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# Facile Kinetic Induction of a Dihydropyridide to Pyrrolide Ring Contraction

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**Reactions between magnesium 1,4-dihydropyridide or 1,2-dihydro-*iso*-quinolide derivatives and carbodiimides, RN=C=NR, generally result in Mg-N insertion and formation of guanidinate complexes. More sterically perturbed systems with *N*-aryl carbodiimide substitution, however, follow a divergent course of reaction initiating heterocyclic ring contraction and pyrrolide formation under unprecedentedly mild conditions.**

Due primarily to their constituent role in biological hydrogen transfer and oxidation-reduction chemistry, the reactivity of dihydropyridine derivatives has attracted considerable attention for over 80 years.[1] Nicotinamide adenine dinucleotide (NADH, Figure 1), for example, is a vital cofactor enabling electron transfer in photosynthesis while Hantzsch esters (HEH) are administered as common vasodilators in the treatment of hypertension and angina.

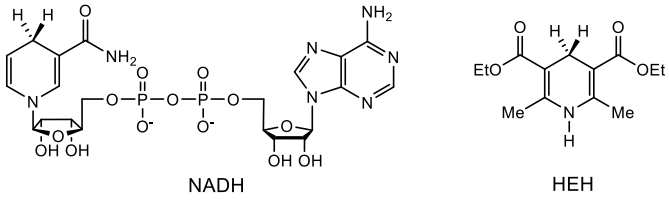
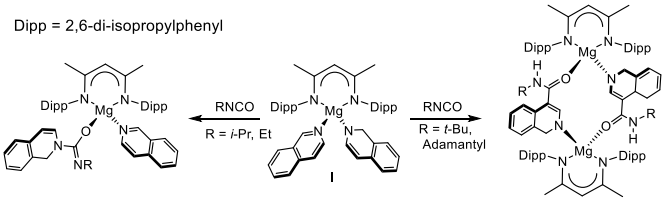



**Figure 1:** Structures of biologically relevant dihydropyridine derivatives

More recent advances have been driven by the ubiquity of reduced pyridine and quinoline cores in other natural products and pharmaceuticals,[2] while a plethora of both main group- and transition metal-centred chemistry has shown that anionic variants, such as Lansbury's reagent, [Li{Al(NC$_5$H$_6$)$_4$}] can display a rich and dynamic chemistry in which hydride transfer and heterocycle re-aromatisation provides only one of sundry potential reaction pathways.[3,4] Our own interest has centred on a study of the reactivity of magnesium compounds such as the β-diketiminato 1,2-dihydro-*iso*-quinolide derivative, compound **I** (Scheme 1).[5] While species such as **I** may be employed as effective pre-catalysts for the facile catalytic hydroborative dearomatisation of a broad scope of pyridine heterocycles,[6] our studies of their stoichiometric reactions with potentially reducible heterocumulenic reagents have indicated that the outcome is subtly dependent on the steric demands and the electronic character of both the dihydropyridide and unsaturated reagents. A case in point is thus provided by the variable reactivity of such magnesium dihydropyridides with alkyl isocyanates. While some evidence for hydride reductive transfer was observed with monocyclic 1,4-dihydropyridides, the majority of these reactions resulted in Mg-N insertion and the formation of the magnesium amidate species. While similar observations also resulted from analogous reactions performed with compound **I**, the introduction of more bulky isocyanate *N*-alkyl groups resulted in a more kinetically favoured nucleophilic attack of the enamide C=C double bond at the electrophilic isocyanate carbon centre (Scheme 1).[5c] In this contribution we extend our studies of magnesium dihydropyridide reactivity with heterocumulenes to isoelectronic carbodiimides. The course of reaction is similarly driven by the steric profile of both the heterocumulene and dihydropyridide reagents to provide a unique and completely specific dihydropyridide to pyrrolide ring contraction reaction.




