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Theoretical and model studies on the chemoselectivity of a Grignard reagent's reaction with a combined aminonitrile–oxazolidine system

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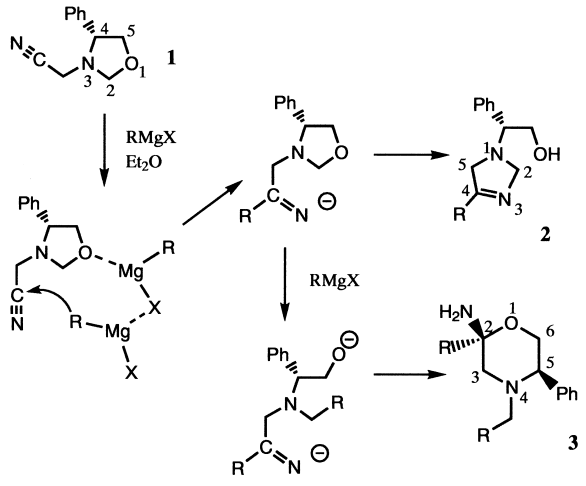
Abstract—Semi-empirical quantum chemical studies using PM3 suggest that the preferred reaction between a Grignard reagent and a combined aminonitrile–oxazolidine system involves initial formation of a Lewis acid–base complex between magnesium and the central nitrogen atom, followed by preferred reaction with the aminonitrile function; model studies confirm that this reaction proceeds by addition rather than substitution.

1. Introduction

Recently, it was shown that Grignard reagents react with combined aminonitrile–oxazolidine systems in a particular fashion.[1,2] The typical case of (*R*)-*N*-cyanomethyl-4-phenyl-oxazolidine **1** is shown in Scheme 1: two products are formed, a Δ^3-imidazoline **2** and a 2-aminomorpholine **3**, resulting, respectively, from intramolecular (imine anion) or intermolecular (Grignard) attack on a common intermediate. To account for the reactivity profiles observed with a series of combined aminonitrile–oxazolidines derived from **1**, a model was proposed in which initial complexation of an associated Grignard species occurred at the oxazolidine oxygen, followed by across-the-ring transfer of the nucleophile to the appropriately-placed nitrile.[2] The predominant formation of the imine anion intermediate implies that the initial reaction between the Grignard reagent and the starting compounds is the highly chemoselective addition of the organometallic nucleophile to the nitrile function; the alternative reactions of substitution at the aminonitrile α-carbon (Bruylants reaction), or substitution at the oxazolidine ring C2, are not observed.

While this model did account for all available data, it was entirely intuitive and lacked independent experimental or theoretical support. In order to gain better insight into the likely origins of the chemoselectivity of these reactions, we decided to undertake a theoretical study of the reaction between **1** and a simple, representative Grignard reagent, methyl magnesium chloride.



Scheme 1.

2. Results and discussion

2.1. Calculations

Frontier orbitals theory postulates that the smallest energy difference between the highest occupied molecular orbital (HOMO) of one reactant and the lowest unoccupied molecular orbital (LUMO) of a second reactant gives information (reactivity indices) about the most favoured

Keywords: theoretical studies; Grignard reagents; aminonitriles; oxazolidines.

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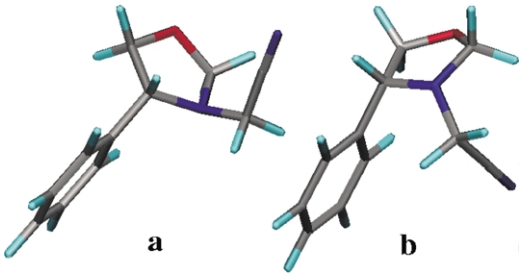
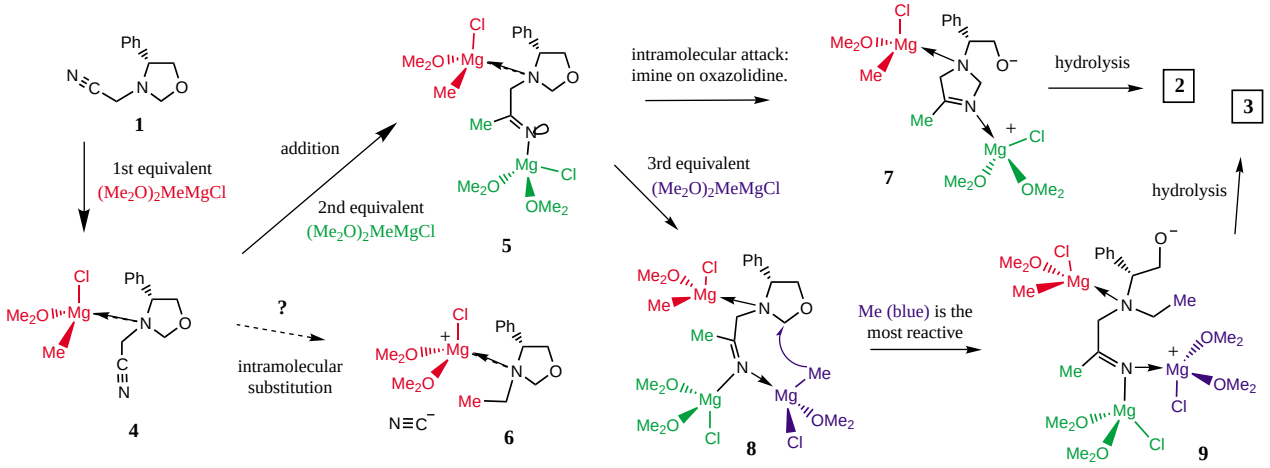


