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for

General Route to Purin-2-yl Magnesium Halides by Metal-Halogen Exchange in Dichloromethane

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General methods

All reagent-grade solvents and chemicals were purchased from standard commercial suppliers and used without further purification. All non-aqueous reactions were carried out under anhydrous conditions using dry solvents. Reactions were monitored by LC-MS or TLC carried out on 0.25 mm silica gel plates (60F-254). TLC plates were visualized using UV light. Flash chromatography was performed using a Biotage Isolera One system with pre-packed column cartridges (Biotage KP-Sil [40+M] or KP-Sil [25+M]). The $^1$H NMR and $^{13}$C NMR spectroscopy data were obtained using a Bruker instrument (400 MHz or 600 MHz for $^1$H NMR and 150 MHz for $^{13}$C NMR; solvent: CDCl$_3$, internal standard: tetramethylsilane $\delta = 0.00$ ppm), and the signals listed have the following meanings: br = broad; s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of a doublet of doublets, m = multiplet, q = quartet, quint = quintet, sext = sextet, sept = septet, dq = doublet of quartets, dt = doublet of triplets. Accurate mass measurement was measured using a Water Q-ToF Premier apparatus under electrospray ionization conditions.

Experimental procedures for the synthesis of 2-ido-9-(4-methylphenyl)-9H-purine (2)

1) Synthesis of 2-chloro-N-(4-methylphenyl)-5-nitropyrimidin-4-amine

Di-isopropyl-ethylamine (DIPEA) (7.18 mL, 41.24 mmol) and then 4-methylaniline (4.42 g, 41.24 mmol) were added slowly to a solution of 2,4-dichloro-5-nitropyrimidine (8 g, 41.24 mmol) in dry dichloromethane (150 mL) at 0 °C under a nitrogen atmosphere. The reaction solution was stirred for 5 h at room temperature and then a sat. solution of Na$_2$CO$_3$ (160 mL) was added. The organic layers were separated, and the aqueous phase was extracted thrice with dichloromethane. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated in-vacuo to give the title compound as a yellow solid (10.9 g, 99% yield), which was used directly in the next step. A sample of this crude material was purified chromatographically (Eluent: CH$_2$Cl$_2$/Heptane 6:4) for accurate NMR and MS characterisation. 

Mp: 113-115 °C. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta =$ 2.38 (s, 3H), 7.24 (d, $J = 9.9$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 9.16 (s, 1H), 10.15 (br s, 1H); $^{13}$C-NMR (150 MHz, CDCl$_3$) $\delta =$ 21.2 (q), 123.0 (d), 126.6 (s), 130.0 (d), 132.9 (s),
2) Synthesis of 2-iodoo-N-(4-methylphenyl)-5-nitropyrimidin-4-amine (3)

![Reaction Diagram](image)

Concentrated hydroiodic acid (57% in H2O) (54 mL, 82.36 mmol) was added dropwise to a solution of 2-chloro-N-(4-methylphenyl)-5-nitropyrimidin-4-amine (10.9 g, 41.18 mmol) in dry acetone (50 mL) at -5 °C under a nitrogen atmosphere. The red brown solution was stirred at -5 °C for 6 hours after which time LC-MS analysis showed that a steady state mixture of starting material and product had been attained. Aqueous NaOH solution (2M) was added until pH 8 was achieved, the acetone was evaporated off under reduced pressure and the remaining aqueous phase was extracted thrice with CH2Cl2. The combined organic phases were washed with brine, dried over Na2SO4, filtered and concentrated in-vacuo to give a mixture of starting material and product which was subjected a second time to the same reaction conditions described above. After 5 hours of stirring, LC-MS analysis showed complete conversion of starting material to product. The mixture was worked up as before to give the title compound 3 as an orange solid (13.9 g, 95% yield) which was used directly in the next step. *Mp*: 147-149 °C. 1H-NMR (600 MHz, CDCl3) δ = 2.38 (s, 3H), 7.24 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 8.89 (s, 1H), 10.05 (br s, 1H); 13C-NMR (150 MHz, CDCl3) δ = 21.2 (q), 122.6 (d), 127.5 (s), 129.9 (d), 133.1 (s), 134.1 (s), 136.6 (s), 151.4 (s), 156.5 (d); HRMS (ESI, m/z): found [M+H]+ 356.9858, C11H10N4O2I requires 356.9835.