**Scheme 1:** Kinetically-directed dihydroquinolide-isocyanate reactivity[5]

It was anticipated that transfer of hydride from the dihydropyridide unit to the central carbon of the carbodiimide to yield formamidinate products would be a competitive process. All reactions of commercially available *N*,*N*'-*iso*-propyl, -cyclohexyl and -*para*-tolyl substituted carbodiimides, however, with a stoichiometric quantity of the monocyclic magnesium dihydropyridide complexes (**II** - **IV**) and the fused ring *iso*-quinolide species (**I**) were found to provide clean

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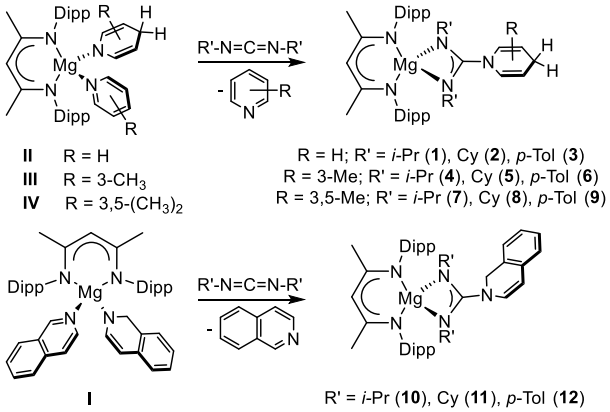
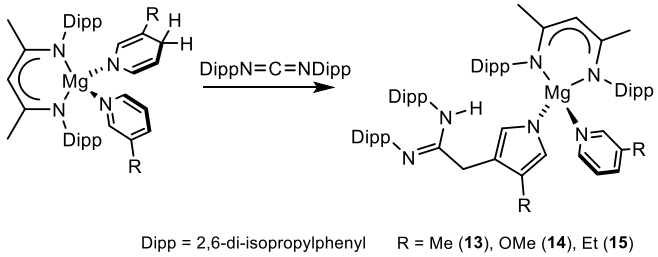
insertion to form guanidinate complexes (**1** – **12)** within minutes at room temperature (Scheme 2). Although, somewhat surprisingly, this approach does not seem to have been adopted in previous syntheses of magnesium guanidinates, closely related reactions with carbodiimides have been reported to yield magnesium alkyl- and formamidinates from reactions with Mg-C or Mg-H bonds.[7]




**Scheme 2:** Synthesis of dihydropyridide-based magnesium guanidinates.

In each case a characteristic downfield shift of ca. 0.5 ppm was noted in the $^1$H NMR spectra for the *ortho*-C*H* protons of the dearomatised ring in compounds **1** - **9**. This occurred in addition to an upfield shift of the dihydropyridide-methylene proton resonances of ca. 0.7 ppm, indicating Mg-N insertion had likely occurred. Confirmation of guanidinate formation was obtained by accurate mass ESI mass spectrometry performed on the hydrolysed products where, in a majority of cases, the parent ion associated with the guanidinate unit or the sodium adduct was observed.

Although further attempted reactions between compounds **II** and **IV** with carbodiimides with higher overall steric demands (*tert*-butyl and 2,6-di-*iso*-propylphenyl, Dipp) failed to provide any evidence of reaction even upon extended heating at 80°C, a reaction between DippN=C=NDipp and compound **III** bearing the 3-methyl-1,4-dihydropyridide ligand provided evidence of divergent reactivity. While no reaction was observed at room temperature, heating of a $C_6D_6$ solution of the two reagents at 60°C for 12 hrs and subsequent analysis by $^1$H NMR spectroscopy indicated a complete loss of those resonances associated with the dearomatised dihydropicolide. The stoichiometric production of a single new species (compound **13**), was characterised by the emergence of five (1H) new singlet resonances in the range δ 4 – 6 ppm (Figure S2). A subsequent $^1$H-$^1$H COSY NMR experiment demonstrated that none of these signals were mutually coupled, whilst a $^1$H-$^{13}$C HSQC correlation revealed that a singlet at δ 4.01 ppm did not arise from a proton attached to a carbon atom (Scheme 3).