Figure 1. Minimum-energy conformers of **1**. (a) *trans*; the N3–C4 dihedral angle is 0.4°; (b) *cis*; the N3–C4 dihedral angle is 11.8°.

cyanomethyl groups. The *trans* conformation is the more stable ($\Delta\Delta H_f$=1.56 kcal mol^{-1}). Subsequent calculations for the reaction with the Grignard reagent were carried out using this minimum-energy conformation of **1**. The sequence of events which is deduced from these calculations (described below), along with the intermediates involved, is summarized in Scheme 2.

The definition of the Grignard reagent system was important in this study. Several computational studies have been performed previously for the addition of a Grignard reagent to an aldehyde or a ketone. The Grignard reagent system is



Scheme 2. Summary diagram of the sequence of reactions between **1** and two or three Grignard reagent molecules, as suggested by the calculations.

interaction between the two species in their ground states.[3] Molecular orbital information is obtained by quantum mechanics. On the basis of the size of our system and our computational power, we decided to use a semi-empirical method. All MO calculations described below were carried out with the MOPAC 6.0 package[4] and the PM3 Hamiltonian, in which the parameters for the magnesium atom have been defined.[5]

The first step was to perform a conformational analysis of **1** to determine the preferred conformation. We use Sybyl[6] to draw four envelope conformations of **1** in which the oxygen atom was at the apex. The difference between these conformers was the position of this oxygen vis-à-vis the phenyl group (*endo* or *exo*) and the relative configuration of the cyanomethyl and phenyl groups (*cis* or *trans*). In addition, two twist conformations were considered, in which O1 and C5 were the out-of-plane atoms. For each conformer we performed a 30° increment grid search on the phenyl and cyanomethyl dihedral angles, and each generated structure was minimized with a conjugate gradient algorithm. The four most stable structures from each series were retained and reminimized with PM3 and the eigen-vector following (EF) algorithm. Four of the six series disappeared to leave only those conformers in which the apex-oxygen was on the opposite face of the envelope to the nitrogen lone pair; this evidently minimizes lone-pair repulsion of the oxygen atom's pseudo-axial lone pair. Fig. 1 shows the most stable conformer from these two remaining series; the two structures differ in the relative configuration of the phenyl and

very often represented as a linear structure without solvent molecules,[7] or with two water molecules[8] to simulate the ether solvent. We decided to use the complex $(Me_2O)_2MeMgCl$ as the representative organometallic species.

The HOMO of this reagent is centred on the bond Mg–CH_3 (E=−9.01 eV) (Fig. 2). The LUMO is principally centred on the magnesium atom (E=−0.16 eV) (Fig. 2). This first unoccupied molecular orbital is bonding, consistent with a Lewis acid character of the Grignard reagent. It is worth noting that only the sp^3 hybridisation state of the magnesium

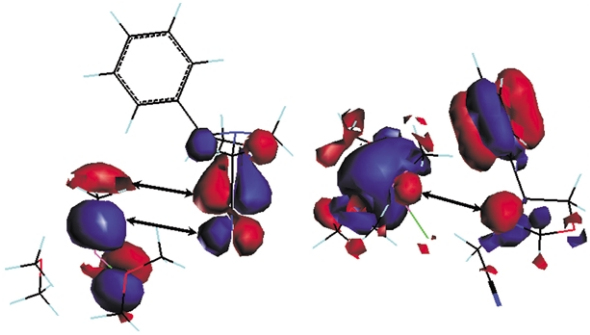


Figure 2. Left: interaction between HOMO−1 of **1** with LUMO of Grignard reagent. Right: interaction between LUMO+3 of **1** and HOMO of Grignard reagent. The left reaction is favoured. MO representations correspond to an isodensity electronic surface of 10^{-2} e$^-$ Å^{-3}; blue: negative lobe, red: positive lobe.

