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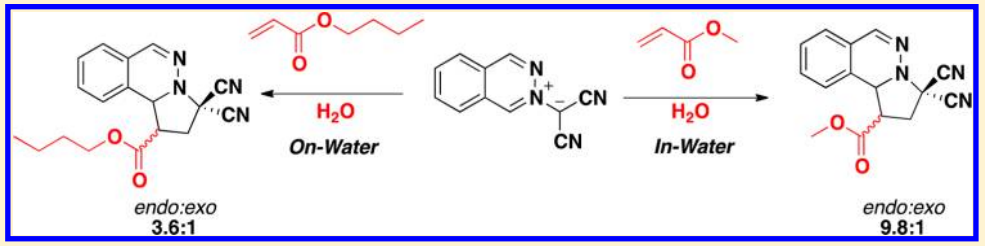
Water and Organic Synthesis: A Focus on the In-Water and On-Water Border. Reversal of the In-Water Breslow Hydrophobic Enhancement of the Normal *endo*-Effect on Crossing to On-Water Conditions for Huisgen Cycloadditions with Increasingly Insoluble Organic Liquid and Solid 2π-Dipolarophiles

Richard N. Butler,*[,†] Anthony G. Coyne,*[,‡] William J. Cunningham,[†] and Eamon M. Moloney[†]

[†]School of Chemistry, National University of Ireland, University Road, Galway, Ireland

[‡]Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom

Supporting Information



ABSTRACT: Measurements of the *endo*/*exo* product ratios for Huisgen cycloadditions with a series of vinyl ketones, alkyl acrylates, and substituted styrenes as dipolarophiles with phthalazinium and pyridazinium dicyanomethanide 1,3-dipoles in acetonitrile and water show that as the reactions change from in-water (large hydrophobic enhancement of *endo*-products) to on-water, the hydrophobic enhancement of the *endo*-products is reduced and partially reversed (relative to acetonitrile). An expected increase of the *endo*-effect with increasing hydrophobic character of the dipolarophile is overcome by decreasing water solubility causing changeover to on-water conditions. On-water reactions do not show increased cycloaddition *endo*-effects (relative to organic solvents) as do in-water reactions.

INTRODUCTION

In recent years there has been an explosion in the use of water as a medium for organic synthesis.[1−11] This remarkable property of water to facilitate organic synthetic reactions even for water-insoluble reactants has led to the seminal introduction of the on-water concept by Sharpless and co-workers.[12] When reactants are soluble in water giving clear solutions, three effects operate simultaneously, (i) the hydrophobic effect, (ii) hydrogen bonding effects, and (iii) solvent polarity effects.[9] For on-water reactions of highly insoluble reactants the main effect is a trans-phase H-bonding catalytic effect due to the penetration by water OH_{free} groups across the water−organic phase boundary[13,14] (see also ref 3). It has been suggested that this could extend to penetration of the phase boundary by a free proton effectively giving acid-catalysis leaving anionic charge at the boundary.[15] For many organic syntheses in the water medium, the reactant molecules are partially soluble, and the reaction medium consists of complicated two or three phase systems.[16] Three phase systems can arise with partially soluble organic liquid and solid reactants, one phase being a dilute aqueous solution with the remaining phases being the undissolved organic liquid and the solid still remaining in the mixture. For such reaction mixtures it is not clear whether the chemical processes occurring arise from in-water or on-water effects. Some methods are needed to distinguish between these alternatives and to explore the borderline regions between in-water and on-water reactions.

Breslow et al. have established that the well-known *endo*-effect, which is observed in Diels−Alder cycloadditions, is significantly enhanced for reactions carried out in water.[17,18] This increased *endo*-enhancement results mainly from the water hydrophobic effect, which favors more compact transition states with reduced exposure to water. Smaller contributions may also come from polarity effects on the *endo*-favoring secondary orbital interactions and charge transfer contributions to the transition state.[17,18] It follows that if the reactants are not within the bulk water medium, i.e., in-water, but rather outside the water medium, i.e., on-water with trans-phase catalysis, then hydrophobic enhancement of the *endo*-effect should not occur. Herein we look at this *endo*-enhancement for a series of increasingly hydrophobic reactants with decreasing water solubilities as probes of the borderline between in-water and on-water modes for multiphase reaction mixtures using a Huisgen cycloaddition that spans the gamut from $4\pi_{HOMO}$ to $4\pi_{LUMO}$ control with accompanying changes in regioselectivity

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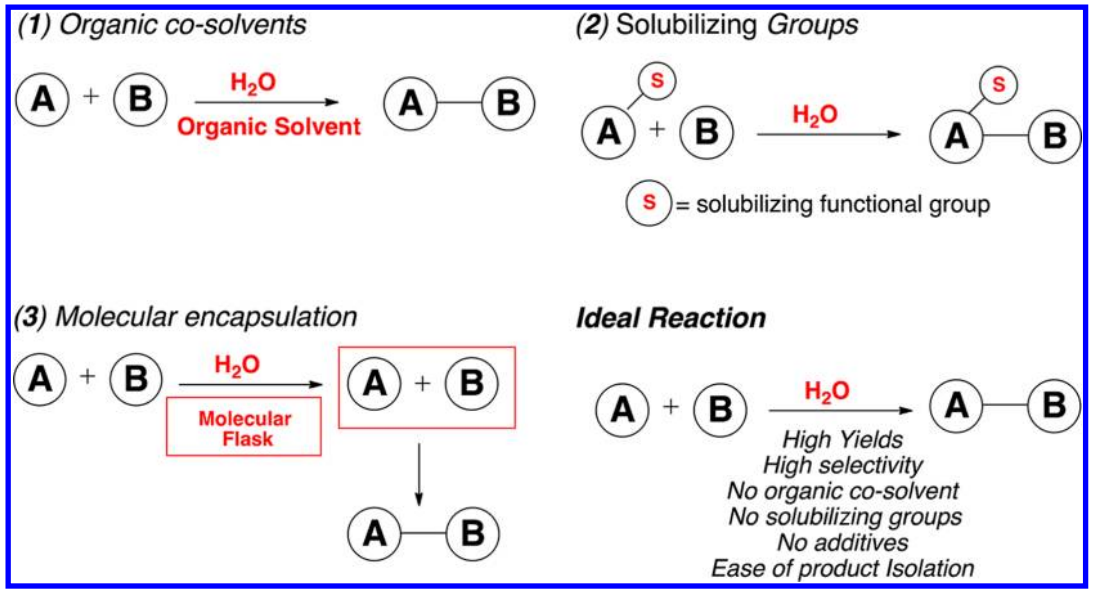

Figure 1. Organic reactions using water as a solvent showing different approaches to solubilizing reactants.

and *endo*–*exo*-selectivity. Such a reaction is particularly fitting for this purpose.

RESULTS AND DISCUSSION

In organic chemistry the majority of synthetic reactions are carried out using a solvent, and in general the solvent will dissolve the reactants. A major criterion for choosing a solvent is that it must not interfere with the reaction and the product should be easily isolated. It is partly because of these requirements that water has not been the solvent of choice for many organic reactions. With the increasing focus on greener aspects of organic synthesis, the use of water as a reaction solvent or medium has greatly expanded in the last two decades. A wide range of reaction types has been explored using water as the reaction solvent, including those which were once considered impossible such as olefin metathesis and cross-coupling reactions.[19,20] While many organic compounds have poor solubility in water, a variety of strategies have been employed in order to overcome this problem.

One approach has been to use water in tandem with an organic solvent, and this has been employed for many different reaction types especially in the area of organocatalysis reactions.[21−23] Another strategy has been to use solubilizing groups on either of the reactants or on catalysts to ensure solubility in water. However a major problem with this is that these functionalities may have to be removed further down the synthetic route. A more recent and interesting approach has been to use molecular encapsulation. This is where self-assembled "molecular flasks" with a nanometer cavity offer a different environment in comparison to the bulk water solvent. These cages have been used to carry out cycloaddition reactions of unactivated dienes and dienophiles. These reactions can be carried out using water as a medium, and the cycloadducts are obtained in excellent yields. A drawback of these reactions is that the self-assembled cage can be specific for certain reactants, which leads to separation problems later in the workup (Figure 1).[24−27]

With all of the above approaches, there has to be a modification of the reactants or other reagents included in order for the reaction to proceed in the water medium. Looking at the simplest case for achieving a reaction, the reactants A and B should undergo reaction in water as solvent so as to give the product in high yield and in high stereo- and regioselectivity. As mentioned, the main drawback is poor solubility of the reactants. However if the solubility of the reactants can be determined, this can give an indication as to whether the reaction is possible using water as a solvent. Aqueous solubilites of organic reactants are not routinely measured in organic chemistry, unlike other areas such as medicinal chemistry where it is a necessity. A number of factors such as temperature, pressure, pH, particle size as well as molecular composition can all affect solubility. In medicinal chemistry, where solubility measurements are necessary, there are a number of methods that can be employed. Thermodynamic solubility measurements are carried out using the solid material, which is directly dissolved in aqueous solutions.[28] This method depends upon the saturation solubility of a compound in equilibrium with an excess of undissolved compound. This is generally carried out over 24−48 h time scale in order to confirm that solution saturation has been achieved. Kinetic solubility measurements are obtained from a predissolved compound (in a solvent such as DMSO), and the solution is added to the water until a precipitation occurs. The kinetic solubility determination is dependent on the supersaturation that occurs within the reaction mixture. While the thermodynamic solubility is the gold standard for solubility measurements, in reality it is very unlikely that this would be carried out as routine for an organic reaction. In recent years, a number of research groups have been looking at determining the solubility of organic compounds in water using computational methods.[29] These methods of solubility determination are still being refined, but the computationally derived solubilities now available provide useful estimates of the solubility of organic compounds in water. This ability to calculate solubilities computationally has been built into the chemical search engine SciFinder, where the solubility of organic compounds for any searchable compound within the CAS have been calculated using the ACD lab software. These solubilities give a good assessment of the solubility of organic compounds in water, and they are the source of the compound solubilities quoted herein. These solubility data are readily available.

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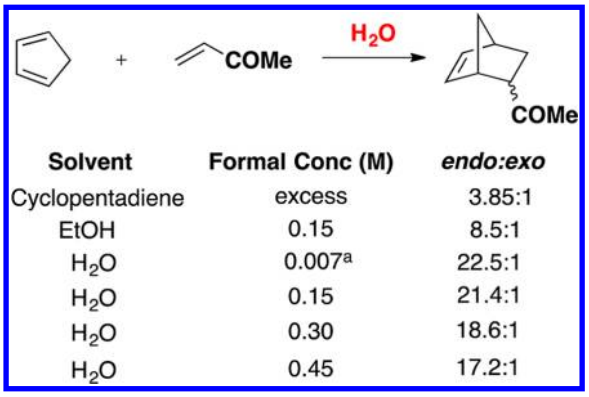
The solubility of the reactants when using water as the reaction medium can have a significant effect on the outcome of the reactions. A number of groups have looked at the effects of concentration on the *endo*:*exo* ratios of Diels–Alder reactions. Breslow et al. examined the Diels–Alder cycloaddition reaction of cyclopentadiene and a range of dienophiles using water as the solvent.[17] For the dienophile methyl vinyl ketone, the reaction was explored using a range of different concentrations (Scheme 1). In excess cyclopentadiene, the product *endo*:*exo* ratio was 3.85:1. When the more polar solvent ethanol was used, the ratio increased to 8.5:1. However when the solvent was changed to water, a much higher *endo*:*exo* ratio of 21.4:1 was observed at a formal concentration of diene and dienophile of 0.15 M. At this concentration the methyl vinyl ketone is fully soluble in water, but the cyclopentadiene is not and is seen as a second phase in the reaction flask. The results are effectively identical to a true solution reaction (0.007 M) where the *endo*:*exo* ratio observed was 22.5:1. At higher formal concentrations of up to 0.45 M, the *endo*:*exo* ratio decreased slightly to 17.2:1; however, in comparison to the reaction in organic solvents, this is a highly enhanced *endo*-selective reaction. In each of these cases the reactions are occurring in-water and exhibiting the enhanced *endo*-effect arising from the hydrophobic effect for reactions occurring in the bulk water. At the higher formal concentrations of reactants, approaching the solubility limit of methyl vinyl ketone, the results herein suggest that some of the reaction with the insoluble cyclopentadiene may have been occurring by the on-water mode, thereby slightly lowering the in-water *endo*-enhancement.[30] Griesbeck reported a study on the reaction of the diene dimethylfulvene and 1,4-benzoquinone using both organic solvents and water.[16] A striking rate enhancement was observed using water as the reaction solvent where the reaction time was cut from 10 days (EtOH) to 11 h using water. Reactions in the water medium relative to ethanol showed enhancement of the *endo*-isomer at normal concentrations paralleling the enhanced *endo*-effect reported by Breslow.

