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The Synthesis of Inward-Facing 3,6-Di(2-Pyridyl)Pyridazine Ligands

Douglas N. Butler,* Paul M. Tepperman, Robert A. Gau

Department of Chemistry, York University, North York, Ontario, M3J 1P3, Canada

Ronald N. Warrener*

Centre for Molecular Architecture, Central Queensland University, Rockhampton, Qld, 4702, Australia

Abstract: A new class of inward-facing bis(dpp-ligands) fused to rigid molecular racks are reported, eg **17** and **19**. The 3,6-di(2-pyridyl)pyridazine ligand units are formed by the reaction of 3,6-di(2-pyridyl)*s*-tetrazine with molrac bis(olefins), eg **11** and **18** (followed by oxidation of the intermediate dihydropyridazines); additionally mono-olefin, mono-pyridazines **14** and **21** are reported. Molecular modelling and comments of the mechanism of product formation are included.
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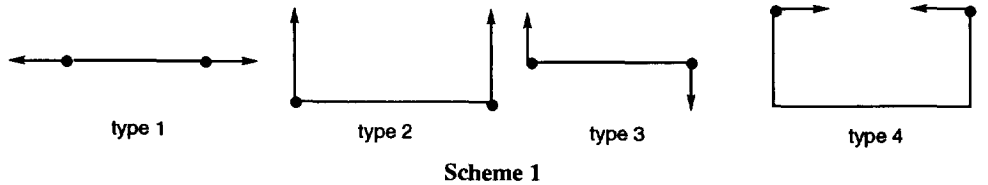
The value of scaffolds for positioning functional groups or effectors has recently been addressed by Voyer and Lamothe in the context of peptides to fulfil this role.[1] The importance of such substances to provide exact molecular geometry is demonstrated in a number of important research areas, eg specific receptors, molecular devices, dendrimers etc. The limitations identified in the use of peptides as scaffolds include a requirement for a minimum number of amino acids to provide specific motifs, eg 6-7 for a β-sheet and 12-13 for an α-helix; in discussing molecular devices they conclude "that scaffolds with a single and rigid conformation will be required for the development of efficient and reliable molecular electronic devices". It is this very arena where the range of geometries and motifs available to molracs[2,3] can complement existing scaffolds and the present report gives an example of how closely positioned chelating functionality can be rigidly attached to the molrac in a new geometry; later work will specifically address the role of molracs in molecular devices. The example provided herein for the conversion of **11** to the inward-facing bis(pyridazine) **17** is pedagogically attractive as the geometry of the system allows clear identification of many of the intermediates and illustrates ring-current and symmetry in a practical way.



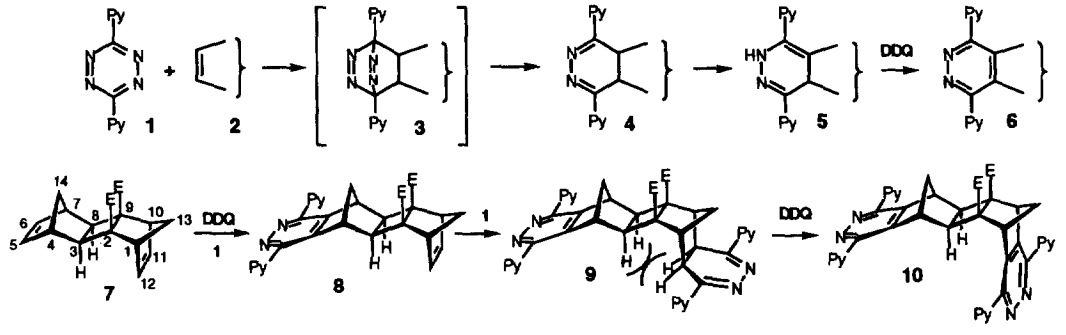
Scheme 1

In a recent report we described the synthesis of a new class of ligands which incorporate two 3,6-di(2-pyridyl)pyridazine (DPP) ligands per molecule.[3] These ligand units were geometrically constrained by virtue of the annelation reaction used to fuse them to the rigid carbocyclic framework of the molrac. Whereas the systems reported to date have the angular relationship of the two DPP ligands ranging from roughly parallel (type 2, Scheme 1) to a fully opposed *anti*-configuration (types 1 and 3, Scheme 1), the present

report deals with systems where the two ligand sites are facing each other through space with the individual ligand units having an *opposed*-relationship (type 4, Scheme 1).