Table 1. Product of the reaction in accordance with MO energies between **1** and the first equivalent of Grignard reagent (Fig. 2)

Grignard reagent $(Me_2O)_2MeMgCl$	**1**	Energy difference (eV)	Product of the HOMO–LUMO interaction
HOMO: −9.01 eV	LUMO+3: +1.24 eV	+10.25	Addition to the nitrile group
LUMO: −0.16 eV	HOMO−1: −9.94 eV	+9.78	Lewis complex **4**: N→Mg

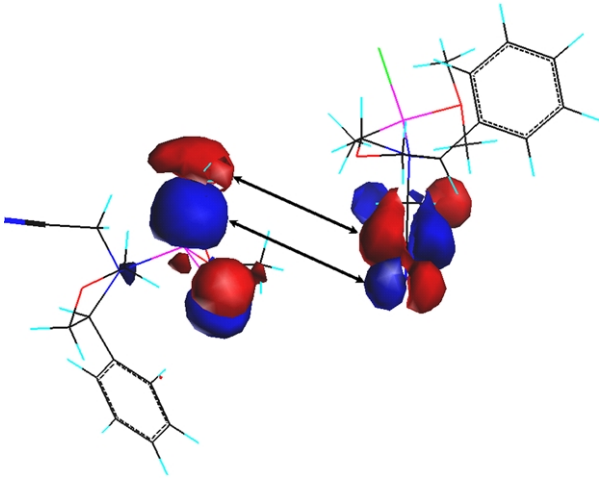


Figure 3. Molecular orbitals of Lewis complex **4**. Interaction between HOMO−1 and LUMO+6 leading to an addition product **5**. MO representations correspond to an isodensity electronic surface of 10^{-2} e$^-$ Å^{-3}; negative lobe, red: positive lobe.

A new PM3/EF calculation was run on the Lewis complex **4**. The HOMO (E=−9.077 eV) is centred on the Cl, C2, N and O atoms. The HOMO−1 (E=−9.41 eV) describes the Mg–CH_3 bond similarly to the HOMO in $(Me_2O)_2MeMgCl$. The LUMO, LUMO+1, +2, +3, +4 are centred on the magnesium atom and/or phenyl group like **1**. The antibonding molecular orbitals which describe the nitrile group, are LUMO+5 (E=+0.71 eV) and LUMO+6 (E=+0.79 eV), which are perpendicular to each other (Fig. 3). Graphical MO analysis suggests two plausible reaction paths.

The first possible reaction is the addition of a second Grignard reagent to the nitrile group, leading to the di-magnesium complex **5** (Table 2 and Fig. 3).

Alternatively, the intramolecular substitution of the nitrile group by the complexed methyl group (the Bruylants reaction) appears possible, giving product **6**. This reaction would imply the interaction of the HOMO−1 (E=−9.41 eV) and the LUMO+7 (E=+1.10 eV) of **4**

Table 2. Product of the reaction in accordance with MO energies between complex **4** and the second equivalent of Grignard reagent (Fig. 3)

Grignard reagent $(Me_2O)_2MeMgCl$	Lewis complex **4**	Energy difference (eV)	Product of the HOMO–LUMO interaction
HOMO: −9.01 eV	LUMO+6: +0.79 eV	+9.80	Addition to nitrile: intermediate **5**
LUMO: −0.16 eV	HOMO−1: −9.41 eV	+9.25	No meaningful interaction

atom can be studied with PM3. However, magnesium has accessible d orbitals and is known, in some cases, to adopt an sp^3d hybridisation,[9] which means that the sp^3 hybridisation is not necessarily the more stable state.

The HOMO (E=−9.85 eV) of **1** is centred on the phenyl group while the HOMO−1 (E=−9.94 eV) is centred on the amine nitrogen and concerns the non-bonding electron pair (Fig. 2). The LUMO and LUMO+1 are centred on the phenyl group. The LUMO+2 and +3 are centred on the nitrile group and describe the two π^* antibonding orbitals (Fig. 2).

After graphical analysis to verify the possible interactions between MOs (the sign should be the same), the smallest HOMO−LUMO energy difference was calculated (Table 1). It was concluded that the first reaction is the formation of an N→Mg Lewis acid–base complex $(Me_2O)MeMgCl$·**1**, called **4** (Scheme 2), between the Grignard reagent (LUMO) and **1** (HOMO−1). No low-energy MOs permit the interaction of the Grignard reagent with the oxazolidine centre, either by O-complexation or by addition to the ring C2.

This initial observation contrasts with the previous suggestion[2] that the initial site of interaction between **1** and a Grignard reagent's magnesium atom might have been at the oxazolidine ring's oxygen (Scheme 1), an assertion often made (with experimental support) in the reactions of Grignard reagents with regular oxazolidine systems.[10,11]

(Fig. 4). Indeed, the LUMO+7 is partly localized on the α-carbon of the aminonitrile moiety. This reaction is slightly less favoured energetically (ΔE=+10.51 eV) than the addition (ΔE=+9.80 eV).

A calculation on the magnesium-imine intermediate **5** showed that the four highest occupied MOs describe the non-bonding electron pair of the imino group, but the AOs of the Mg, C and Cl atoms from the first Grignard reagent

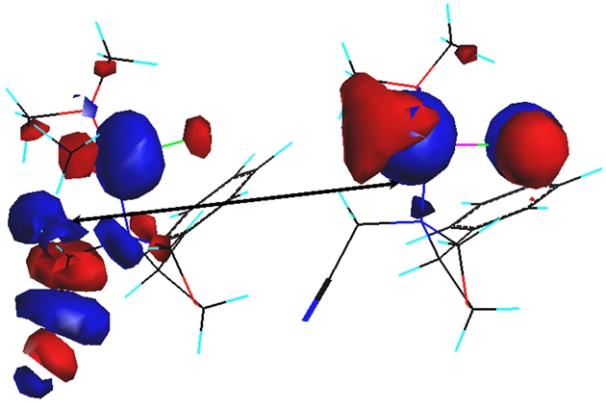


Figure 4. Molecular orbitals of Lewis complex **4**. Intramolecular interaction between HOMO−1 and LUMO+7 leading to a Bruylants substitution product **6**. MO representations correspond to an isodensity electronic surface of 10^{-2} e$^-$ Å^{-3}; blue: negative lobe, red: positive lobe.

