Stereochemistry of Knoevenagel Condensation Products from Cyanoacetates and Aromatic Aldehydes

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The C-13 long-range selective proton decoupling method and X-ray crystallographic analysis were employed to determine the stereochemistry of the caffeic acid derivatives, extremely potent 12-lipoxygenase inhibitors, synthesized from cyanoacetates and aromatic aldehydes. The ester group of 1 and 2 was found to be *trans* to the phenyl group.

Keywords stereochemistry; Knoevenagel condensation; X-ray crystallographic analysis; caffeic acid derivative; 12-lipoxygenase; 12-lipoxygenase inhibitor; C-13 NMR long-range selective proton decoupling (LSPD); E-regioisomer; *Z*-regioisomer; regioselectivity

Little work has been done on the stereochemistry of Knoevenagel condensation products obtained from cyanoacetates and aldehydes. Hayashi *et al.* studied the stereochemistry of α-cyano-β-alkoxy-β-alkylacrylic esters by nuclear magnetic resonance (NMR) spectroscopy and concluded that they were mixtures of *cis* and *trans* isomers.[1] Schwarz reported the stereochemistry of ethyl alkylidenecyanoacetates.[2] On the other hand, Zabicky examined ethyl arylidenecyanoacetates by infrared (IR) spectroscopy and suggested that the cyano group should be *cis* to the phenyl group.[3]

In connection with a synthetic study of 12-lipoxygenase inhibitors,[4] we needed to confirm the stereochemistry of condensation products of cyanoacetates with 3,4-dihydroxybenzaldehyde. We employed the ^{13}C-NMR LSPD (^{13}C-nuclear magnetic resonance long-range selective proton decoupling) method to determine the chemical structure. From a Newman projection, it seemed likely that the large ester group should be opposite to the bulky phenyl group, and *trans* elimination of water would occur to give a caffeic acid derivative. However, confirmation of the stereochemistry was required by ^{13}C-NMR spectroscopy and X-ray crystallographic analysis, because compound **1** exhibited the most potent 12-lipoxygenase-inhibitory activity among compounds reported so far.[4] Thus, we chose two compounds **1** and **2**, synthesized by condensation to give regioselectively a single isomer, and took the ^{13}C-NMR spectra to compare the coupling constants between the cyano carbon or ester carbon and the olefinic proton. Upon irradiation of the olefinic proton, three-bond couplings were observed at those carbons. Thus, the coupling constant of carbon *trans* to the olefinic proton is about 13—14 Hz in both **3** and **4**, while that of the ester carbon *cis* to the olefinic proton is 3 Hz in compound **4** and that of the cyano carbon *cis* to the proton is 8 Hz in compound **3**. The long-range three-bond coupling constants of **1** and **2** between the olefinic proton and the ester carbon (δ 164.52 in compound **1** and δ 164.55 in compound **2**) and 3 and 6.3 Hz, respectively. Moreover, upon irradiation of the olefinic proton, 15% nuclear Overhauser effect (NOE) was observed at the carbon at δ 164.52 in compound **1**.

The ^{13}C-NMR LSPD technique described above to determine the stereochemistry of the three-substituted olefinic bond seems to be useful and should be generally applicable to amides, aldehydes, *etc.* These results suggested that the ester group should be *trans* to the phenyl group and the chemical structures of the caffeic acid derivatives can be drawn as **1** and **2**. A fine crystal of compound **2** was obtained and subjected to X-ray crystallographic analysis. The ORTEP drawing of **2** is shown in Fig. 2, confirming that the phenyl group is *trans* to the ester group.

Experimental

Synthesis of Phenethyl 2-Cyano-3-(3,4-dihydroxyphenyl)-2-propenoate (2) i) EDC Reaction: To a stirred solution of 3.68 g (30 mmol) of phen-

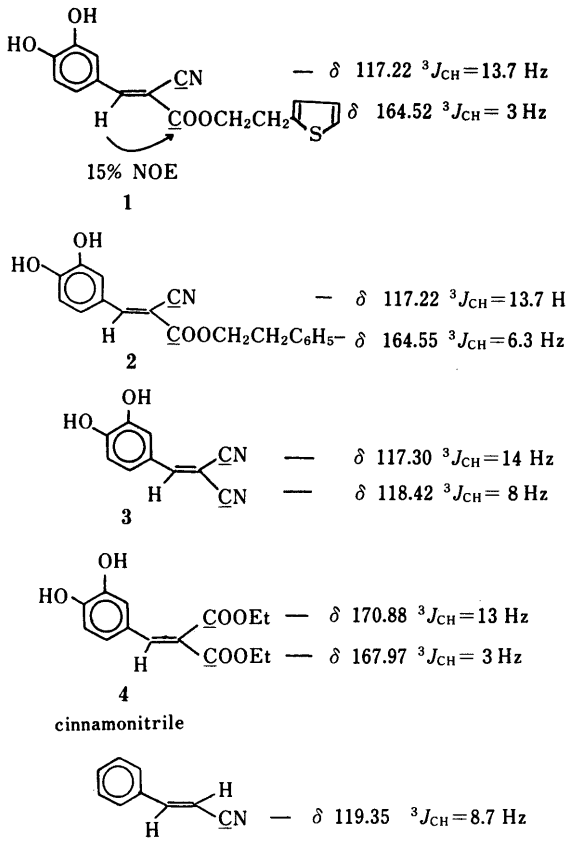

Fig. 1. The Chemical Shifts of Cyano and Ester Carbons and Three-Bond Coupling Constants between Olefinic Proton and Carbon

