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The synthesis of new framework structures containing rigidly-linked pyrimidines suitable for uracil and cytosine elaboration [1]

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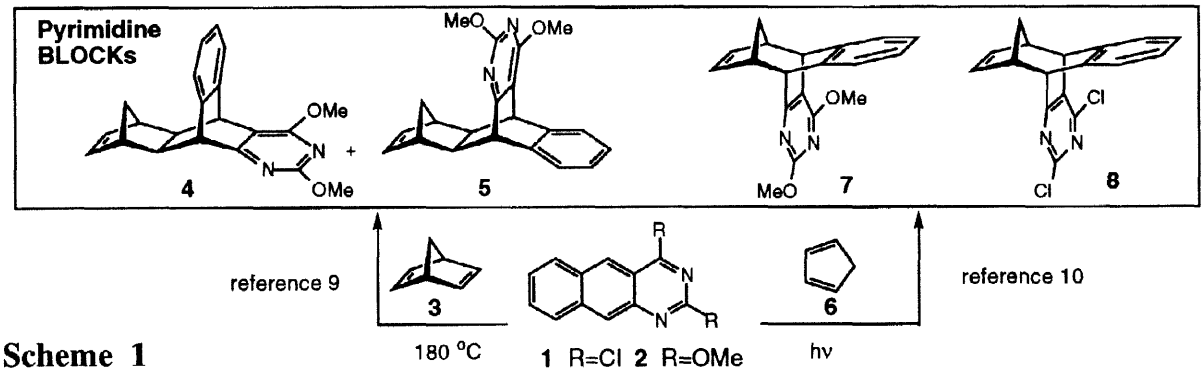
Abstract:

Fused norbornenes and tricyclo[4.2.2.1^{2,5}]undec-3,7,9-trienes containing 2,4-dichloropyrimidine and 2,4-dimethoxy pyrimidine units are coupled with norbornadiene, benzonorbornadienes and dimethoxynaphthaleno norbornadienes using *s*-tetrazines or ACE coupling techniques to afford framework structures where different geometrical interrelationships can be attained between the chromophores.

Keywords: cycloaddition; pyrimidines; stereochemistry; epoxides

Uracil and cytosine, two naturally occurring pyrimidines, have major roles in complementary recognition of nucleic acid purine bases through H-bonding [2]. As such, they are important targets in artificial systems seeking to mimic nature's H-bonding motifs [3-5]. Accordingly, these pyrimidine types have been specifically targeted for incorporation into alkene building BLOCKs for use in coupling protocols developed recently in our laboratory [6,7]. We now demonstrate the coupling profiles of new pyrimidine BLOCKs and their application to the synthesis of ribbon systems typified by their linkage to dimethoxy naphthalenes, a prototype chromophore suitable for energy transfer studies [8]. Of course, linking to other effectors is feasible as instanced in some of our recent work with crown ethers, porphyrins, ligands and their metal complexes [7].



Scheme 1

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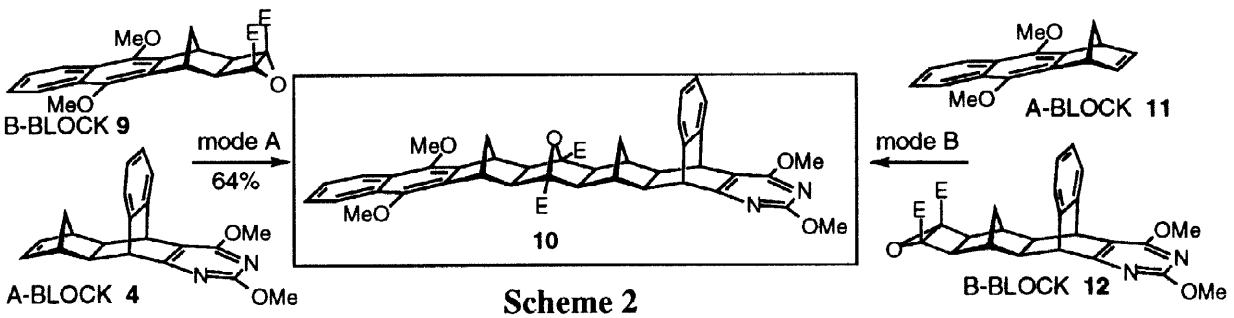
Two types of building BLOCKs have been used in this study (Scheme 1). The first are the fused norbornenes **4** and **5**, which contain the 2,4-dimethoxy pyrimidine ring. These were prepared from the thermal addition of norbornadiene **3** to 2,4-dimethoxy-1,3-diazaanthracene **1** using published methods [9]. The others are the tricyclo[4.2.2.$1^{2,5}$] undec-3,7,9-trienes **7** and **8** which are formed by photochemical addition of cyclopentadiene to 1,3-diazaanthracenes **1** and **2** using methods described in the accompanying letter [10].