Table 3. Product of the reaction in accordance with MO energies between imine **5** and the third equivalent of Grignard reagent (Fig. 5)

Grignard reagent $(Me_2O)_2MeMgCl$	Imino-magnesium **5**	Energy difference (eV)	Product of the HOMO–LUMO interaction
HOMO: −9.01 eV	LUMO+9: +1.30 eV	+10.31	Addition to imine group
LUMO: −0.16 eV	HOMO−1: −8.64 eV	+8.48	Tri-magnesium complex **8**

have a significant contribution. Graphical analysis of these MOs (not shown) reveals them to be very similar except for the lobe signs.

Two reaction pathways appear to be open for **5**, depending on the availability of further Grignard reagent molecules. In the first case, assuming a sufficient quantity of the reagent, the LUMO of a third Grignard molecule may interact with the HOMO of **5**, leading to the intermediate tri-magnesium complex **8** (Table 3 and Fig. 5). An alternative process, in which the Grignard reagent adds to the imine π bond, seems possible but energetically disfavoured (Table 3 and Fig. 5). This is consistent with the experimental observation that nitriles generally only undergo addition of 1 equiv. of Grignard, even in the presence of excess reagent.[12]

A different situation obtains for **5** if no further Grignard reagent is available (Fig. 6). An intramolecular reaction involving HOMO−2 (E=−9.05 eV) centred on the imine and LUMO+16 (E=+2.48 eV) centred on the oxazolidine C2 can occur, leading directly to the Δ^3-imidazoline skeleton **7** and thus to product **2**. The energy difference for this reaction (ΔE=+11.53 eV) compared with that for the intermolecular reaction with the third Grignard molecule to give **8** (ΔE=+8.48 eV) suggests that the latter may be preferred.

A final calculation on the tri-magnesium intermediate **8** shows that the HOMO (E=−8.49 eV) is situated on the CH_3–Mg bond of the third magnesium centre. This MO can interact with the LUMO+22 (E=+2.33 eV) centred on the C2–N bond of the oxazolidine ring (Fig. 7). Since all lower unoccupied MOs describe only the three magnesium atoms, the LUMO+22 can be considered the first reactive unoccupied MO. This interaction (ΔE=+10.82 eV) leads to **9** by ring opening, and thus to the final product **3** after hydrolytic treatment and spontaneous cyclization to the hemi-aminal.

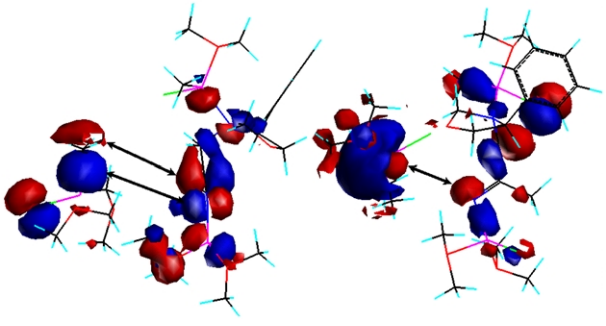


Figure 5. Reaction of intermediate **5** with a third equivalent of Grignard reagent. Left: interaction between HOMO of **5** and LUMO of Grignard reagent, leading to a tri-magnesium complex **8**. Right: interaction between LUMO+9 of **5** and HOMO of Grignard reagent. The reaction on the left is more favourable. MO representations corresponds to an isodensity electronic surface of 10^{-2} e$^-$ Å^{-3}; blue: negative lobe, red: positive lobe.

To summarize the results of the theoretical calculations, then, Grignard reagent complexation at the central nitrogen of **1** (not at the more electronegative oxygen) is the preferred initial interaction. Nucleophilic attack of a second Grignard molecule occurs on the nitrile to give the key intermediate **5**. Depending on the availability of a third Grignard molecule, **5** may evolve to give either imidazoline **2** or aminomorpholine **3**.

