STUDIES IN THE DIHYDROPYRIDINE SERIES III[1]. PIPERIDEINE SYNTHONS BY NUCLEOPHILIC SUBSTITUTION TO DIHYDROPYRIDINETRICARBONYL CHROMIUM (0) COMPLEXES.

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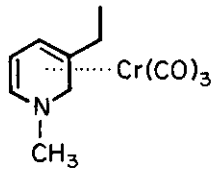
Abstract - Overall nucleophilic substitution of N-methyl-3-ethyl-1,2-dihydropyridinetricarbonylchromium (0) complex afforded the corresponding 2,5-disubstituted, complexed, unit. Oxidative work-up conditions provided the parent heterocycles. In a similar fashion, N-methyl-3-ethyl-1,6-dihydropyridinetricarbonylchromium (0) provided 3,5-disubstituted products.

Previous reports from these laboratories described the preparation of the stable complexes N-methyl-3-ethyl-1,2-dihydropyridinetricarbonylchromium (1), and N-methyl-3-ethyl-1,6-dihydropyridinetricarbonylchromium (2)[2]. An extension of this work allowed the stabilisation of other, more complicated dihydropyridines related to[3], and including[4] the elusive dehydrosecodine (3).



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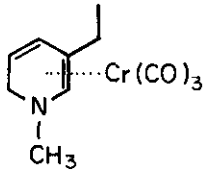

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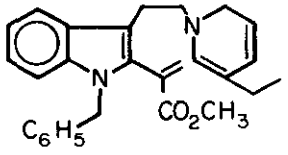

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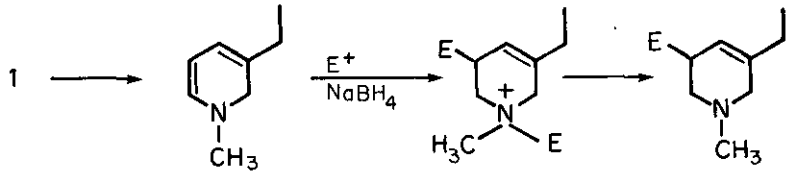
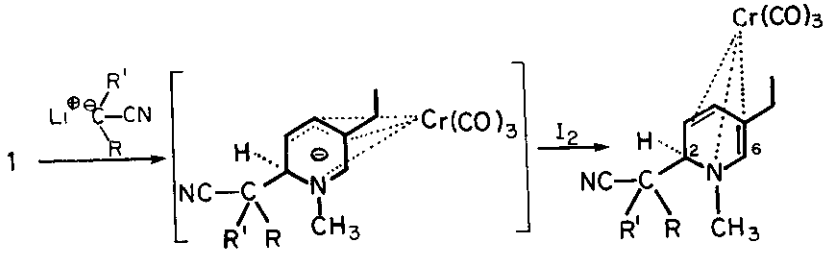
Use of the simple complexes (1) and (2) enabled release of the labile dihydropyridine ligand from the metal, and subsequent alkylation β- to the nitrogen provided 3,5-disubstituted piperideines according to eq. (1)[1].



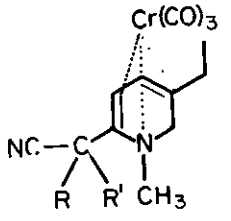
Semmelhack[5-7] has shown that π-benzenoid tricarbonylchromium (0) complexes are sufficiently electron deficient at the ring carbons to allow nucleophilic addition to the system by a variety of nucleophiles. Subsequent oxidative cleavage of the metal from the so formed intermediates

gave substituted arenes via an overall nucleophilic substitution. Reduced pyridines have an obvious potential as intermediates in alkaloid synthesis and the facility of nitrogen extrusion from such systems points to a further utility of such synthons in other areas of organic synthesis. The work outlined here shows that the analogous heterocyclic π-complexes exemplified by (1) and (2) also undergo nucleophilic addition reactions and that the carbon-carbon bond formation is, at least for these simple systems, regiospecific.