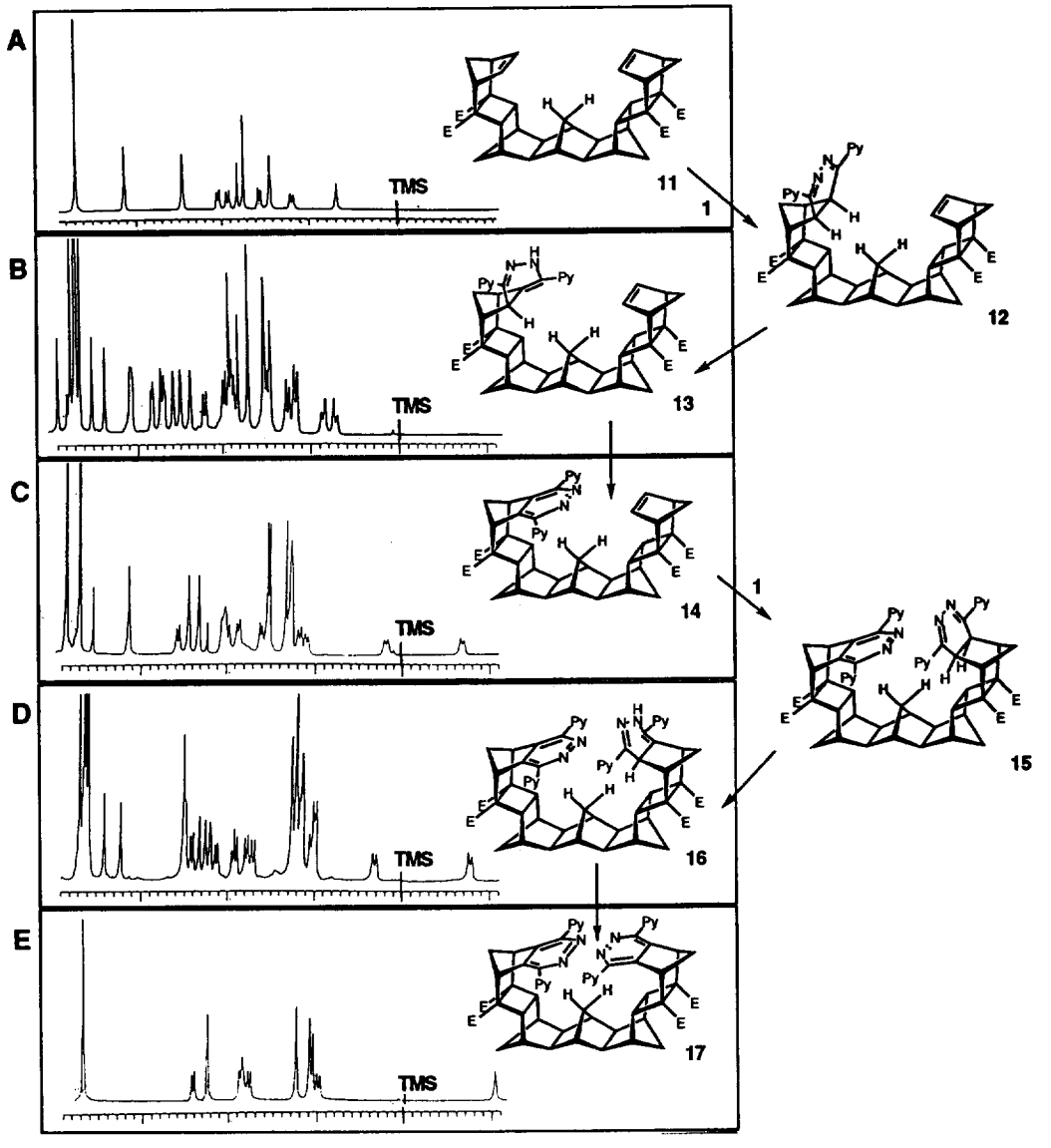
The basic reaction used to introduce the DPP ligand proceeds according to the reaction sequence illustrated with prototype olefin **2** and 3,6-di(2-pyridyl)-*s*-tetrazine **1**, followed by oxidation of the dihydropyridazine intermediate(s) with DDQ (Scheme 2). The first adduct **3** is never observed, indeed there is some suggestion that it may be no more than a transition state in the formation of the 1, 2-dihydropyridazine **4**.[4] 1, 2-Dihydropyridazines of this type are isolated in some cases, eg fused cyclopropanes and cyclobutanes, while isomerisation to the 1,4-dihydropyridazine **5** is facile in others and is common in norbornenes.[5] Oxidation with DDQ on either dihydropyridazine to the pyridazine **6** is readily achieved, and pyridazines are often the product of reaction with sluggish olefins and *s*-tetrazine where aerial oxidation or the *s*-tetrazine itself effect the dehydrogenation.[6]

The reaction of 3,6-di(2-pyridyl)-*s*-tetrazine **1** with the carbocyclic diene **7**, which has been described previously,[3] puts the present reactions into context. While reaction of **1** occurs rapidly with **7** in chloroform solution at ambient temperature at the $\Delta^{5,6}$ π-bond, the reaction can only be made to proceed at the *bent* ($\Delta^{11,12}$-type) π-bond of **8** after heating under reflux in $CHCl_3$ for several days whence bis(pyridazine) **10** can be isolated following DDQ oxidation (Scheme 2). This shows that the *bent* norbornene π-bond in substrate **7** is much less reactive than its *extended* norbornene counterparts and this has been established as a general rule. One explanation for this reduced reactivity can be attributed to the steric crowding which occurs in the transition state between the protons at C11,12 as they develop sp^3 geometry and approach those at C3,8. These observations are pertinent to the present study of reaction of *s*-tetrazine **1** with molrac olefins **11**, **18**, and **20** since all the inward-facing norbornene π-bonds in this series are of the *bent* type.