In this communication, we demonstrate that each of these types of alicyclic A-BLOCK alkenes (Scheme 2) can participate in ACE (Alkene plus Cyclobutene Epoxide) coupling [6] or *s*-tetrazine coupling [11] procedures, thereby opening opportunities for the preparation of new framework structures containing naturally occurring pyrimidine subunits linked to other effector groups.

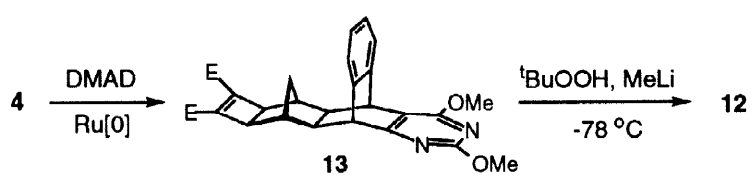
ACE Coupling

ACE coupling of norbornene A-BLOCKs has established itself as a key method for the stereocontrolled assembly of multi-functionalised framework structures. In the present context, we show (Scheme 2, mode A) that the 2,4-dimethoxy pyrimidine component can be delivered by the A-BLOCK **4** to the dimethoxynaphthalene B-BLOCK **9** [6] under photochemical conditions (acetone, 300 nm, 3h) to provide the mixed-coupled product **10**[1] {mp 256-260 °C, 64% isolated yield, ^{1}H NMR δ -0.63 (d, J = 11.3 Hz, 1H), 1.38 (d, J = 9.2 Hz, 1H), 1.64 (d, J = 11.3 Hz, 1H), 1.77 (m, 2H), 1.93 (s, 2H), 1.99 (s, 1H), 2.01 (s, 1H), 2.28 (s, 2H), 2.69 (d, J = 9.2 Hz, 1H), 3.55 (s, 2H), 3.92 (s, 3H), 3.95 (s, 9H), 3.957 (s, 3H), 3.963 (s, 3H), 4.22 (d, J = 2.5 Hz, 1H), 4.44 (d, J = 2.5 Hz, 1H), 7.15 (m, 4H), 7.44 (m 2H), 8.06 (m, 2H)}.



Scheme 2

Further support for the structure of **10** comes from its separate synthesis by reaction of alkene **11** with the cyclobutene epoxide **12** (Scheme 2, mode B) under thermal conditions (49% yield). The required epoxide **12** {mp 283-285 °C, 59% yield, ^{1}H NMR δ -0.25 (d, J = 12.3 Hz, 1H), 0.95 (d, J = 12.3 Hz, 1H), 1.78 (m, 2H), 2.22 (s, 2H), 2.55 (s, 1H), 2.57 (s, 1H), 3.72 (s, 6H), 3.94 (s, 3H), 3.96 (s, 3H), 4.29 (d, J = 2.6 Hz, 1H), 4.52 (d, J = 2.6 Hz, 1H), 7.16 (m, 2H), 7.25 (m, 2H)} is prepared in two steps from **4** (Scheme 3).

