

Pyridines via Solid-Supported [2+2+2] Cyclotrimerization

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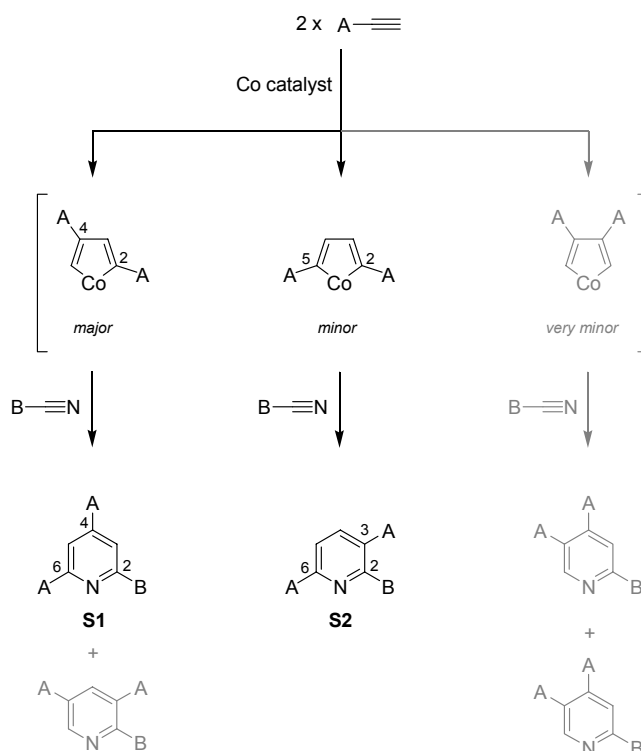
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Supplementary Data

Mechanistic Explanation of Regioisomer Formation

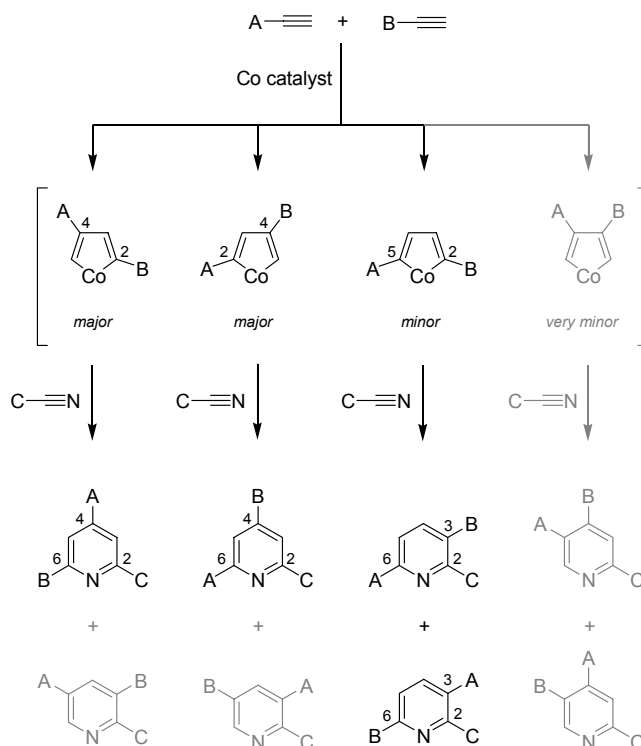
A wide variety of homogeneous catalysts are available for [2+2+2] cyclotrimerizations. As a result, numerous mechanistic pathways have been established for the different versions of this process, each characteristic for the metal involved in the particular system. The most common relies on metallacyclopentadienes, derived from the metal atom and two alkynes, as intermediates. Upon opening a coordination site, these intermediates – especially in case of a Co(III) center – readily complex a nitrile, which then inserts in a way that the nitrogen center is bound to the metal atom and a new carbon-carbon bond is formed. In this sequence regioselectivity can be seen to occur at two stages: 1) in the formation of the metallacyclopentadiene, and 2) in the subsequent insertion of the nitrile.

In case of a *homo* [2+2+2] cyclotrimerization, symmetrically disubstituted alkynes give rise to penta-substituted pyridines. In the case of monosubstituted (or unsymmetrically disubstituted) alkynes regioselectivity of these reactions becomes a major issue: both 2,4,6- and 2,3,6-trisubstituted pyridines are generated in substantial amounts (Scheme S1). Ratios of about 2:1 in favor of the 2,4,6-trisubstituted pyridine are typical. Therefore both, the 2,4- and 2,5-disubstituted cobaltacyclopentadiene intermediates participate in the cyclotrimerization, with the former being the predominant reactive species. Insertion of the nitrile is generally regioselective, leading to bond formation with the less sterically hindered carbon atom attached to the metal.