2.2. Model studies

An interesting matter raised by the theoretical work concerned the importance of the number of Grignard reagent molecules available in the system. Two molecules,

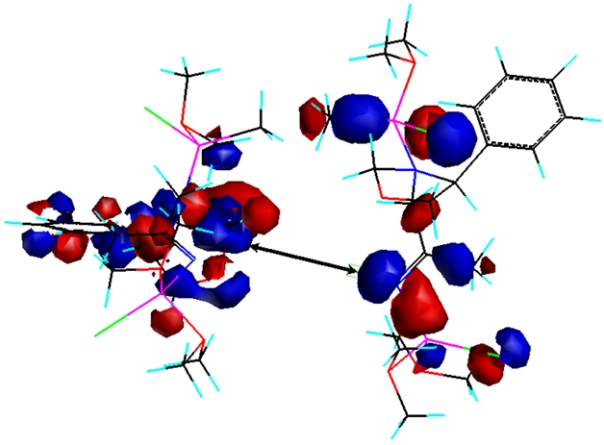


Figure 6. Intramolecular reaction between the HOMO−2 imine and LUMO+16 imine. To aid viewing, the HOMO−2 and the LUMO+16 are shown for two identical species **5** having different spatial orientations. MO representations correspond to an isodensity electronic surface of 10^{-2} e$^-$ Å^{-3}; blue: negative lobe, red: positive lobe.

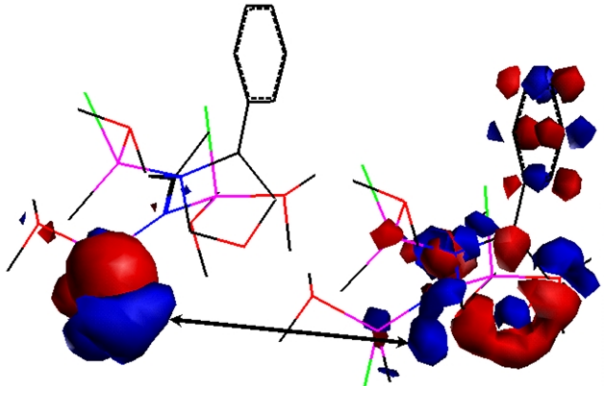
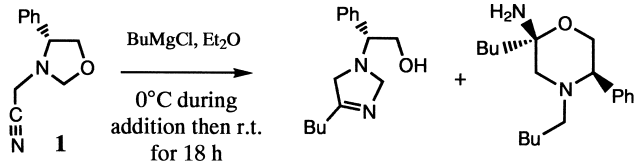
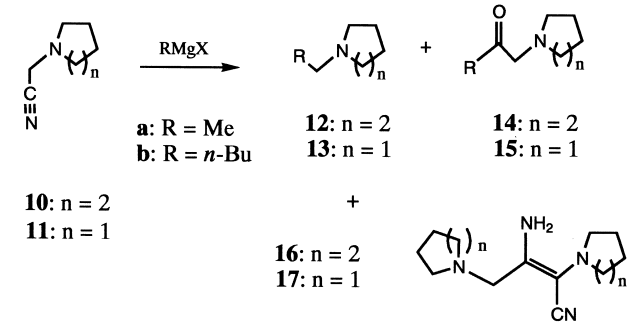


Figure 7. Intramolecular reaction between the HOMO and LUMO+22 of **8**. To aid viewing, the HOMO and the LUMO+22 are shown for two identical species having identical spatial orientations. MO representations correspond to an isodensity electronic surface of 10^{-2} e$^-$ Å^{-3}; blue: negative lobe, red: positive lobe.



conditions:	product ratio:	
2 equiv. Grignard added slowly (over 2 h) to **1**	83	17
1 added slowly (over 2 h) to 3 equiv. Grignard	32	68

Scheme 3.



Scheme 4.

in theory, are sufficient for the transformation of **1** into **2**, whereas three (or more) should favour formation of **3**. On the basis of this hypothesis, we carried out reactions of **1** with *n*-butyl magnesium chloride under conditions which were designed to favour one or other of the two possible products (Scheme 3). Thus, slow addition of 2 equiv. of Grignard reagent to **1** minimized local excesses of the nucleophile and led to a marked preference for formation of the imidazoline. On the other hand, inverse addition of **1** to 3 equiv. of Grignard maintained the nucleophile in excess as much as possible and led to majority formation of the aminomorpholine. In the real system, it cannot be expected that 100% selectivity for one or other of the possible reaction pathways should be achieved, so these observations offer reasonable support for the reaction stoichiometry suggested by the calculations.

One question not resolved by the theoretical work is why a substitution reaction (replacement of the nitrile by the organometallic radical) does not take place. This reaction, often called the Bruylants reaction,[13] has often been used as a synthetic method for preparing diverse tertiary amine moieties, sometimes incorporated in quite complex molecular structures.[14] Most of the applications of the Bruylants reaction, however, have been to cases where the α-carbon of the aminonitrile has been substituted by one or two alkyl or aryl functions; very little work has been done using aminonitriles with an unsubstituted α-carbon (i.e. with a CH_2 group between the amine and the nitrile), as pertains for **1**. Early literature suggests that such aminonitriles are much less susceptible to undergo Bruylants-type substitution, with addition reactions (leading to ketones) competing.[13,15–17] Details are sparse, however, and concern mostly cases where the amine nitrogen is not part of a cyclic system. Furthermore, both Bruylants[13a] and Stevens[15] report that the piperidine derivative **10** behaves in a contradictory manner, giving only the substitution product (Bruylants reaction) when treated with a methyl Grignard reagent. Thies et al., however, reported that **10** reacted by addition with an *n*-butyl Grignard reagent.[17]

We therefore decided to carry out comparative studies using a model aminonitrile **11** having the five-membered ring of **1** but lacking the reactivity of a combined oxazolidine. At the same time, we carried out a reevaluation of the higher homologue, **10**. In standard experiments, each aminonitrile was treated in ether solution with 2 equiv. of methyl or *n*-butyl Grignard reagent, over a period of 18 h then hydrolysed with mild acid (Scheme 4). The product mixture was analysed directly by glc to determine the presence of tertiary amines **12/13**, ketones **14/15** and dimers **16/17**. Results are presented in Table 4.

