Cyclization of *N*-Acetyl-*N*-(*ortho*-chlorophenyl)-4-aminobut-2-enenitrile with Zerovalent Nickel Complexes: Conformational Analysis of the *N*-3-Cyanoprop-2-enyl Chain

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Cyclization of *N*-acetyl-*N*-(*ortho*-chlorophenyl)-4-aminobut-2-enenitrile with zerovalent nickel complexes, prepared from bis(acetylacetonate)nickel(II), with either pyridine or triphenylphosphine as ligands, and triethylaluminium as reducing agent has been carried out. The α-methylene protons show a diastereotopic effect which could be explained by a rigid bridged hydrogen bound through the oxygen atom of the acetanilide group to one of the α-methylene protons and partially hindered rotation around the *N*-phenyl bond, due to the *ortho*-substitution. Conformational analysis of the fragments of the *N*-3-cyanoprop-2-enyl chain has been carried out using the Sternhell treatment.

N-Alk-2-enyl-*ortho*-chloroanilines are efficiently converted into indole and indoline derivatives by reaction with zerovalent nickel complexes. This intramolecular cyclization reaction has been the subject of some of our previous papers.[1,2]

Moreover, the protons of the methylene group and the olefinic protons of the *N*-3-cyanoprop-2-enyl chain in some of these compounds show a complex ^{1}H NMR spectrum. This is a common feature to compounds having a N–C=O anilide group, a *N*-β-cyanoethyl chain with a terminal CN group, and an *ortho*-substituted aromatic ring.[3,4] In this paper we present a conformational analysis of the protonic systems of the *N*-3-cyanoprop-2-enyl chain and discuss its role in the mechanism of the intramolecular cyclization reaction.

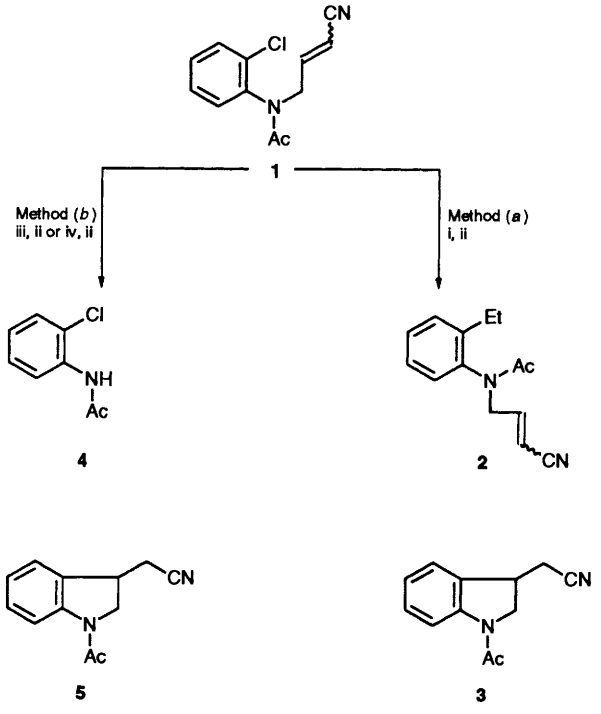
Results and Discussion

N-Acetyl-*N*-(*o*-chlorophenyl)-4-aminobut-2-enenitrile **1** (*E*:*Z*, 81:19) was prepared from *o*-chloroacetanilide and a mixture of the *E*- and *Z*-isomers of 4-bromobut-2-enenitrile,[5] with sodium hydride as base, in anhydrous THF, at room temperature.[1]

The reaction of compound **1** with zerovalent nickel complexes prepared *in situ* is shown in Scheme 1. Method (*a*), treatment of compound **1** with bis(acetylacetonate)nickel(II) with pyridine as ligand in the presence of the reducing agent triethylaluminium in anhydrous THF, afforded the nitrile **2** (42%) and the dihydroindole **3** (34%). The formation of compound **2** can be explained by nucleophilic substitution of the chlorine atom of the aromatic ring, in a π-aryl–nickel intermediate, by an ethyl anion of the triethylaluminium, which is in excess.[1]