*Scheme S1. Mechanism leading to two major regioisomeric pyridines **S1** and **S2** in a homo [2+2+2] cycloaddition reaction of two identical alkynes. A and B are different substituents on the alkyne and the nitrile, respectively. Ligands on the Co-atom are omitted for clarity and very minor isomers are shown in grey.*

In case of a *crossed* [2+2+2] cyclotrimerization with two different terminal alkynes, a multitude of regioisomers can be expected (as depicted in Scheme S2). The major reactive cobaltacyclopentadienes are the 2,4-isomers. The 2,5-isomer represents a minor intermediate and the 3,4-isomer is probably not present due to sterical interactions of the two substituents A and B. Since the incorporation of two different alkynes leads to unsymmetrically substituted cobaltacyclopentadienes, the nitrile can react in two different orientations furnishing the potential formation of eight different pyridines. However, minimizing sterical interactions leads to the predominant generation of four major pyridines (the previously observed 2,4,6- and 2,3,6-isomers).

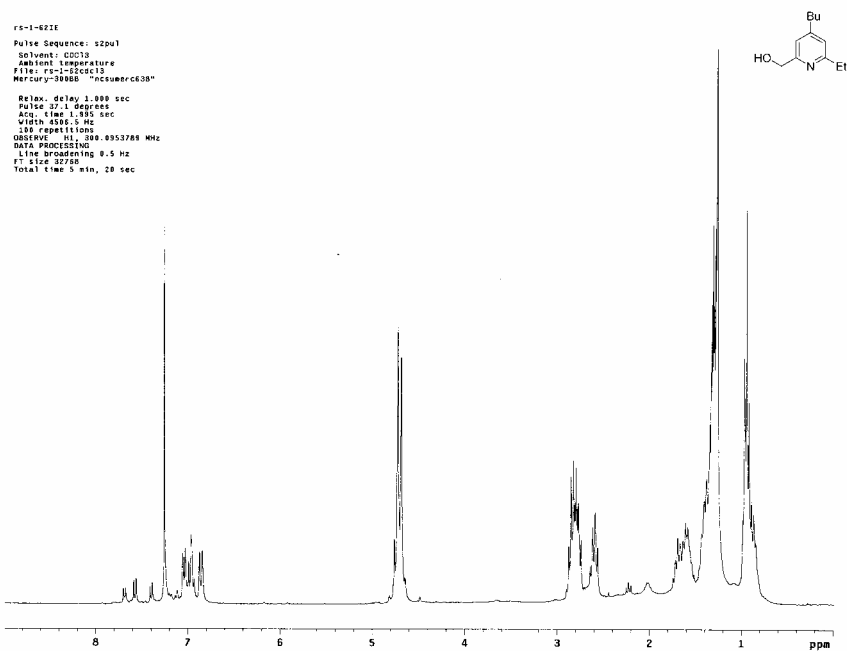
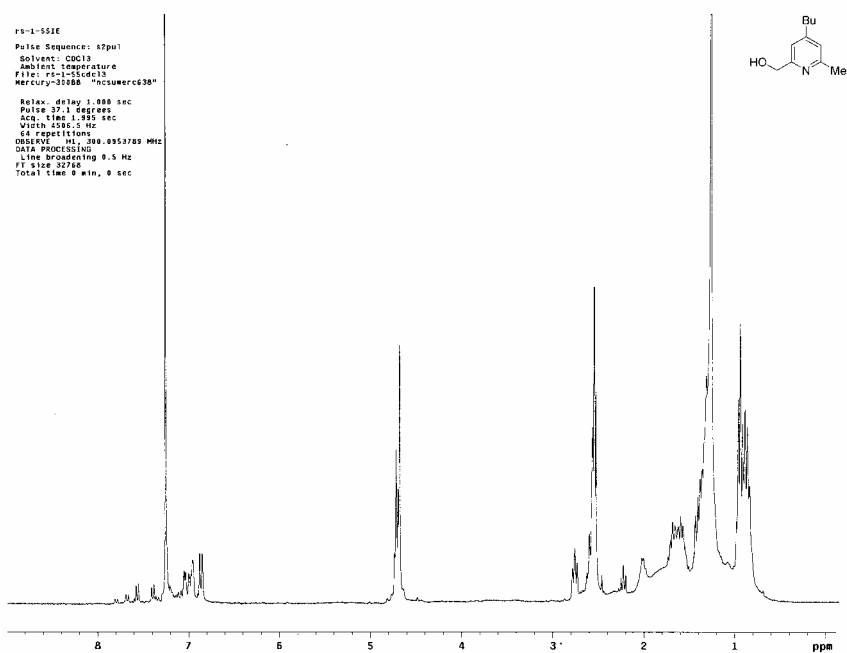


