Reissert Compound Studies LXVI [1]. Regioselective Synthesis of Pyridine Reissert Analogs [2]

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The reaction of ethyl chloroformate and pyridine with diethylaluminum cyanide as the cyanide source gave the Reissert analog, 1-ethoxycarbonyl-4-cyano-1,4-dihydropyridine and not the expected 1,2-dihydro regio isomer. Under the same conditions, 3-bromopyridine also directly gave the corresponding 1,4-dihydro Reissert analog. Reinvestigation of trimethylsilylcyanide, as the cyanide source, resulted in the observation that both regio isomers are formed and the ratio of these isomers are affected by both solvent polarity and by copper(I) iodide.

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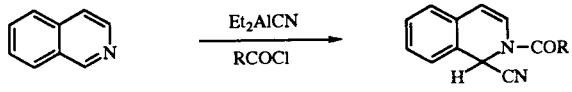
We have recently reported that diethylaluminum cyanide [3] serves as a cyanide source to give Reissert compounds [4] (for example see Scheme 1). We now report that

Scheme 1



the reaction of pyridine with diethylaluminum cyanide and ethyl chloroformate in methylene chloride did not give the expected Reissert analog **1**. Rather, the regio isomer, 1-ethoxycarbonyl-4-cyano-1,4-dihydropyridine (**2**) was obtained.

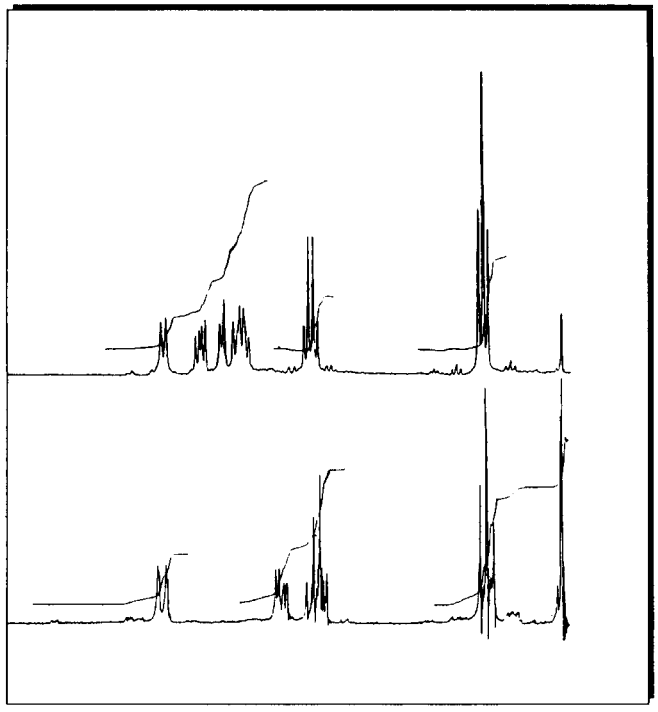
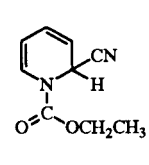


Figure 1. The pmr spectra of the 1,2-dihydro regio-isomer (top) and of the 1,4-dihydro isomer.

The pmr spectra of **1** (see Figure 1) exhibits a doublet at 6.6 ppm due to the proton on the 6-position of the pyridine ring. The pmr spectra of **2** shows a doublet at 6.9 ppm due to protons on the 2- and 6-positions of the pyridine ring. A doublet of doublet assigned to H-4, a doublet due to the H-2 proton and a multiplet due to the H-3 and H-5 protons are in the range of 5.3 to 6.3 ppm in **1**. In contrast, the pmr spectra of **2** shows no signals in this region of the pmr spectrum. Compound **2** shows a doublet of doublet assigned to H-3 and H-5 at 4.8-5.0 ppm. The spectra of both compounds show the typical triplet and quartet signals of the ethyl group. The H-4 proton of **2** is buried underneath the right shoulder of the quartet due to the methylene protons of the ethyl group. It should be noted that the above mentioned pmr of **2** is consistent with the pmr pattern observed for 1-diphenylcarbamoyl-4-cyano-1,4-dihydropyridine (**3**) [5] and *N*-alkyl-4-cyano-1,4-dihydropyridines [6]. The mass spectra of both isomers was determined to be in accordance with the mass spectra of Reissert compounds [7].