In all cases, there was an overwhelming preference for the addition reaction leading to the ketone, rather than the Bruylants substitution reaction. This observation confirms that aminonitriles which are unsubstituted on the α-carbon, undergo addition reactions, not substitutions. We find that piperidine **10** respects this rule, as suggested by Thies et al.,[17] in contrast with previous reports.[13a,15] This being the case, it is not surprising that the molecule which is the focus of our attention here, **1**, should also react by addition; once the reaction centre has been determined as being the aminonitrile function, not the oxazolidine ring, **1** simply evolves (via **4**) as would a typical aminonitrile.

Small amounts of dimers **16** and **17** were observed, with the former[17] probably being the unidentified higher-boiling product reported originally by Bruylants.[13a] Dimerization results from deprotonation of one molecule of aminonitrile by Grignard reagent and attack of the resulting anion on the nitrile function of a second aminonitrile molecule. Base-promoted aminonitrile dimerization of this type has been reported before.[18,19]

3. Conclusions

In conclusion, semi-empirical theoretical calculations have

Table 4. Products obtained in the reactions of Grignard reagents with model aminonitriles (see Scheme 4)

Aminonitrile	Grignard reagent	Amine (yield%)	Ketone (yield%)	Dimer (yield%)
10	MeMgBr	**12a** (1)	**14a** (89)	**16** (9)
10	*n*-BuMgCl	**12b** (5)	**14b** (46)	**16** (6)
11	MeMgBr	**13a** (1)	**15a** (76)	**17** (1)
11	*n*-BuMgCl	**13b** (2)	**15b** (78)	**17** (2)

been used to show that a Grignard reagent's reaction with the combined aminonitrile–oxazolidine system **1** can be at least partly explained in terms of preferred molecular orbital interactions. The stoichiometry of the two reactants has a dramatic influence on the product ratios with the passage from 2 to 3 equiv. of the organometallic reagent being the critical point. In any event, the reaction commences via an initial *N*-complex by nucleophilic addition to the nitrile moiety, in a manner which is typical of standard unsubstituted aminonitriles, as shown by model studies. This scenario leads logically to the question of what factors determine the addition/substitution selectivity in Grignard-aminonitrile reactions, and what the precise mechanism of each of these processes might be; these matters will be addressed in a future study.

4. Experimental

4.1. Calculation methods

All calculations were carried out on a Silicon Graphics Indigo2 workstation equipped with a R8000 Mips processor operating at 75 MHz. Within the Sybyl package,[6] conformational analyses were performed using the Tripos Force Field with Gasteiger–Hückel charges, the distance dielectric function, a dielectric constant of 4.2 (corresponding to ether) and a cutoff of 8 Å. All conformations were minimized with a conjugate gradient algorithm. Semi-empirical calculations were carried out using the MOPAC 6.0 package.[4] The eigen-vector following algorithm was used for minimization. Molecular orbitals generated by these calculations were analysed graphically.[20]

4.2. General methods

NMR spectra were measured in $CDCl_3$ solution on a Bruker AC-400 spectrometer, operating at 400 MHz for ^1H and 100 MHz for ^{13}C, using residual solvent signals as reference. Chemical shifts (δ) are reported in ppm, J values are given in hertz, and phasing observed in ^{13}C J-modulation experiments is indicated as up (+) or down (−). Infrared spectra were recorded neat on a Perkin–Elmer 881 spectrometer; only structurally important peaks (ν) are presented in cm^{-1}. Low-resolution mass spectra were recorded on an HP 5989B spectrometer in chemical ionisation mode (150 eV) using methane as the ionisation gas.

Solvent ether and THF were distilled from sodium-benzophenone under argon. Ether solutions of butylmagnesium chloride (2 M) and methylmagnesium bromide (3 M) were obtained commercially and used as freshly delivered; dilutions in ether were made immediately before reactions were carried out. (*R*)-*N*-Cyanomethyl-4-phenyloxazolidine (**1**)[21] and *N*-(cyanomethyl)piperidine (**10**)[22] were prepared as previously described. Other reagents, including *N*-(cyanomethyl)pyrrolidine (**11**) and *N*-ethylpiperidine (**12a**), were commercially available.

