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Regioselective Addition of Mesitol to a 2,4-Dichloropyridine

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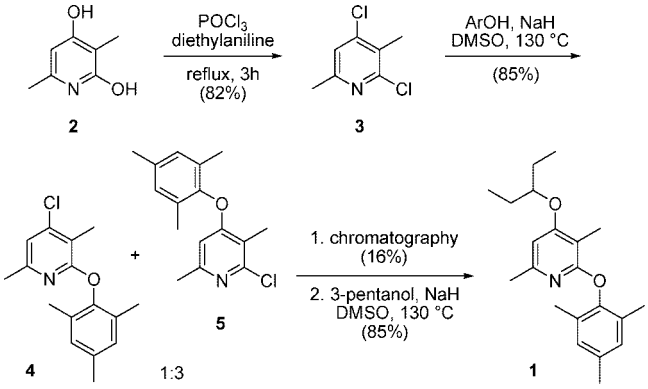
Abstract:

The regioselectivity of the addition of 2,4,6-trimethylphenol to 2,4-dichloro-3,6-dimethylpyridine can be controlled by the proper choice of catalyst and solvent. The use of catalytic copper(I) salts and pyridine as solvent results in exclusive addition at C-2. In their absence, a mixture of regioisomers is obtained in which addition at C-4 is dominant.

Introduction

Corticotropin-releasing factor (CRF) antagonists have been suggested for use in many therapeutic areas, including depression, anxiety and stress-related diseases.[1] 4-(1-Ethylpropoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)pyridine (**1**) is a potent CRF antagonist discovered at Pfizer.[2] The original synthetic route is shown in Scheme 1. 2,4-Dihydroxy-3,6-dimethylpyridine[3] (**2**) was converted to its dichloro analogue[4] (**3**) by reaction with $POCl_3$/diethylaniline. Aryl ether formation was achieved by addition of 2,4,6-trimethylphenol (mesitol) sodium salt in DMSO, but the undesired C-4 regioisomer was the major product of the reaction. On laboratory scale, the regioisomers could be separated by column chromatography, and the minor isomer (**4**) was reacted with the sodium or potassium salt of 3-pentanol in DMSO to give the desired compound. The low overall yield and chromatographic separation were not optimal for the preparation of larger quantities needed for clinical development. This prompted an investigation into the control of regioselectivity of the chloride displacement by aryloxides and alkoxides.

Scheme 1. **Original Synthesis of 1**



A seemingly trivial improvement to the regioselectivity issue would be to reverse the order of oxygen nucleophile additions and add 3-pentoxide first to the dichloropyridine. Unfortunately, the sodium salt of 3-pentanol added preferentially at C-2, affording **7** as the major isomer in a 6:1 ratio (Scheme 2).

At this point, a more thorough investigation examining the effects of counterion and solvent in the addition of mesitol to **3** was undertaken. The highlights of that investigation are shown in Table 1. In most cases, simply altering the counterion, whether an alkali metal or a quaternary ammonium salt, had little of the desired effect on the regioselectivity, and polar, high-boiling solvents were required to get reasonable conversion

Scheme 2. **Addition of 3-pentanol to 2-4-dichloro-3,6-dimethylpyridine**

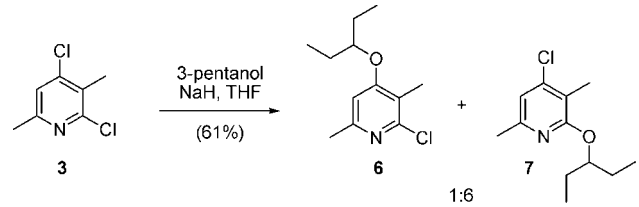


Table 1. **Addition of 2,4,6-trimethylphenol to 2-4-dichloro-3,6-dimethylpyridine**[a]