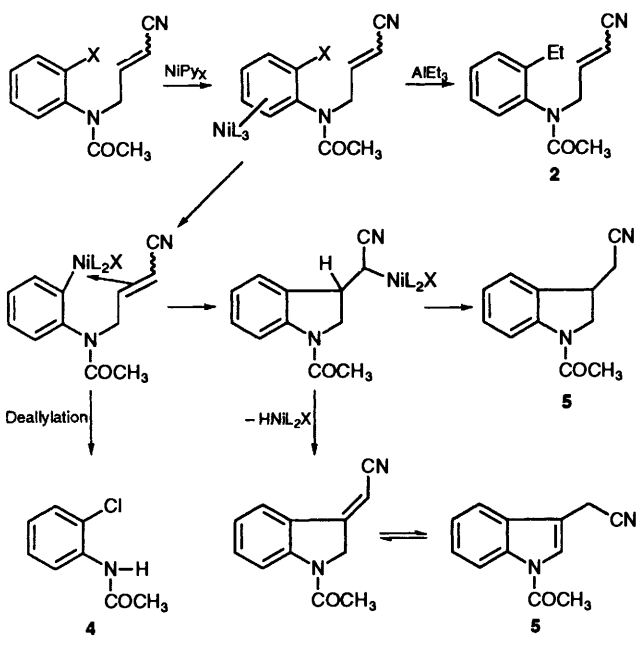
The nature of the products obtained by Method (*b*) [treatment of compound **1** with bis(acetylacetonate)nickel(II), triethylaluminium and triphenyl phosphine in THF] was determined by the relative ratio of the reagents. Thus treatment of the isomer compound (*E*)-**1** with tetrakis(triphenylphosphine)nickel(0), prepared *in situ* from a 3:1 molar ratio of triethylaluminium and bis(acetylacetonate)nickel(II), gave only the deallylation product **4** (80%), identified as *o*-chloroacetanilide. Deallylation of compound **1** is likely to be caused by transfer from a coordinated C=O–Al species. Treatment of compound **1** with the complex obtained from a 1:1 mixture of triethylaluminium to bis(acetylacetonate)nickel(II) decreased the yield of the deallylation product **4** (40%) and afforded the indole **5** (50%).

An approach to the reaction mechanism is shown in Scheme 2. The σ-nickel intermediate complex for (*E*)- or (*Z*)-isomers, in the intramolecular reaction, requires the approach of the π-C=C double bond close to the plane of the σ-bond between the aromatic carbon and nickel and this conformational position of the alkenyl chain is reached by thermal motion of the molecule (reaction temp. 80 °C). In this molecular orientation minimal steric hindrance arises from the substituents in either (*E*)- and (*Z*)-isomers.



Scheme 1 *Reagents and conditions:* Method (*a*) i, $Ni(acac)_2$, py, $AlEt_3$, THF; ii, NH_4Cl (aq.). Method (*b*) iii, $Ni(acac)_2$, Ph_3P, $AlEt_3$ (1:4:3), THF; iv, $Ni(acac)_2$, Ph_3P, $AlEt_3$ (1:4:1), THF.

The (*E*)- and (*Z*)-isomers of the compound **1** and also the compound (*Z*)-**2** show a complex ^{1}H NMR spectrum for the protons of the *N*-3-cyanoprop-2-enyl chain, $NCH_2CH{=}CHCN$; the α-methylene protons are diastereotopic. Fig. 1(*a*) shows the ^{1}H NMR spectrum of the *N*-3-cyanoprop-2-enyl fragment of compound (*E*)-**1**. A first-order AMRX proton system is generally shown by compounds bearing a CON anilide group, a



Scheme 2

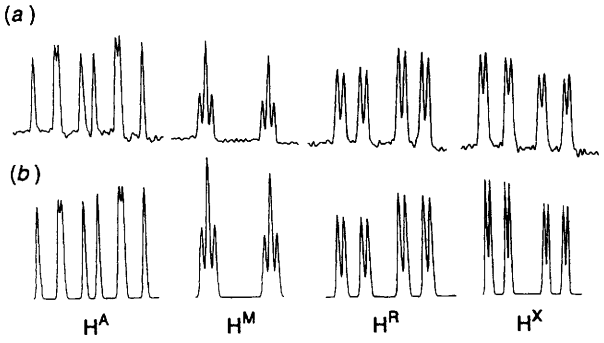


Fig. 1 ^{1}H NMR spectrum of the AMRX proton coupling system. Experimental (*a*) and computer simulated (*b*) spectra for the CH_2–CH=CH fragment of the compound (*E*)-**1**.

