis was developed for the preparation of 2,2′-bipyrimidine (**1**) using the Ullmann coupling of 2-iodopyrimidine. The new procedure was also used for the preparation of 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine (**2**) and 5,5′-dibromo-2,2′-bipyrimidine (**3**).

2,2′-Bipyrimidine (**1**) has been used as a ligand in inorganic and organometallic chemistry[1] and exhibits a remarkable stability in acidic medium. Periana has shown that the (2,2′-bipyrimidine)PtX_2 (X = Cl,[1b] OSO_3H) complexes are extremely stable in *oleum* during the catalytic functionalization of methane at 180 °C.[2] Since the reproducibility of the published procedures[3−5] for the synthesis of 2,2′-bipyrimidine was rather low, we have developed a high-yield synthesis using the Ullmann coupling of 2-iodopyrimidine. In addition, the new procedure was used for the preparation of 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine (**2**) and 5,5′-dibromo-2,2′-bipyrimidine (**3**) as well.

2,2′-Bipyrimidine (**1**) was first synthesized by Bly and Mellon utilizing the Ullmann coupling of 2-bromopyrimidine in the presence of metallic copper.[3] Since the reported reproducibility of this procedure was rather low and the yields varied from 10 to 50%, we have first tested a Ni-assisted coupling of 2-chloropyrimidine.[4] Unfortunately, we were unable to reproduce the reported 60% yield. In fact, only a trace amount of **1** was formed when we used the published 1:1 ratio between 2-chloropyrimidine and $NiCl_2 \cdot 6H_2O$ (Table 1). It has been reported that the yield of the in situ formed coupling species $Ni(PPh_3)_4$ could be very low in the presence of water.[6] Therefore, we tried to modify the procedure by removing the water from the solution of $NiCl_2 \cdot 6H_2O$ in DMF by azeotropic distillation with toluene, but the formation of **1** could not be detected. A similar result was obtained when the water-free nickel precursor $Ni(acac)_2$ was used. Next, we changed the ratio between 2-chloropyrimidine and $NiCl_2 \cdot 6H_2O$ from 1:1 to 2:1, which resulted in 21% yield. Further increase of the ratio between 2-chloropyrimidine and $NiCl_2 \cdot 6H_2O$ up to 4:1 did not give higher yields. It should be noted that a similar yield (16%) was reported for the Ni-assisted coupling of 4-methyl-2-bromopyrimidine.[5] In general, the reactivity of iodoaryl compounds is much higher in cross-coupling reactions than that of chloroaryl compounds. Accordingly, the Ni-assisted coupling of 2-iodopyrimidine[7] resulted in 33% 2,2′-bipyrimidine (**1**).

Since it is also well established that iodoaryl compounds could readily undergo Ullmann coupling,[8] we have finally investigated the reactivity of 2-iodopyrimidine. The Ullmann coupling was started by reacting 2-iodopyrimidine with activated copper powder in absolute DMF between 80 and 85 °C. After 7 h, the temperature was increased to 120−130 °C for 2 h. The suspension was then cooled to 0 °C, and the coordinated copper was removed with potassium cyanide in a 25% aqueous solution of ammonia to give 2,2′-bipyrimidine (**1**) in 90% yield.



It should be emphasized that the careful activation of the metallic copper, described in the Experimental Section, is very important to achieve a high yield.

The new procedure was also tested for the coupling of 4,6-dimethyl-2-iodopyrimidine[8,9] and 5-bromo-2-iodopyrimidine[10−12] resulting in 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine (**2**) and 5,5′-dibromo-2,2′-bipyrimidine (**3**) in 50 and 38% isolated yield, respectively.

Experimental Section

2-Chloropyrimidine (97%), 2-hydroxypyrimidine hydrochloride, and 57% aqueous solution of hydriodic acid were obtained from commercial sources. DMF was either distilled from calcium

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TABLE 1.