Scheme 1. Diels–Alder Reaction of Cyclopentadiene and Methyl Vinyl Ketone Using Water as a Reaction Solvent and the Role of Concentration[17]



Solvent	Formal Conc (M)	*endo*:*exo*
Cyclopentadiene	excess	3.85:1
EtOH	0.15	8.5:1
H_2O	0.007[a]	22.5:1
H_2O	0.15	21.4:1
H_2O	0.30	18.6:1
H_2O	0.45	17.2:1

[a]All reactants dissolved in water layer.

The solubility of the high melting point (252–254 °C) yellow azinium dicyanomethanide 1,3-dipole **1** in water is $\leq 5 \times 10^{-6}$ mol L^{-1} at 37 °C. This limit was measured from the UV spectra of saturated neat water solutions using the λ_{max} of 413 nm and the extinction coefficient of solutions of **1** in H_2O–MeCN (9:1 v/v), which were used previously for kinetic studies.[31,32] This solubility limit is well below that required for normal in-water synthetic reactions. Nevertheless, high yield synthetic reactions were readily achieved by vigorous stirring at ambient temperatures of a wide range of 2π-reactants with suspensions of **1** in water, Scheme 2.

For the series of alkyl vinyl ketones (Table 1, entries 1–5) where the alkyl groups contain 1–5 carbon atoms, high yield reactions in the water medium gave mixtures of *endo*- and *exo*-isomers of compounds **2**–**6**. As the carbon number of the alkyl group is increased, the vinyl ketones become more hydrophobic in character, and an increasing hydrophobic enhancement of the *endo*/*exo* ratio would be expected for reactions in the bulk water medium, i.e., for in-water reactions. This is observed for alkyl substitutents containing up to two carbon atoms where the water solubilities of the vinyl ketones are greater than 0.2 mol L^{-1} (Table 1, entries 1–3). For alkyl substituents containing 3–5 carbons where the water solubilities of the vinyl ketones fall below 0.1 mol L^{-1}, there is no enhancement of the *endo*-isomer in the water medium, and the *endo*/*exo* ratio is slightly reduced relative to the acetonitrile solvent (Table 1, entries 4, 5). In Table 1 the percent *endo*-enhancement is quoted as the percentage increase in the *endo*/*exo* ratio, and when this ratio decreases the percent *enhancement* of the normal *endo*-effect (compared to MeCN solvent) is then a negative number. A similar sequence is observed for a series of alkyl acrylate esters (Table 1, entries 8–13). With methyl acrylate as dipolarophile (water solubility 0.46 mol L^{-1}), hydrophobic enhancement of the *endo*-isomer occurs for an in-water reaction in which the insoluble 1,3-dipole **1** is passing through the solution in an equilibrium shifted process (Table 1, entry 8). As the carbon number of the ester alkyl substituent is increased to 2, 3, 4 and a phenyl group, with an accompanying fall in water solubility, there is no increase in the product *endo*/*exo* ratio. As the water solubilities of the acrylates decrease below 0.1 mol L^{-1}, the reaction changes to the on-water mode with reductions in the product *endo*/*exo* ratios (relative to MeCN as solvent) (Table 1 entries 10–13). Among the alkyl vinyl ketone series in Table 1, entries 6 and 7 represent a special case. *p*-Chlorobenzylidine acetone gives the product **7** from the cycloaddition reaction with compound **1**. We have discussed this reaction in detail previously.[9c] The products are mixtures of the *endo*- and *exo*-isomers of compound **7** where the aryl group is at the 1-position and the acetyl group at the 2-position of the 1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine products. The reactant *p*-chlorobenzylidine acetone is a solid (mp 62 °C) that is highly insoluble in water (10^{-4} mol L^{-1}), and when it is vigorously stirred with solid 1,3-dipole **1** (solubility $<10^{-6}$ mol L^{-1}) in water at ambient temperature, unsurprisingly no reaction occurs. However when the temperature of the water is raised to 75 °C, above the melting point of *p*-chlorobenzylidine acetone, melting occurs providing an oily liquid phase, and the on-water phenomenon takes over with a high yield reaction producing a 6.2:1 *endo*(aryl):*exo* ratio of compound **7**. In acetonitrile at the same temperature, the reaction produces the same products in lower yield with a 10.4:1 *endo*(aryl)/*exo* ratio (Table 1, entries 6 and 7). This is a classic on-water reaction, and there is no enhancement of the favored *endo*(aryl) isomer, but it is reduced as for the other cases. We note that McErlean et al. have recently reported a similar necessary liquefaction of a highly water insoluble solid allyl aryl ether above its melting point in order to achieve an on-water Claisen rearrangement for synthetic purposes.[33] Our experience has been that organic solid reactants with water

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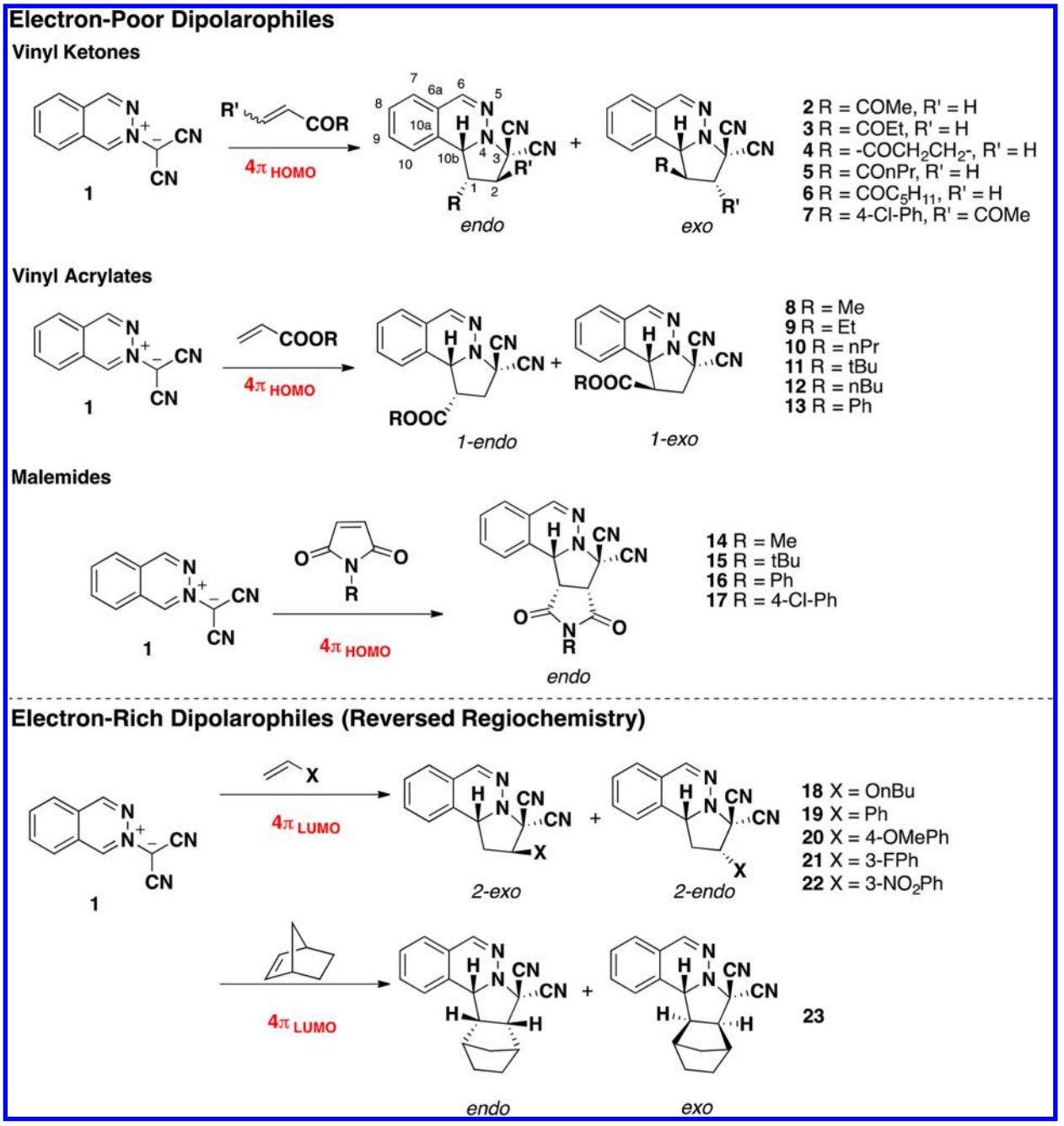
Scheme 2. Huisgen Cycloaddition Reaction of Phthalazinium-2-dicyanomethanide 1,3-Dipole with a Range of Electron-Rich and Electron-Poor Dipolarophiles



solubilities of 10^{-4} mol L^{-1} do not display on-water reactions without liquefaction of one of them.,[9a]

The series of N-substituted maleimides in Table 1 (entries 14−17) represents cases where the *endo*-transition states are fully dominant and only *endo*-products are formed for both on-water and in-water conditions. The designation of the reactions as in-water and on-water (Table 1) is based on the solubilities, by comparison with the other cases. There are no steric constraints in the *endo*-transition states of these cycloadditions. We have observed exclusive *endo*-reactions in acetonitrile for a series of maleimides with N-substituents ranging from Me, aryl, *t*Bu and adamantyl.[34b] Four cases with appropriate water solubility were chosen for comparison in the water medium (Table 1, entries 14−17).

All of the substrates in Table 1 (entries 1−17) contain a C═O group bonded to the 2π-reaction site. Could hydrogen bonding be playing a significant role in these results? The generally accepted explanation for the on-water phenomenon is a catalytic trans-phase H-bonding effect due to the presence of OH_{free} groups at the oil−water interface. In previous kinetic and theoretical studies, we have shown that strong water H-bonding occurs at the C═O of the vinyl ketones in the cycloaddition *endo*-transition state and that structured water clusters grow around this from the initially H-bonded water molecules.[31]

Similar strong H-bonding does not arise with the cycloadditions of acrylate esters. The water rate enhancement for vinyl ketones in these reactions is 10 times greater than for acrylates because of this H-bonding.[31,32] The H-bonding

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Table 1. Huisgen Cycloaddition Reaction of Phthalazinium-2-dicyanomethanide 1 with a Range of Electron-Poor and Electron-Rich Dipolarophiles