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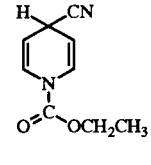

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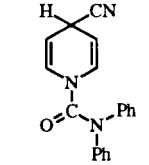

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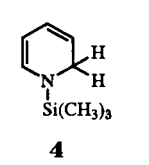

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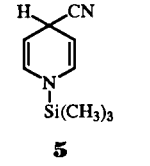

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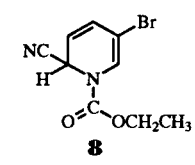

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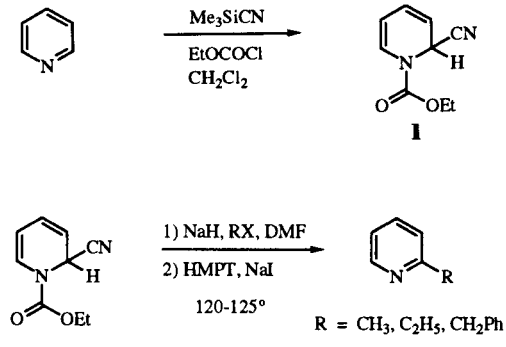
Further evidence for the structure of **2** can be found in the ir spectra of **2**. Cook and Lyons [8] demonstrated, in

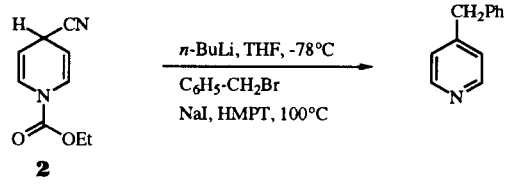
their study of dihydropyridines from silylation of pyridines, that the ir spectra may be used as a diagnostic for the identification of 1,2- *vs* 1,4-dihydropyridines. The assigned olefinic stretch (-C=C-N-C=C-) of *N*-trimethylsilyl-1,4-dihydropyridine (**5**) was observed at 1675 cm^{-1} compared to 1625 cm^{-1} observed for the same stretch (-C=C-C=C-N-) of *N*-trimethylsilyl-1,2-dihydropyridine (**4**). The same tendency was established for *N*-trimethylsilyl-3-methyl-1,2-(and 1,4)-dihydropyridines. Winters and co-workers [6] observed the same trend in their study of cyano adducts of 1-substituted pyridinium salts. The olefinic stretch for **1** was observed at 1650 cm^{-1} [5] and at 1686 cm^{-1} for **2** and thus are consistent with the fore mentioned trends of ir olefinic stretch in dihydropyridines.

Alkylation of the 1,2-dihydro Reissert analog **1** using sodium hydride in a dimethylformamide solution followed by hydrolysis with sodium iodide in HMPT gives the 2-substituted pyridines [5] (Scheme 2). No 4-substituted pyridines were observed suggesting that isomerization of the generated 1,2-dihydro anion to the 1,4-dihydro anion does not occur. Attempts to alkylate the 1,4-dihydro Reissert analog **2** using sodium hydride failed. However, alkylation with benzylbromide using *n*-butyllithium in tetrahydrofuran at -78° gave after hydrolysis 4-benzylpyridine (Scheme 3).

Scheme 2

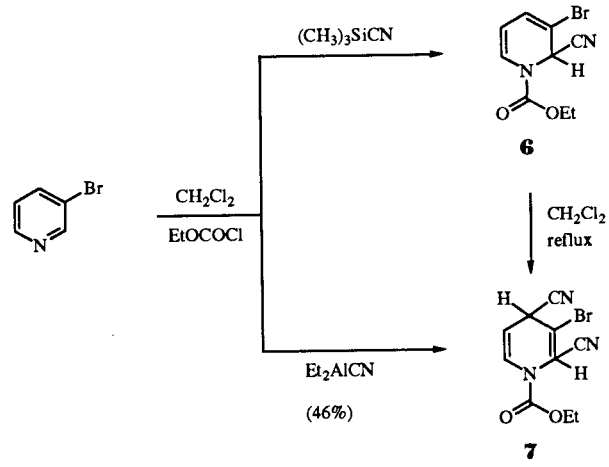


Scheme 3



It has been reported [5] that 3-bromopyridine, trimethylsilylcyanide, and ethyl chloroformate generates the expected 1,2-dihydro Reissert analog **6** (Scheme 4). When the 1,2-dihydro species **6** is refluxed in methylene chloride the isomerization of the 1,2-dihydro compound to the 1,4-dihydro structural isomer **7** takes place. In contrast, use of diethylaluminum cyanide as the cyanide source directly gave the 1,4-dihydro Reissert analog **7** from 3-bromopyridine and ethyl chloroformate (Scheme 4). Reaction of one equivalent of diethylaluminumcyanide with two equivalents each of 3-bromopyridine and ethyl chloroformate gave the 1,4-dihydro Reissert analog. To assure that no isomerization was occurring during the workup process the solvent was removed at low temperature. This still gave only the 1,4-dihydro Reissert analog.