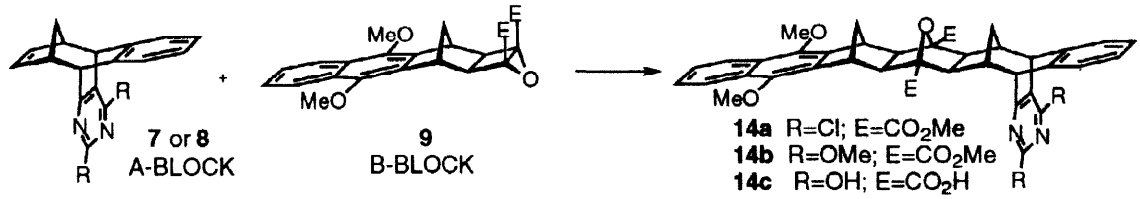


Scheme 3

The ability of the π-bond of tricyclo[4.2.2.$1^{2,5}$]undeca-3-enes to undergo BLOCK coupling was demonstrated by the formation of the pyrimidine-containing compounds **14a** (mp 360-362 °C, 77% yield, ^{1}H NMR δ 0.85 {d, J = 13.1 Hz, 1H), 1.42 (d, J = 9.5 Hz, 1H), 1.97 (m, 3H), 2.24 (m, 2H), 2.49 (m, 2H), 2.69 (d, J = 9.5 Hz, 1H), 3.58 (brs, 2H), 3.97 (s, 12H), 4.27 (d, J = 9.3

[1] All compounds exhibited ^{13}C NMR, MS and/or analytical data consistent with structure.

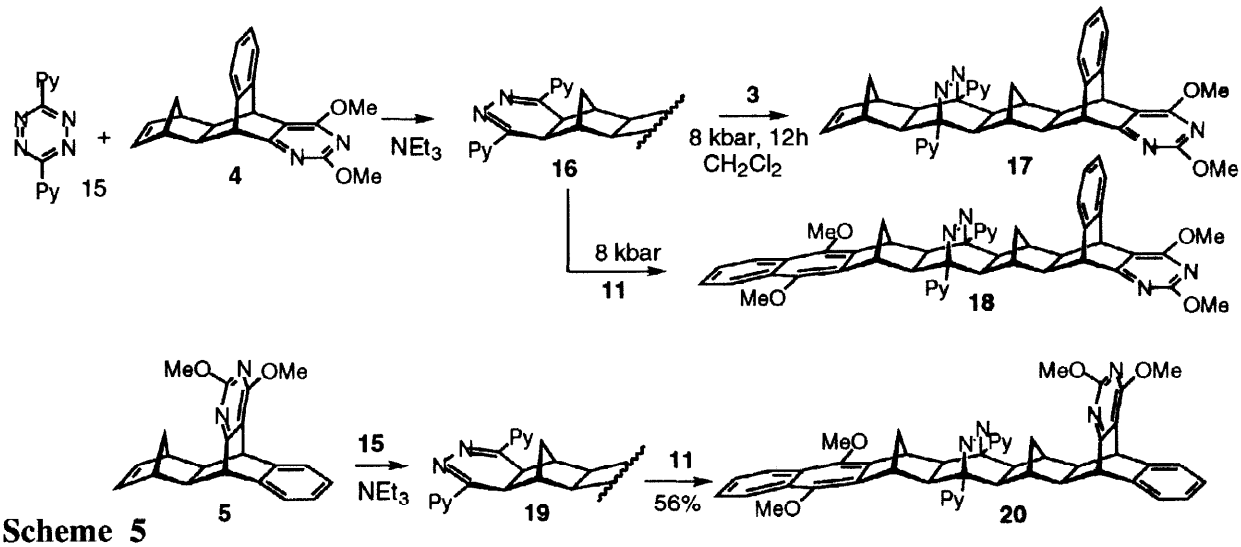
Hz, 1H), 4.47 (d, J = 9.1 Hz, 1H), 7.20 (narrow m, 4H), 7.43 (m, 2H), 8.05 (m, 2H)} and **14b** {43% yield, ^{1}H NMR δ 0.81 (d, J = 13.1 Hz, 1H), 1.42 (d, J = 9.4 Hz, 1H), 1.94 (m, 1H), 2.03 (d, J = 7.1 Hz, 1H), 2.11 (d, J = 7.1 Hz, 1H), 2.22 (brs, 2H), 2.37 (m, 2H), 2.70 (d, J = 9.4 Hz, 1H), 3.63 (brs, 2H), 3.89 (s, 3H), 3.92 (s, 3H), 3.961 (s, 3H), 3.964 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 4.07 (d, J = 9.3 Hz, 1H), 4.30 (d, J = 9.3 Hz, 1H), 7.15 (narrow m, 4H). 7.45 (m, 2H), 8.07 (m, 2H)} by ACE coupling of alkenes **7** or **8** respectively with cyclobutene epoxide **9** (Scheme 4).