coupling precursor (mmol)	2-X-pyrimidine (mmol)	PPh_3 (mmol)	Zn (mmol)	solvent (mL)	time (h)	yield (%)
$NiCl_2 \cdot 6H_2O$ (8.73)	X = Cl; 8.73	34.9	121.5	45	5	trace
$Ni(acac)_2$ (6.56)	X = Cl; 8.73	26.2	9.36	45	5	0
$NiCl_2 \cdot 6H_2O$ (6.56)	X = Cl; 13.1	26.2	9.35	60	5	21
$NiCl_2 \cdot 6H_2O$ (1.45)	X = I; 1.94	5.83	2.08	10	5	33
copper (338)	X = I; 72.8	0	0	60	9	90

hydride at atmospheric pressure under N_2 and stored on molecular sieves (3 Å) or degassed by purging with N_2. Copper (fine powder, >230 mesh, 25 g) was activated by washing it on a glass filter with a 1:1 mixture of acetone and 37% aqueous solution of hydrochloric acid (100 mL), acetone (100 mL), distilled water (100 mL), 5% aqueous solution of ammonia (100 mL), absolute ethanol (until the filtrate's blue color disappeared), acetone (100 mL), and diethyl ether (250 mL). Finally, all residual solvents were removed in a vacuum.

Preparation of 2-Iodopyrimidine. Hydroiodic acid (160.0 mL, 57%), precooled to 0 °C, was added to solid 2-chloropyrimidine (40.0 g, 194 mmol) in a 500 mL round-bottomed flask. The mixture was kept and vigorously stirred at 0 °C for 50 min. The light brownish green suspension was quickly neutralized at 0 °C with a saturated aqueous solution of potassium carbonate and decolorized with potassium disulfite at 0 °C. The aqueous solution was extracted with diethyl ether (5 × 300 mL), dried over desiccated magnesium sulfate, filtered, and evaporated under reduced pressure. The light yellow oil was dissolved in a minimal amount of boiling petroleum ether (bp 30−50 °C) and crystallized at 0 °C to give 60.5 g (84%) of colorless 2-iodopyrimidine: mp 30−32 °C (uncorrected; lit.[7] mp 30−32 °C). Anal. Calcd for $C_4H_3IN_2$: C, 23.32; H, 1.47; N, 13.60. Found: C, 23.60; H, 1.60; N, 14.05. ^{1}H NMR ($CDCl_3$): δ 8.45 (d, J = 4.90 Hz), 7.32 (t, J = 4.90 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 158.9, 130.0, 121.0.

Preparation of 2,2′-Bipyrimidine (1) by Ullmann Coupling. 2-Iodopyrimidine (15.0 g, 72.8 mmol) and activated copper powder (17.5 g, 275 mmol) were placed in a 250 mL double-necked flask fitted with a reflux condenser, a N_2 inlet, and a magnetic stirrer. Absolute DMF (60 mL) was added, and the flask was flushed with N_2 for 10 min. The reaction mixture was heated to 80 °C with vigorous stirring and the temperature kept between 80 and 85 °C. After 3.5 h, 4.0 g (63.0 mmol) of activated copper powder was added to the mixture, and the N_2 inlet was replaced with a calcium chloride tube. After another 3.5 h, the temperature was increased to 120−130 °C and the stirring was continued for 2 h. The suspension was then cooled to 0 °C, carefully drowned into a solution of 23.0 g potassium cyanide in 115 mL of 25% aqueous solution of ammonia, and filtered. The solid residue on the filter was extracted with the same amount of cyanide solution and filtered again. The combined filtrates were treated with 1.2 g of potassium cyanide and extracted with chloroform (5 × 300 mL). The organic phases were dried over desiccated potassium carbonate, filtered, and evaporated to dryness. Re-crystallization of the crude product from ethyl acetate/methanol 19:1 with addition of petroleum ether (bp 40−70 °C) gave 5.16 g (90%) of pale tan 2,2′-bipyrimidine (**1**). Mp: 112−114 °C (uncorrected; lit.[3] mp 113−115 °C). Anal. Calcd for for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.42. Found: C, 60.37; H, 3.88; N, 35.71. ^{1}H NMR ($CDCl_3$): δ 8.95 (d, J = 4.90 Hz), 7.42 (t, J = 4.90 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 163.3, 158.2, 121.8. IR: 3049 w, 2979 w, 1565 m, sh, 1557 s, 1403 vs, 1142 w, 989.9 w, 808.5 w, 773.7 w. EIMS: 158 (M, base peak), 159 (M − H).

Preparation of 4,6-Dimethyl-2-hydroxypyrimidine Hydrochloride.[9] Urea (12.0 g, 0.20 mol) in 100 mL of boiling ethanol was treated with acetylacetone (20.0 g, 0.20 mol), and the hot solution was treated with 27 mL of concentrated hydrochloric acid with stirring. The mixture was refluxed for 24 h, after which time 24.0 g (75%) of 4,6-dimethyl-2-hydroxypyrimidine hydrochloride was isolated by filtration and subsequent washing with cold ethanol and diethyl ether.