Scheme 4



Theoretical computations on both the 1,2- and 1,4-dihydro Reissert analog were performed for the purpose of gaining some insight as to the stability and reactivity of these regio-isomers. These calculations revealed that the 1,4-dihydro species (ΔH_f = -18.25 kcal/mole) was more stable than the 1,2-dihydro species (ΔH_f = -12.17 kcal/mole). These results suggest that the 1,4-dihydro species is the more thermodynamically stable product, while the 1,2-dihydro moiety is the more kinetically favored product. Furthermore, the 1,4-dihydro (3.76 Debye) regioisomer structure also has a higher dipole moment than the 1,2-regioisomer (2.43 Debye) compound implying that the 1,4-dihydro isomer is the more polar. A similar relationship was observed for the 1,2-dihydro and 1,4-dihydro Reissert analogs of 3-bromopyridine.

The calculated heat of formations of the bromo substituted pyridine Reissert analog coincide with the observation that the 1,2-dihydro compound isomerized to the more stable 1,4-dihydro moiety. However, the 1,6-dihydro

Table 1
Summary of AM1 Calculations

Regio isomer	ΔH_f (kcal/mole)	Dipole (Debye)
1 (1,2-dihydro)	-12.17	2.43
2 (1,2-dihydro)	-18.25	3.76
6 (3-bromo-1,2-dihydro)	-6.37	2.25
8 (3-bromo-1,6-dihydro)	-7.19	2.95
7 (3-bromo-1,4-dihydro)	-12.42	4.12

species **8**, having the mid range theoretical stability of the other regioisomers was not observed. Furthermore, thermal isomerization for the non-substituted pyridine Reissert analog was also not observed. These calculated values of heat of formation and dipole moments are summarized in Table 1.

According to the calculated dipoles, compound **2** has the higher polarity and suggests that reaction in a polar medium would favor formation of **2**. Reinvestigation of the earlier work [5] showed that both isomers were formed using trimethylsilylcyanide in methylene chloride. Solvent studies were therefore implemented to observe the solvent and catalyst effect on the formation of the pyridine Reissert compounds. These results are summarized in Table 2.

Table 2

1 *vs* **2** Pyridine Reissert Compound Formation As a Function of Solvent and Catalyst

% CH_2Cl_2 (with Me_3SiCN)	% Toluene	Composition of regio-isomer (by pmr) **1**, (1,2)	**2**, (1,4)	Overall Yield (%)
100	0	69	31	62
75	25	79	21	90
50	50	86	14	27
25	75	100	0	66
0	100	100	0	65
Et_2AlCN, toluene		0	100	54
Et_2AlCN, toluene, 24 hours		0	0	0
ME_3SiCN, neat $CH_3CH_2CO_2Cl$		67	33	6
ME_3SiCN, CuI, CH_2Cl_2		100	0	53
ME_3SiCN, CuI, THF		100	0	65
ME_3SiCN, dimethoxyethane		0	0	0
ME_3SiCN, acetonitrile		100	0	21

Various toluene and methylene chloride compositions (vol/vol) were studied. As the polarity of the solvent system decreases (*e.g.* increase amount of toluene used) the amount of the 1,4-dihydro Reissert analog observed in the pmr becomes less while the amount of the 1,2-dihydro regioisomers increase. This would seem to be readily explained in terms of **2** being more polar than **1** and therefore would be favored in the more polar solvent system. However, repeating the reaction in neat ethyl chloroformate, much more polar than methylene chloride or toluene, yielded no significant increase of regioisomers than using methylene chloride itself. Dimethoxyethane yielded no Reissert compound while acetonitrile gave only **1** in low yield. Anhydrous copper(I) iodide [9], which has been used as a catalyst to selectively yield *N*-acyl-4-alkyl-1,4-dihydropyridine compounds from Grignard reagents, yielded only the 1,2-dihydro pyridine Reissert analogs. The reagent diethylaluminumcyanide, in toluene only, gave the expected 1,4-dihydro isomer 54% yield. Extension of the reaction time to 24 hours gave only a inseparable mixture of compounds.