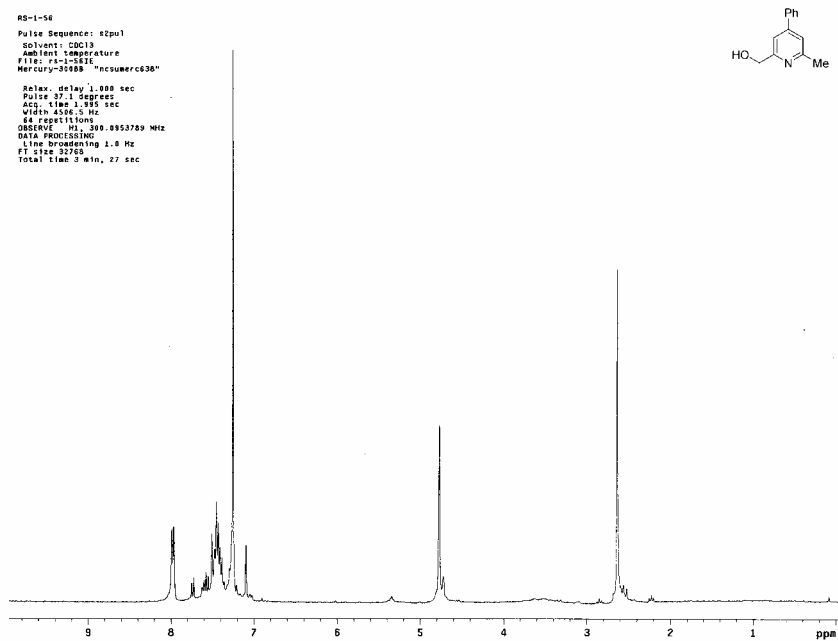
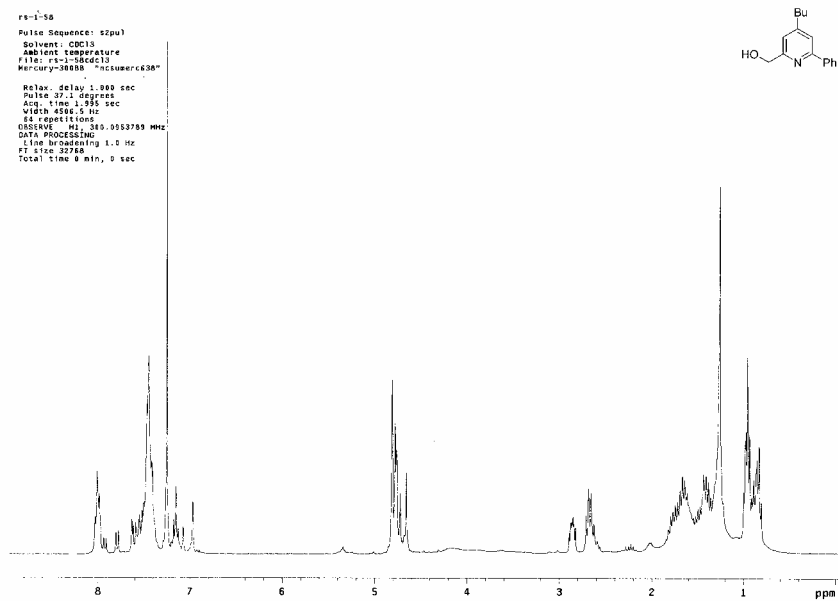
Scheme S2. Mechanism leading to eight possible regioisomers in a crossed [2+2+2] cycloaddition yielding pyridines. A, B, and C are different substituents on the alkynes and nitrile, respectively. Ligands on the Co-atom are omitted for clarity and very minor isomers are shown in grey.

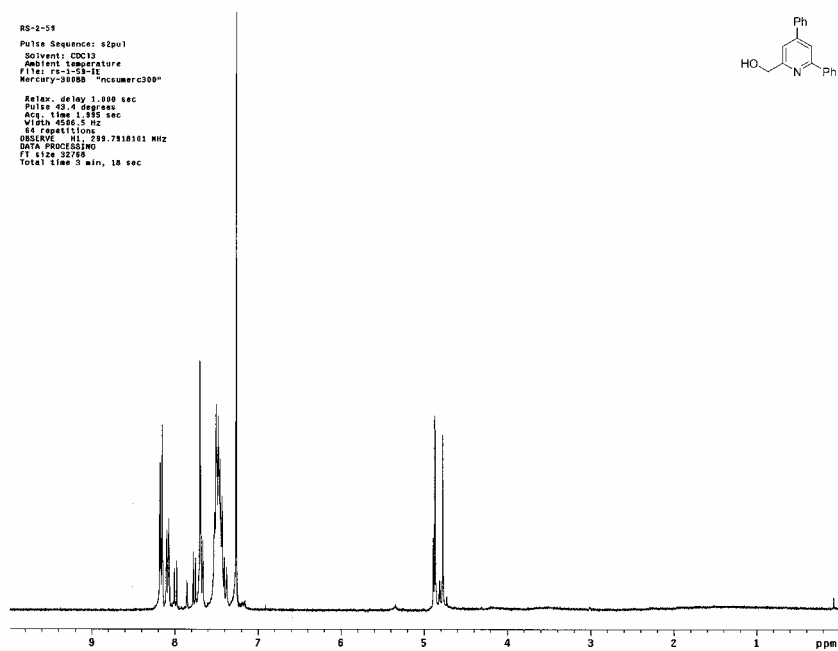
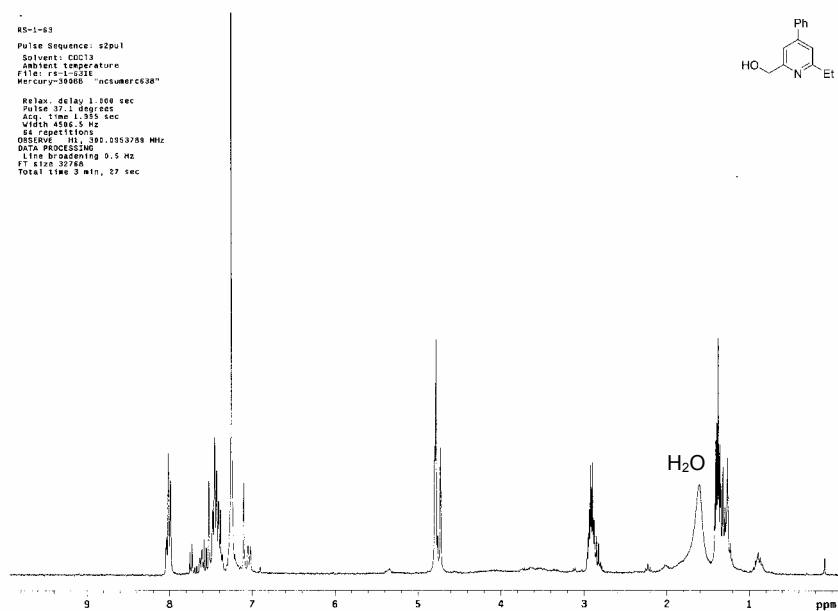
Sample Cyclotrimerization Protocol