Table 1 ^{1}H NMR frequencies (in ppm), coupling constants (in Hz) and r.m.s. error values for the AMRX type proton system of the compounds (*E*)-**1**, (*Z*)-**1** and (*Z*)-**2**

	(*E*)-**1** Cl	(*Z*)-**1** Cl	(*Z*)-**2** CH_2CH_3
δH^A	6.74	6.67	6.64
δH^M	5.44	5.42	5.42
δH^R	4.72	4.70	4.94
δH^X	4.03	4.49	4.12
J_{AM}	16.32	11.00	11.00
J_{AR}	5.96	6.73	5.80
J_{AX}	6.88	6.99	7.75
J_{MR}	−1.59	−1.49	−1.56
J_{MX}	−1.46	−1.44	−1.42
J_{RX}	−15.85	−15.70	−15.52
r.m.s.	0.040	0.059	0.052
CO–CH_3	1.84	1.86	1.80
ArH	7.63–7.23	7.55–7.21	7.40–7.00
CH_2	—	—	2.58 (*J* 7.65)
CH_3	—	—	1.26 (*J* 7.65)

N-β-cyanoethyl chain and an *ortho*-substituted (chloro, methyl or ethyl) aromatic ring.[3,4] The replacement of the *N*-β-cyanoethyl chain by the *N*-3-cyanoprop-2-enyl fragment leads to a similar diastereotopic effect for the α-methylene protons. Also, replacement of the chlorine atom in the *ortho* position of the aromatic ring by methyl or ethyl groups, does not affect the ^{1}H NMR spectrum of the compound (*Z*)-**2**, which shows an analogous proton system.

^{1}H NMR Analysis.—First-order AMRX proton systems of this type have been analysed using the iterative computer program LAOCOON III.[6] The frequencies, coupling constants and r.m.s. error values (differences between observed and calculated line positions) are given in Table 1. The agreement between the observed (*a*) and computer simulated (*b*) spectra, for compound (*E*)-**1**, confirms the analysis and assignment of the protons (Fig. 1 and Table 1).

The absolute values of $J_{allylic,cis}$ [compound (*E*)-**1**] are greater than those of $J_{allylic,trans}$ [compounds (*Z*)-**1** and (*Z*)-**2**], as has been previously reported for acyclic systems.[7]

Conformational Analysis.—By comparison with similar proton systems in *ortho*-(chloro or methyl)-*N*-β-cyanoethylanilides by ^{1}H NMR and monocrystal X-ray diffraction,[2] the diastereotopic effect shown in the methylene group of the *N*-3-cyanoprop-2-enyl fragments of compounds **1** and **2** can be explained by hindered rotation around the N-phenyl bond due to the *ortho*-substitution. This steric crowding pushes the oxygen atom of the strongly polarized N–C=O acetanilide group close to H^R of the methylene group, causing a deshielding effect on the H^R proton, which therefore appears at lower field. We have observed previously by single crystal X-ray diffraction techniques that the intramolecular contact between a methylenic proton and the oxygen atom of a N–C=O anilide group was 2.40 Å (hydrogen bridged bond).[3] We took this assumption as a starting point for the conformational analysis of the *N*-3-cyanoprop-2-enyl fragment $NCH_2CH{=}CHCN$ in the compounds (*E*)-**1**, (*Z*)-**1** and (*Z*)-**2** which was carried out using the system of eqns. (1)–(3), where J_{MR} and J_{MX} are the experimental

