Synthesis and Reactivity of Pyridylpyridone Derivatives

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Introduction

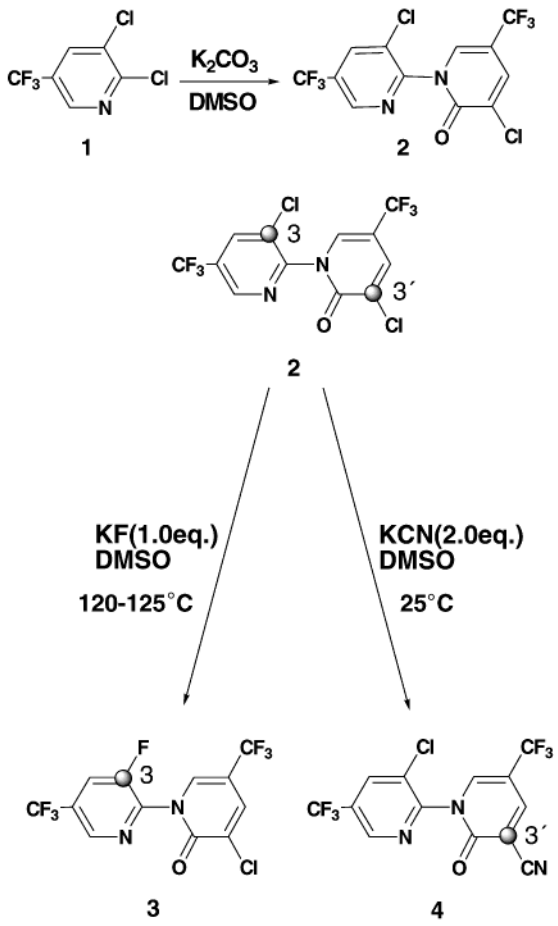
It is well-known that the incorporation of fluorine atoms into biologically active molecules often leads to increased activity compared to that of the parent compounds. 2,3-Dichloro-5-(trifluoromethyl)pyridine (**1**) is an important starting material for various agrochemicals and pharmaceuticals.[1] The very high levels of activity of compounds derived from **1** can in part be attributed to the presence of the trifluoromethyl group. In our continuing research to find new insecticides, we synthesized the novel insecticidal dimeric product **2**.[2] Further modification of compound **2** via nucleophilic substitution reactions with KF and KCN proceeded in a highly regioselective manner to afford the novel pyridylpyridones **3** and **4**, respectively.

Results and Discussion

The dimeric product **2** was initially obtained accidentally in low yield (30%) from 2,3-dichloro-5-(trifluoromethyl)pyridine 1 (DMF−CH_3CO_2Na, 120 °C). However, an alternative procedure (**1**, K_2CO_3 in DMSO, 120 °C, 24 h) led to the isolation of the desired product in greatly improved yield (82%) (Scheme 1).[3]

Further investigations for the derivatives of **2** revealed that **2** undergoes facile and highly regioselective nucleophilic substitution with KF and KCN to give the novel pyridylpyridone **3** and **4**, respectively (Scheme 1). We initially assumed that the **3** and **4** were pyridylpyiridones arising from substitution at the 3′-carbon atom of the pyridone ring, which is activated by α-carbonyl group. In fact, KCN did indeed react (25 °C, 12 h) at the 3′-carbon atom of **2** to give the corresponding 3′-cyano compound **4** in good yield (71%). However, KF unexpectedly reacted at the 3-carbon atom of 2 (120 °C, 5 h) to give the novel pyridylpyridone **3**. The yield of **3** was moderate (40%), but no other fluorine-containing compounds, for example, 3′-fluoro-substituted or 3,3′-difluoro-substituted pyridylpyridones were detected. The structures of both new compounds were confirmed by means of X-ray analysis.

Scheme 1



Nucleophilic substitution at the 3-position of pyridine derivatives under such mild reaction conditions is unusual—such reactions typically require temperatures in excess of 200 °C. Thus we were very interested in the nucleophilic substitution of the chlorine atom by fluorine at the 3-position on the pyridine ring.

First, we attempted to relate the chemical regioselectivity to a particular MO index such as charges, electron densities, orbital energies, and heats of formation. In addition, we studied the comparison of energies of Meizenheimer-type intermediates. These procedures, however, did not account for the regioselectivity of a fluoride anion nor a cyanide anion to the pyridylpyridone **2**.

Second, we turned our attention to the HSAB principles.[4] It is well-known that a fluoride anion is a hard base and a cyanide anion is a soft base, and hard bases prefer to coordinate with hard acids and soft bases prefer soft acids. Klopman and Fleming showed that hard acids are recognized, as small sized, highly positively charged, not easily polarizable, and characterized by a low value for the frontier electron density of LUMO.[5] On the other

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Table 1. Maximum LUMO Density ($Ø_{LUMO}^2$), Electrostatic Potential, and Net Charges of 3- and 3′-Carbon Atoms in 2

	max. LUMO density ($Ø_{LUMO}^2$)	electrostatic potential (atomic unit)	net charges	
			Mulliken	CHELPG
3-C	2.26×10^{-4}	−0.0148 to +0.0481	−0.178	−0.232
3′-C	2.89×10^{-4}	−0.0021 to +0.0345	−0.303	−0.282

hand, soft acids are defined as those possessing the reverse properties.[5] Therefore, to investigate the properties of 3- and 3′-carbon atoms, the possible reacting centers, we calculated the maximum LUMO densities, electrostatic potentials and net charges of 3- and 3′-carbon atoms in **2**.[6] The results are summarized in Table 1.