Here addition (at -78°) of α-lithioisobutyronitrile to a solution of the red complex (1) in THF gave an immediate pale yellow solution which regained the deep red colour on treatment with iodine (1 equiv). Removal of the solvent and chromatography on silica gel gave the crystalline red complex (4) (R = R^1 = CH_3) (54%), mp. 115° (decomp). The infrared spectrum confirmed the presence of the carbon monoxide ligands with absorbances at 1850, 1875 and 1950 cm^{-1}, while a weak band at 2220 cm^{-1} indicated the inclusion of a nitrile function. The molecular formula $C_{15}H_{18}CrN_2O_3$ was defined by elemental analysis and high resolution mass spectrometry. The substitution pattern was determined from the 270 MHz 'Hmr spectrum (C_6D_6) δ: 4.55 (1H, d, J = 7 Hz, C_4-H), 4.34 (1H, s, C_6-H), 2.75 (1H, bt, J ≈ 7 Hz, C_3-H), 2.65 (1H, d, J = 6 Hz, C_2-H), 2.00 (2H, m, $-CH_2CH_3$), 1.86 (3H, s, $-NCH_3$), 0.88 (3H, t, J = 7 Hz, $-CH_2CH_3$), 0.14 (3H, s, $-CH_3$), 0.07 (3H, s, $-CH_3$). Double irradiation experiments confirmed this assignment. The orientation of the substituent in (4) is presumed "trans" as a consequence of the recognised steric bulk of the coordinated metal[7] which perhaps explains the absence of the double bond isomer (5) also derivable from an intermediate such as (6).

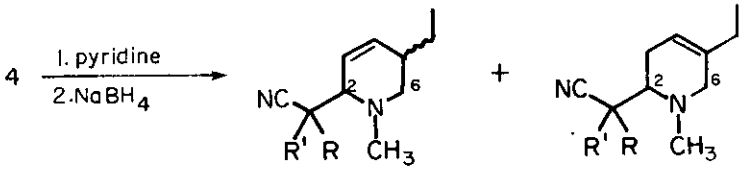


6, R = R' = CH_3
9, R = H, R' = CH_3



5, R = R' = CH_3

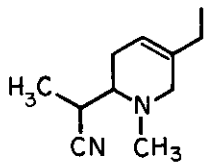
As in earlier work[1], pyridine could be used to liberate the labile ligand from the coordinated metal. Thus reaction of (4) with pyridine in dry ether followed by reduction with sodium borohydride gave a mixture of the tetrahydropyridines: (7) [(34%) as a mixture of diastereoisomers; ν_{max}: 2230 cm^{-1}; $C_{12}H_{20}N_2$ requires 192.1626, found 192.1622. 'Hmr δ: ($CDCl_3$) 6.07 (0.5 H, bd, J = 10 Hz, C_3-H), 6.00 (0.5 H, bd, J = 10 Hz, C_3-H), 5.85 (0.5 H, dt, J = 10, 3 Hz, C_4-H), 5.68 (0.5 H, dt, J = 10, 3 Hz, C_4-H), 2.9 - 3.05 (1H, m, C_2-H), 2.58 (1.5 H, s, $-NCH_3$), 2.50 (1.5 H, s, $-NCH_3$), 1.37 (6H, s, 2 x $-CH_3$), 0.95 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$)] and (8) [(8%); ν_{max}: 2240 cm^{-1}; M^+ found 192.1619; 'Hmr δ($CDCl_3$): 5.52 (1H, bs, C_4-H), 3.45 - 3.70 (1H, m, C_2-H), 3.10 (1H, bd, J = 16 Hz, C_6-H), 2.65 - 2.85 (1H, m, C_6-H), 2.50 (3H, bs, $-NCH_3$), 1.95 (2H, q, J = 7 Hz, $-\underline{CH_2}CH_3$), 1.51 (3H, s, $-CH_3$), 1.40 (3H, s, $-CH_3$), 1.00 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$)].



7, R = R' = CH_3 8, R = R' = CH_3

A more efficient route to (8) (67%) was found by reaction of the complex (1) with the anion of isobutyronitrile, as before, followed by protonation of the intermediate (6) with trifluoroacetic acid and subsequent oxidative cleavage with iodine.