Scheme 2

The reactions involved in the conversion of cavity diene **11** to cavity bis(pyridazine) **17** (Scheme 3) are clearly followed by ^1H NMR spectroscopy and provide a pleasing pedagogic example of symmetry and anisotropy (Fig 1). In particular, the ester groups in **11** (and subsequent intermediates) yield information regarding both σ-planes in the C_{2v} starting and C_{2v} finishing product while the intracavity methylene protons serve as the probe for anisotropy and the short axis σ-plane. Thus the starting material **11** exhibits only one resonance corresponding to all four ester methyl groups and a singlet for the central methylene protons (Fig 1A). The first equivalent of *s*-tetrazine **1** adds slowly ($CHCl_3$ at reflux, 5 days) to form the 1,4-dihydropyridazine **13** is which is devoid of symmetry: the ester methyls appear as four separate singlets and the methylene as a pair of doublets (δ 0.74, 0.86) (Fig 1B). Significantly neither resonance is upfield confirming the lack of appreciable ring current in the dihydropyridazine ring. Oxidation (DDQ) provides the

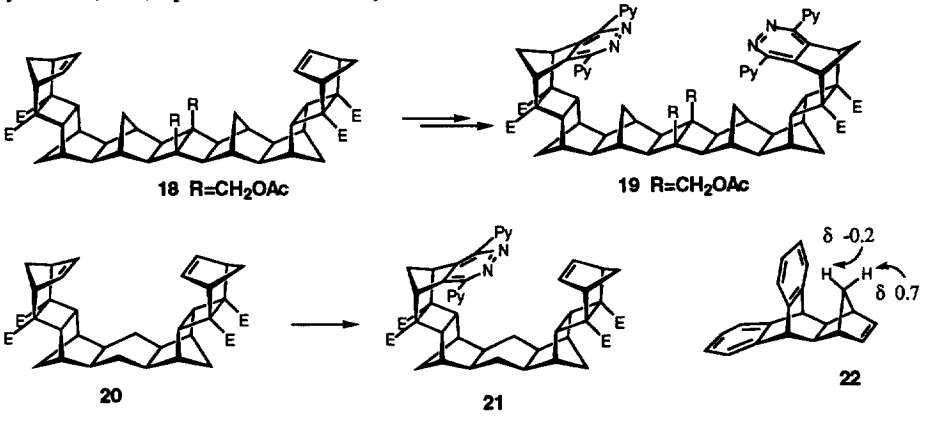


Scheme 3 and Fig 1. ^{1}H NMR Spectra (δ -1 to 4) of compounds **11, 13, 14, 16, 17.**

pyridazine **14** where some symmetry is restored (Cs) which is characterised by the two sets of ester methyl resonances and a new pair of doublets for the methylene protons (Fig 1C). Now one of the methylene doublets resonates at δ -0.7 and indicates its proximity to, and the anisotropy of, the pyridazine ring. Further reaction of **14** with **1** is only observed after protracted heating (reflux in $CHCl_3$, 12 days). The unsymmetrical intermediate **16** can be identified (Fig 1D) where all four ester methyl are different and the methylene retains well separated resonances for the two methylene protons. Complete conversion to the bis(pyridazine) **17** occurs without incident upon treatment with DDQ and the C_{2v} symmetry of the product is restored (singlet for ester methyls and for the methylene protons) (Fig 1E). These methylene protons resonate at δ -1.05 as they are

now under the influence of both pyridazine ring currents. Examples of such high field methylene resonances are provided by the anthracene adduct of norbornadiene **22**[7] and more recently, that resulting from porphyrin shielding.[8]

Cavity-molecule **18** in which the π–centres are significantly further separated (13.35Å, calculated by AM1)[9] than **11** (6.56Å, X-ray)[10] is still slow in its reaction with *s*-tetrazine **1** ($CHCl_3$, 5 days at reflux) but ^1H NMR analysis shows that dihydropyridazine formation has occurred at both π-centres; oxidation (DDQ) to the bis(pyridazine) **19** (m.p. 138-140 °C; 59% yield) occurs without undue difficulty (Scheme 4).



Scheme 4

In contrast, the cyclohexane-based molrac diene **20**, where the π-bonds are separated by only 4.41Å (X-ray)[10] is much more sluggish in its reaction with *s*-tetrazine **1**. Addition of the first equivalent of *s*-tetrazine **1** is still incomplete after heating in chloroform at reflux for 5 days (note that **11** had reacted completely at the first π-bond in this time). Oxidation of the reaction mixture and separation of the acid-soluble components yielded the monopyridazine **21** (m.p. 220 °C, 68%). All attempts to force reaction at the π-bond of **21** with *s*-tetrazine **1** were unsuccessful and this is attributed to steric congestion in the transition state leading to attack at the π-bond by **1** owing to the proximity of the pyridazine and its substituents.

Acknowledgements

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