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Functionalised Rigid Rods - Dream or Reality

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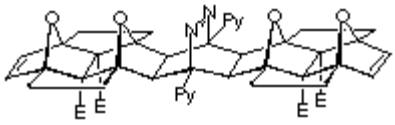
Abstract

Approaches to the synthesise of rigid molecular rods containing syn-facially positioned 7-oxa functionality the building BLOCK **12** was identified by molecular modelling as a suitable starting substrate. However, once synthesised, **12** was found to be unstable under the reaction conditions used in an attempt to create rigid rods. This included such coupling protocols as the epoxide based ACE reaction as well as the *s*-tetrazine system. The foundations have now been laid for future incorporation of **12** into rigid rods.



1. Introduction

During the past several years *molracs*[1] have been employed as the structural backbone for the positioning of various moieties in well defined geometries. These have included such entities as pyrimidines[2], phenanthrolines[3,4], crown ethers[5] and porphyrins[2]. The synthesis of these backbones has evolved from serial cycloaddition strategies into those incorporating functionalised building BLOCKs and appropriate coupling reactions[6,7]. With the stereoselectivity of the oxadiazole (OD), ACE and *s*-tetrazine based coupling reactions well established, the design of larger supramolecular structures using the molrac concept now centres around building BLOCK design. In particular, the shape and

positioning of functionality within the BLOCK is all important since these characteristics are retained in the target molrac.

A particularly relevant variation on the usual curved molrac topology was the inclusion of the pentacyclic bis-norbornene unit **1** to create rigid rods[8]. Application of the various coupling strategies mentioned above facilitated the synthesis of extended rods with little or no curvature.

As a further extension of this methodology, we sought a BLOCK that would allow functionality to be positioned in the all important 7- position of the norbornene skeleton as well as facilitate the synthesis of linear rigid systems utilising the known coupling procedures. Herein we report that **12** has been identified as a BLOCK fulfilling the above requirements and discuss its synthesis as well as several attempts to incorporate **12** into various linear architectures.

2. BLOCK Modelling

Molecular modelling is an invaluable aid in determining suitable materials for inclusion into molrac structures. Several BLOCK candidates are shown in Figure 1 and contain various degrees of curvature as indicated by the comparison between the calculated (AM1) C-C and H-H distances shown. The curvature of the system may be expressed in the difference between these distances, with a large difference implying high curvature. The Paquette-based system **1**[8], containing two one carbon bridges directly linked, possesses the least curvature of any of the BLOCKs shown, whereas the bisnorbornane skeleton **2** has the highest. The inclusion of oxygen in BLOCK **3** still results in a certain degree of curvature. However, the Cram-based system **4**,[10] while still containing two functionalities, is still reasonably linear in geometry and represents an excellent combination of functionality and shape. The system **4** was thus identified as a suitable target for inclusion within the molrac structure.