Scheme 4

s-Tetrazine Coupling

The norbornene **4** participates in the *s*-tetrazine reaction with alacrity even at room temperature and by conducting the reaction in the presence of triethylamine, yields the dihydropyridazine **16** (Scheme 5). Coupling of **16** occurs with norbornadiene **3** under high pressure (8 kbar) to form the *exo*-fused norbornene **17** {mp 279 °C, 68% yield, ^{1}H NMR δ -1.04 (d, J = 12.3 Hz, 1H), 0.30 (d, J = 12.3 Hz, 1H), 0.63 (d, J = 9.0 Hz, 1H), 1.21 (d, J = 9.0 Hz, 1H), 1.55 (s, 1H), 1.58 (s, 1H), 1.79 (m, 2H), 2.18 (s, 2H), 2.60 (s, 2H), 2.61 (s, 2H), 3.92 (s, 6H), 4.03 (d, J = 2.6 Hz, 1H), 4.27 (d, J = 2.6 Hz, 1H), 5.91 (s, 2H), 6.97 (narrow m, 4H), 7.33 (m, 2H), 7.89 (m, 2H), 8.54 (m, 2H), 8.80 (m, 2H)}. When the reaction was conducted on a mixture of **4** and **5**, it was possible to form both stereoisomeric pyrimidines (combined yield 56%) linked to a dimethoxynaphthalene unit by reaction with A-BLOCK **11**.