Preparative chromatography was carried out using silica gel (40–63 μm). Gas chromatographic analyses were carried out on a Delsi Nermag instrument equipped with a Carbowax column (Machery-Nagel Optima 1, 0.20 μm, 25 m×0.20 mm i.d.) using hydrogen as the vector gas and the following program: initial temperature 80°C for 5 min, increasing by 4°C min^{-1} to final temperature 200°C, maintained for 15 min.

Product retention times were as follows:

- *N*-(cyanomethyl)piperidine (**10**)=6 min 34 s.
- *N*-(cyanomethyl)pyrrolidine (**11**)=4 min 32 s.
- *N*-ethylpiperidine (**12a**)=2 min 3 s.
- *N*-pentylpiperidine (**12b**)=8 min 33 s.
- *N*-ethylpyrrolidine (**13a**)=2 min 8 s.
- *N*-pentylpyrrolidine (**13b**)=6 min 19 s.
- *N*-(2-oxopropyl)piperidine (**14a**)=6 min 49 s.
- *N*-(2-oxohexyl)piperidine (**14b**)=16 min 36 s.
- *N*-(2-oxopropyl)pyrrolidine (**15a**)=4 min 31 s.
- *N*-(2-oxohexyl)pyrrolidine (**15b**)=13 min 30 s.
- *N*-(cyanomethyl)piperidine dimer (**16**)=35 min 52 s.
- *N*-(cyanomethyl)pyrrolidine dimer (**17**)=31 min 29 s.

4.3. Reaction of *n*-butyl magnesium chloride with 1

This reaction was carried out on a 4 mmol scale and at 1 M concentration (for **1**) on the basis of the previously described procedure,[1,2] with the appropriate modifications as indicated in Scheme 3. Product ratios were determined by integration of convenient ^1H NMR spectroscopic signals, and product identities were confirmed by comparison with previously prepared compounds.[1]

4.4. General procedure for reaction of a Grignard reagent with 10 or 11

A 1 M solution of aminonitrile (4 mmol) in ether was added dropwise to a stirred 1 M solution of Grignard reagent (8 mmol) in ether at 0°C under argon. The reaction mixture was left to warm to ambient temperature overnight and was then quenched with saturated aqueous ammonium chloride solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (4×10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude reaction mixture was analysed directly by GC. Subsequent column chromatographic separation and/or distillation gave pure samples of ketones **14/15** and dimers **16/17**. Yields are given in Table 4.

4.4.1. *N*-(2-Oxopropyl)pyrrolidine. Bp 60°C (9 mmHg); IR ν 1715; ^1H NMR δ 1.62–1.65 (m, 4H, $2CH_2\beta$), 1.98 (s, 3H, CH_3), 2.39–2.42 (m, 4H, $2CH_2\alpha$), 3.20 (s, 2H, NCH_2CO); ^{13}C NMR δ 23.3 (2C; +), 27.3 (−), 53.9 (+), 65.9 (+), 206.3 (+); MS *m/z*: 128 $[MH]^+$.

4.4.2. *N*-(2-Oxopropyl)piperidine.[23] Bp 80°C (5 mmHg); IR ν 1730; ^1H NMR δ 1.39–1.43 (m, 2H, $CH_2\gamma$), 1.56–1.62 (m, 4H, $2CH_2\beta$), 2.13 (s, 3H, CH_3), 2.37–2.39 (m, 4H, $2CH_2\alpha$), 3.11 (s, 2H, NCH_2CO); ^{13}C NMR δ 23.9 (+), 25.8 (2C; +), 27.7 (−), 54.8 (2C; +), 69.2 (+), 207.5 (+); MS *m/z*: 142 $[MH]^+$.

4.4.3. *N*-(2-Oxohexyl)pyrrolidine. Bp 140°C (1 mmHg); IR ν 1720; ^1H NMR δ 0.83 (t, J=7.3 Hz, 3H, CH_3), 1.25 (sext, J=7.4 Hz, 2H), 1.50 (quint, J=7.6 Hz, 2H),

1.68–1.77 (m, 4H, $2CH_2\beta$), 2.35 (t, J=7.6 Hz, 2H), 2.44–2.52 (m, 4H, $2CH_2\alpha$), 3.28 (s, 2H); ^{13}C NMR δ 13.0 (−), 21.5 (+), 23.2 (2C; +), 25.6 (+), 39.1 (+), 53.2 (2C; +), 64.6 (+), 207.6 (+); MS *m/z*: 170 $[MH]^+$.

4.4.4. *N*-(2-Oxohexyl)piperidine.[17] Bp 120°C (2 mmHg); IR ν 1715; ^{1}H NMR δ 0.84 (t, J=7.3 Hz, 3H, CH_3), 1.24 (sext, J=7.5 Hz, 2H, $MeCH_2$), 1.35 (m, 2H, $CH_2\gamma$), 1.48 (quint, J=7.4 Hz, 2H), 1.54 (m, 4H, $2CH_2\beta$), 2.35 (m, 6H, $2CH_2\alpha$ and RCH_2CO), 3.09 (s, 2H, NCH_2CO); ^{13}C NMR δ 13.8 (−), 22.4 (+), 23.8 (+), 25.6 (2C; +), 25.8 (+), 40.0 (+), 54.7 (2C; +), 68.3 (+), 209.2 (+); MS *m/z*: 184 $[MH]^+$.