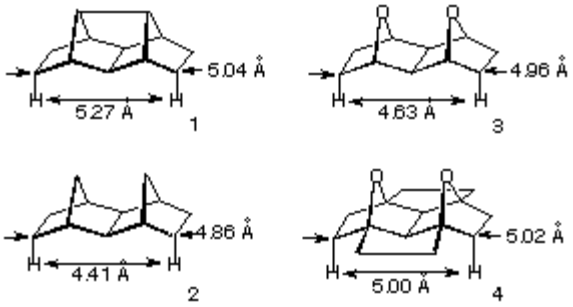
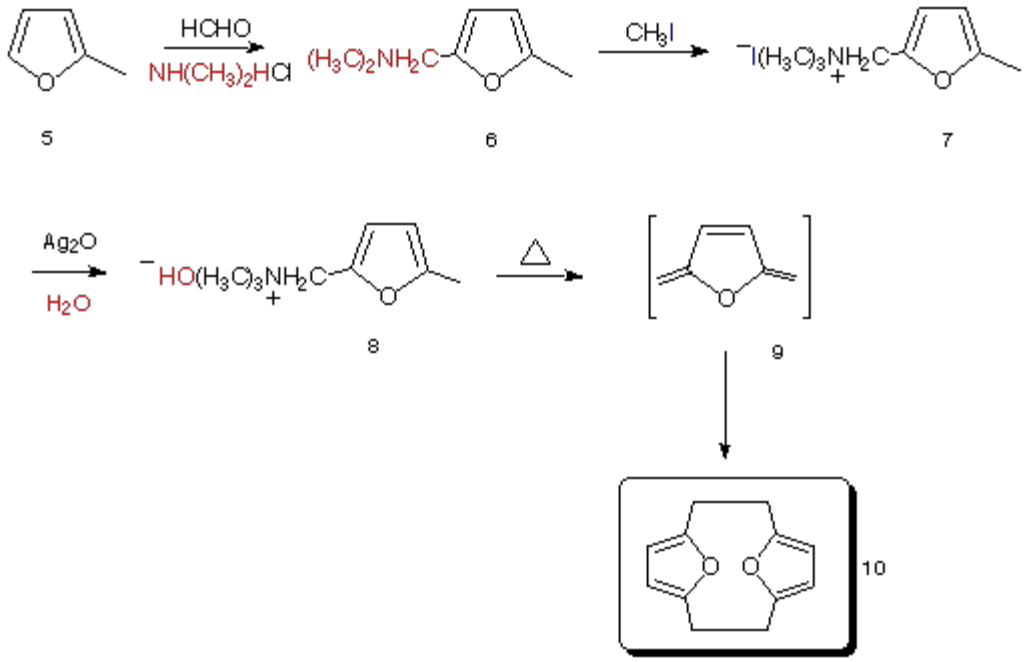


Figure 1: *Molecular models of the various BLOCKs carried out at the AM1 level of theory. Distances are in Angstroms (Å).*

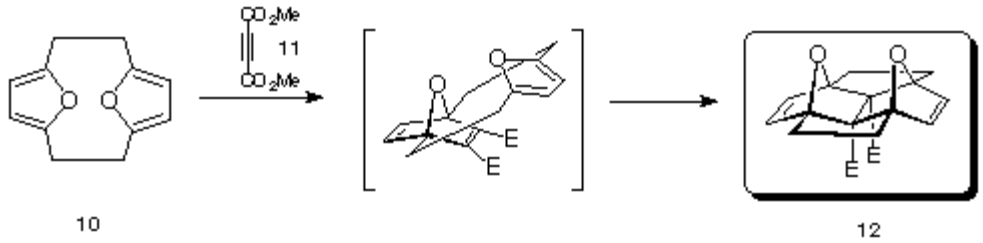
3. BLOCK Synthesis

The synthesis of **12** followed that first developed by Cram[10] and is outlined in Schemes 1 and 2. Treatment of 2-methylfuran **5** under Mannich conditions resulted in the isolation of the adduct **6** which was subsequently quatternised with methyl iodide to yield **7**, which after being subject to counterion exchange produced **8** (Scheme 1). Pyrolysis of **8** (via Hoffman elimination) resulted in the formation of the transient exocyclic diene **9**, which dimerises *in situ* to yield the product bisfuranocyclophane **10** in reasonable yield. The reaction sequence was carried out on a multi-gram scale.



Scheme 1

Once isolated, the furanocyclophane **10** was allowed to react with dimethylacetylene dicarboxylate **11** (DMAD) to give the pincer cycloaddition adduct **12** (Scheme 2). The intermediate 1:1 adduct between **11** and DMAD has the possibility of forming both "pincer" and "domino" adducts, yet the "pincer" adduct **12** was the only isomer observed.



Scheme 2

4. Molrac Modelling

The curvatures of the various molrac structures were initially examined by molecular modelling at the AM1 level of theory. Shown in figures 2, 3 and 4 are various modelled structures based on the **1**, **2** and **4** BLOCKs. In all instances the pronounced curvature of the molecules constructed with the **2** BLOCK is apparent. In contrast the use of **1** or **4** creates a more linear system with **1** producing more linear structures than **4**.