The maximum value of the electrostatic potential around 3-carbon atom is greater than that around 3′-carbon atom, and the net charges of 3-carbon atom obtained from both Mulliken and CHELPG methods are relatively more positive than those on 3′-carbon atom. On the other hand, the maximum density of LUMO (ϕ_{LUMO}^2) around 3′-carbon atom is greater than that around 3-carbon atom. These results indicate that 3-carbon atom on the pyridyl pyridone **2** is a harder acid, and 3′-carbon atom on the pyridylpyridone **2** is a softer acid.

Thus a fluoride anion (a hard nucleophile) reacted at 3-carbon atom (a harder electrophile) on the pyridylpyridone **2** to give the pyridyl pyridone **3** and a cyanide anion (a soft nucleophile) reacted at 3′-carbon atom (a softer electrophile) on the pyridylpyridone **2** to give the pyridyl pyridone **4**. All pyridylpyridones **2**−**4** show significant insecticidal activity, and the results will be published in future.

Experimental Section

General. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kiesegel 60 F_{254} plates (Merck) using reagent grade solvents. Chromatography was performed using Kieselgel 60 (70−230 mesh). ^{1}H NMR was performed at 300 MHz in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm downfield from internal tetramethylsilane. ^{19}F NMR were performed at 282 MHz in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm downfield from internal fluorotrichloromethane.

[1(2*H*)-3-Chloro-5-(trifluoromethyl)-3′-Chloro-5′-(trifluoromethyl)-2′-bipyridin]-2-one (2). A solution of 2,3-dichloro-5-(trifluoromethyl)pyridine (20.0 g, 92.6 mmol) and potassium carbonate (6.40 g, 46.3 mmol) in *N*,*N*-dimethylformamide (50 mL) was stirred at 140 °C for 30 h. The reaction was cooled to room temperature. The reaction mixture was poured into water (100 mL) and then extracted with ethyl acetate. The organic extracts were combined, washed with water and saturated aqueous sodium chloride solution, dried over $MgSO_4$, and filtered, and the solvent was evaporated, yielding a residue that was chromatographed on silica gel. Elution with 5% EtOAc/hexane yielded the title compound **2** as white crystals: 13.30 g (76.0% yield); mp 107.8 °C; IR ($CHCl_3$) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (bs, 1H), 7.77 (bs, 1H), 8.20 (bs, 1H), 8.80 (bs, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −63.3 (s, CF_3), −62.8 (s, CF_3). Anal. Calcd for $C_{12}H_4Cl_2N_2O$: C, 38.22; H, 1.07; N, 7.43. Found: C, 38.33; H, 1.16; N, 7.46.

[1(2*H*)-3-Fluoro-5-(trifluoromethyl)-3′-chloro-5′-(trifluoromethyl)-2′-bipyridin]-2-one (3). A solution of **2** (0.963 g, 2.55 mmol) and spray-dried KF (0.155 g, 2.67 mmol) in dimethyl sulfoxide (10 mL) was stirred at 120−125 °C for 5 h. The reaction was cooled to room temperature. The reaction mixture was poured into water (50 mL) and then extracted with ethyl acetate. The organic extracts were combined, washed with water and saturated aqueous sodium chloride solution, dried over $MgSO_4$, and filtered, and the solvent was evaporated, yielding a residue (0.879 g) that was chromatographed on silica gel. Elution with 5% EtOAc/hexane yielded crude compound **3** (0.403 g). Recrystallization from hexane furnished the title compound **3** as a white crystals: 0.368 g (40.0% yield); mp 110.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.77 (d, J = 35.5 Hz, 1H), 7.94−7.53 (m, 3H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −62.2 (s, CF_3), −63.5 (s, CF_3), −115.9 (s, 1F) Anal. Calcd for $C_{12}H_4ClFN_2O$: C, 39.97; H, 1.12; N, 7.77. Found: C, 39.65; H, 1.22; N, 7.84.

[1(2*H*)-3-Chloro-5-(trifluoromethyl)-3′-cyano-5′-(trifluoromethyl)-2′-bipyridin]-2-one (4). A solution of **2** (0.954 g, 2.53 mmol) and potassium cyanide (0.173 g, 2.66 mmol) in dimethyl sulfoxide (10 mL) was stirred at room temperature for 12 h. The reaction mixture was poured into water (50 mL) and then extracted with ethyl acetate. The organic extracts were combined, washed with water and saturated aqueous sodium chloride, dried over $MgSO_4$, and filtered, and the solvent was evaporated, yielding a residue that was chromatographed on silica gel. Elution with 5% EtOAc/hexane yielded the title compound **4** as a white crystals: 0.659 g (71.0% yield); mp 144.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00 (bs, 1H), 8.08 (bs, 1H), 8.22 (bs, 1H), 8.81 (bs, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −63.1 (s, CF_3), −62.9 (s, CF_3). Anal. Calcd for $C_{13}H_4ClN_3O$: C, 42.45; H, 1.09; N, 11.43. Found: C, 42.64; H, 0.96; N, 11.24.

Supporting Information Available: Copies of ORTEP diagrams and X-ray crystallographic data for compound **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Ab initio molecular orbital calculations were performed with the GAUSSIAN94 program.[7] Geometries were fully optimized at the HF/6-31G* level. The electrostatic potential and the density of LUMO ($Ø_{LUMO}^2$) were obtained at 167 points around the 3-carbon and 204 points around the 3′-carbon in compound **2**. These points were on the 2 Å radius spheres the centers of which were the 3-carbon and 3′-carbon, respectively. There were 1632 points primarily located on each sphere uniformly, and the points more than 2 Å apart from any other nuclei were selected as the surface points of each atom. The net charges of the atoms were calculated by using the method of Mulliken and the CHELPG method of Breneman and Wiberg.[8]

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