What has been determined, with respect to regio selectivity in the synthesis of *N*-acyl-1,X-dihydropyridine (X = 1 or 4) Reissert analogs is as follows: First, the reagent diethylaluminum cyanide is specific for attack at the 4-position of the *N*-acyl-pyridinium salt. This allows the synthesis of 4-substituted pyridines, however, the process does limit itself in that attempted scale up to large scale reactions yield inseparable mixtures. Secondly, solvent polarity does affect the ratio of 1,2- to 1,4-dihydro pyridine Reissert compound analogs, using trimethylsilylcyanide. The more non-polar solvents favoring the 1,2-dihydro regio isomer.

EXPERIMENTAL

All melting points were determined on a Thomar-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 710B spectrometer. Proton magnetic resonance spectra were determined on a Hitachi Perkin Elmer 12-R-24B intrument. Pyridine was dried over potassium hydroxide, methylene chloride and toluene were dried over molecular sieves. Microanalysis was performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. High resolution mass spectra was obtained from the Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln, Lincoln, Nebraska (NSF, Biology Division Grant No. DIR9017262). Molecular weights are within 5 ppm of calculated values.

Computations.

Theoretical calculations were performed using the AM1 [10] semi-empirical method as implemented in the AMPAC 2.1 [11] series of programs. The geometry was fully optimized with no constraints on geometry. Force constants were computed to characterize each point on the potential surface as a minima [12]. Computations were carried out on the UMKC VAX 6460 from Digital Equipment Corporation.

Preparation of 1-Ethoxycarbonyl-2-cyano-1,4-dihydropyridine (**1**).

Using the procedure reported by Kant and Popp [5], except no aluminum chloride was used, equimolar amounts of pyridine, trimethylsilyl cyanide, and ethyl chloroformate gave **1** as a near colorless oil; pmr (deuteriochloroform): δ 1.3 (t, 3H), δ 4.3 (q, 2H), δ 5.6 (m, 2H), δ 5.9 (d, 1H), δ 6.3 (dd, 1H), δ 6.9 (d, 1H); ms: m/z (%) 178.07410 (12.69, $C_9H_{10}N_2O_2$, M^+), 133.04001 (2.61, $C_7H_5N_2O$), 119.06139 (3.69, $C_7H_7N_2$), 105.04492 (18.88, $C_6H_5N_2$), 79.04283 (100, C_5H_5N).

Preparation of 1-Ethoxycarbonyl-4-cyano-1,4-dihydropyridine (**2**).

All glassware was preheated, assembled hot, and allowed to cool with an atmosphere of nitrogen. While maintaining the nitrogen atmosphere, 12 ml (12 mmoles) of 1 *M* diethylaluminum cyanide dissolved in toluene was added over 10 minutes to 30 ml of dry methylene chloride containing 0.48 g (6.07 mmoles) of pyridine and 1147 μl (12 mmoles) ethyl chloroformate. The reaction was stirred for 3 hours and poured onto 100 g of ice containing 100 ml 5% sodium hydroxide. The mixture was stirred until the ice melted (*ca.* 1 hour) followed by extracting with methylene chloride (3 x 50 ml). The organic solvent was then washed with 5% sodium hydroxide (1 x 25 ml), water (1 x 25 ml), 10% hydro-

chloric acid (1 x 25 ml), brine (1 x 25 ml), dried over anhydrous magnesium sulfate (24 hours). Evaporation of the methylene chloride under reduced pressure and placing under vacuum overnight yielded 0.11 g (10%) of **2** as a reddish-brown oil; ir (thin film): 2240 (weak), 1721, 1686 cm^{-1}; pmr (deuteriochloroform): δ 1.3 (t, 3H), δ 4.1-4.5 (m, 3H), δ 4.8-5.0 (dd, 2H), δ 6.9 (d, 2H).

The reddish-brown oil, after further drying over anhydrous magnesium sulfate for a period of one week and placed under vacuum for 48 hours, gives a brown precipitate. Eluting the brown precipitate through a small silica gel plug with methylene chloride gives a white powder which sublimes (ambient temperature, *ca.* 5 mm Hg) giving colorless elongated rods having the same pmr as the oil product, mp 58-59°; ms: m/z (%) 178.07471 (46.52, $C_9H_{10}N_2O_2$, M^+), 152.07114 (5.62, $C_8H_{10}NO_2$), 149.03537 (2.18, $C_7H_5N_2O_2$), 133.03987 (7.11, $C_7H_5N_2O$), 119.06050 (7.86, $C_7H_7N_2$), 106.05270 (14.59, $C_6H_6N_2$), 105.04528 (100, $C_6H_5N_2$), 79.04239 (90.37, C_5H_5N), 52.03115 (10.37, C_4H_4).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.67; N, 15.71. Found: C, 60.49; H, 5.83; N, 15.29.