In a similar manner, α-lithiopropionitrile provided the anion (9) which on protonation and oxidation gave (10) [(57%), ν_{max}: 2235 cm^{-1}; $C_{11}H_{18}N_2$ required 178.1470, found 178.1464; 'Hmr ($CDCl_3$) δ: 5.41 (1H, bs, C_4-H), 3.16 (1H, d, J = 16 Hz, C_6-H), 3.10 (1H, d, J = 16 Hz, C_6-H), 2.93 (1H, quintet, J = 7 Hz, $-\underline{CH}(CN)CH_3$), 2.69 (1H, m, C_2-H), 2.35 (3H, s, $-NCH_3$), 1.92 (2H, q, J = 7 Hz, $-\underline{CH_2}CH_3$), 1.31 (3H, d, J = 7 Hz, $-CH\underline{CH_3}$), 0.99 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$)]. The use of the anion of acetonitrile gave a 55% yield of (11) [ν_{max}: 2240 cm^{-1}; $C_{10}H_{16}N_2$ requires 164.1313, found 164.1313; 'Hmr ($CDCl_3$) δ: 5.40 (1H, bs, C_4-H), 2.94 (2H, bs, $-CH_2CN$), 2.40 (3H, s, $-NCH_3$), 1.95 (2H, q, J = 7 Hz, $-\underline{CH_2}CH_3$), 1.00 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$)].



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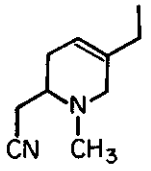

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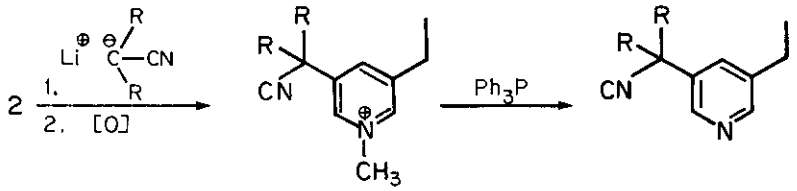
Alternatively, reaction of the 1,6-dihydropyridine complex (2) with α-lithioisobutyronitrile as before, gave a pale yellow solution which, on reaction with iodine and subsequent treatment with excess silver nitrate (methanol solution at -78°) gave the pyridinium salt (12); ^{1}Hmr (D_2O) δ: 8.77 (1H, s, C_6-H), 8.65 (1H, s, C_2-H), 8.52 (1H, s, C_4-H), 4.35 (3H, s, $-NCH_3$), 2.87 (2H, q, J = 7 Hz, $-\underline{CH_2}CH_3$), 1.86 (6H, s, $-C(\underline{CH_3})_2CN$), 1.26 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$). The 3,5-disubstituted pattern indicated by this nmr spectrum confirmed the expected position of nucleophilic addition to (2). Thus the overall process resembles conjugate addition to the enamine of an α,β-unsaturated carbonyl compound.

Subsequently, the parent heterocycle (13) was available by reaction of (12) with triphenylphosphine in acetonitrile (150°, sealed tube), [^{1}Hmr ($CDCl_3$) δ: 8.2 - 8.8 (2H, broad envelope C_2-H and C_6-H), 7.64 (1H, s, C_4-H), 2.71 (2H, q, J = 7 Hz, $-\underline{CH_2}CH_3$), 1.76 (6H, s, $-C(CH_3)_2CN$), 1.28 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$); ν_{max}: 2230 cm^{-1}; ms, m/e: 174.1161 (M^+, $C_{11}H_{14}N_2$ requires 174.1159), 159, 144, 106], providing a route to 3,5-disubstituted pyridines.

For the analogous benzenoid cases a wide variety of nucleophiles were found suitable; in general carbanions derived from carbon acids of pK_a = 25 or higher could be used[5]. In the present work, thus far, ester enolates and carboxylic acid dianions did not show any observable reaction with (1).



12, R = CH_3 13, R = CH_3

Although further studies are required to determine the overall scope of this approach the method described here does provide regiospecific substitution of dihydropyridinetricarbonylchromium (0) complexes and a route to substituted reduced pyridines. Further aspects of this work are currently under investigation.

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References and Notes

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