(a) Electron Rich Dipolarophiles: $4\pi_{HOMO}$ Reactions

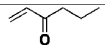
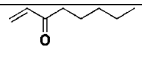
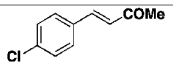
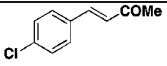
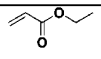
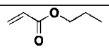
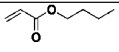
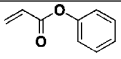
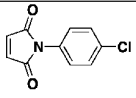
Entry	2π Reactant	Solubility (H_2O, mol L^{-1})	2π Phase [a]	Product	Temp (°C)[b]	MeCN Yield (%) 1-Isomer *1-endo:exo*		H_2O Yield (%) 1-Isomer *1-endo:exo*		*endo* enhancement	Reaction Mode
1		0.58	Liquid	**2**	20	96	3.2:1	95	7:1	+121%	in-water
2		0.23	Liquid	**3**	20	94	3:1	96	11:1	+258%	in-water
3		0.27	Liquid	**4**	82	80	3:1	95	16:1	+433%	in-water
4		0.094	Liquid	**5**	20	86	7.6:1	90	7.4:1	-3%	on-water borderline
5		0.016	Liquid	**6**	20	99	8.7:1	92	8.2:1	- 5%	on-water
6		1.2×10^{-2}	(Solid)[c]	**7**	75	57	10.4:1	86	6.2:1	-40%	on-water
7		1.2×10^{-4}	Solid	**7**	20	0	-	0	-	-	-
8		0.46	Liquid	**8**	20	65	8.3:1	91[d]	9.8:1	+18%	in-water
9		0.18	Liquid	**9**	20	69	6.6:1	82[d]	6.4:1	-3%	on-water borderline
10		0.075	Liquid	**10**	20	79	5.6:1	81[d]	4.1:1	-26%	on-water
11		0.039	Liquid	**11**	20	76	2.8:1	95[d]	2.1:1	-25%	on-water
12		0.031	Liquid	**12**	20	95	5.3:1	88[d]	3.6:1	-32%	on-water
13		0.012	Liquid	**13**	20	88	7.8:1	90	6.8:1	-10%	on-water
14		0.27	Solid	**14**	20	87	1:0	89	1:0	0	in-water
15		0.025	Liquid	**15**	20	80	1:0	90	1:0	0	in-water borderline
16		4.4×10^{-3}	Solid	**16**	20	88	1:0	96	1:0	0	on-water
17		2.0×10^{-3}	Solid	**17**	20	92	1:0	94	1:0	0	on-water

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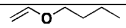
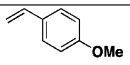
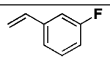
Table 1. continued

(b) Electron Rich Dipolarophiles: $4\pi_{LUMO}$ Reactions

Entry	2π Reactant	Solubility (H_2O, mol L^{-1})	2π Phase [a]	Product	Temp (°C)[b]	MeCN Yield (%) 2-Isomer *2-endo:exo*		H_2O Yield (%) 2-Isomer *2-endo:exo*		*endo* enhancement	Reaction Mode
18		0.078	Liquid	**18**	82	86	0:1	87	0:1	0	on-water borderline
19		2.9×10^{-3}	Liquid	**19**	82	87	1:5.7	78	1:6.1	-7%	on-water
20		8.0×10^{-3}	Liquid	**20**	82	71	1:7.8	87	1:8.6	-10%	on-water
21		5.1×10^{-3}	Liquid	**21**	82	91	1:5.1	82	1:6.4	-25%	on-water
22		2.0×10^{-3}	Liquid	**22**	82	79	1:6.2	82	1:7	-13%	on-water
23		2.4×10^{-3}	Solid	**23**	20	92	1:1.8	91[e]	1:2.3	-28%	on-water

[a]Physical state of dipolarophile at ambient temperature. [b]Ambient temperature is 20 °C. [c]Liquid at 75 °C. [d]In the case of entries 8−12, a small amount (<2%) of the reverse isomer was detected by NMR. In the case of entry 13, none of this minor isomer was detected by NMR. [e]With entry 23, the reaction in MeCN occurred in 16 h. In the case of the reaction using water, no reaction was observed after 48 h; this was then heated to 82 °C, where it was stirred for a further 48 h, and the reaction was deemed complete.

catalytic effect for on-water processes is much stronger than for in-water reactions,[14] but the H-bond acceptor sites are the same in both cases. Hence, if the H-bonding were influencing the *endo/exo* ratios, the *endo*-isomers should be more favored for on-water reactions, the reverse of the experimental results. Furthermore, similar results are obtained with substituted styrenes and norbornene (Table 1, part B), where there are no H-bond acceptor sites on the dipolarophiles.

Compound **1** is an example of a Sustmann Type II 1,3-dipole, which can react also with electron rich dipolarophiles through inverse electron demand $LUMO_{Dipole}$ interactions in the transition state.[31,32,34] Examples of such reactions are shown in Table 1 part B. For these cases the regioselectivity is reversed, and the products **18**−**22** are 2-substituted pyrrolo-[2,1-*a*]phthalazines. When *endo/exo*-isomer pairs are formed, the *exo*-isomers are the major products because for the inverse demand transition state this is the favored orientation.[34] With *n*-butyl vinyl ether as the dipolarophile, the *exo*-isomer is exclusively formed in acetonitrile and water (Table 1, entry 18). Solubilities suggest that this reaction is on the borderline of both in-water and on-water processes. For the series of hydrophobic styrenes and norbornene (Table 1, entries 19−23), both isomers were formed with measurable *endo/exo* ratios. These liquid reactants (which do not have a H-bond acceptor sites) are all highly insoluble in water (ca. 10^{-3} mol L^{-1}), and the reactions with insoluble compound **1** are on-water processes where catalytic trans-phase H-bonding can only occur at compound **1**. In each case there is again no increase in the *endo/exo* ratio when going from acetonitrile to water but rather a decrease, which is recorded as a minus *endo*-enhancement in Table 1.

Some comparable reactions of the 1,3-dipole **1A** pyridazinium dicyanomethanide are shown in Scheme 3. Compound **1A** is soluble in water at small scale synthetic levels. In Scheme 3, for entries 1−4 there is the expected hydrophobic-based large increase in the *endo/exo* product ratio on moving from acetonitrile to water, where the reactions are occurring in-water. Only with styrene, where the reaction is necessarily on-water, is there again a decrease in the *endo/exo* ratio. The contrasting behavior of acrylonitrile and styrene (entries 3 and 5) is of added interest. It is likely hydrogen bonding would have little effect in either case, and it could not account for the fall in the *endo*-effect for the on-water reaction with styrene.

Some reactions with alkyne dipolarophiles in acetonitrile and water are compared in Scheme 4. There is no steric component here, and the designation of the reactions as in-water and on-water are based on solubilities and the above examples. The reactions with solid diphenylacetylene (mp 61 °C) are again of special interest (entries 3, 4). At ambient temperatures, since both solid reactants diphenylacetylene and compound **1** have very low water solubilities ($<10^{-5}$ mol L^{-1}), not surprisingly no reaction occurs for vigorous stirring over 24 h. However on raising the temperature above the melting point of diphenylacetylene, an oily phase is produced in the mixture, and this again allows the on-water process to occur giving a good yield of product **31** (71%) for 24 h of stirring and better than in acetonitrile (60%).

■ CONCLUSION

For organic synthesis in the water medium, hydrophobic enhancement of the preferred endo isomer from cycloadditions arises for reactions in the bulk water solution (relative to organic solvents), but it does not occur with water insoluble reactants when on-water processes prevail. This allows the *endo/exo* product ratios to be used to distinguish between in-water and on-water conditions. Successful synthetic reactions between two insoluble organic solids can be achieved by the on-water process if one is liquefied to provide an oily layer in the water mixture.

■ EXPERIMENTAL SECTION

Melting points were measured on an electrothermal apparatus. IR spectra were measured using an FT-IR instrument. All the NMR spectra were measured on either a 400 or 500 MHz instrument for ^{1}H NMR and 100 or 125 MHz for ^{13}C NMR. The NMR spectra were

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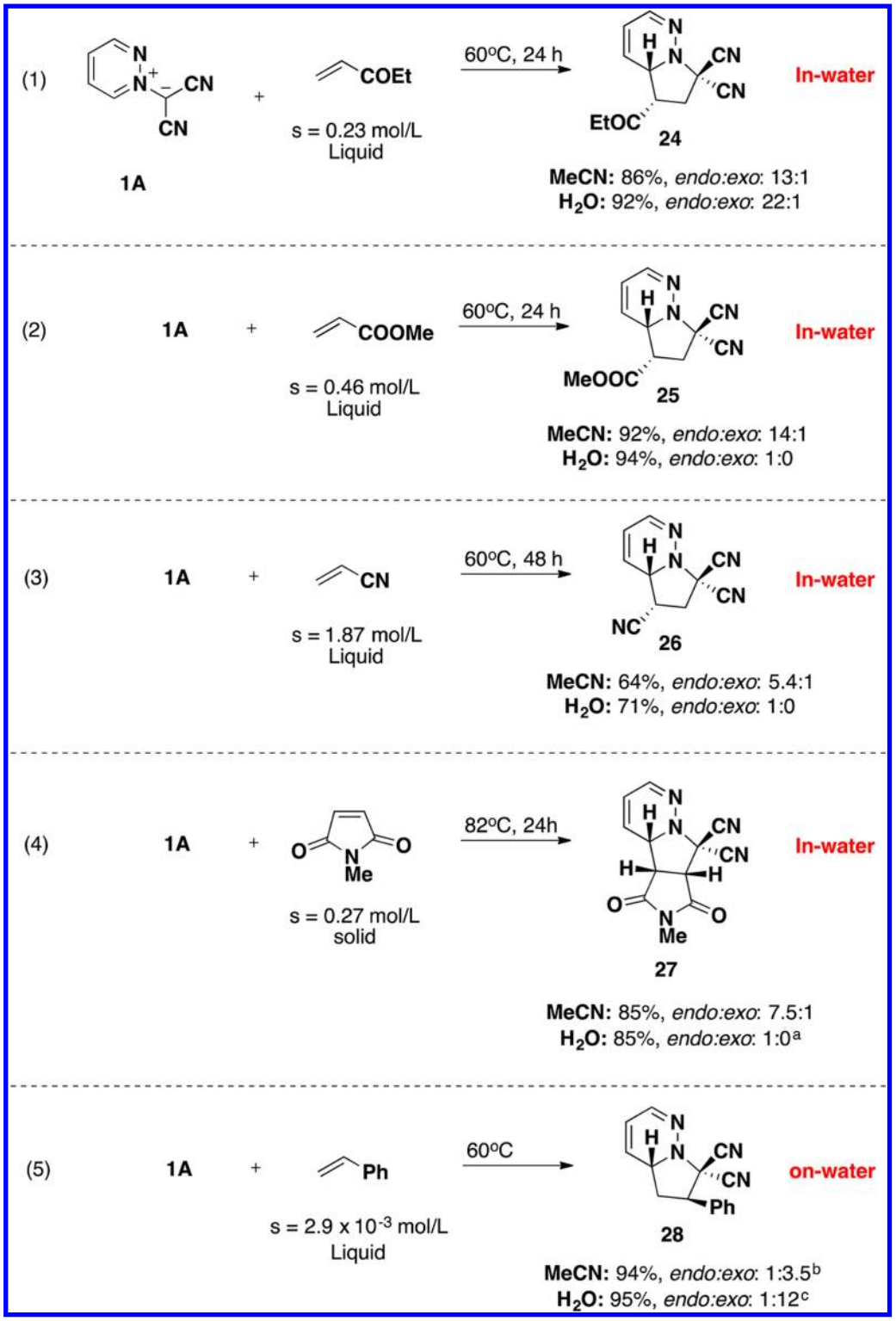
Scheme 3. Huisgen Cycloaddition Reaction of Pyridazinium Dicyanomethanide 1a with a Range of Dipolarophiles (s = Dipolarophile Solubility in Water)



[a]Stirring at ambient temperature (96 h). [b]Stirring for 7 days (168 h). [c]Stirring for 96 h.

measured with tetramethylsilane as an internal reference and either $CDCl_3$ or DMSO-d_6 as a solvent. The structures were also examined using COSY, NOEDS and DEPT. *J* values are given in Hertz (Hz). The dipole **1** was prepared as previously described.[35] The pyridazinium dicyanomethanide dipole **1A** was prepared by the same procedure. The phenyl-substituted maleimides were prepared according to the literature procedure.[36] Water used for synthesis was ultrapure grade. The stereochemistries of the *endo*-products and their *exo*-isomers were established from NOE difference spectra (NOEDS), which showed strong (7−10%) enhancements from H-10b to the *cis*-H-1 in the *endo*-compounds and the absence of a through-space enhancement for the *exo*-products. Isomer ratios (*endo*−*exo*) for product solutions in acetonitrile solvent were determined by NMR analysis. For reactions in the water medium, the water insoluble