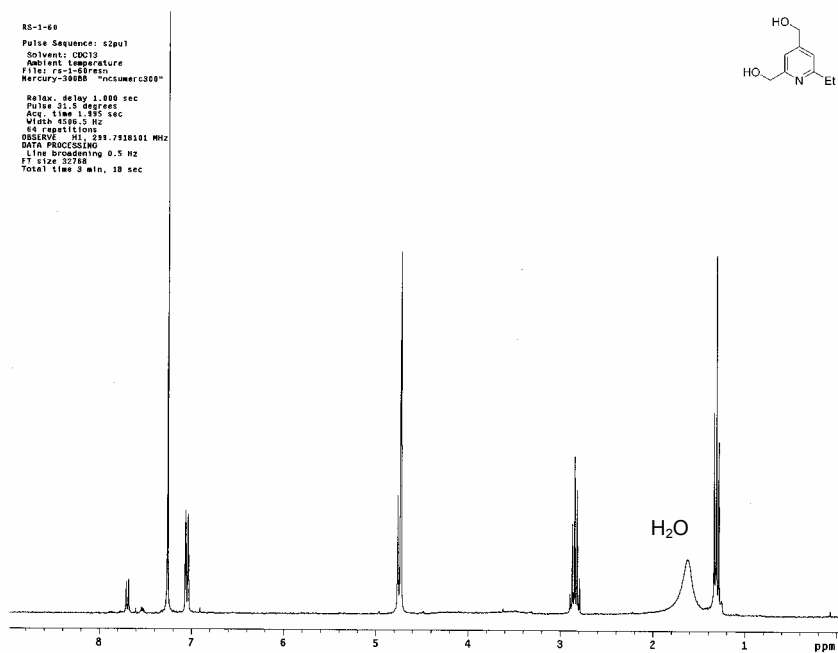
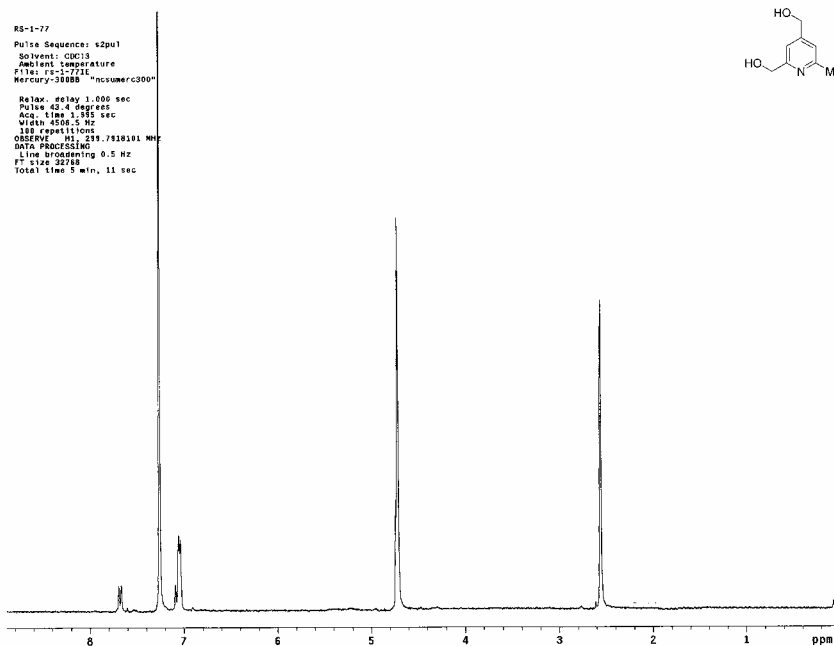
Trimethylamine oxide (0.1 eq.) was added to a flame dried vial containing the propargyl alcohol derivatized trityl resin (50mg), the nitrile (100 eq.), the soluble alkyne (10 eq.), and toluene (2 mL). The solution was degassed, the Co catalyst was added (0.25 eq), and the reaction was heated to 80 °C. The catalyst addition was repeated every 12 h for 48 h. The resin was transferred to a syringe filter and washed with DCM and MeOH (4 alternating rinses with 4 mL each). The product was then cleaved from the resin by treatment with 1% TFA (DCM, 1 h), filtered into a short DowexWX8-100 column (200 mg) and eluted with ammonia in methanol (2 M, 2 mL) to yield the cyclotrimerization product.