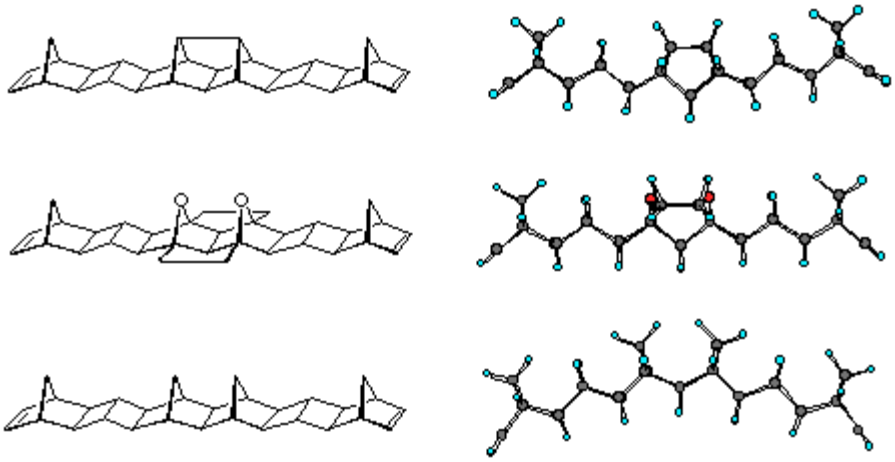


Figure 2: *Quadricyclane adducts*

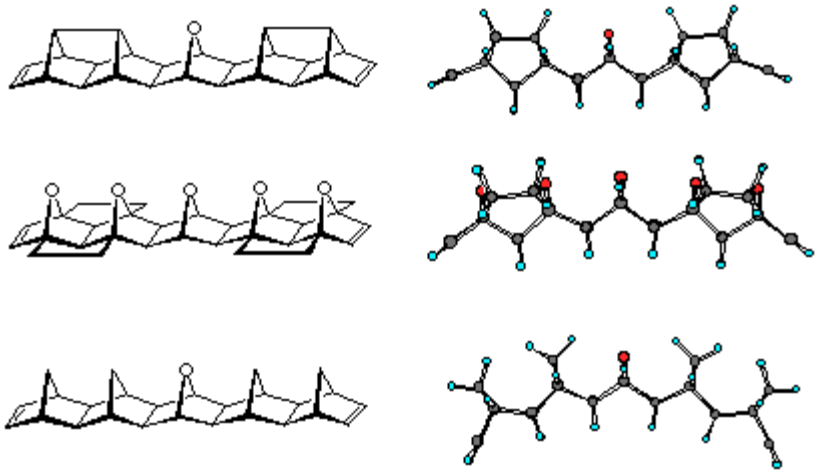


Figure 3: *Oxadiazole or ACE coupled products*

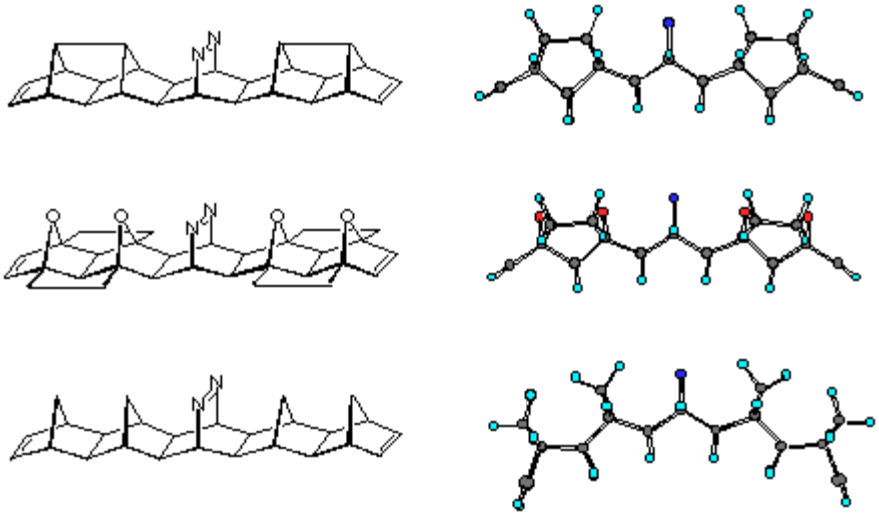
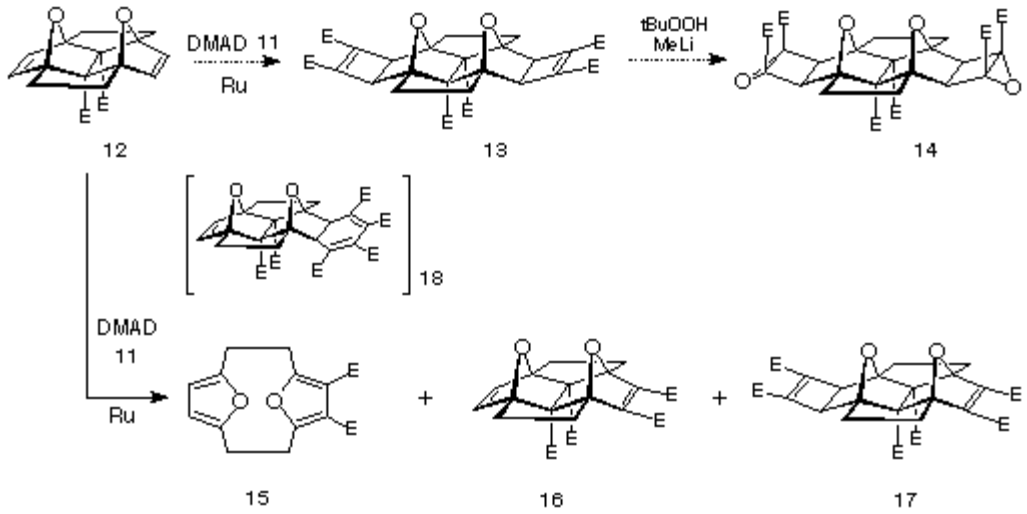


Figure 4: *Tetrazine coupled adducts*

5. Molrac Synthesis

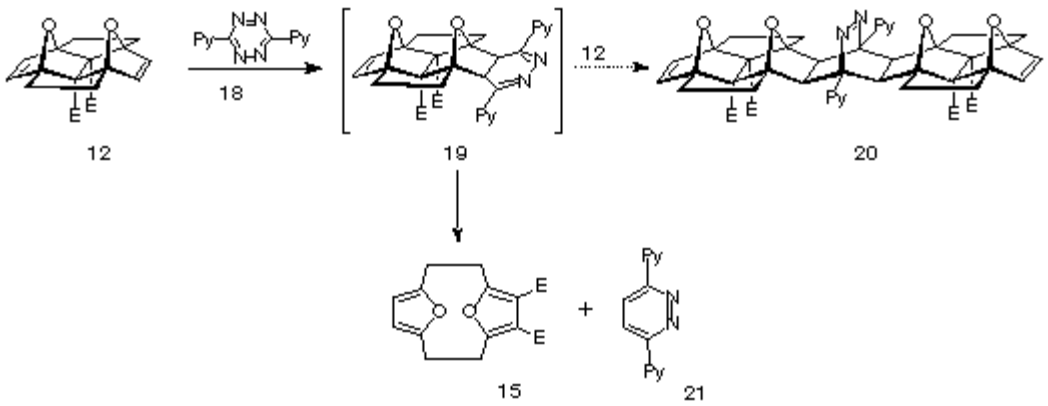
The first coupling method to be examined using **12** was the epoxide based ACE procedure[11]. While the stereoselectivity of the ACE reaction is well known for norbornene terminated substrates, the use 7- oxa containing BLOCKs results in the isolation of both *exo,exo*- and *exo,endo*- adducts[12]. Thus, for the stereoselective use of **12** the epoxide functionality must be contained within **12** and this necessitated the synthesis of **14** via the DMAD adduct **13** (Scheme 3). However, several attempts to prepare **13** have proved ineffective with only very minor amounts of material produced. Instead a complex mixture containing **15, 16** and **17** along with other unidentified products. Such materials presumably result from an intermediate **18** (by analogy with the *s*-tetrazine coupling reaction intermediate, Scheme 4) to produce **15** which subsequently undergoes reaction with DMAD under the reaction conditions to form the tetraester **16**. Further reaction of **16** with DMAD under ruthenium catalysed conditions yields the hexaester **17**. The conversion of **16** to **17** has been verified in a separate experiment starting with pure **16**.