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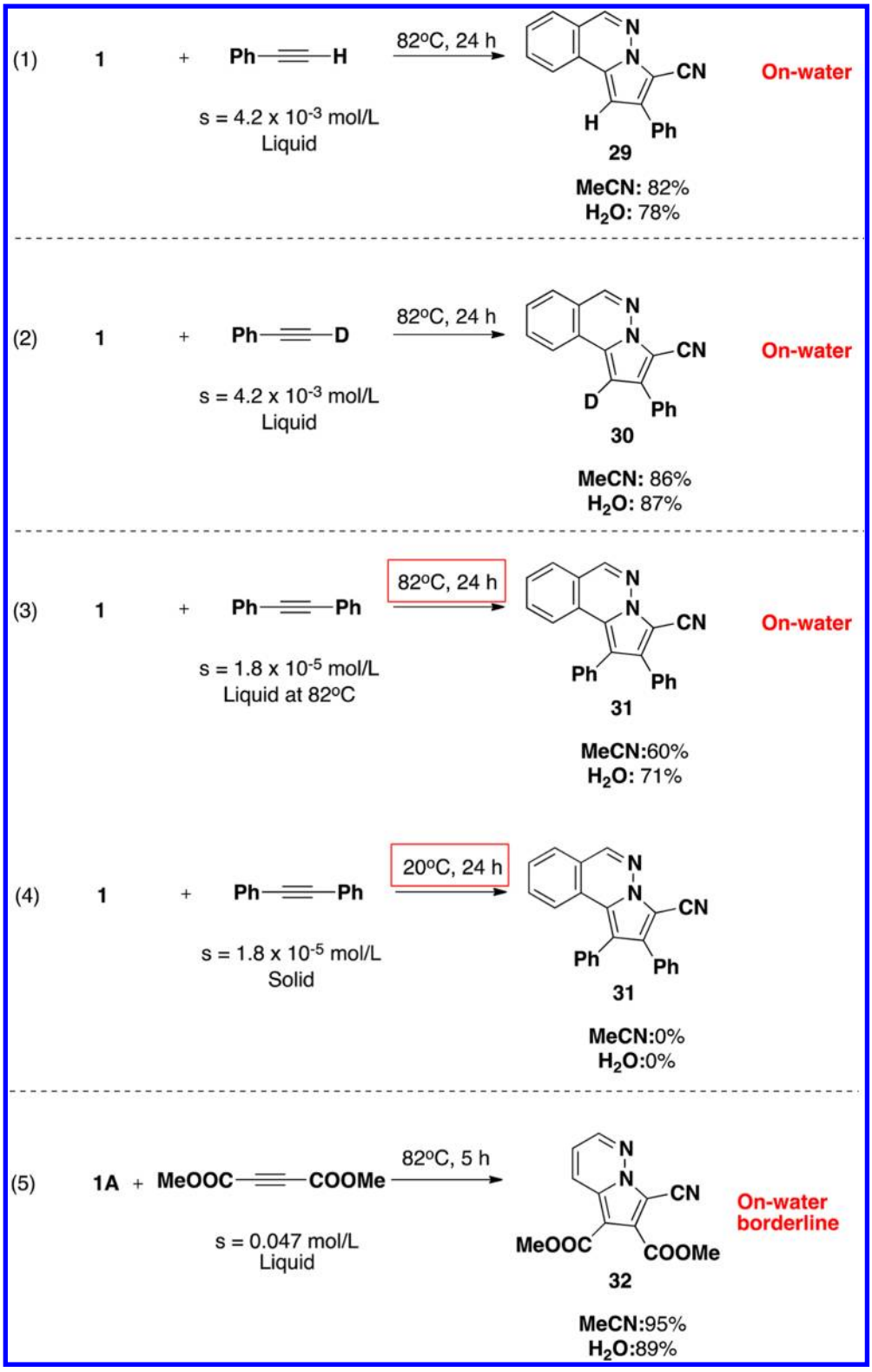
Scheme 4. Huisgen Cycloaddition Reaction of Phthalazinium-2-dicyanomethanide 1 and Pyridizanium Dicyanomethanide 1A with a Range of Electron Rich and Electron Poor Dipolarophiles (s = Dipolarophile Solubility in Water)



product mixtures were separated and each product isolated as described after prior NMR estimation of the isomer ratio. All of the reactions described herein in the water medium were carried out in the formal concentration ranges 0.077−1.38 mol L^{-1}. Because of the low water solubilities of the reactants, the reaction milieu appeared as insoluble multiphase mixtures in water. X-ray crystal structures of products from earlier work in MeCN solvent are also available in refs 31, 32, and 34.

Synthesis of Tetracyanoethylene Oxide.[35] A solution of tetracyanoethylene (3.0 g, 34 mmol) in acetonitrile (22 mL) was cooled to −5 °C in an acetone−ice bath. Hydrogen peroxide (30%) (2.66 mL, 34 mmol) was added dropwise at such a rate that the temperature of the reaction remained between 10 and 12 °C. When

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the addition was complete, the reaction mixture was stirred for a further 5 min and then diluted with ice cold water (150 mL). The precipitated solid was collected by filtration and washed with water. The solid was left to dry on a suction pump for 1 h and then used immediately. The product was obtained as a white solid (3.62 g, 74%), mp 177−179 °C (sealed tube) (lit mp 177−178 °C);[35] (Found C, 50.0; N, 38.7, C_6N_4O requires C, 50.0; N, 38.9%). ***Caution!*** *Both TCNE and TCNEO evolve hydrogen cyanide when exposed to water. All operations must be carried out in a fumehood.*

Phthalazinium-2-dicyanomethanide 1,3-dipole (1).[35] A solution of phthalazine (0.91 g, 7.0 mmol) in ethyl acetate (40 mL) was cooled to below 0 °C in an ice-bath. This was treated dropwise with a cooled ethyl acetate solution (5 mL) of TCNEO (1.0 g, 7.0 mmol). The yellow product precipitated immediately and was collected by filtration (1.25 g, 92%): mp 263−265 °C (acetonitrile); (Found C, 67.9, H, 3.1; N, 28.7, $C_{11}H_6N_4$ requires C, 68.0, H, 3.1, N, 28.9%); ν_{max} (mull)/cm^{-1} 2191, 2159 (C≡N); δ_H (400 MHz, DMSO-d_6, 80 °C) 7.92−7.96 (m, 1H, H-5), 8.02−8.06 (m, 1H, H-8), 8.18−8.24 (m, 2H, H-6 and H-7), 9.40 (s, 1H, H-4), 9.60 (s, 1H, H-1); δ_C (100 MHz, DMSO-d_6, 80 °C) 63.5 (methanide C), 117.2 (C≡N), 122.8 (C-8a), 126.4, 128.0 (C-6 and C-7), 129.8 (C-4a), 132.8 (C-8), 135.5 (C-5), 150.9 (C-1), 153.9 (C-4).

Pyridazinium dicyanomethanide 1,3-dipole (1A).[35] A solution of pyridazine (0.98 mL, 7.0 mmol) in ethyl acetate (20 mL) was cooled to below 0 °C in an ice-bath. This was treated dropwise with a cooled ethyl acetate solution (5 mL) of TCNEO (1.0 g, 7.0 mmol). The yellow product precipitated from the solution and was collected in three crops as the 1,3-dipole gradually separated from the solution (0.69 g, 70%): mp 208−210 °C (methanol); ν_{max} (nujol mull)/cm^{-1} 2194, 2166 cm^{-1} (C≡N); (Found C, 58.0; H, 2.5; N, 39.1, $C_7H_4N_4$ requires C, 58.3; H, 2.8; N, 38.8%); δ_H (400 MHz, DMSO-d_6) 7.46−7.49 (m, 1H, H-4), 8.00−8.04 (m, 1H, H-5), 8.77 (d, 1H, J = 5.9, H-3), 8.95 (d, 1H, J = 5.2, H-6); δ_C (100 MHz, DMSO-d_6) 65.5 (methanide C), 116.1 (C≡N), 122.3 (C-4), 130.7 (C-5), 134.4 (C-6), 152.0 (C-3).

1-*endo*-Acetyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine and 1-*exo*-Acetyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (2).[32] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with an excess of methyl vinyl ketone (0.64 mL, 7.7 mmol) and stirred at ambient temperature for 4 h to give a pale yellow solution. The solvent was removed under reduced pressure, and the residue was placed on a flash column of silica gel (230−400 mesh ASTM) and eluted with dichloromethane to give both the *endo*- and *exo*-isomers. Overall yield: 96% (1-*endo*:1-*exo* 3.2:1). **1-*endo*-isomer:** (73%, 0.31 g) mp 152−154 °C (ethanol); (Found C, 68.0;, H, 4.3; N 21.2; $C_{15}H_{12}N_4O$ requires C, 68.2; H, 4.5; N, 21.2%); ν_{max} cm^{-1} (nujol mull) 1715 (C═O); δ_H (400 MHz, $CDCl_3$) 2.05 (s, 3H, CH_3), 3.63−3.67 (m, 1H, H-1$_{exo}$), 2.93 (dd, 1H, J = 3.4, 14.6, H-2$_{endo}$), 3.09 (dd, 1H, J = 8.7, 14.6, H-2$_{exo}$), 4.80 (d, 1H, J = 6.8, H-10b), 7.27−7.46 (m, 3H, H-7 to H-9), 7.65 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 29.4 (CH_3), 38.5 (C-2), 50.5 (C-1), 55.2 (C-3), 58.5 (C-10b), 113.1, 113.3 (C≡N), 124.6 (C-10a), 127.1, 129.3, 124.8 (C-8 to C-10), 130.7 (C-6a), 132.0 (C-7), 145.3 (C-6) 205.5 (C═O). **1-*exo*-isomer:** 23%, 0.098 g gum; ν_{max} cm^{-1} (CCl_4 liquid cell) 1716 (C═O); δ_H (400 MHz, $CDCl_3$) 2.93 (s, 3H, CH_3), 2.95 (dd, 1H, J = 5.8, 13.9, H-2$_{endo}$), 3.10 (dd, 1H, J 11.7, 13.9, H-2$_{exo}$), 4.53 (d, 1H, J = 9.2, H-10b), 7.03 (d, 1H, J = 6.8, H-10), 7.28- 7.48 (m, 3H, H-7 to H-9), 7.76 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 29.2 (CH_3), 37.8 (C-2), 49.8 (C-1), 57.6 (C-10b), 112.8, 113.1 (C≡N) 123.5 (C-10), 124.8 (C-10a), 126.2 (C-9), 128.9 (C-8), 129.3 (C-6a), 131.2 (C-7), 146.4 (C-6), 203.9 (C═O).

Synthesis in Water. The reaction was carried out under identical conditions using water as the reaction medium. Overall yield: 95% (*endo*:*exo* ratio 7:1).

1-*endo*-Propionyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo-[2,1-*a*]phthalazine and 1-*exo*-Propionyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine. (3).[32] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with ethyl vinyl ketone (0.76 mL, 7.7 mmol) and stirred at room temperature for 4 h. After which time the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (3 mL). The residue was placed onto a flash column of silica gel (230−400 mesh ASTM) and eluted with a mixture of dichloromethane:petroleum spirit (bp 40−60 °C) in the gradient 1:1 to 1:0. Overall yield: 94% (*endo*:*exo* 3.0:1) **1-*endo*-isomer:** (71% 0.31 g) mp 123−125 °C (ethanol); (Found C, 68.6; H, 5.1; N, 19.9, $C_{16}H_{14}N_4O$ requires C, 69.0; H, 5.0; N, 20.1%); ν_{max} cm^{-1} (Nujol mull) 1712 (C═O); δ_H (400 MHz, $CDCl_3$) 0.79 (t, 3H, J = 7.3, CH_3), 2.34 (q, 2H, J = 7.3, CH_2), 2.92 (dd, 1H, J = 3.9, 14.2, H-2), 3.05 (dd, 1H, J = 9.2, 14.2, H-2), 3.65−3.69 (m, 1H, H-1$_{exo}$), 2.82 (d, 1H, J = 7.3, H-10b), 7.08 (d, 1H, J = 6.8, H-10), 7.26−7.45 (m, 3H, H-7 to H-9), 7.62 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 7.3 (CH_3), 35.6 (CH_2), 38.8 (C-2), 49.8 (C-1), 58.7 (C-10b), 113.2, 113.3 (C≡N), 124.9 (C-10a), 125.0 (C-10), 127.0 (C-9), 129.3 (C-8), 130.9 (C-6a), 131.9 (C-7), 144.8 (C-6), 208.3 (C═O). **1-*exo* isomer:** (23% 0.098 g gum); ν_{max} cm^{-1} (CCl_4 liquid cell) 1725 (C═O); δ_H (400 MHz, $CDCl_3$) 1.16 (t, 3H, J = 6.8, CH_3), 2.65 (q, 2H, J = 6.8, CH_2), 2.92 (dd, 1H, J = 6.3, 13.9, H-2$_{endo}$), 3.06 (dd, 1H, J = 10.9, 13.9, H-2$_{exo}$), 3.55−3.62 (m, 1H, H-1$_{endo}$), 4.60 (d, 1H, J = 9.3, H-10b), 6.99 (d, 1H, J = 7.3, H-10), 7.26−7.49 (m, 3H, H-7 to H-9), 7.76 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 7.5 (CH_3), 35.7 (CH_2), 38.3 (C-2), 49.1 (C-1), 58.1 (C-10b), 112.5, 113.1 (C≡N), 123.2 (C-10a), 125.6 (C-10), 126.3 (C-9), 128.7 (C-6a), 132.0 (C-7), 146.2 (C-6), 206.7 (C═O).