entry	base	additive	solvent	conversion	**4**:**5**[b]
1	NaH	–	DMSO	>99%	1:3
2	NaH	–	toluene	trace	100:0
3	LiOH	–	DMF	20%	0:100
4	KO*t*-Bu	–	DMAc	93%	1:4
5	Cs_2CO_3	–	DMSO	91%	1:4
6	*n*-Bu_4NOH[c]	–	DMSO	85%	1:4
7	NaH	Ag_2CO_3	DMSO	0%	–
8	NaH	BF_3•OEt_2	THF	0%	–
9	NaH	CuBr	DMSO	50–67%	2:1
10	NaH	$CuBr_2$	DMSO	33%	2:3
11	*n*-BuLi	CuCl	diglyme	trace	100:0
12	NaH	CuBr	DMSO/py	33%	8:1
13	KO*t*-Bu	Cu bronze	DMF/py	30%	1:3
14	KO*t*-Bu	–	pyridine	>95%	4:1
15	–	CuBr	pyridine	0%	–
16	**KO*t*-Bu**	**Cu(I)**[d]	**pyridine**	**100%**	**100:0**[e]

[a] Typical reaction conditions: Equimolar amounts of **3** and the phenol were mixed with 1.1 equiv of the base in the solvent and heated to reflux if the bp of the solvent was <120 °C or 120–150 °C if high-boiling solvents were employed. The additives were initially screened using 1.0 equiv, and were added prior to heating. Conversions shown are generally after 18–24 h. [b] Ratios determined by GC/MS. [c] *n*-Tetrabutylammonium salt of phenol was preformed separately and isolated prior to reaction. [d] CuCl, CuBr, and CuI were used interchangeably. [e] No **5** was observed; however, the product of double displacement was seen.

At this point, a more thorough investigation examining the effects of counterion and solvent in the addition of mesitol to **3** was undertaken. The highlights of that investigation are shown in Table 1. In most cases, simply altering the counterion, whether an alkali metal or a quaternary ammonium salt, had little of the desired effect on the regioselectivity, and polar, high-boiling solvents were required to get reasonable conversion

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(entries 1, 3−6); nonpolar solvents seemed to favor the desired isomer, but the reaction was extremely slow. The major product where good conversion was achieved was the undesired C-4 isomer, **5**. However, in our investigation of additive counterions, we noted that addition of copper salts (entry 9) to the standard reaction had a beneficial effect on the regioselectivity and inverted the ratio in favor of attack at C-2 to give **4** as the major isomer. In another experiment, adding a small amount of pyridine to the reaction in order to solubilize the copper salts further increased the ratio of products in favor of **4** (entry 12). In an attempt to separate counterion from solvent effects, we ran the reaction with potassium *tert*-butoxide in pyridine in the absence of copper catalyst (entry 14). Desired isomer **4** was still the major one, but to a lesser extent. When pyridine was used as solvent with potassium *tert*-butoxide and a catalytic amount of a copper salt, none of the undesired regioisomer could be detected. The only other product of the reaction arose from displacement of both chlorides by the phenol. The amount of the bis-adduct formed could be minimized by adjusting the stoichiometry of mesitol and base relative to **3**. Under the optimized conditions (1.1 equiv of each), <5% of this bis-adduct was formed, and was largely purged during isolation.

A rate enhancement was also observed. In all the other reactions shown, the ether formation was sluggish, and often failed to go to completion even after 24 h. Under the preferred conditions (25 mol % catalyst), the reaction was complete within 2 h. As little as 5 mol % was sufficient to drive the reaction to completion, but a tailing in conversion was observed, and the reaction required overnight reflux to consume the starting materials. All of the copper(I) halide sources tried gave equivalent results. Copper(0) or -(II) sources were not effective in reversing the regioselectivity to a useful degree. Potassium carbonate could also be used as the base, but a minimum of two equivalents were required for good conversion.

The reason for the changes in selectivity observed is not entirely clear. There are a few examples reported in the literature in which alkoxide anions add with high or exclusive selectivity to the C-4 position of polychloropyridines. The best results are obtained when the alkoxide is small and the reaction is carried out at lower temperatures.[5] Increasing the size of the nucleophile tends to lead to mixtures of regioisomers,[6] and this is usually observed with phenols.[7] More examples have been reported for dichloroquinolines[8] and other related heterocycles, [9] and in some cases the regioselectivity can be controlled by reaction conditions,[10] but the kinetic selectivity is opposite to that observed for the pyridines (C-2 > C-4[11]), making it difficult to draw analogies.