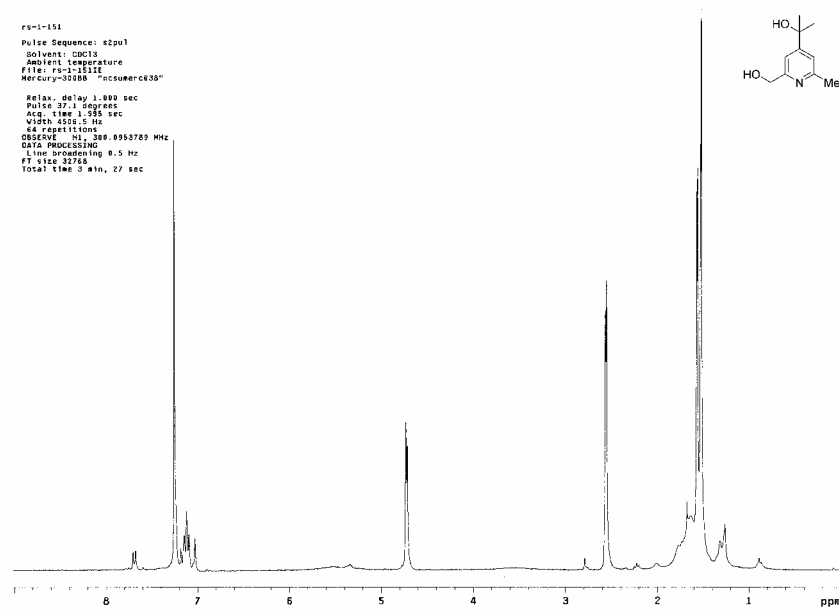
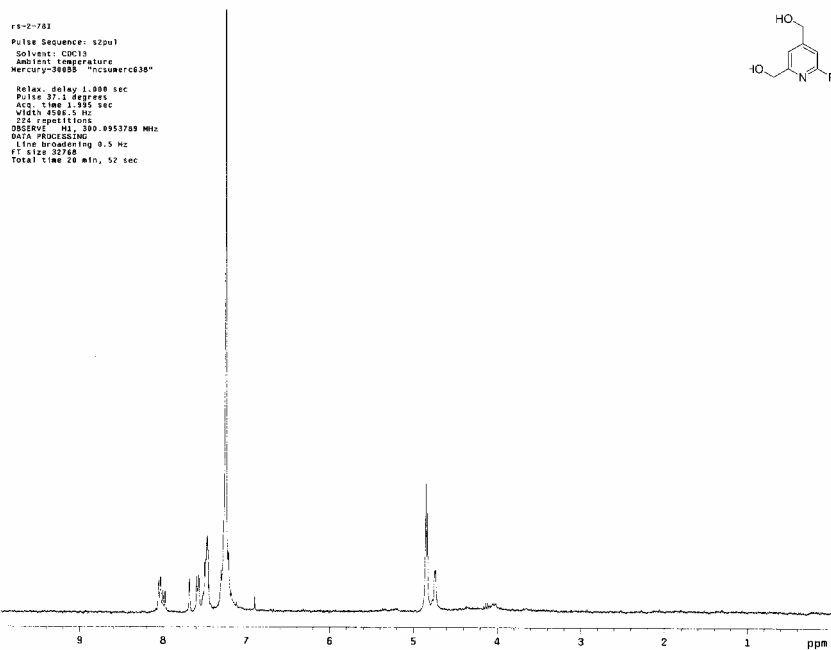
¹H NMR Spectra of Synthesized Pyridines