Synthesis in Water. The reaction was carried out under identical conditions using water as the reaction medium. Overall yield 96% (*endo*:*exo* ratio 11:1).

***endo*-3,3-Dicyano-1,2-cyclopentano-5-one-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine and *exo*-3,3-Dicyano-1,2-cyclopentano-5-one-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]-phthalazine (4).**[32] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with an excess of 2-cyclopenten-1-one (0.64 mL, 7.7 mmol) and was stirred under reflux for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (3 mL). This was placed on a flash column of silica gel (230−400 mesh ASTM) and eluted with a petroleum spirit (bp 40−60 °C)/dichloromethane mixture in the gradient 1:1 to 0:1. The products were eluted from the column as follows. Overall yield: 80% (*endo*:*exo* 3:1). ***endo*-isomer:** (60%, 0.27 g) mp 228−229 °C (ethanol); (Found C, 69.8; H, 4.1; N, 19.8, $C_{16}H_{12}N_4O$ requires C, 69.5; H, 4.4; N, 20.2%); ν_{max} cm^{-1} (Nujol mull) 1748 (C═O); δ_H (400 MHz, DMSO-d_6) 2.08−2.58 (m, 4H, H-3′ and H-4′), 3.55 (dd, 1H, H-1), 3.80−3.82 (m, 1H, H-2), 4.72 (d, 1H, J = 6.3, H-10b), 7.37−7.55 (m, 3H, H-7 to H-9), 7.56 (d, 1H, J = 7.3, H-10), 7.82 (s, 1H, H-6); δ_C (100 MHz, DMSO-d_6) 24.5 (C-3′), 38.2 (C-2), 38.5 (C-4′), 47.6 (C-1), 60.5 (C-10b), 112.8, 113.5 (C≡N), 124.4 (C-10a), 126.6 (C-10), 127.1 (C-9), 130.7 (C-8), 131.3 (C-7), 131.2 (C-6a), 146.6 (C-6), 213.6 (C═O). ***exo*-isomer:** 20%, 0.09 g, Gum (recolumed crude sample); ν_{max} /cm^{-1} (CCl_4 Liquid cell) 1734 (C═O); δ_H (400 MHz, DMSO-d_6) 2.20−2.52 (m, 4H, H-3′ and H-4′), 3.49 (dd, 1H, H-1), 3.83−3.85 (m, 1H, H-2), 4.19 (d, 1H, J = 9.2, H-10b), 7.34−7.78 (m, 4H, H-7 to H-10), 7.89 (s, 1H, H-6); δ_C (100 MHz, DMSO-d_6) 22.9 (C-3′), 37.8 (C-4′), 51.1 (C-1), 57.0 (C-10b), 60.4 (C-3), 112.2, 114.3 (C≡N), 124.5 (C-10), 126.3 (C-9), 128.9 (C-8), 132.5(C-7), 133.2 (C-6a), 146.7 (C-6), 211.2 (C═O).

Synthesis in Water. The reaction was carried out using water as the reaction medium by heating at 82 °C, and products were isolated as described. Overall yield: 95% (*endo*:*exo* ratio 16:1).

1-*endo*-Butyryl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo-[2,1-*a*]phthalazine and 1-*exo*-Butyryl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (5). A suspension of compound **1** (0.10 g, 0.51 mmol) in acetonitrile (7 mL) was treated with an excess of 1-hexen-3-one (0.288 mL, 2.56 mmol) and stirred at ambient temperature for 4 h to give a pale yellow solution. The solvent was removed under reduced pressure, and the residue was placed on a flash column of silica gel (230−400 mesh ASTM). The *endo*/*exo*-isomers proved difficult to isolate separately. The characterization given is for the mixture of the *endo*- and *exo*-isomers, and the ratio of *endo*/*exo*-isomers was determined through integration of the H-10b signals. **1-*endo*- and 1-*exo*-isomers:** (0.128 g, 86%, *endo*:*exo* 7.6:1),

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Gum; HRMS (ESI) calcd for $C_{17}H_{16}N_4O$ $(M + H)^+$ 293.1403, found 293.1417; δ_H (500 MHz, $CDCl_3$) 0.65 (t, 3H, J = 7.4, CH_3 endo), 0.96−1.00 (m, 3H, CH_3 exo), 1.30−1.38 (m, 2H, CH_3 endo), 1.68−1.77 (m, 2H, CH_2 endo) 2.23−2.37 (m, 2H, CH_2 exo), 2.59−2.63 (m, 2H, CH_2 exo), 2.89−2.93 (m, 1H endo, 1H exo, H-2), 3.01−3.11 (m, 1H endo, 1H exo, H-2), 3.55−3.59 (m, 1H, H-1 exo), 3.62−3.66 (m, 1H, H-1 endo), 4.60 (d, 1H, J = 9.2, H-10b exo), 4.82 (d, 1H, J = 7.4, H-10b endo), 6.98 (d, 1H, J = 7.6, H-10 exo), 7.09 (d, 1H, J = 7.1, H-10 endo), 7.30−7.53 (m, H-7 to H-9 endo and H-7 to H-9 exo), 7.62 (s, 1H, H-6 endo), 7.76 (s, 1H, H-6 exo); δ_C (125 MHz, $CDCl_3$) 13.4 (CH_3 endo), 13.6 (CH_3 exo), 16.5 (CH_2 endo), 16.8 (CH_2 exo), 38.3 (C-2 exo), 38.9 (C-2 endo), 44.2 (CH_2 endo and exo), 49.9 (C-1 exo), 50.0 (C-1 endo), 54.7 (C-3 exo), 55.8 (C-3 endo), 58.0 (C-10b exo), 58.5 (C-10b endo), 112.9, 113.2 (C≡N exo), 113.0, 113.5 (C≡N endo), 123.6 (C-10a exo), 124.7 (C-10a endo), 125.0 (C-10 exo), 125.2 (C-10 endo), 126.3 (C-9 exo), 127.1 (C-9 endo), 128.9 (C-8 exo), 129.4 (C-8 endo), 130.5 (C-6a endo and exo) 131.9 (C-7 endo), 132.1 (C-7 exo), 144.8 (C-6 endo), 145.9 (C-6 exo), 206.2 (C═O exo), 207.6 (C═O endo). The terms *endo* and *exo* refer to the isomers to which the signal belongs. Some of the *exo*-isomer peaks are missing in the ^{13}C NMR due to overlap with the major *endo*-isomer

Synthesis in Water. The reaction was carried out under identical conditions using water as the reaction medium. Overall yield 90% (*endo*:*exo* ratio 7.4:1).

1-*endo*-Hexanoyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo-[2,1-*a*]phthalazine and 1-*exo*-Hexanoyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (6). A suspension of compound **1** (0.100 g, 0.51 mmol) in acetonitrile (6.4 mL) was treated with an excess of 1-octen-3-one (0.38 mL, 0.255 mmol) and stirred at ambient temperature for 4 h to give a pale yellow solution. The solvent was removed under reduced pressure, and the residue was placed on a flash column of silica gel (230−400 mesh ASTM The *endo*/*exo*-isomers proved difficult to isolate separately. The characterization given is for the mixture of the *endo*- and *exo*-isomers, and the ratio of *endo*/*exo*-isomers was determined through integration of the H-10b signals. **1-*endo*- and 1-*exo*-isomers:** (0.161 g, 99%, *endo*:*exo* 8.7:1), Gum; HRMS (ESI) calcd for $C_{19}H_{20}N_4O$ $(M + H)^+$ 321.1716, found 321.1725; δ_H (500 MHz, $CDCl_3$) 0.75 (t, 3H, CH_3 endo), 0.87−0.98 (m, 2H CH_2 endo, 3H CH_3 exo), 1.06−1.14 (m, 2H, CH_2 endo), 1.22−1.36 (m, 2H, CH_2 endo, 2H, CH_2 exo), 1.64−1.73 (m, 2H, CH_2 exo), 2.25−2.30 (m, 2H, CH_2 exo), 2.29−2.32 (m, 2H, CH_2 endo, 2H CH_2 exo), 2.88−2.92 (m, 1H endo, 1H exo, H-2), 3.03 (dd, 1H, J = 13.8, 9.1, H-2 endo), 3.10 (dd, 1H, J = 13.8, 11.2, H-2 exo), 3.55−3.60 (m, 1H, H-1 endo), 3.64−3.68 (m, 1H, H-1 exo), 4.50 (d, 1H, J = 9.4, H-10b exo), 4.81 (d, 1H, J = 7.5, H-10b endo), 6.97 (d, 1H, J = 7.8, H-10 exo), 7.09 (d, 1H, J = 7.4, H-10 endo), 7.26−7.53 (m, 3H, H-7 to H-9 endo, 3H, H-7 to H-9 exo), 7.57 (s, 1H, H-6 endo), 7.73 (s, 1H, H-6 exo); δ_C (125 MHz, $CDCl_3$) 13.8 (CH_3 endo), 13.9 (CH_3 exo), 22.1 (CH_2 endo), 22.7 (CH_2 exo), 23.1 (CH_2 exo), 22.3 (CH_2 endo), 30.8 (CH_2 exo), 30.9 (CH_2 endo), 38.2 (C-2 exo), 38.8 (C-2 endo), 42.5 (CH_2 endo), 42.3 (CH_2 exo), 49.2 (C-1 exo), 50.0 (C-1 endo), 55.9 (C-3 endo), 58.0 (C-10b exo), 58.9 (C-10b exo), 112.9, 113.3 (C≡N exo), 113.1, 113.6 (C≡N endo), 123.6 (C-10a exo), 124.6 (C-10a endo), 125.3 (C-10 endo), 126.2 (C-9 exo), 127.0 (C-9 endo), 128.9 (C-8 exo), 129.3 (C-8 endo), 130.5 (C-6a), 131.8 (C-7 endo), 132.0 (C-7 exo), 144.5 (C-6 endo), 146.3 (C-6 exo), 207.1 (C═O exo), 208.0 (C═O endo). The terms *endo* and *exo* refer to the isomers to which the signal belongs. Some of the *exo*-isomer peaks are missing in the ^{13}C NMR due to overlap with the major *endo*-isomer.

Synthesis in Water. The reaction was carried out under identical conditions using water as the reaction medium. Overall yield 92% (*endo*:*exo* ratio 8.2:1).