**Scheme 3:** Synthesis of compounds **13** - **15**.

The origin of these observations was resolved by a single crystal X-ray analysis on a sample of compound **13** (isolated yield 69%) that was grown by slow evaporation of a toluene solution at room temperature. This revealed (Figure 2) that the dihydropicolide unit of compound **III** had undergone an unexpected ring contraction to form a coordinated pyrrolide with the remaining dihydropicolide carbon (C35), now external to the new $C_4N$ ring system as a methylene group which forms a new C-C bond to the central carbon of the carbodiimide-derived and protonated amidine unit. The formation of this latter moiety also accounts for the non-carbon bound singlet resonance observed at δ 4.01 ppm in the $^1$H NMR spectrum. Compound **13** contains a 4-coordinate magnesium centre, in which two of the coordination sites are occupied by the bidentate β-diketiminate ligand with further augmentation of the coordination sphere provided by a neutral 3-picoline molecule and the resulting ring contracted pyrrolide anion. The pyrrolide ring is delocalised around the *N*-heterocycle [N(4)-C(30) 1.337(3) Å, C(30)-C(31) 1.376(3) Å, C(31)-C(33) 1.417 (3) Å, C(33)-C(34) 1.381(3) Å, C(34)-N(4) 1.371(3) Å], while the remaining carbon centre, C(35), arising from the original dihydro-3-picolide ligand, displays unambiguous tetrahedral *sp*$^3$ hybridisation. The formation of the new C-C bond is confirmed to have single bond character [C(35)-C(36) 1.517(3) Å], whilst the reduced carbodiimide contains both localised single [N(5)-C(36) 1.374(3) Å] and double carbon-nitrogen bonds [N(6)-C(36) 1.285(2) Å]. Although transformations of dihydropyridines to pyrrole derivatives have been described previously,[8] these earlier processes required highly energetic thermal conditions (>230°C), provided low yields and were unselective for the production of a single reaction product.

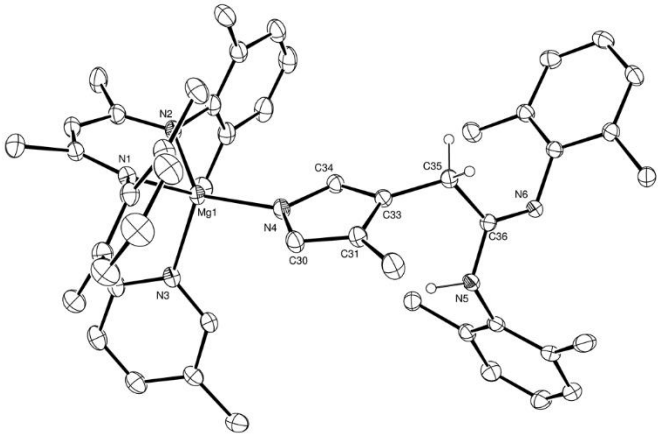


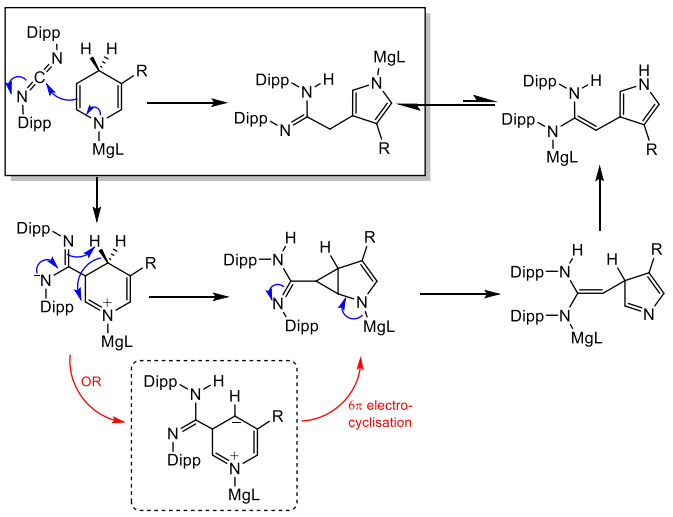

**Figure 2:** ORTEP representation of compound **13** with thermal ellipsoids set at 25% level of probability. Hydrogen atoms except those attached to C(35) and N(5) along with *iso*-propyl groups of the *β*-diketiminate 2,6-di-*iso*-propylphenyl substituents are removed for clarity. Selected bond lengths (Å) and angles (°): Mg(1)-N(1) 2.0500(18), Mg(1)-N(2) 2.0438(18), Mg(1)-N(3) 2.1290(19), Mg(1)-N(4) 2.0042(18), N(4)-C(34) 1.371(3), C(34)-C(33) 1.381(3), C(33)-C(35) 1.505(3), C(35)-C(36) 1.517(3), C(36)-N(5) 1.374(3), C(36)-N(6) 1.285(2), C(33)-C(35)-C(36) 116.06(17), N(5)-C(36)-N(6) 118.69(18), C(36)-N(5)-C(49) 121.00(17).