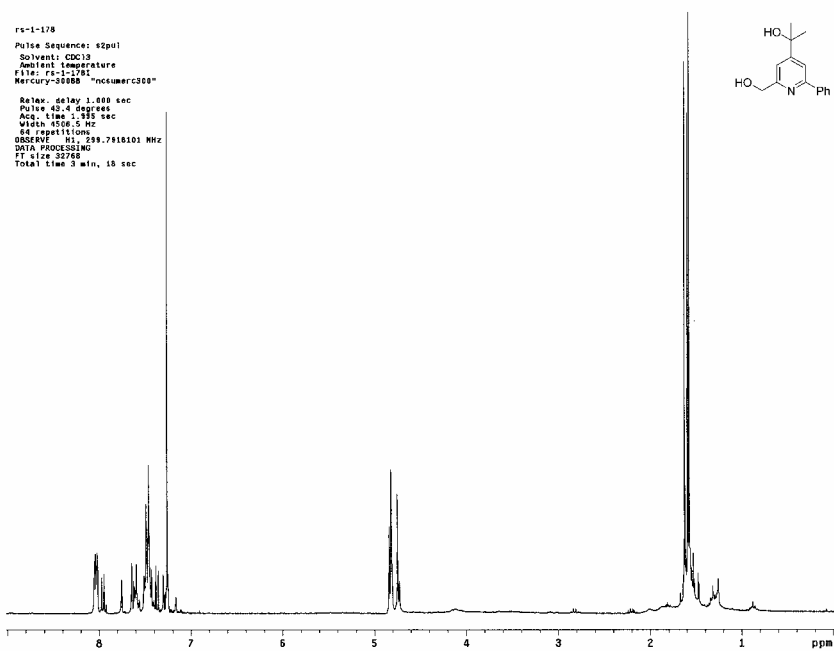
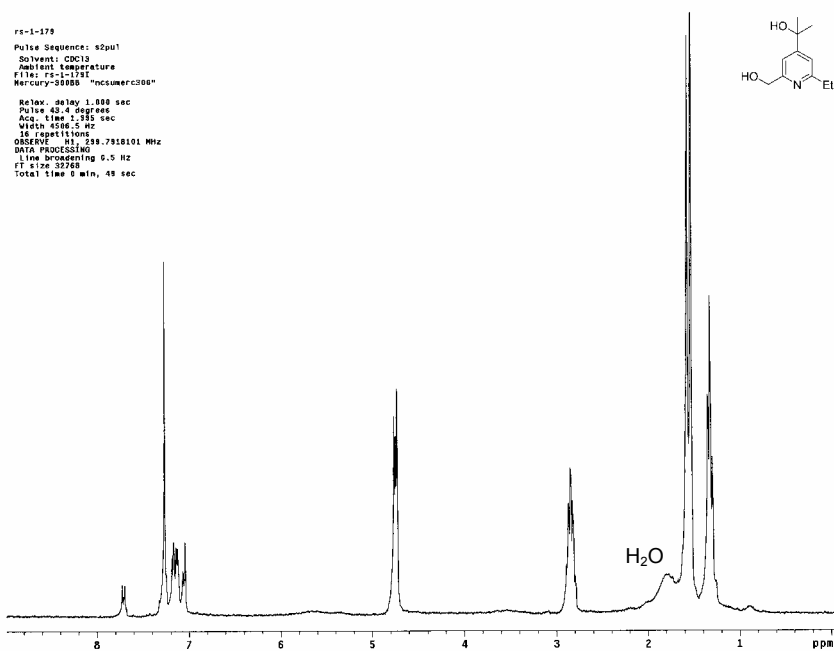