1-*endo*-2-*exo*-2-Acetyl-1-(4-chlorophenyl)-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine-3,3-dicarbonitrile and 1-*exo*-2-*endo*-2-Acetyl-1-(4-chlorophenyl)-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine-3,3-dicarbonitrile (7).[9c] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with 4-(4-chlorophenyl)-3-buten-2-one (0.834 g, 4.62 mmol) and stirred under reflux for 4h. The solvent was removed under reduced pressure, and the residue was taken up in ice-cold Et_2O, which caused the major product to separate as a yellow solid. The ethereal filtrate contained the minor isomer as well as traced on the major isomer and some intractable gum. ^1H NMR analysis of this mixture, combined with separation by flash chromatography on silica gel using petroleum ether (bp 40−60 °C)/dichloromethane in the gradient 1:1 to 1:0 afforded the separated regioisomers. Overall yield: 57% (*endo*-aryl:*exo*-aryl 10.4:1). **major isomer (*endo* *p*-ClC_6H_4):** Yield 52%, colorless solid, 162−163 °C (ethanol); ν_{max}/cm^{-1} 761 (C−Cl) 1725 (C═O); HRMS (ESI) calcd for $C_{21}H_{15}N_4OCl$ $(M + H)^+$ 375.1013, found 375.1048; δ_H (400 MHz, $CDCl_3$) 1.87 (s, Me); 3.86 (dd, J = 7.8, 7.3, H-1), 4.26 (d, J = 7.8, H-2), 5.25 (d, J = 7.3, H-10b), 7.21 (d, J = 7.3, H-10), 7.34 (d, J = 7.3, H-7), 7.41−7.47 (m, H-8 and H-9, H-2′ and H-3′), 7.63 (s, H-6); δ_C (100 MHz, $CDCl_3$) 31.6 (Me), 57.2 (C-10b), 58.9, 59.4 (C-1, C-2), 65.9 (C-3), 111.2, 111.9 (C≡N), 124.3 (C-10a), 126.2 (C-10), 127.5 (C-9), 129.3 (C-1′), 129.8 (C-2′), 129.9 (C-8), 130.1 (C-3′), 130.4 (C-6a), 132.1 (C-7), 136.1 (C-4′), 144.6 (C-6), 204.5 (C═O). **minor isomer (*exo* *p*-ClC_6H_4):** Yield 5%; δ_H (400 MHz, $CDCl_3$) mixture with the major isomer; key signals 3.67 (dd, 8.7, 8.3, H-1), 4.19 (d, J = 7.3, H-2), 4.66 (d, J = 8.7, H-10b).

Synthesis in Water. A suspension of compound **1** (0.20 g, 1.03 mmol) and 4-(4-chlorophenyl)-3-buten-2-one (0.19 g, 1.05 mmol) in water (10 mL) was stirred vigorously at 75 °C for 24 h. During this time the suspended solids compacted into a sticky mass surrounding the stir bar and were converted to the products, which were collected by filtration and scraping from the stir bar to give a mixture of compounds. Overall yield 86%, *endo*-aryl:*exo*-aryl isomer ratio 6.2:1.

***endo*-1-Methoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrollo[2,1-*a*]phthalazine and *exo*-1-Methoxycarbonyl isomer and *endo*-2-Methoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (8).**[34b] A suspension of the compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with methyl acrylate (0.69 mL, 7.7 mmol) stirred at ambient temperature for 12 h, giving a pale yellow solution. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed on a flash column of silica gel (230−400 mesh ASTM) and eluted with a gradient mixture of dichloromethane and petroleum spirit (bp 40−60 °C) in the range 1:1 to 1:0. The products from the column were isolated in the following order. Overall yield 65% (1-isomer) (1-*endo*:1-*exo* 8.3:1). **2-*endo*-isomer:** (0.008 g, 2%); gum (recolumned crude sample); ν_{max}(CCl_4 liquid cell)/cm^{-1}, 1742 (C═O); δ_H (400 MHz, $CDCl_3$) 2.53−2.98 (m, 2H, H-1), 3.96 (s, 1H, OMe), 3.90−3.96 (m, 1H, H-2_{exo}), 4.34 (dd, 1H, J = 8.6, 8.5, H-10b), 7.13−7.53 (m, 4H, H-7 to H-10), 7.81 (s, 1H, H-6). **1-*exo*-isomer:** (0.03 g, 7%), gum (recolumned crude sample); ν_{max}(CCl_4 liquid cell)/cm^{-1}, 1751 (C═O); δ_H (400 MHz, $CDCl_3$) 3.00−3.22 (m, 2H, H-2), 3.86 (s, 3H, OMe_{endo}), 3.54−3.59 (m, 1H, H-1_{exo}), 4.46 (d, 1H, J = 8.8, H-10b), 7.40−7.61 (m, 4H, H-7 to H-10), 7.89 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 42.3 (OMe), 58.7 (C-10b), 113.2, 113.5 (C≡N), 123.4, 124.9, 126.0, 128.8 (C-7 to C-10), 131.5 (C-6a), 145.8. **1-*endo* isomer:** (0.25 g, 58%); white crystalline solid, mp 132−133 °C (ethanol); (Found C, 63.9; H, 4.3; N, 19.9. $C_{15}H_{12}N_4O_2$ requires C, 64.3; H, 4.3; N, 19.9%) ν_{max}(mull)/cm^{-1} 1742 (C═O); δ_H (400 MHz, $CDCl_3$) 2.99−3.05 (m, 1H, H-2_{exo}), 3.12−3.16 (m, 1H, H-2_{endo}), 3.55 (s, 3H, OMe_{endo}), 3.63−3.68 (m, 1H, H-1_{exo}), 4.82 (d, 1H, J = 6.6, H-10b), 7.26−7.45 (m, 4H, H-7 to H-10), 7.66 (s, 1H, H-6); δ_C (400 MHz, $CDCl_3$) 39.2 (C-2), 42.9 (OMe), 52.4 (C-1), 55.8 (C-3), 59.2 (C-10b), 113.3, 113.9 (C≡N), 124.7 (C-10a), 125.1,126.1, 127.1(C-8 to C-10), 129.7 (C-7), 130.2 (C-6a), 144.4 (C-6), 170.6 (C═O).

Synthesis in Water. The product and was stirred at ambient temperature and isolated as described. Overall yield 91% (1-*endo*:*exo* ratio 9.8:1). A small amount (<2%) of the 2-*endo*-isomer was observed by ^1H NMR.

***endo*-1-Ethoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrollo[2,1-*a*]phthalazine and *exo*-1-Ethoxycarbonyl isomer and *endo*-2-Ethoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (9).**[34b] A suspension of the compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with ethyl acrylate (0.83 mL, 7.7 mmol) stirred at ambient

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temperature for 24 h, giving a pale yellow solution. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed on a flash column of silica gel (230−400 mesh ASTM) and eluted with a gradient mixture of dichloromethane and petroleum spirit (bp 40−60 °C) in the range 1:1 to 1:0. The products from the column were isolated in the following order. Overall yield 69% (1-isomer) (1-*endo*:1-*exo* 6.6:1) **2-*endo*-isomer:** (0.018 g, 4%), gum (recolumned crude sample); ν_{max}(CCl_4 Liquid cell)/cm^{-1} 1743 (C═O); δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, CH_3), 2.96−3.05 (m, 1H, H-2), 3.18−3.23 (m, 1H, H-2), 3.51−3.56 (m, 1H, H-1), 4.31 (q, 2H, CH_2), 4.45 (dd, 1H, *J* = 10.8, 6.9, H-10b), 7.40−7.60 (m, 4H, H-7 to H-10), 7.78 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 38.2 (CH_2), 58.8 (C-10b), 62.5 (C-2) 112.6, 113.2 (C≡N), 128.7, 128.9, 133.1 (C-7 to C-10), 148.8 (C-6), 170.4 (C═O). **1-*exo*-isomer:** (0.04 g, 9%), gum (recolumned crude sample); ν_{max}(CCl_4 Liquid cell)/cm^{-1} 1752 (C═O); δ_H (400 MHz, $CDCl_3$) 1.42 (t, 3H, CH_3), 2.51−2.57 (m, 1H, H-1), 2.92−2.99 (m, 1H, H-1), 3.83−3.89 (m, 1H, H-2), 4.36 (q, 2H, CH_2), 4.46 (d, 1H, *J* = 9.2, H-10b), 7.13−7.15 (d, 1H, H-10), 7.26−7.53 (m, 3H, H-7 to H-9), 7.80 (s, 1H, H-6). **1-*endo*-isomer:** (0.27 g, 60%), 130−131 °C (ethanol); Found C, 65.7; H, 4.4; N, 19.2. $C_{16}H_{14}N_4O_2$ requires C, 65.3; H, 4.7; N, 19.1; ν_{max}(mull)/cm^{-1} 1753 (C═O); δ_H (400 MHz, $CDCl_3$) 1.07 (t, 3H, CH_3), 2.90−3.03 (m, 1H, H-2), 3.13−3.17 (m, 1H, H-2), 3.60−3.64 (m, 1H, H-1), 4.00 (q, 2H, CH_2), 4.85 (d, 2H, *J* = 6.2, H-10b), 7.20−7.43 (m, 4H, H-7 to H-10), 7.60 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 39.2 (CH_2), 39.5 (C-2), 55.0 (C-3), 59.2 (C-10b), 61.8 (C-1), 113.9 (C≡N), 124.7 (C-7), 125.5 (C-6a), 126.6 (C-9), 129.4 (C-7), 131.4 (C-10), 144.1 (C-6), 170.1 (C═O).

Synthesis in Water. The product and was stirred at ambient temperature and isolated as described. Overall yield 82% (1-isomer) (1-*endo*:1-*exo* ratio 6.4:1). A small amount <2% of the 2-*endo*-isomer was observed by ^{1}H NMR.

endo*-1-Propoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrollo[2,1-*a*]phthalazine and *exo*-1-Propoxycarbonyl isomer and *endo*-2-Propoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (10).** A suspension of compound **1** (0.10 g, 0.51 mmol) in acetonitrile (6.4 mL) was treated with an excess of *n*-propylacrylate (0.316 mL, 2.56 mmol) (Caution!*** *n-propylacrylate is a severe lachrymator and should be handled in a fumehood*) and stirred at ambient temperature for 4 h to give a pale yellow solution. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed on a flash column of silica gel (230−400 mesh ASTM) and eluted with a gradient mixture of dichloromethane and petroleum spirit (bp 40−60 °C) in the range 30:70 to 100:0. The products from the column were isolated in the following order. Overall yield 79% (1-isomer) (1-*endo*:1-*exo* 5.6:1). **1-*exo*-isomer:** gum (0.018 g, 12%) ν_{max}(neat)/cm^{-1} 1731(C═O); δ_H (500 MHz, $CDCl_3$) 0.87−0.98 (m, 3H, CH_3), 1.31−1.47 (m, 2H, CH_2), 2.91−2.98 (m, 1H, H-1), 3.83−3.89 (m, 2H, H-2), 4.21−4.36 (m, 2H, CH_2), 4.39 (d, 1H, *J* = 9.1, H-10b), 7.25−7.53 (m, 4H, H-7 to H-10), 7.80 (s, 1H, H-6). The 1-*exo*- and 2-*endo*-products were isolated as a mixture and could not be separated using column chromatography. The 2-*endo*-isomer was present at 5% as observed by ^{1}H NMR; however, because of overlap, it was not possible to fully assign the *endo*-2-isomer. **1-*endo*-isomer:** off-white solid (0.105 g, 67%) mp 122−124 °C (ethanol); (Found C, 66.4; H, 5.2; N,18.0, $C_{17}H_{16}N_4O_2$ requires C, 66.2; H, 5.2; N, 18.2%); ν_{max} (neat)/cm^{-1} 1721 (C═O); δ_H (500 MHz, $CDCl_3$) 0.75 (t, 3H, *J* = 7.5, CH_3), 1.39−1.49 (m, 2H, CH_2), 3.01 (dd, 1H, *J* = 14.2, 8.4, H-2_{endo}), 3.15 (dd, 1H, *J* = 14.2, 2.9, H-2_{exo}), 3.61−3.64 (m, 1H, H-1), 3.83−3.88 (m, 1H, CH_2), 3.91−3.96 (m, 1H CH_2), 4.83 (d, 1H, *J* = 6.7, H-10b), 7.25−7.43 (m, 4H, H-7 to H-10), 7.58 (s, 1H, H-6); δ_C (125 MHz, $CDCl_3$) 10.1 (CH_3), 21.6 (CH_2), 39.5 (C-2), 43.3 (CH_2), 54.9 (C-3), 59.2 (C-10b), 67.4 (C-1), 113.3, 113.9 (C≡N), 124.8 (C-8), 125.3 (C-6a), 126.6 (C-9), 129.1 (C-7), 130.4 (C-10a), 131.5 (C-10), 144.2 (C-6), 170.2 (C═O).