$$J_{MR} = X_I J^I_{MR} + X_{II} J^{II}_{MR} + X_{III} J^{III}_{MR} \quad (1)$$

$$J_{MX} = X_I J^I_{MX} + X_{II} J^{II}_{MX} + X_{III} J^{III}_{MX} \quad (2)$$

$$X_I + X_{II} + X_{III} = 1 \quad (3)$$

values of the allylic coupling constants; X_I, X_{II} and X_{III} are the molar fractions of the conformations **I**, **II** and **III**; and J^i_{MR} and J^i_{MX} (i = **I**–**III**) are the theoretical values of the allylic coupling constants in conformations **I**–**III** resulting from the Sternhell treatment,[7] which relates the allylic coupling constants J_{trans} and J_{cis} with the dihedral angles showed in Fig. 2 for the (*E*)- and (*Z*)-isomers of compounds **1** and **2**:

$$J_{cis} = 3.00\sin^2\theta - 3.00,\ 0 < \theta < 180° \quad (4)$$
$$J_{cis} = 4.75\sin^2\theta - 3.00,\ 180 < \theta < 360°$$

$$J_{trans} = 4.25\sin^2\theta - 3.50,\ 0 < \theta < 180° \quad (5)$$
$$J_{trans} = 6.00\sin^2\theta - 3.50,\ 180 < \theta < 360°$$

These equations were deduced from the Sternhell graphical relationship of J_{cis} and J_{trans} *vs.* θ using the computer program 'DERIVE'.[8] Fig. 2 shows the Newman projections of the conformations **I**, **II** and **III**; in the conformer **I**, the anchorage of H^R of the methylene group to the oxygen atom of the N–C=O acetanilide group is represented by a dashed line.

Table 2 gives the results of the conformational analysis of the *N*-3-cyanoprop-2-enyl fragment in the compounds **1** and **2**. The conformational equilibria in all the cases shows the preference order **I** > **II** > **III**, which is in agreement with the steric hindrance of the substituents observed by 'crystal structure' molecular models.

The strongly electronegative –CN group decreases the bond

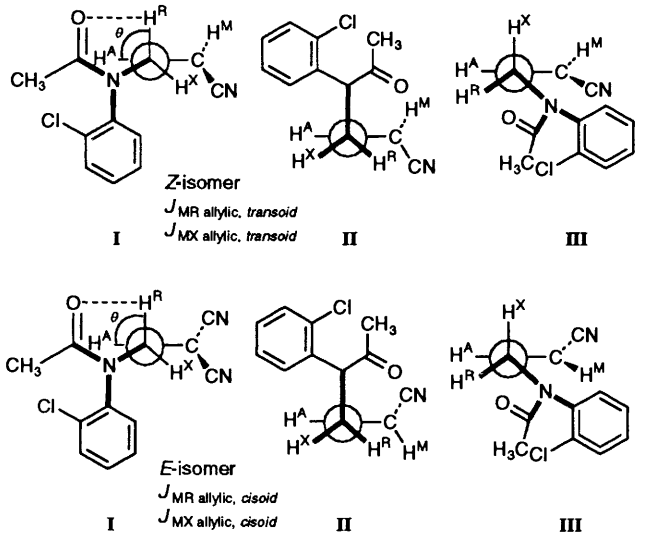


Fig. 2 Newman projections of the conformations **I**, **II** and **III** for compounds **1** and **2**. Dihedral angles between the H^R–C–C= (or H^X–C–C=) and H^M–C=C– planes.

Table 2 Conformational populations from the J_{MR} and J_{MX} values of Table 1

Compound	I(%)	II(%)	III(%)
(*E*)-**1**	58.0	35.4	6.6
(*Z*)-**1**	52.9	38.8	8.3
(*Z*)-**2**	54.7	37.8	7.5

order of the double bond, and also the absolute magnitude of the negative allylic coupling constants found experimentally. There is no data available for –CN, but for CHO *vs.* CH_2CH_3 this decrease ranges in magnitude from $\Delta J = 0.25$ for J_{cis} to $\Delta J = 0.15$ for J_{trans}.[7b,9] Eqns. (4) and (5) do not take into account this electronegative effect to calculate the theoretical values of allylic coupling constants for conformations **I**, **II** and **III**. Also, the ArNHCO substituent on the methylene group may influence the value of *J* through steric or polar effects. These facts could be considered as a drawback of this method. However, in spite of the above limitations the magnitude of allylic coupling constants may be utilized for the determination of conformational populations, since the effects of the electronegative substituents are not so big as to reverse the conformational preference.[9] Conformation **I** in (*E*)- and (*Z*)-isomers represents an approach to the reactive position in the intermediate σ-nickel complex, closing the plane of π-double bond onto the σ-arylnickel bond.