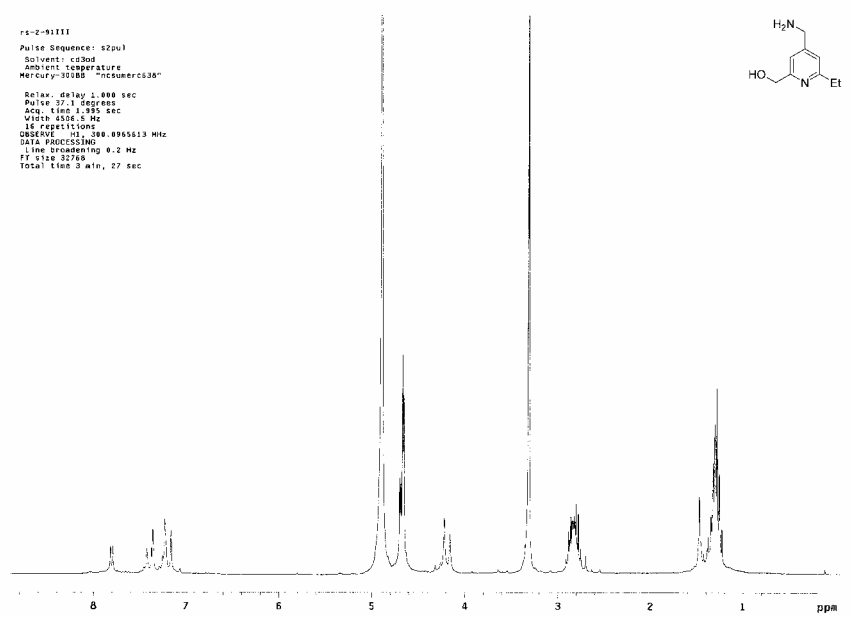
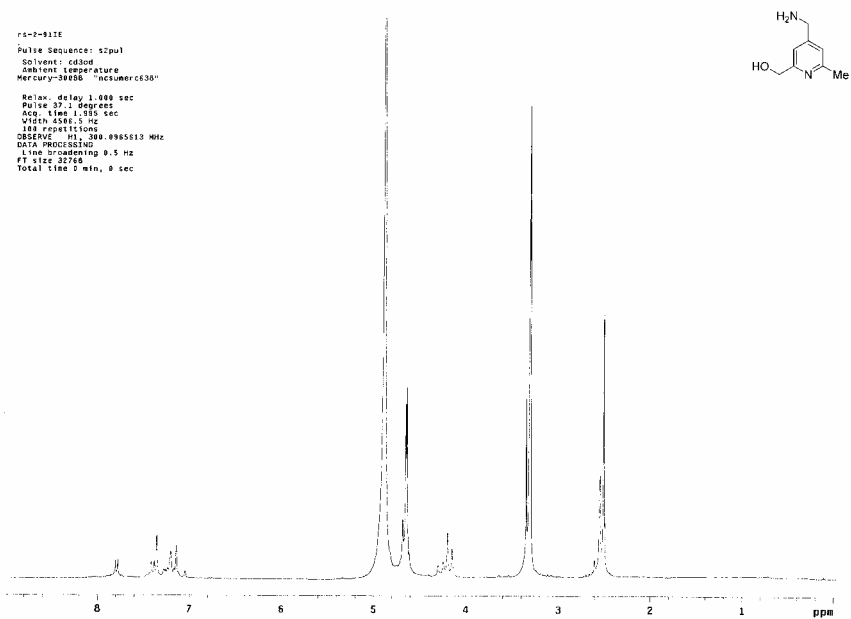


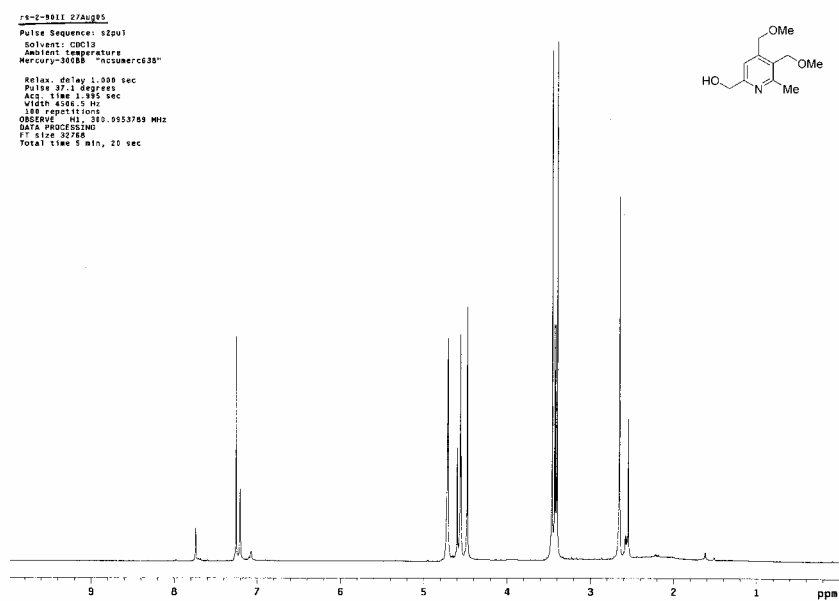
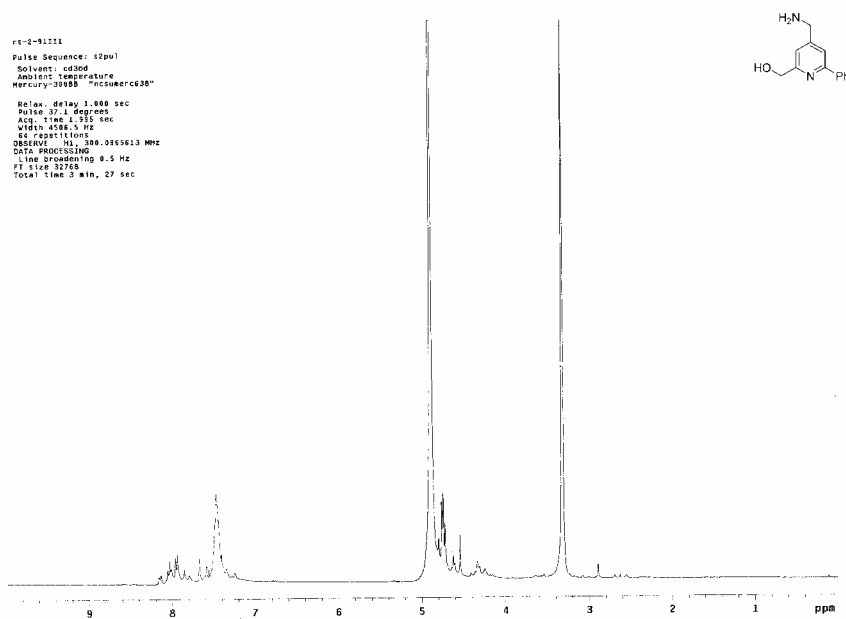