Preparation of 4-Benzylpyridine from **2**.

Compound **2** (0.11 g, 0.62 mmole), in *ca.* 20 ml of tetrahydrofuran was placed in a dry ice/acetone bath (-78°). To the solution was added 0.40 ml (0.64 mmole) of *n*-butyllithium and after 5 minutes 76.1 μl of benzyl bromide (0.64 mmole) was added. The mixture was stirred for 3.5 hours in the cold and then allowed to stir at room temperature for *ca.* 19 hours. The reaction mixture was quenched with 100 ml of water and extracted with chloroform (4 x 50 ml). The chloroform was removed under reduced pressure. To the recovered material was added 0.46 g (3.07 mmoles) of sodium iodide and 1 ml HMPT. The mixture was stirred at 120°-125° for 3.25 hours after which time the reaction mixture was poured into *ca.* 50 g of ice. The aqueous solution was extracted with methylene chloride (2 x 50 ml). The methylene chloride was washed with brine (1 x 50 ml) and dried over anhydrous magnesium sulfate. Removal of the methylene chloride under reduced pressure yielded a semi-solid material which was washed with anhydrous ether. The ether was evaporated yielding 0.040 g (40%) of 4-benzylpyridine as a light brown liquid; pmr (deuteriochloroform): δ 8.5 (d, 2H), δ 7.0-7.4 (m, 7H), δ 3.95 (s, 2H); picrate, mp 140-141° lit [13] 140-141°.

Preparation of 1-Ethoxycarbonyl-3-bromo-4-cyano-1,4-dihydropyridine (**7**).

Diethylaluminumcyanide (2 ml, 2 mmoles) was added dropwise over a five minute time period into a methylene chloride (*ca.* 30 ml) solution containing 0.16 g (1 mmole) of 3-bromopyridine and 191 μl (2 mmoles) of ethyl chloroformate. Workup proceeded as in preparation of **2** yielding 0.08 g (46%) of **5** which on trituration with hexanes gave a beige color solid which was eluted through a short column of silica gel with methylene chloride. Evaporation of the methylene chloride gave **5** as a white powder; pmr (deuteriochloroform): δ 7.15 (s, 1H), δ 6.85 (d, 1H), δ 4.75 (dd, 1H), δ 4.35 (m, 3H), δ 1.30 (t, 3H); ir (potassium bromide): 2278, 1726, 1686 cm^{-1}; mp 66-67°, lit 66-67.5° [5].

Solvent and Catalyst Reactions.

To 30 ml of solvent (with the appropriate solvent composition) containing 1 equivalent of pyridine, 2 equivalents of trimethylsilylcyanide, and 0.01 equivalent of aluminum chloride 2 equivalents of ethyl chloroformate was slowly added dropwise. The reaction mixture was stirred for 2.25 hours, after which time the mixture was poured into 25 ml of 5% sodium hydroxide containing ice (*ca.* 100 g). After the ice melted, *ca.* 150 ml of methylene chloride was added and the phases separated. Those mixtures containing 75% and 100% toluene were diluted with more toluene instead of methylene chloride. The organic layers were washed with water (25 ml), 10% hydrochloric acid (25 ml), brine (25 ml) and dried over anhydrous magnesium sulfate. The organic solvents were removed under reduced pressure and placed under vacuum for at least 2 hours. The composition of regioisomers was determined by pmr which consisted of comparison of the integrated area of proton H-6 of **1** versus the area of either H-3 or H-5 proton of **2**.

The catalyst reactions used 0.07 mole % of copper(I) iodide in either methylene chloride or tetrahydrofuran with trimethylsilylcyanide as the cyanide source and a reaction time of 1.5 hours. All reactions were carried out at ambient temperature with the reaction using tetrahydrofuran being carried out under an atmosphere of nitrogen. Compound **1** was isolated as mentioned above.

All other reactions in toluene, dimethoxyethane, and acetonitrile maintained a molar ratio of 1:2:2 with respect to pyridine, ethyl chloroformate, and to the cyanide source (Et_2AlCN or Me_3SiCN) except for the reaction which was carried out in neat ethyl chloroformate. Isolation of **1** or **2** was accomplished as mentioned above.

Acknowledgement.

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