Experimental

Melting points were measured on a hot-stage microscope and are uncorrected. The IR spectra were recorded on a Pye Unicam SP1100 spectrophotometer. The ^1H NMR spectra were registered in a 200 MHz Brucker WH-200-SY instrument, in deuteriated chloroform using tetramethylsilane as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in hertz (Hz). Mass spectra were obtained in a Hewlett-Packard 5985 A GC–MS system, at an ionizing energy of 70 eV.

Elemental analyses were carried out in a Perkin-Elmer 2400CHN instrument. Preparative TLC was carried out on silica gel Merck 60 PF_{254}. Column chromatography was done on silica gel Merck 60 (70–230 mesh ASTM, 0.063–0.200 nm) and TLC on silica gel Merck 60 F_{254}. The solvents used were purified and dried by standard methods.

Reaction of N-*Acetyl*-N-(o-*chlorophenyl*)-4-*aminobut*-2-*enenitrile with Zerovalent Nickel Complexes.—Method* (a) *with zerovalent* (*pyridine*)$_x$*nickel complex. General procedure.* The compound **1** (0.13 g, 0.5 mmol), in dried THF, was added to a solution of zerovalent (pyridine)$_x$nickel complex, prepared from bis(acetylacetonate)nickel(II) (0.14 g, 0.5 mmol), anhydrous pyridine (0.21 g, 2.5 mmol, 0.22 cm^3) and triethylaluminium (0.12 g, 1.0 mmol, 0.30 cm^3 of a 50% solution in anhydrous toluene), in dried THF. The mixture was stirred under reflux at 80 °C for 5 h, and later hydrolysed with a saturated aq. solution of ammonium chloride. The organic layer was separated, dried ($MgSO_4$), and the solvent removed at reduced pressure. The crude product was purified by preparative TLC on silica gel, eluting with toluene–ethyl acetate (6:1). Two main products were isolated and identified: (*Z*)-*N*-acetyl-*N*-(*o*-ethylphenyl)-4-aminobut-2-enenitrile, **2**, yellowish oil, 47.7 mg (42%) (Found: C, 73.4; H, 6.85; N, 12.1. $C_{14}H_{16}N_2O$ requires C, 73.7; H, 7.1; N, 12.3); ν_{max}(neat)/cm^{-1} 2250 (–CN), 1680 (C=O) and 770 (C–H Ar); *m*/*z* 228 (M^+, 22%), 213 (12), 199 (13), 171 (18), 157 (40), 144 (19), 132 (34), 130 (29), 120 (89), 107 (40), 91 (34) and 43 (100). 1-Acetyl-2,3-dihydroindole-3-acetonitrile, **3**, brown oil, 34.1 mg (34%) (Found: C, 72.8; H, 5.35; N, 13.9. $C_{12}H_{11}N_2O$ requires C, 72.3; H, 5.6; N, 14.1%); ν_{max}(neat)/cm^{-1} 2250 (–CN), 1655 (CON) and 760 (*o*-subst); δ_H($CDCl_3$; 200 MHz) 8.27 (d, H-C7, 1 H, *J* 8.77), 7.42–7.05 (m, ArH, 3 H), 4.30 [dd, CH(1)-N, 1 H, *J* –10.74, 9.0], 3.84 [dd, CH(2)-N, 1 H, *J* –10.74, 4.49], 3.13 (m, H-C3, 1 H), 2.76 [dd, CH(4)-CN, 1 H, *J* –16.74, 5.43], 2.62 [dd, CH(5)-CN, 1 H, *J* –16.74, 8.03] and 2.26 (s, Me–C=O, 3 H); *m*/*z* 200 (M^+, 15%), 185 (M^+ – 15, 4), 158 (M^+ – 42, 20), 118 (100), 103 (5), 91 (8) and 43 (21).