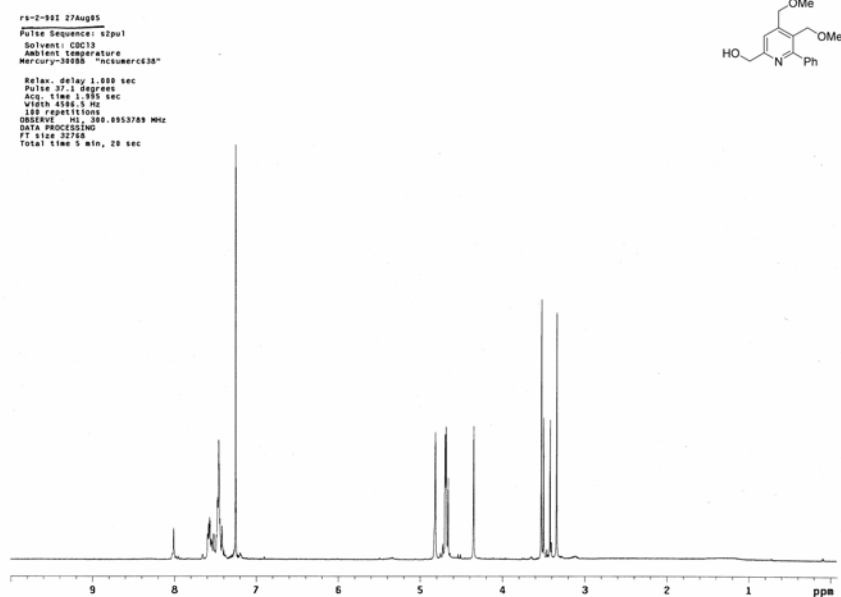
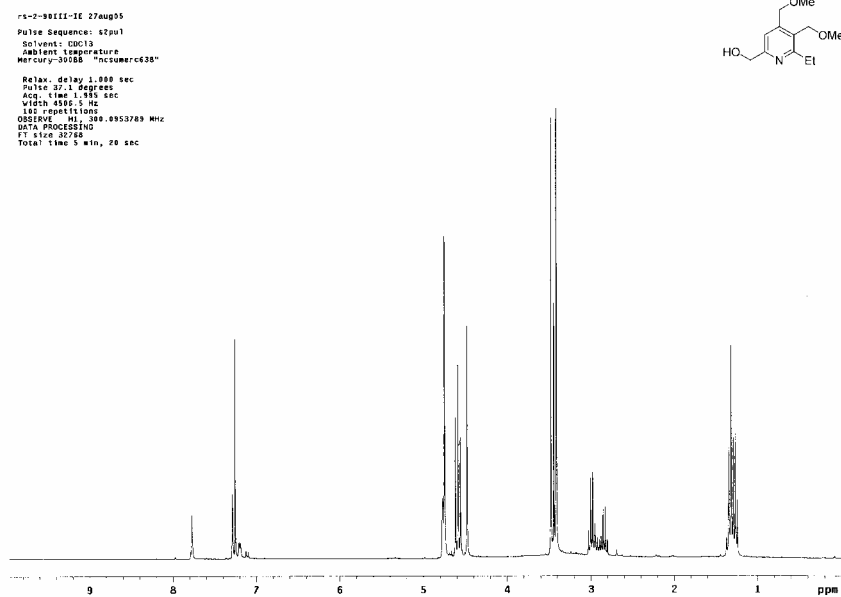












MS Data of Synthesized Pyridines

High Resolution Exact Mass measurements of either the molecular or the protonated molecular ions were carried out using electric field scanning and fast-atom bombardment with a JEOL (Tokyo, Japan) HX 110HF mass spectrometer (resolving power 10000, accelerating voltage 10 keV and ion source temperature 40°C) using polyethylene glycol ions in the appropriate mass range as a reference standard. Low Resolution Mass measurements were conducted with the same instrument

Compound	m/z [M+H] ⁺ (calculated)	m/z [M+H] ⁺ (found) ^a
15	180.1388	180.1380
16	194.1545	194.1546
17	242.1545	242.1553
18[#]	200.2	200.2
19	214.1232	214.1222
20	262.1232	262.1242
21[#]	153.2	153.1
22	168.1025	168.1013
23	216.1025	216.1027
24[#]	182.2	182.2
25	196.1338	196.1322
26	244.1338	244.1348
27[#]	153.2	153.2
28[#]	167.2	167.2
29[#]	215.3	215.2
30	212.1287	212.1289
31	226.1443	226.1448
32	274.1443	274.1429

[#] Only low-res MS data could be obtained.