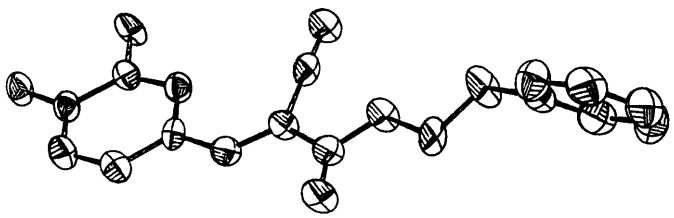

Fig. 2. ORTEP Drawing of Compound **2**

ethyl alcohol in 30 ml of *N,N*-dimethylformamide (DMF) was added a solution of 2.55 g (30 mmol) of cyanoacetic acid in 20 ml of DMF at 0 °C. To the stirred solution were added successively both solutions of 4.66 g (30 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in 5 ml of DMF and 0.37 g (3 mmol) of 4-dimethylaminopyridine (DMAP) in 10 ml of DMF at 0 °C. The solution was stirred for 18 h at room temperature. After DMF was removed *in vacuo*, the residue was quenched with brine and extracted with Et_2O. The organic layer was washed with brine, dried over anhyd. $MgSO_4$ and evaporated to leave the residue, which was purified by SiO_2 column chromatography (hexane : AcOEt = 4 : 1) to give 2.49 g (44%) of phenethyl cyanoacetate.

ii) Knoevenagel Reaction: To a solution of 1.73 g (12.5 mmol) of 3,4-dihydroxybenzaldehyde in 3 ml of DMF and 30 ml of benzene was added a solution of 2.49 g (13.2 mmol) of phenethyl cyanoacetate in 70 ml of benzene. After addition of 3 drops of piperidine, the solution was refluxed with a Dean–Stark apparatus for 2 h. After evaporation of the solvents under reduced pressure, water was added to the concentrated residue. After collection of the precipitated crude crystals, recrystallization from EtOH–H_2O afforded 3.5 g (91%) of the desired compound, mp 171—172 °C (yellow crystals). IR (Nujol): 2230, 1730 cm^{-1}. ^{1}H-NMR (270 Mz, CD_3OD) δ: 3.03 (2H, t, J=7 Hz), 4.45 (2H, t, J=7 Hz), 6.86 (1H, d, J=9 Hz), 7.15—7.39 (6H, m), 7.63 (1H, d, J=2 Hz), 8.05 (1H, s). *Anal.* Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.92; H, 4.93; N, 4.39. Similarly, 2-(2-thienyl)ethyl 2-cyano-3-(3,4-dihydroxyphenyl)-2-propenoate (**1**) was synthesized, mp 168—170 °C (yellow crystals). IR (Nujol): 2220, 1680 cm^{-1}. ^{1}H-NMR (270 MHz, CD_3OD) δ: 3.27 (2H, t, J=7 Hz), 4.45 (2H, t, J=7 Hz), 6.83 (1H, d, J=9 Hz), 6.68—6.99 (2H, m), 7.18—7.27 (1H, m), 7.35 (1H, dd, J=8, 2 Hz), 7.65 (1H, d, J=2 Hz), 8.08 (1H, s). *Anal.* Calcd for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.15; N, 4.44. Found: C, 60.99; H, 4.17; N, 4.40.

^{13}C-NMR Spectra ^{13}C-NMR spectra were measured on GN-300 instrument (75.5 MHz for ^{13}C). LSPD was obtained by selective decoupling of the olefinic proton during data acquisition. Steady-state NOE was observed by selective irradiation prior to data acquisition, with subtraction of a reference spectrum.[5]

X-Ray Crystallographic Analysis Crystal Data For Compound **2**: $C_{18}H_{15}NO_4$, MW = 309.32. The crystals were recrystallized from EtOH–H_2O, mp 171—172 °C. Yellow crystals, orthorhombic, space group $P2_12_12_1$ a=10.291 (1), b=32.323 (3), c=4.610 (1) Å, $\alpha=\beta=\gamma=90°$, U=1533.4(3) Å^3, Z=4, D_c=1.34 g/cm^3, F (000)=147, μ(Cu K_α)=5.28 mm^{-1}. X-Ray diffraction intensity data from the crystal (0.1 × 0.05 × 0.2 mm) were obtained on a Rigaku AFC diffractometer equipped with a rotating anode X-ray generator (50 kV—200 mÅ), using graphite-monochromated Cu K_α radiation (λ=1.5418 Å). A total of 1506 independent reflections with $2\theta<126°$ were collected in the ω scanning mode ($2\theta<45°$) and $\omega/2\theta$ scanning mode ($2\theta>45°$). The structure was solved by the direct method using MULTAN 84.[6] Hydrogen atoms were not determined. The refinement was carried out by the block-diagonal, least-squares method with anisotropic thermal parameters. The *R*-factor was reduced to 0.080 using 1422 reflections. All calculations were performed on a PANAFACOM U-1200 II in the Rigaku RASA-5RP system.

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