Scheme 3

Cram has indeed reported that **12** undergoes a partial retro Diels-Alder reaction at 100°C resulting in the formation of an equilibrium between **12** and the bisfuranocyclophane **10** after a 3-4 hours. Further attempts at the synthesis of **13** utilising lower reaction temperatures were unsuccessful.

The thermal instability of **12** eliminated the possibility of the OD coupling procedure (140°, 20 hours, sealed tube) and hence attention was turned to the use of *s*-tetrazine as a coupling reagent since low temperatures and high pressures have been found to be favourable for its use[13]. The proposed synthesis of molrac **20** using tetrazine is outlined in Scheme 4.



Scheme 4

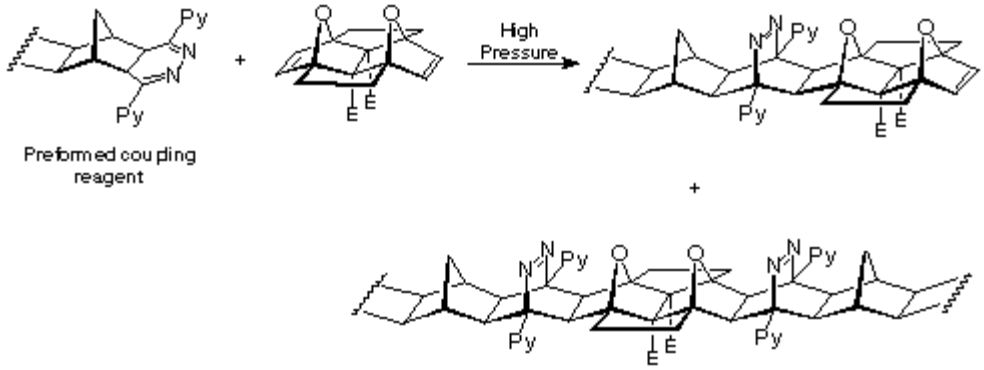
Combination of two equivalents of **12** with one equivalent of *s*-tetrazine **18** in DCM revealed the loss of the characteristic red colour of **18** within several minutes, an phenomena usually expected to be associated with the rapid

formation of the intermediate dihydropyrazine **19** in this case. However, subsequent application of high pressure failed to yield the product **20**, but rather gave the tetrazine byproduct **21** and **15**. Similar decomposition reactions have been observed previously by Battiste for a bis-7-aza linked pincer material[14].

6. Conclusion

While we have identified a suitable BLOCK containing the desired structural features using molecular modelling, it does not immediately follow that such material will be stable under the coupling procedures necessary to produce molrac materials. Attempted syntheses of the bisepoxide ACE reagent precursor **14** failed to yield the desired material in any quantity but instead yielded several unexpected materials. Similar results were also observed in attempts to utilise the *s*-tetrazine based coupling protocol.

Since the application of coupling procedures starting with **12** and working outwards have been found to be ineffective, future work must necessarily couple from outside reagents onto **12** (Scheme 5). In particular, the ambient temperature photoACE[12] reaction may prove useful as well as *s*-tetrazine coupling reactions with addition of **12** after dihydropyrazine formation has already been carried out on a second BLOCK.

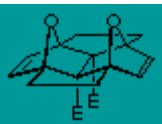


Scheme 5

7. Experimental

Molecular modelling was undertaken using Silicon Graphics workstations (O_2) and Spartan 5.2 software utilising the AM1 level of theory. Cram's diene **12** and the relevant precursors were synthesised according to literature procedures[10]. ^{1}H and ^{13}C NMR spectroscopy was obtained on Bruker AMX300 or Avance400 spectrometers using standard Bruker pulse programs. Spectra are referenced relative to tetramethylsilane.