Method (b) *with tetrakis*(*triphenylphosphine*)*nickel*(0). *General procedure.* Triethylaluminium (0.34 g, 3 mmol, 0.81 cm^3 of a 50% solution in toluene) was added to a solution of bis(acetylacetonate)nickel(II) (0.25 g, 1 mmol) and triphenylphosphine (1.05 g, 4 mmol) in anhydrous toluene (10 cm^3), under an argon atmosphere, with external cooling in an ice–ammonium chloride bath. After the initial vigorous reaction had subsided, the mixture was stirred at room temperature for 30 min, when the characteristic dark-red colour of tetrakis(triphenylphosphine)nickel(0) was observed. A solution of the *N*-β-alkenyl-*o*-chloroaniline derivative (1 mmol), in toluene (10 cm^3), was then added dropwise, and the mixture was warmed within the range 60–80 °C for 4–5 h. Finally, the complex was hydrolysed with saturated aq. ammonium chloride. The organic layer was extracted and dried ($MgSO_4$), and the crude product was purified by successive chromatographic runs on silica gel (column and thin layer) to afford the pure products.

With molar ratio of Al:Ni = 3:1. To a solution of zerovalent tetrakis(triphenylphosphine)nickel, obtained from bis(acetylacetonate)nickel(II) (0.69 g, 2.3 mmol), triphenylphosphine (2.43 g, 9.2 mmol) and triethylaluminium (0.79 g, 6.9 mmol, 1.8 cm^3 of a solution 50% in toluene), in anhydrous toluene, was added a solution of the compound (*E*)-**1** (0.54 g, 2.3 mmol) in toluene. The mixture was warmed to 60–70 °C for 5 h. After hydrolysis with saturated aqueous ammonium chloride and work-up, the crude product was purified by chromatography on silica gel, eluting with toluene–ethyl acetate (6:1) to give *o*-chloroacetanilide (0.40 g, 80%), m.p. 88 °C (identified by comparison with an authentic sample); ν_{max}(Nujol)/cm^{-1} 3300 (NH), 1660 (CONH) and 750 (*o*-subst-Ar); δ_H($CDCl_3$; 200 MHz) 8.25 (br d, H-C3, 1 H, *J* 8), 7.60 (br s, NH, 1 H), 7.40–6.80 (m, ArH, 3 H) and 2.20 (s, CH_3CO, 3 H).

With molar ratio of Al:Ni = 1:1. A solution of bis(acetylacetonate)nickel(II) (0.3 g, 1.2 mmol), triphenylphosphine (1.26 g, 4.8 mmol) and triethylaluminium (0.14 g, 1.2 mmol, 0.3 cm^3 of a solution 50% in toluene), in anhydrous toluene was stirred at room temperature for 1 h. Afterwards, a solution of the

compound (*E*)-**1** (0.28 g, 1.2 mmol) in toluene was added. The mixture was warmed at 60–70 °C for 5 h. After hydrolysis with saturated aqueous ammonium chloride and work-up, two products were isolated by chromatography on silica gel: *o*-chloroacetanilide **4** (82 mg, 40%), as in the preceding run, and 1-acetylindole-3-acetonitrile **5** (0.113 g, 50%), which crystallized from carbon tetrachloride as a white solid,[10] m.p. 114–115 °C (Found: C, 72.4; H, 4.95; N, 13.9. $C_{12}H_{10}N_2O$ requires C, 72.7; H, 5.1; N, 14.13%); ν_{max}(Nujol)/cm^{-1} 2270 (CN) and 1710 (CON); δ_H($CDCl_3$; 200 MHz) 7.58–7.13 (m, ArH, 5 H), 3.80 (d, CH_2CN, 2 H, *J* 1) and 2.67 (s, CH_3CON, 3 H); *m*/*z* 198 (M^+, 37%), 155 (M^+ − 43, 100), 130 (60), 128 (32), 115 (11), 103 (18), 102 (19), 89 (11), 77 (30), 63 (12), 51 (14) and 43 (83).

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