4.4.5. *N*-(Cyanomethyl)pyrrolidine dimer. Bp 200°C (1 mmHg); IR ν 1650, 2180, 3350, 3480; ^{1}H NMR δ 1.83–1.85 (m, 8H), 2.61–2.64 (m, 4H), 2.72–2.75 (m, 4H), 3.42 (s, 2H), 5.27 (br s, 2H, NH_2); ^{13}C NMR δ 23.6 (2C; +), 24.2 (2C; +), 51.6 (2C; +), 53.8 (2C; +), 54.7 (+), 92.5 (+), 117.5 (+), 153.1 (+); MS *m/z*: 221 $[MH]^+$.

4.4.6. *N*-(Cyanomethyl)piperidine dimer.[17] Bp 220°C (0.7 mmHg); IR ν 1645, 1635, 2180, 3360, 3490; ^{1}H NMR δ 1.43–1.44 (m, 4H), 1.53–1.64 (m, 8H), 2.37 (m, 4H), 2.54–2.57 (m, 4H), 3.16 (s, 2H), 5.24 (br s, 2H, NH_2); ^{13}C NMR δ 23.1 (+), 23.9 (+), 25.6 (2C; +), 26.4 (2C; +), 52.6 (2C; +), 54.3 (2C; +), 57.8 (+), 95.9 (+), 117.6 (+), 152.0 (+); MS *m/z*: 249 $[MH]^+$.

4.5. General procedure for preparation of tertiary amines

A modification of the method of Alunni and Tijskens[24] was used for the preparation of the following tertiary amines.

4.5.1. *N*-Ethylpyrrolidine.[24] To a solution of pyrrolidine (14.4 mmol) and triethylamine (28.0 mmol) in THF (5 mL) was added dropwise bromoethane (17.0 mmol). The reaction mixture was stirred at rt for 4 days, then filtered. The solids were washed through with THF (15 mL) and the combined filtrate distilled at atmospheric pressure to give the title amine as a yellow liquid (1.14 g; 80%). Bp 103°C (760 mmHg); ^{1}H NMR δ 0.96 (t, J=7.1 Hz, 3H, CH_3), 1.78 (br s, 4H, $2CH_2\beta$), 2.41–2.46 (m, 6H, $MeCH_2$ and $2CH_2\alpha$); ^{13}C NMR δ 14.0 (−), 23.3 (2C; +), 50.1 (+), 53.8 (2C; +); MS *m/z*: 100 $[MH]^+$.

4.5.2. *N*-Pentylpyrrolidine.[25] To a solution of pyrrolidine (14.4 mmol) and triethylamine (28.0 mmol) in THF (5 mL) was added dropwise 1-bromopentane (16.1 mmol). The reaction mixture was stirred at rt for 5 days, filtered, and the filtrate evaporated. The residue was treated with distilled water (10 mL) and extracted with dichloromethane (4×8 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated, and the residual oil distilled under reduced pressure to give the title amine as a yellow liquid (1.70 g; 83%). Bp 53°C (10 mmHg); ^{1}H NMR δ 0.89 (t, J=6.9 Hz, 3H, CH_3), 1.28–1.35 (m, 4H), 1.48–1.55 (quint, J=7.5 Hz, 2H), 1.76–1.80 (m, 4H, $2CH_2\beta$), 2.39–2.42 (dd, J=7.7 and 7.9 Hz, 2H, NCH_2), 2.46–2.48 (m, 4H, $2CH_2\alpha$); ^{13}C NMR δ 14.0 (−), 22.6 (+), 23.3 (2C; +), 28.8 (+), 29.9 (+), 54.2 (2C; +), 56.7 (+); MS *m/z*: 142 $[MH]^+$.

4.5.3. *N*-Pentylpiperidine.[26] To a solution of piperidine (12.1 mmol) and triethylamine (24.4 mmol) in THF (5 mL) was added dropwise 1-bromopentane (13.7 mmol). The reaction mixture was stirred at rt for 5 days, filtered, and evaporated. The residue was treated with distilled water (10 mL) and extracted with dichloromethane (4×8 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated, then distilled under reduced pressure to give the title amine as a yellow liquid (1.53 g; 82 %). Bp 67°C (9 mmHg); ^{1}H NMR δ 0.82 (t, J=7.3 Hz, 3H, CH_3), 1.16–1.28 (m, 4H), 1.36–1.46 (m, 4H), 1.49–1.51 (m, 4H, $2CH_2\beta$), 2.19 (dd, J=7.8 and 5.5 Hz, 2H, NCH_2), 2.31 (m, 4H, $2CH_2\alpha$); ^{13}C NMR δ 14.0 (−), 22.6 (+), 24.5 (+), 26.0 (2C; +), 26.7 (+), 30.0 (+), 54.6 (2C; +), 59.7 (+); MS *m/z*: 154 $[MH]^+$.

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