Synthesis of **12**:

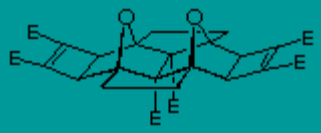


A solution of bisfuranocyclophane **10** (1.0 g) and DMAD **11** (3.0 g) in chloroform (2 ml) was heated overnight in a stainless steel high pressure vessel overnight. The solvent was removed *in vacuo* and the residue separated by radial chromatography (petroleum spirit-ethyl acetate 5:1 to 2:1) to afford **12** (410 mg) and a second product **16** as a yellow coloured solid (400 mg, m.p. 187-189 °C).

^{1}H-NMR ($CDCl_3$): 2.35 - 2.45 (8H, m); 2.59 - 2.83 (4H, m); 2.91 - 3.08 (4H, m); 3.55 (6H, s); 3.80 (6H, m); 6.80 (2H, s).

^{13}C-NMR ($CDCl_3$): 29.0; 29.4; 1.9; 52.1; 81.2; 97.3; 97.6; 138.9; 147.7; 163.1; 168.8; HRMS calc for $C_{22}H_{22}O_{10}$: 446.1213, found: 446.1203.

Synthesis of **13**:



A solution of **12** (0.85 g) DMAD **11** (3.0 g) and $RuH_2CO(PPh_3)_3$ catalyst (200 mg) in benzene (20 ml) were refluxed overnight under an nitrogen atmosphere. Purification was achieved by flash chromatography (silicagel, petroleum spirit - ethyl acetate 3 :1 with increasing ethyl acetate), followed by radial chromatography (2x) to afford small amounts of **13**, which was recrystallised twice from methanol to afford product as a colourless solid (40 mg, 2.5 %, m.p. 200-202 °C).

^{1}H-NMR ($CDCl_3$): 2.17-2.26 (4H, m); 2.34 - 2.43 (4H, m); 3.55 (4H, s); 3.75 (6H, s); 3.77 (12H, s).

^{13}C-NMR: 28.9; 47.7; 52.3; 52.6; 76.47; 94.5; 141.23; 161.5; 168.8.

HRMS calc for $C_{30}H_{30}O_{14}$: 614.1638, found: 614.1647.

Synthesis of **17**:

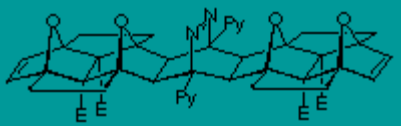
A mixture of tetraester **16** (200 mg), DMAD **11** (2.0 g) and $RuH_2CO(PPh_3)_3$ catalyst (200 mg) in benzene (10 ml) was refluxed for 3 days. The reaction mixture was separated by flash chromatography (silicagel, petroleum ether - ethyl acetate 3 :1, with increasing ethyl acetate), to afford product **17** as a colourless solid (30 mg, m.p. 191-3 °C)

^{1}H-NMR ($CDCl_3$): 1.80 - 1.90 (2H, m); 2.48 - 2.51 (2H, m); 2.63 - 2.77 (2H, m); 3.18 (2H, s); 3.35 - 3.42 (2H, m); 3.78 (6H, s); 3.79 (6H, s); 4.05 (6H, s).

^{13}C-NMR ($CDCl_3$): 26.4; 31.5; 51.9; 52.6; 53.0; 53.3; 87.4; 117.2; 139.4; 140.5; 162.4; 163.5; 165.8.

HRMS calc for $C_{28}H_{28}O_{14}$: 588.1479, found: 588.1486.

Attempted Synthesis of **20**:



A solution of **12** (50 mg, 0.151 mmol) in DCM (1 ml) was treated with *s*-tetrazine **18** (36 mg, 0.151 mmol). The pink color of the tetrazine disappeared within several minutes. The ^{1}H-NMR of crude mixture revealed that all **12** had been converted to **15** (83%, m.p. 137-9 °C).

^{1}H-NMR ($CDCl_3$) (obtained from crude spectrum): 2.56 - 2.59 (4H, m); 2.81 - 2.84 (4H, m); 3.58 (6H, s); 6.07 (2H, s)

^{13}C-NMR ($CDCl_3$):30.3, 30.8, 52.3, 109.4, 115.6, 156.7, 163.3, 164.3.

HRMS calc for $C_{16}H_{16}O_6$: 304.0947, found: 304.0944.

8. References

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