Synthesis in Water. The reaction was carried out under identical conditions using water as the reaction medium. Overall yield 81% (1-isomer) (1-*endo*:1-*exo* ratio 4.1:1).

***endo*-1-*tert*-Butoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrollo[2,1-*a*]phthalazine and *exo*-1-*tert*-Butoxycarbonyl isomer and *endo*-2-*tert*-Butoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (11).** A suspension of the compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with *t*-butyl acrylate (1.12 mL, 7.7 mmol) stirred at ambient temperature for 24 h, giving a pale yellow solution. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed on a flash column of silica gel (230−400 mesh ASTM) and eluted with a gradient mixture of dichloromethane and petroleum spirit (bp 40−60 °C) in the range 30:70 to 100:0. The products from the column were isolated in the following order. Overall yield 76% (1-isomer) (1-*endo*:1-*exo* 2.8:1). **2-*endo*-isomer:** (0.05 g, 10%), gum (recolumned crude sample); ν_{max}(CCl_4 Liquid cell)/cm^{-1} 1725 (C═O); δ_H (400 MHz, $CDCl_3$) 1.48 (s, 9H, *t*-Bu), 2.40 (dd, 1H, *J* = 12.9, 22.9, H-1_{exo}), 2.82 (dd, 1H, *J* = 12.9, 5.8, H-1_{endo}), 3.68 (dd, 1H, *J* = 5.8, 5.9, H-2_{exo}), 4.23 (dd, 1H, *J* = 8.7, 8.5 H-10b), 7.06 (d, 1H, *J* = 7.3, H-10), 7.25−7.46 (m, 3H, H-7 to H-9), 7.43 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 27.9 (*t*-Bu), 51.2 (C-10b), 55.6 (C-2), 85.0 ($\underline{C}(CH_3)_3$), 112.0, 113.1 (C≡N), 123.3 (C-10a), 134.6 (C-6a), 132.1(C-7), 128.1, 126.1, 129.0 (C-8 to C-10), 147.0 (C-6), 165.9 (C═O). **1-*exo*-isomer:** (0.10 g, 20%), gum (recolumned crude sample); ν_{max}(CCl_4 Liquid cell)/cm^{-1} 1732 (C═O); δ_H (400 MHz, $CDCl_3$) 2.50 (s, 9H, *t*-Bu), 2.93 (dd, 1H, *J* = 13.6, 11.2, H-2_{exo}), 3.15 (dd, 1H, *J* = 13.6, 5.3, H-2_{endo}), 3.43 (m, 1H, H-1), 4.36 (d, 1H, *J* = 8.8, H-10b), 7.31 (d, 1H, *J* = 6.8, H-10), 7.39−7.67 (m, 3H, H-7 to H-9), 7.75 (s,1H, H-6); δ_C (100 MHz, $CDCl_3$) 27.8 (*t*-Bu), 38.1 (C-2), 43.5 (C-1), 53.1 (C-3), 59.0 (C-10b), 84.3 ($\underline{C}(CH_3)_3$), 112.5, 113.2 (C≡N), 123.4 (C-10a), 125.0, 126.0, 128.8 (C-7 to C-9), 132.1 (C-10a), 133.7 (C-6a), 146.7 (C-6), 169.4 (C═O). **1-*endo*-isomer:** (0.28 g, 56%) white crystalline solid; mp 142−143 °C (ethanol); (Found C, 67.1; H, 5.8; N,17.2. $C_{18}H_{18}N_4O_2$ requires C, 67.0; H, 5.6, N, 17.3%); ν_{max}(mull)/cm^{-1} 1721 (C═O); δ_H (400 MHz, $CDCl_3$) 2.10 (s, 9H, *t*-Bu), 2.96 (dd, 1H, *J* = 14.1, 8.3, H-2_{endo}), 3.10 (dd, 1H, *J* = 14.1, 2.9, H-2_{exo}), 3.48−3.53 (m, 1H, H-1_{exo}), 4.83 (d, 1H, *J* = 6.3, H-10b), 7.28 (d, 1H, *J* = 8.3, H-10), 7.31−7.45 (m, 3H, H-7 to H-9), 7.56 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 27.7 (*t*-Bu), 39.7 (C-2), 44.6 (C-1), 55.1 (C-3), 59.3 (C-10b), 83.0 ($C(CH_3)_3$), 113.5, 114.2 (C≡N), 124.3 (C-10a), 130.3 (C-6a), 131.4 (C-7), 126.1, 126.7, 129.1 (C-8 to C-10), 143.8 (C-6), 166.0 (C═O).

Synthesis in Water. The product and was stirred at ambient temperature and isolated as described. Overall yield 95% (1-isomer) (1-*endo*:1-*exo* ratio 2.1:1).

***endo*-1-Butoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrollo[2,1-*a*]phthalazine and *exo*-1-Butoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrollo[2,1-*a*]phthalazine (12).** A suspension of compound **1** (0.10 g, 0.512 mmol) in acetonitrile (6.4 mL) was treated with an excess of *n*-butylacrylate (0.364 mL, 2.56 mmol) and stirred at ambient temperature for 5 h to give a pale yellow solution. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed on a flash column of silica gel (230−400 mesh ASTM) and eluted with a gradient mixture of dichloromethane and petroleum spirit (bp 40−60 °C) in the range 30:70 to 100:0. The products from the column were isolated in the following order. Overall yield 95% (1-isomer) (1-*endo*:1-*exo* 5.3:1). **1-*exo*-isomer:** gum (0.025 g, 15%); ν_{max}(neat)/cm^{-1} 1721(C═O); δ_H (500 MHz, $CDCl_3$) 0.86 (t, 3H, *J* = 7.1, CH_3), 1.30−1.41 (m, 2H, CH_2), 1.55−1.68 (m, 2H, CH_2), 3.03−3.13 (m, 2H, H-2), 4.10−4.29 (m, 3H, CH_2 and H-1), 4.38 (d, 1H, *J* = 9.3, H-10b), 7.27−7.44 (m, 4H, H-7 to H10), 7.72 (s, 1H). The 1-*exo* and 2-*endo* products were isolated as a mixture and could not be separated using column chromatography. The 2-*endo*-isomer was present at 4% as observed by ^{1}H NMR; however, because of overlap, it was not possible to fully assign the 2-*endo*-isomer. **1-*endo*-isomer:** off-white solid (0.128 g, 80%) mp 79−81 °C (ethanol); (Found C, 67.2; H, 5.4; N, 17.5. $C_{18}H_{16}N_4O_2$ requires C, 67.1; H, 5.6; N, 17.4%); ν_{max}(neat)/cm^{-1} 1720 (C═O); δ_H (500 MHz, $CDCl_3$) 0.77 (t, 3H, *J* = 7.1, CH_3), 1.10−1.23 (m, 2H, CH_2), 1.32−1.46 (m 2H, CH_2), 3.00 (dd, 1H, *J* = 13.5, 8.4, H-1_{endo}), 3.13 (dd, 1H, *J* = 14.1, 2.7, H-2_{exo}), 3.60−3.64 (m, 1H, H-1_{exo}), 3.86 (m, 1H, CH_2), 3.96−

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4.01 (m, 1H, CH_2), 4.81 (d, 1H, J = 6.4, H-10b), 7.25−7.42 (m, 4H, H-7 to H-10), 7.58 (s, 1H, H-6); δ_c (500 MHz, $CDCl_3$) 13.5 (CH_2), 30.0 (CH_2), 39.2 (C-2), 43.2 (CH_2), 54.8 (C-3), 59.2 (C-10b), 65.6 (C-1), 113.4, 114.0 (C≡N), 124.8 (C-8), 125.3 (C-6a), 126.1 (C-9), 129.0 (C-7), 129.2 (C10a), 130.4 (C-10), 144.1 (C-6), 170.2 (C═O).

Synthesis in Water. The reaction was carried out under identical conditions using water as the reaction medium. Overall yield 88% (1-isomer) (1-*endo*:1-*exo* ratio 3.6:1).

***endo*-1-Phenoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrollo[2,1-*a*]phthalazine and *exo*-1-Phenoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrollo[2,1-*a*]-phthalazine (13).** A suspension of compound **1** (0.10 g, 0.51 mmol) in acetonitrile (6.4 mL) was treated with an excess of phenyl acrylate (0.352 mL, 2.56 mmol) and stirred at ambient temperature for 12 h to give a pale yellow solution. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed on a flash column of silica gel (230−400 mesh ASTM) and eluted with a gradient mixture of dichloromethane and petroleum spirit (bp 40−60 °C) in the range 30:70 to 100:0. The products from the column were isolated in the following order. Overall yield 88% (1-isomer) (1-*endo*:1-*exo* 7.8:1). **1-*exo*-isomer:** Gum (0.017 g, 10%) ν_{max}(neat)/cm^{-1} 1750 (C═O); δ_H (500 MHz, $CDCl_3$) 3.14 (m, 1H, H-2_{endo}), 3.27 (dd, 1H, J = 14.2, 5.3, H-2_{exo}), 3.68−3.74 (m, 1H, H-2_{endo}), 4.55 (d, 1H, J = 9.2, H-10b), 6.74 (d, 1H, J = 8.6, 1H, Ph), 7.09−7.48 (m, 6H, H-7 to H-9, Ph), 7.74 (s, 1H, H-6). **1-*endo*-isomer:** off-white solid (0.156 g, 78%) mp 126−128 °C (ethanol); (Found C, 70.2; H, 4.2; N,16.5. $C_{20}H_{14}N_4O_2$ requires C, 70.1; H, 4.1; N, 16.4%); ν_{max}(neat)/cm^{-1} 1748 (C═O); δ_H (500 MHz, $CDCl_3$) 3.11 (dd, 1H, J = 13.7, 8.1, H-2_{endo}), 3.24 (dd, 1H, J = 13.7, 3.1, H-2_{exo}), 3.82−3.86 (m, 1H, H-1_{exo}), 4.97 (d, 1H, J = 6.7, H-10b), 6.60 (d, 2H, J = 7.8, Ph), 7.16 (d, 1H, J = 7.3, H-10), 7.23−7.26 (m, 2H, Ph), 7.31−7.33 (m, 1H, Ph), 7.40−7.48 (m, 3H, H-7 to H-9), 7.60 (s, 1H, H-6); δ_C (125 MHz, $CDCl_3$) 39.6 (C-2), 43.7 (C-3), 55.3 (C-10b), 59.5 (C-1), 113.1, 113.9 (C≡N), 120.9 (Ph), 124.8 (C-8), 125.8 (C-6a), 126.4 (C-9), 126.9 (Ph), 129.4 (C-7), 129.9 (C-10a), 131.7 (Ph), 144.1 (C-6), 149.9 (Ph), 169.0 (C═O).

Synthesis in Water. The reaction was carried out under identical conditions using water as the reaction medium. Overall yield 90%(1-isomer) (1-*endo*:1-*exo* ratio 6.8:1).

***endo*-1,2(Dicarboxy-*N*-methylimido)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (14).**[34b] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with *N*-methylmaleimide (0.17 g, 1.54 mmol) and stirred at ambient temperature for 24 h. The solvent was removed under reduced pressure to give the title compound (0.41 g, 87%): 233−235 °C (ethanol); (Found C, 62.9; H, 3.7; N, 23.2, $C_{16}H_{11}N_5O_2$ requires C, 62.9; H, 3.6; N, 22.9); ν_{max} /cm^{-1} 2300 (C≡N), 1785, 1716 (C═O); δ_H (400 MHz, DMSO-d_6) 2.78 (s, 3H, CH_3), 4.18 (dd, 1H, J = 7.9, 7.7, H-1), 4.45 (d, 1H, J = 7.7, H-2), 4.85 (d, 1H, J = 7.9, H-10b), 7.45−7.55 (m, 3H, H-7 to H-9), 7.77 (d, 1H, J = 7.7, H-10), 7.91 (s, 1H, H-6); δ_C (100 MHz, DMSO-d_6) 25.4 (CH_3), 43.4 (C-2), 50.0 (C-1), 57.4 (C-3), 58.7 (C-10b), 110.9, 112.1 (C≡N), 124.0 (C-10a), 127.0, 127.7, 129.0 (C-8 to C-10), 130.2 (C-6a), 131.7 (C-7), 147.6 (C-6), 171.2, 173.2 (C═O).