Synthesis of 2-iodo-N4-(4-methylphenyl)pyrimidine-4,5-diamine

![Reaction Diagram](image)
Concentrated hydrochloric acid (6.5 mL, 76.94 mmol) was added slowly at 0 °C to a stirred solution of 3 (13.7 g, 38.47 mmol) in dry methanol (219 mL) under a nitrogen atmosphere. After 5 minutes tin (II) chloride dihydrate (26.9 g, 119.26 mmol) was added at 0°C, and the reaction mixture was stirred at room temperature for 3 h. The mixture was cooled to 0 °C and quenched slowly with a saturated solution of NaHCO₃ until pH 8 was achieved. After removal of methanol under reduced pressure, the residue was diluted with water (100 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filerated and concentrated in vacuo to give a brown solid. Trituration with CH₂Cl₂ afforded the title compound as a pale grey solid (10.9 g, 87% yield), which was carried forward to the next step without further purification. A sample of this crude material was purified by HPLC for accurate NMR and MS characterisation. **Mp:** 212-215 °C. **¹H-NMR** (600 MHz, CDCl₃) δ = 2.34 (s, 3H), 3.06 (br s, 2H), 6.84 (br s, 1H), 7.16 (d, J = 7.4 Hz, 2H), 7.43 (d, J = 7.9 Hz, 2H), 7.66 (s, 1H); **¹³C-NMR** (150 MHz, CDCl₃) δ = 20.8 (q), 117.8 (s), 119.9 (d), 124.8 (s), 129.3 (d), 133.4 (s), 135.1 (s), 144.1 (d), 152.9 (s); **HRMS** (ESI, m/z): found [M+H]+ 235.0746, C₁₁H₁₂N₄Cl requires 235.0750.

**Synthesis of 2-iodo-9-(4-methylphenyl)-9H-purine (2)**

Pyridinium p-toluenesulfonate (18.9 g, 75.3 mmol) was added to a suspension of 2-iodo-N⁴-(4-methylphenyl)pyrimidine-4,5-diamine (8.4 g, 25.75 mmol) in triethylorthoformate (168.1 mL, 1.03 mol) at rt under a nitrogen atmosphere. The reaction mixture was stirred at rt for 6 hours after which time TLC (4:1 EtOAc/Hept) showed complete conversion. Ethanol was evaporated in vacuo at room temperature and the residue was diluted with NaHCO₃ and extracted 4 times with CH₂Cl₂. The combined organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to give a brown solid. Trituration with a small amount of CH₂Cl₂ afforded the title compound 2 as a pale brown solid (5.1 g, 59% yield). **Mp:** 181-184 °C. **¹H-NMR** (600 MHz, CDCl₃) δ = 2.45 (s, 3H), 7.39 (d, J = 7.9 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 8.25 (s, 1H), 8.95 (s, 1H); **¹³C-NMR** (150 MHz, CDCl₃) δ = 21.2 (q), 120.1 (s), 123.4 (d), 130.6 (d), 131.2 (s), 134.4 (s), 139.1 (s), 144.4 (d), 150.2 (d), 152.1 (s); **HRMS** (ESI, m/z): found [M+H]+ 336.9948, C₁₂H₁₀N₄I requires 336.9950.
$^1$H and $^{13}$C-NMR of 2-chloro-N-(4-methylphenyl)-5-nitropyrimidin-4-amine (400 MHz, 150 MHz, CDCl$_3$)
$^1$H and $^{13}$C-NMR of 2-iodo-N-(4-methylphenyl)-5-nitropyrimidin-4-amine (3) (600 MHz, 150 MHz, CDCl₃)
$^{1}$H and $^{13}$C-NMR of 2-iodo-N$^4$-(4-methylphenyl)pyrimidine-4,5-diamine (600 MHz, 150 MHz, CDCl$_3$)
$^1\text{H}$ and $^{13}\text{C}$-NMR of 2-iodo-9-(4-methylphenyl)-9H-purine (2) (600 MHz, 150 MHz, CDCl$_3$)
$^1$H and $^{13}$C-NMR of (6-chloro-9-isopropyl-9H-purin-2-yI)(phenyl)methanol (4a) (600 MHz, 150 MHz, CDCl$_3$)
$^1$H and $^{13}$C-NMR of (6-chloro-9-isopropyl-9H-purin-2-yl)(3-nitrophenyl)methanol (4b) (600 MHz, 150 MHz, CDCl$_3$)
$^1$H and $^{13}$C-NMR of (6-chloro-9-isopropyl-9H-purin-2-yl)(2-furyl)methanol (4c) (400 MHz, 150 MHz, CDCl$_3$)
$^1$H and $^{13}$C-NMR of 1-(6-chloro-9-isopropyl-9H-purin-2-yl)-2-methylpropan-1-ol (4d) (600 MHz, 150 MHz, CDCl$_3$)
$^1\text{H}$ and $^{13}\text{C}$-NMR of [9-(4-methylphenyl)-9H-purin-2-yl](phenyl)methanol (5a) (600 MHz, 150 MHz, CDCl$_3$)
$^1$H and $^{13}$C-NMR of methyl 4-{hydroxy[9-(4-methylphenyl)-9H-purin-2-yl]methyl}benzoate (5b) (600 MHz, 150 MHz, CDCl$_3$)
$^1$H and $^{13}$C-NMR of 1,3-benzodioxol-5-yl[9-(4-methylphenyl)-9H-purin-2-yl]methanol (5c) (600 MHz, 150 MHz, CDCl$_3$)
$^1$H and $^{13}$C-NMR of 2-(benzyloxy)-1-[9-(4-methylphenyl)-9H-purin-2-yl]ethanol (5d) (600 MHz, 150 MHz, CDCl$_3$)