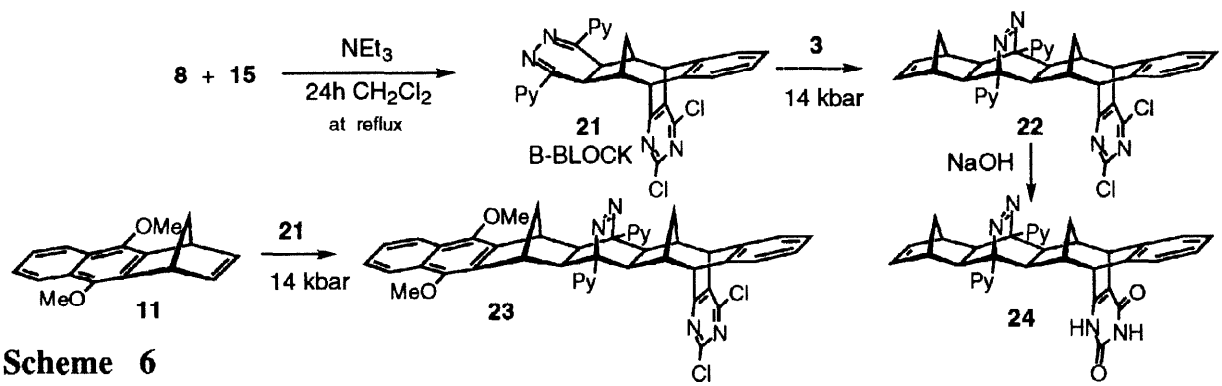


Scheme 5

The extended-frame product **18** {mp 254-257 °C, ^{1}H NMR δ -1.00 (d, J = 11.9 Hz, 1H), 0.37 (d, J = 11.9 Hz, 1H), 0.96 (d, J = 10.4 Hz, 1H), 1.60 (s, 1H), 1.61 (d, J = 10.4 Hz, 1H), 1.63 (s, 1H), 1.73 (m, 2H), 2.57 (s, 2H), 2.97 (s, 2H), 3.15 (s, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 3.90 (s, 6H), 4.02 (d, J = 2.5 Hz, 1H), 4.26 (d, J = 2.5 Hz, 1H), 7.01 (narrow m, 4H), 7.41 (m, 4H), 7.98 (m, 4H), 8.70 (m, 2H), 8.81 (m, 2H)} was isolated by fractional crystallisation, while the bent-frame isomer **20** {mp 264-266 °C (decomp), ^{1}H NMR δ -0.42 (d, J = 12.3 Hz, 1H), 0.56 (d, J = 12.3 Hz, 1H), 0.97 (d, J = 9.7 Hz, 1H), 1.60 (brs, 2H), 1.75 (d, J = 9.7 Hz, 1H), 1.76 (s, 1H), 1.82 (s, 1H), 2.53 (d, J = 9.1 Hz, 1H), 2.61 (d, J = 8.9 Hz, 1H), 2.93 (d, J = 9.1 Hz, 1H), 2.99 (d, J = 8.9 Hz, 1H), 3.13 (s, 1H), 3.18 (s, 1H), 3.72 (s, 3H), 3.76 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.01 (brs 1H), 4.29 (brs, 1H), 7.01

(m, 2H), 7.11 (m, 2H), 7.40 (m, 4H), 7.99 (m, 4H), 8.82 (m, 4H)} with orthogonally-related chromophores was separated by reverse phase HPLC (C18 NOVA pack, MeOH, H_2O=90:10).

In contrast with norbornene **4**, the π-bonds of the tricyclo[4.2.2.$1^{2,5}$]undeca-3-ene **7** and **8** are far less reactive towards 3,6-(di-2-pyridyl)-*s*-tetrazine **15** [12] and the required heating under reflux in methylene chloride for 24 hours to achieve conversion to the dihydropyridazine **21**; this reaction was conducted in the presence of triethylamine to avoid prototropic isomerisation of **21** to the deconjugated 1,4-isomer. Pressurising **21** with norbornadiene **3** (14 kbar, 12 h, RT) gave the coupled azo-bridged product **22** {mp 264-265 °C, 62% yield, ^{1}H NMR δ 0.43 (d, J = 14.1 Hz, 1H), 0.70 (d, J = 9.2 Hz, 1H), 0.85 (m, 1H), 1.27 (d, J = 9.2 Hz, 1H), 2.16 (m, 2H), 2.21 (brs, 2H), 2.42 (brs, 2H), 2.78 (m, 2H), 4.09 (d, J = 9.3 Hz, 1H), 4.29 (d, J = 9.3 Hz, 1H), 5.92 (brs, 2H), 6.99 (m, 2H), 7.09 (m, 2H), 7.37 (m, 2H), 7.92 (m, 2H), 8.59 (m, 2H), 8.87 (m, 2H)} (Scheme 5). A similar coupling of naphthalenonorbornadiene **11** with B-BLOCK **21** leads to **23** {mp 327-328 °C, 62% yield, ^{1}H NMR δ 0.46 (d, J = 14.0 Hz, 1H), 0.89 (m, 1H), 1.03 (d, J = 10.7 Hz, 1H), 1.67 (d, J = 10.7 Hz, 1H), 2.20 (m, 2H), 2.69 (d, J = 8.5 Hz, 1H), 2.78 (d, J = 8.5 Hz, 1H), 2.83 (s, 2H), 3.16 (s, 2H), 3.66 (s, 3H), 3.71 (s, 3H), 4.04 (d, J = 9.4 Hz, 1H), 4.25 (d, J = 9.4 Hz, 1H), 7.00 (m, 2H), 7.10 (m, 2H), 7.38 (m, 2H), 7.43 (m, 2H), 7.99 (m, 4H), 8.73 (m, 2H), 8.87 (m, 2H)} where the pyrimidine is linked to the dimethoxynaphthalene chromophore.



Scheme 6

Hydrolysis: Preliminary Results

Uracil and cytosine BLOCKs can be prepared by nucleophilic displacements of the chlorine substituents in BLOCK **8**, however, these products have poor solubility, so it is preferable to conduct the functional group interchanges after coupling has been completed. Thus, reaction of the linked dichloropyrimidine **14a** with alkali produces the linked uracil derivative **14c**; in this case, the ester groups are also hydrolysed in the course of reaction. The azo-bridged product **22** which lacks the ester groups is converted to the uracil **24** by base hydrolysis, this time without secondary group modification. Other studies in this area will be described later.

References

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