There have been reports on the use of copper catalysis in biaryl ether formation from halopyridines,[12] but none that address the issue of regioselectivity in 2,4-chloropyridines. The beneficial effect of pyridine, either as a ligand or as solvent, has been well-demonstrated in nonpyridyl Ullmann couplings,[13] but this example appears to be unique, since the pyridine appears to play a role even in the absence of copper. It is possible that pyridine is adding to form a transient pyridinium species, but literature precedent[14] suggests that such activation would occur at C-4, and would be more likely to enhance the electrophilicity of that carbon rather than block it. One reaction was run in which collidine was substituted for pyridine, and in that instance, almost no conversion was observed after extensive reaction times. However, a trace of a product was observed by GC that had a mass consistent with displacement of one of the chlorides by collidine. If the pyridinium adduct is forming, the role of the copper is still not explained. Wright and co-workers have described the isolation of macrocyclic 2-pyridyl copper complexes,[15] which may help explain the directing effect noted in this case, but would not explain the solvent effect. Finally, an electron-transfer mechanism cannot be ruled out; the reactions with copper(I) are highly colored and, as noted previously, occur at a much faster rate than those without it.

The final step of the process was modified to avoid the use of sodium hydride. Replacement with potassium *tert*-butoxide gave clean displacement of the remaining chloride by 3-pentanol, and the solvent was changed from DMSO to DMAc to reduce potential handling issues. The order of addition and temperature were found to have a large effect on the conversion. The base had to be added to a mixture of the starting materials at a minimum of 120 °C. Running the reaction at lower temperatures or premixing all the reagents and heating gave <60% conversion. A THF solution of the base was used to avoid having to open the reactor under these conditions, with continuous distillation of the THF from the reaction mixture to maintain the temperature. The need for these conditions to obtain good conversion is presumed to be due to steric hindrance, since any residual methanol not removed after the isolation of **4** gave the corresponding methoxy-substituted product at much lower temperatures.

The optimized conditions are shown in Scheme 3. During scale-up, a silica pad filtration was carried out after the first coupling to ensure removal of the copper salts. The recovery for both steps was less than the inherent yield because of the very high solubility of both **4** and **1** in all solvents screened for isolation.

In conclusion, a method for regioselective addition of mesitol to the C-2 position of 2,4-dichloro-3,6-dimethylpyridine has been described. The use of a copper(I) salt and pyridine as solvent are key to achieving the desired selectivity.

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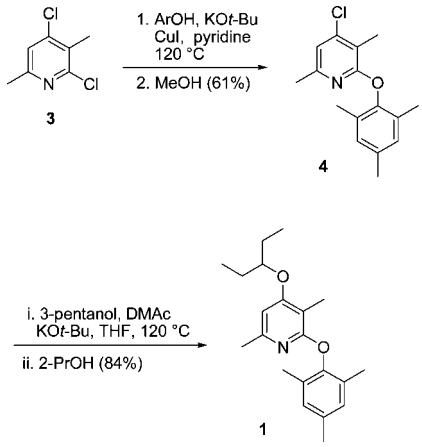
Scheme 3. **Optimized synthesis**



Experimental Section

General. All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. All reactors were glass-lined steel vessels. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by HPLC or GC/MS. HPLC analyses were performed using a Zorbax SB-CN 4.6 mm × 150 mm column and a gradient mobile phase consisting of 0.02% phosphoric acid (A) and acetonitrile (B) (A/B 95/5 to 25/75 at 10 min, hold to 14 min, to 95/5 at 15.5 min, flow 0.5 mL/min, temp 30 °C). GC analyses were performed on a DBWaxEtr (15 m × 0.25 mm ID × 0.25 μm film). Proton and carbon NMR spectroscopy was performed on a Bruker-Spectrospin Avance 400 MHz instrument. Elemental analyses were performed by Quantitative Technologies Inc. of Whitehouse, NJ.