Preparation of 4,6-Dimethyl-2-chloropyrimidine.[9] The mixture of 4,6-dimethyl-2-hydroxypyrimidine hydrochloride (20.0 g, 0.125 mol) and phosphorus oxychloride (110 mL) was refluxed for 10 h, after which time the residual phosphorus oxychloride was removed in vacuo. The residual oil was poured into 50 g of ice and neutralized below 10 °C with a concentrated aqueous solution of potassium hydroxide. The resulting mixture and 300 mL of diethyl ether was vigorously stirred for 10 h. The organic extract was evaporated to dryness. The residual crude product was recrystallized from a minimal amount of petroleum ether (bp 40−70 °C) giving 13.8 g (77%) of 4,6-dimethyl-2-chloropyrimidine as colorless plates. Mp: 37−38 °C (uncorrected; lit.[9] mp 38−39 °C). ^{1}H NMR ($CDCl_3$): δ 6.89 (s), 2.37 (s).

Preparation of 4,6-Dimethyl-2-iodopyrimidine.[8] The heterogeneous mixture of 4,6-dimethyl-2-chloropyrimidine (2.0 g, 14.0 mmol) and hydroiodic acid (5.0 mL, 57%) was vigorously stirred in a capped round-bottomed flask at room temperature for 5 h. The brownish green suspension was neutralized at 10 °C with saturated aqueous solution of potassium carbonate and decolorized with potassium disulfite. The white precipitate was collected and recrystallized from petroleum ether (bp 40−70 °C) giving 2.05 g (62%) of 4,6-dimethyl-2-iodopyrimidine as snow-white needles. Mp: 128−129 °C (uncorrected; lit.[8] mp 128−129 °C). ^{1}H NMR ($CDCl_3$): δ 6.98 (s), 2.40 (s).

Preparation of 4,4′,6,6′-Tetramethyl-2,2′-bipyrimidine (2). 4,6-Dimethyl-2-iodopyrimidine (0.300 g, 1.28 mmol) and activated copper powder (480 mg, 7,55 mmol) were placed in a 4 mL flask fitted with a reflux condenser, a N_2 inlet, and a magnetic stirrer. Absolute DMF (1.5 mL) was added, and the flask was flushed with N_2 for 10 min. The reaction mixture was heated to 85 °C with vigorous stirring and the temperature kept between 85 and 90 °C. After 3.5 h, 120 mg (1.89 mmol) of activated copper powder was added to the mixture, and the N_2 inlet was replaced with a calcium chloride tube. After another 3.5 h, the temperature was increased to 120−130 °C and the stirring was continued for 2 h. The suspension was then cooled to 0 °C, carefully drowned into a solution of 1.0 g potassium cyanide in 5 mL of 25% aqueous solution of ammonia, and filtered. The solid residue on the filter was extracted with the same amount of cyanide solution and filtered again. The combined filtrates were treated with 50 mg of potassium cyanide and extracted with chloroform (5 × 20 mL). The organic phases were dried over desiccated potassium carbonate, filtered, and evaporated to dryness. Recrystallization of the crude product from ethyl acetate−petroleum ether (bp 40−70 °C) gave 69 mg (50%) of pale tan 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine (**2**). Mp: 131−132 °C (uncorrected; lit.[4a] mp 131−132 °C). ^{1}H NMR ($CDCl_3$): δ 7.12 (s), 2.62 (s).

Preparation of 2-Hydroxypyrimidine Bisulfate. The solution of 2-hydroxypyrimidine hydrochloride (26.54 g, 0.200 mol) in 50 mL of distilled water was mixed with 95% sulfuric acid (20.67 g, 0.200 mol) and evaporated to dryness at 100 °C under reduced pressure. Drying in a vacuum with desiccated potassium hydroxide gave 39.0 g (~100%) of crystalline 2-hydroxypyrimidine bisulfate.

Preparation of 2-Hydroxypyrimidine. 2-Hydroxypyrimidine bisulfate (39.0 g, 0.200 mol) was dissolved in 300 mL of distilled water , added to a solution of barium acetate (51.3 g, 0.201 mol) in 400 mL of distilled water, treated with gasous carbon dioxide, and filtered through Celite500. The resulted solution was evaporated to dryness at 100 °C under reduced pressure. Drying in a vacuum with desiccated potassium hydroxide gave 18.8 g (97.5%) 2-hydroxypyrimidine as a light yellow powder. ^{1}H NMR (DMSO-d_6): δ 8.26 (d, J = 5.0 Hz), 6.36 (t, J = 5.0 Hz).