The effects of varying the electronic nature and steric demands of this system were examined through the *in situ* preparation of two further analogues of compound **III**, which were derived by the dearomatisation of 3-methoxy- and 3-ethylpyridine. Heating of the

reaction mixtures formed by addition of DippN=C=NDipp to these β-diketiminato magnesium 3-methoxy-1,4-dihydropyridide and 3-ethyl-1,4-dihydropyridide complexes at 60°C for 12 hrs again resulted in the formation of the respective pyrrolide species **14** and **15**. Both compounds were readily identified through the emergence of 5 new singlet resonances in the relevant $^{1}$H NMR spectra reminiscent of those observed for compound **13**. We, thus, suggest that an analogous ring contraction mechanism is operant during the formation of all three compounds, **13** – **15**.

Monitoring of a further reaction of compound **III** with 1 equivalent of DippN=C=NDipp through the acquisition of $^{1}$H NMR spectra at 15 minute intervals over the course of the 12 hour reaction period, showed the loss of the proton resonances pertaining to the dearomatised 3-picolide anion concurrent with an increase in the new singlet resonances arising from compound **13**. No other potential intermediates or reaction products were observed during the course of the reaction, suggesting that the ring contraction ensues through a concerted mechanism involving rapid rearrangement to the pyrrolide fragment. Further insight into the potential mechanism of these reactions was provided through the preparation of the magnesium 1,4-hydro-3-picolide($d_7$) complex (**III**-$d_7$), which was formed *in situ* in an analogous fashion to that utilised during the synthesis of **III** but with the replacement of the 3-picoline reagent by its perdeuterated analogue, 3-picoline-($d_7$). Analysis of the $^{1}$H NMR spectrum provided by the reaction of **III**-$d_7$ with an equimolar quantity of DippN=C=NDipp at 60°C for 24 hrs revealed the presence of the expected β-diketiminate ligand resonances along with one further singlet signal at δ 4.00 ppm that was deduced to have originated from the single $^{1}$H hydride of the 1,4-hydro-3-picolide($d_7$) unit of **13**-$d_7$ (Figure S3). This latter signal was identified as the proton transferred to the amidine N-*H* bond, both by comparison to the analogous spectrum obtained from the protio derivative **13** along with a further $^{1}$H-$^{14}$N HSQC NMR experiment, which demonstrated a clear correlation between this singlet resonance and the amidine nitrogen nucleus observed at δ 70 ppm in the $^{14}$N NMR spectrum (Figure S4).




**Scheme 4:** Proposed mechanism for the ring contraction to form compounds **13** – **15**

Based on these observations, a proposed mechanism for the ring contraction of magnesium-supported 3-substituted-1,4-dihydropyridides through reaction with DippN=C=NDipp is shown in Scheme 4. This is suggested to proceed *via* initial nucleophilic enamide attack at the central carbon of the carbodiimide substrate, which is crucially more electrophilic than similar bulky *N*-alkyl derivatives. The reaction is further directed by both the steric demands of the 2,6-di-isopropylphenyl substituents and the 3-substitution of the relevant 1,4-dihydropyridide heterocycles. The initially formed intermediate undergoes subsequent and rapid ring contraction to form a cyclopropanamidate species either directly or *via* a 6π electrocyclisation. Further rearrangement to form the pyrrolide ring, and finally tautomerisation yields the more stable methylene pyrrolide complexes.

In conclusion, we have observed that magnesium dihydropyridide derivatives display divergent reactivity with carbodiimide reagents of varying steric demands. While smaller *N*-alkyl or –aryl substitution results in the anticipated formation of magnesium guanidinate derivatives, the use of more bulky *N*-aryl reagents induces an unprecedented 1,4-dihydropyridide to pyrrolide ring contraction reaction.

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