2,4-Dichloro-3,6-dimethylpyridine (3). To a vessel were charged 8.8 kg (63.2 mol) of 2,4-dihydroxy-3,6-dimethylpyridine and 10.0 L (62.8 mol) of *N*,*N*-diethylaniline. Phosphorus oxychloride (41.2 L) was added, allowing the mixture to exotherm. The mixture was heated to 90−95 °C and held for 2 h, then checked for reaction completion by GC. The excess phosphorus oxychloride was removed by distillation under vacuum, and then the crude residue was poured onto water (176 L) with good stirring. Hexanes (176 L) were added, and the pH of the mixture was adjusted to 2.5 with 50% NaOH. After separation of the layers, the organics were washed with 2 × 176 L of 1 N HCl and 2 × 176 L of 1 M NaOH. The solution was dried over sodium sulfate, and the solvent was removed under vacuum. The crude residue was pushed through a small plug of silica with hexanes and isolated by concentration to obtain 8.0 kg (72%) of the product as a clear amber oil. HPLC anaylsis showed the material to be 97.6% pure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H), 2.40 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.4, 151.4, 145.6, 127.6, 123.0, 23.5, 16.4. Anal. Calcd. for $C_7H_7Cl_2N$: C, 47.76; H, 4.01; Cl, 40.28; N, 7.96. Found: C, 47.81; H, 3.96; Cl, 39.94; N, 7.75.

4-Chloro-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)pyridine (4). A vessel was charged with 4.94 kg (36.3 mol) of 2,4,6-trimethylphenol, 29 L of pyridine, 4.07 kg (36.3 mol) of potassium *tert*-butoxide, 1.57 kg (8.2 mol) of copper(I) iodide, and 5.81 kg (33.0 mol) of **3**. The mixture was heated to reflux for 2 h and then cooled to 0 °C. The reaction was poured into a mixture of hexanes (58.3 L) and saturated NH_4Cl (116.2 L), and stirred at room temperature overnight. The layers were separated, and the organic layer was washed with 2 × 15 L of 1 M NH_4OH, 3 × 29 L of 3 N NaOH, 1 × 29 L of 1 N HCl and 1 × 29 L of water. The organic layer was dried over sodium sulfate and filtered, washing with hexanes. The filtrate was concentrated under vacuum to a brown oil and then pushed through a small plug of silica with hexanes. After removal of the solvent under vacuum, the residue was stirred in methanol (8.0 L) to precipitate the product. The slurry was filtered, and the solids were dried under vacuum to obtain 3.9 kg (43%) of **4**. In order to obtain a second crop, the filtrate was concentrated under vacuum to an oil, and the residue was slurried in minimal methanol at 0 °C and filtered under vacuum. The solids were dried to give an additional 1.6 kg (18%) of **4** for an overall yield of 61%. HPLC analysis showed the product to be 99.1% pure with 0.6% of the bis-adduct. ^{1}H NMR ($CDCl_3$): δ 6.88 (s, 2H), 6.78 (s, 1H), 2.40 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H), 2.04 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 161.1, 154.0, 148.9, 145.0, 134.2, 130.7, 129.2, 117.8, 115.4, 23.9, 21.1, 16.8, 12.3. Anal. Calcd. for $C_{16}H_{18}ClNO$: C, 69.68; H, 6.58; N, 5.08; Cl, 12.86.. Found: C, 70.03; H, 6.54; N, 5.00; Cl, 12.49.

4-(1-Ethylpropoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)pyridine (1). A vessel was charged with 3.88 kg (14.1 mol) of **4,** 2.1 kg (23.8 mol) of 3-pentanol, and 46.4 L of DMAc. The mixture was heated to 120 °C, and a 1 M solution of potassium *tert*-butoxide in THF (34.7 L, 34.7 mol) was added over 4 h with simultaneous removal of the THF by distillation. After the addition was complete, the mixture was cooled and partitioned between hexanes (77.6 L) and water (77.6 L). The organics were washed with water (2 × 39 L) and dried over sodium sulfate. The hexanes were displaced with isopropanol under vacuum to a final volume of 12 L. The resulting slurry was cooled to −10 °C, and the solids were isolated by filtration. After drying, 3.9 kg (84%) of **1** was obtained that was 99.4% pure by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 2H), 6.29 (s, 1H), 4.19 (p, J = 5.8 Hz, 1H), 2.30 (s, 3H), 2.20 (s, 6H), 2.08 (s, 6H), 1.76−1.69 (m, 4H), 0.97 (td, J = 7.5, 0.8 Hz, 6H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.7, 161.9, 154.0, 149.4, 133.6, 131.1, 129.0, 104.3, 102.5, 80.2, 26.3, 24.8, 21.1, 16.9, 9.7, 8.2. Anal. Calcd. for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.66; H, 8.93; N, 4.22.

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