Preparation of 5-Bromo-2-hydroxypyrimidine.[10] 2-Hydroxypyrimidine (18.58 g, 0.193 mol) was added to a stirred

solution of bromine (33.5 g, 0.210 mol) in 7400 mL of water at room temperature. After 5 min, the water was removed in vacuo, and the residual brownish yellow oil was treated with water leading to the precipitation of crude 5-bromo-2-hydroxypyrimidine. The off-white powder was recrystallized from 90% aqueous ethanol giving 16.8 g (50%) of 5-bromo-2-hydroxypyrimidine. Anal. Calcd for $C_4H_3BrN_2O$: Br, 45.66. Found: Br, 45.43. ^{1}H NMR (DMSO-d_6): δ 8.46 (s), ~3.4 (s, broad).

Preparation of 5-Bromo-2-chloropyrimidine.[11] 5-Bromo-2-hydroxypyrimidine (16.75 g, 95.7 mmol), phosphoroxy chloride (125 mL), and *N*,*N*-dimethylaniline (4.2 mL) were refluxed for 4 h. The cooled reaction mixture was poured onto 500 g of ice and extracted with diethyl ether (5 × 200 mL). The extract was neutralized with aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and evaporated to dryness. The recrystallization of the crude product from a minimal amount of diethyl ether gave 13.5 g (73%) of 5-bromo-2-chloropyrimidine. Mp: 78−79 °C (uncorrected; lit.[11] mp 79−80 °C). ^{1}H NMR ($CDCl_3$): δ 8.70 (s).

Preparation of 5-Bromo-2-iodopyrimidine.[12] Precooled (−10 °C) 57% hydroiodic acid (48 mL) was added drowise to a cooled, stirred solution of 5-bromo-2-chloropyrimidine (13.50 g, 69.8 mmol) in dichloromethane (42 mL). The mixture was stirred at 0 °C for 5 h, neutralized carefully with solid potassium carbonate, and decolorized with a saturated aqueous solution of sodium disulfite. Water was added until the solution was formed. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (5 × 100 mL), dried over potassium carbonate, filtered, and evaporated to dryness. The crude product was recrystallized from petroleum ether (bp 40−70 °C) yielding 14.5 g (73%) of 5-bromo-2-iodopyrimidine. Mp: 101 °C (uncorrected; lit.[12] mp 101−102 °C).

Preparation of 5,5′-Dibromo-2,2′-bipyrimidine (3). 5-Bromo-2-iodopyrimidine (2.40 g, 8.42 mmol) and activated copper powder (2.00 g, 31.5 mmol) were placed in a 20 mL double-necked flask fitted with a reflux condenser, a N_2 inlet, and a magnetic stirrer. Absolute DMF (7 mL) was added, and the flask was flushed with N_2 for 10 min. The reaction mixture was heated to 90 °C with vigorous stirring and the temperature kept between 90 and 95 °C. After 3.5 h, 0.35 g (5.5 mmol) of activated copper powder was added to the mixture, and the N_2 inlet was replaced with a calcium chloride tube. After another 3.5 h, the temperature was increased to 120−130 °C, and the stirring was continued for 2 h. The suspension was then cooled below 10 °C, carefully drowned in a solution of 2.7 g potassium cyanide in 14 mL of 25% aqueous solution of ammonia, and filtered. The solid residue on the filter was extracted with the same amount of cyanide solution and filtered again. The combined filtrates were treated with 0.1 g of potassium cyanide and extracted with chloroform (6 × 70 mL). The organic phases were dried over desiccated potassium carbonate, filtered, and evaporated to dryness. Recrystallization of the crude product from ethyl acetate/chloroform 9:1 with addition of petroleum ether (bp 40−70 °C) and refrigeration gave 0.51 g (38%) of pale tan 5,5′-dibromo-2,2′-bipyrimidine (**3**). ^{1}H NMR ($CDCl_3$): δ 9.06 (s). IR (in KBr): 3014 m, 1540 w, 1523 vs, 1411 vs, 1361 m, 1236 w, 1137 vs, 1008 s, 932 w, 758 s, 641 s. EIMS: 314−316−318 (M, base peak, triplet by two isotopes of bromine atom).

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