Synthesis in Water. The product and was stirred at ambient temperature and isolated as described. Overall yield 89% (*endo*:*exo* ratio 1:0).

Synthesis of *endo*-1,2-(Dicarboxy-*N*-*tert*-butylimido)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (15).[34b] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with *N*-*tert*-butylmaleimide (0.24 mL, 1.54 mmol) and stirred at ambient temperature for 24 h. The solvent was removed under reduced pressure to give the title compound (80%): white crystalline solid; mp 212−214 °C (ethanol); (Found C, 65.5; H, 5.0; N, 19.8. $C_{19}H_{17}N_5O_2$ requires C, 65.7; H, 4.9; N, 20.2%); ν_{max} (mull)/cm^{-1} 2263 (C≡N) 1702, 1774 (C═O); δ_H (400 MHz, DMSO-d_6), 1.35 (9H, s, ^{t}Bu protons), 3.92−3.95 (1H, dd, J = 7.7, 7.8, H-1), 4.29 (1H, d, J = 7.8, H-2), 4.93 (1H, d, J = 7.7, H-10b), 7.44−7.57 (3H, m, H-7 to H-9), 7.67 (1H, d, J = 7.3, H-10), 7.87 (1H, s, H-6); δ_C (100 MHz, DMSO-d_6) 27.3 (C($\underline{C}H_3$)), 44.4 (C-2), 50.8 (C-1), 58.2 ($\underline{C}(CH_3)_3$), 59.2 (C-1), 59.5 (C-3), 110.8, 112.4 (C≡N), 123.6 (C-10a), 126.9, 127.6, 129.1 (C-8 to C-10), 129.8 (C-6a), 131.7 (C-7), 146.5 (C-6), 171.6 and 173.8 (C═O).

Synthesis in Water. The product was prepared and isolated as described. Overall yield: 90% (*endo*:*exo* ratio 1:0). This structure of this compound was confirmed previously by an X-ray crystal structure.

***endo*-1,2-(Dicarboxy-*N*-phenylimido)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine. (16).** A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with *N*-phenylmaleimide (0.26 g, 1.54 mmol) and stirred at ambient temperature for 24 h. During this time the product precipitated from solution and was collected by filtration to give the title compound (0.51 g, 88%): mp 252−253 °C (ethanol); HRMS (ESI) calcd for $C_{21}H_{13}N_5O_2$ $(M + H)^+$ 368.1148, found 368.1175; ν_{max} cm^{-1} (nujol mull) 1715, 1795 (C═O); δ_H (400 MHz, DMSO-d_6) 4.41 (dd, 1H, J = 7.8, 7.6, H-1), 4.77 (d, 1H, J = 7.8, H-2), 5.19 (d, 1H, J = 7.6, H-10b), 7.19 (d, 2H, J = 7.1, H-2′ of N-Ph), 7.51−7.66 (m, 6H, H-3′ and H-4′ of N-Ph and H-7 to H-9), 7.82 (d, 1H, J = 7.8, H-10), 8.07 (s, 1H, H-6); δ_C (100 MHz, DMSO-d_6) 45.3 (C-2), 51.3 (C-1), 59.2 (C-3), 59.7 (C-10b), 110.8, 112.4 (C≡N) 123.9 (C-10a), 128.9 (C-1′ of N-Ph), 129.6 (C-6a), 131.9 (C-7), 126.5, 127.1, 127.8, 129.2, 131.5 (C-8 to C-10 and C-2′ and C-3′ of N-Ph respectively), 146.8 (C-6), 170.4, 172.4 (C═O).

Synthesis in Water. Product was prepared in water as described and isolated by direct filtration. Yield 96% (*endo*:*exo* ratio 1:0).

***endo*-1,2-(Dicarboxy-*N*-*p*-chlorophenylimido)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (17).**[34c] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with *N*-(*p*-chlorophenyl)maleimide (0.32 g, 1.54 mmol) and stirred at ambient temperature for 24 h. During this time the product precipitated from solution and was collected by filtration to give the title compound (0.53 g, 92%): mp 237−238 °C (ethanol); (Found C, 62.9; H, 3.1; N, 17.4, $C_{21}H_{12}N_5O_2Cl$ requires C, 62.7; H, 3.0; N, 17.4%); ν_{max} cm^{-1} (nujol mull) 1781, 1716 (C═O); δ_H (400 MHz, DMSO-d_6) 4.31 (dd, 1H, J = 7.8, 8.1, H-1), 4.68 (d, 1H, J = 7.8, H-2), 5.07 (d, 1H, J = 7.8, H-10b), 7.13 (d, 2H, J = 8.8, H-2′ of N−C_6H_4Cl), 7.41−7.57 (m, 5H, H-3′ of C_6H_4Cl and H-7 to H-9), 7.71 (d, 1H, J = 7.3, H-10), 7.95 (s, 1H, H-6); δ_C (100 MHz, DMSO-d_6) 45.2 (C-2), 51.2 (C-1), 59.1 (C-3), 59.8 (C-10b), 110.6, 112.2 (C≡N), 123.5 (C-10a), 127.0, 127.7, 129.2 (C-8 to C-10), 129.3, 128.8, 133.3 (C-1′, C-2′, C-4′ of C_6H_4Cl respectively), 130.2 (C-6a), 131.8 (C-7), 146.7 (C-6), 170.2, 172.4 (C═O).

Synthesis in Water. the product was prepared in water as described and isolated by direct filtration, Yield 94% (*endo*:*exo* ratio 1:0).

***exo*-2-Butoxy-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (18).**[34b] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with *n*-butyl vinyl ether (1.47 mL, 15.4 mmol) and stirred under reflux for 12 h. The solvent was removed under reduced pressure to give the title compound. Yield: 86%, white crystalline solid, mp 140−141 °C (ethanol); (Found C, 69.3; H, 6.2; N, 19.0. $C_{17}H_{18}N_4O$ requires C, 69.1; H, 6.1; N, 18.9%); δ_H (400 MHz $CDCl_3$) 0.96 (t, 3H, CH_3); 1.42−1.49 (m, 2H, CH_2), 1.65−1.70 (m, 2H, CH_2), 2.39−2.45 (m, 1H, H-1_{exo}), 2.64−2.72 (m, 1H, H-1_{endo}), 3.65−3.71 (m, 1H, H-1 *n*-Bu), 3.83−3.89 (m, 1H, H-1 *n*-Bu), 4.44 (dd, 1H, J = 8.3, 8.1, H-10b), 4.58−4.61 (m, 1H, H-2), 7.07 (d, 1H, J = 7.3, H-10), 7.28−7.50 (m, 3H, H-7 to H-9), 7.72 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 13.6 (CH_3), 18.8 (CH_2), 31.7 (CH_2), 32.9 (C-1), 55.2 (C-10b), 61.6 (C-3), 72.2 (CH_2), 83.8 (C-2), 110.2, 113.9 (C≡N), 123.4 (C-10), 124.7 (C-10a), 126.1, 128.5,125.9 (C-8 to C-10) 132.1(C-7), 134.2(C-6a), 146.3 (C-6).

Synthesis in Water. The reaction was carried out under identical conditions as to that in acetonitrile. The reaction was carried out by heating at 82 °C. The product was isolated by direct filtration, Yield 87% (2-*endo*:2-*exo* 0:1).

This structure of compound **18** was confirmed by an X-ray crystal structure.

***exo*-2-Phenyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine and *endo*-2-Phenyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (19).**[9c] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated

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with styrene (0.352 mL, 3.08 mmol) and stirred under reflux for 24 h. After this time the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed onto a flash column of silica gel (ASTM 230−400 mesh) packed with petroleum spirit (bp 40−60 °C)/dichloromethane in the ratio 1:1. The products were eluted with a mixture of petroleum spirit (bp 40−60 °C)/dichloromethane in the range 1:1 to 0:1 with a 2.5% (v/v) changing gradient. The products came off the column as follows. **2-*exo*-isomer:** (0.34 g, 74%), mp 158−160 °C (ethanol); (Found C, 76.2; H, 4.4; N, 18.5; $C_{19}H_{14}N_4$ requires C, 76.5; H, 4.7; N, 18.7%); ν_{max} (mull)/cm^{-1} 666, 759 (-Ph); δ_H (400 MHz, $CDCl_3$) 2.74−2.85 (m, 2H, H-1), 4.15 (dd, 1H, J = 10.7, 7.3, H-2), 4.52 (dd, 1H, J = 8.8, 8.5, H-10b), 7.18 (d, 1H, J = 7.3, H-10), 7.25−7.54 (m, 8H, H-7, H-8, H-9 and Ph), 7.80 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 29.7 (C-1), 52.2 (C-2), 56.3 (C-10b), 63.7 (C-3), 110.8, 113.3 (C≡N), 123.1 (C-10), 125.1 (C-10a), 126.0 (C-9), 128.7, 129.2, 134.7 (Ph, C-1′ to C-4′), 129.4 (C-8), 132.0 (C-7), 133.7 (C-6a), 146.5 (C-6), C-4′ signal masked by C-3′. **2-*endo*-isomer:** (0.06 g, 13%) isolated as a gum; δ_H (400 MHz, $CDCl_3$) 2.56−2.64 (m, 1H, H-1$_{endo}$), 2.99−3.03 (m, 1H, H-1$_{exo}$), 4.18 (dd, 1H, J = 8.8, 8.3, H-2), 4.54 (dd, 1H, J = 10.2, 5.8, H-10b), 7.13−7.57 (m, 9H, H-7 to H-10 and Ph), 7.78 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 33.5 (C-1), 53.2 (C-2), 56.3 (C-10b), 111.7, 113.2 (C≡N), 122.9 (C-10), 128.7, 129.2, 136.7 (Ph, C-1′, C-2′, C-3′), 124.2, 129, 132.2 (C-7 to C-10), 145.9 (C-6), C-3 signal was too weak to be seen with the small quantity available.

Synthesis in Water. The reaction was carried out by stirring at 82 °C. For the work up the reaction was allowed to cool, and the products were extracted into dichloromethane (2 × 10 mL) and dried over $MgSO_4$. The purification step was identical to the reaction carried out in acetonitrile. Overall yield 78% (2-*endo*:2-*exo* 1:6.1).

***exo*-2-(4-Methoxyphenyl)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine and *endo*-2-(4-Methoxyphenyl)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (20).**[9c] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with 4-methoxystyrene (0.410 mL, 3.08 mmol) and stirred under reflux for 24 h. After this time the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed onto a flash column of silica gel (ASTM 230−400 mesh) packed with petroleum spirit (bp 40−60 °C)/dichloromethane in the ratio 1:1. The products were eluted with a mixture of petroleum spirit (bp 40−60 °C)/dichloromethane in the range 1:1 to 0:1 with a 2.5% (v/v) changing gradient. The products came off the column as follows. **2-*exo*-isomer:** (0.32 g, 63%), mp 159−162 °C (ethanol); (Found C, 72.8; H, 4.5; N, 17.2; $C_{20}H_{16}N_4O$ requires C, 73.15; H, 4.9; N, 17.1%); ν_{max} (mull)/cm^{-1} 831 (−C_6H_4), 1036, 1260 (C−O−C), 2213 (C≡N); δ_H (400 MHz, $CDCl_3$) 2.69−2.87 (m, 2H, H-1), 3.85 (s, 3H, CH_3) 4.13(dd, 1H, J = 11.3, 6.8, H-2), 4.52 (dd, 1H, J = 8.7, 8.3, H-10b), 6.98−7.77 (m, 8H, H7 to H-10 and H-2′, H-3′), 7.80 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 29.8 (C-1), 51.7 (C-2), 55.3 (OCH_3), 56.3 (C-10b), 63.5 (C-3), 111.0, 113.5 (C≡N), 114.6 (C-3′), 123.4 (C-10), 125.0 (C-10a), 125.5 (C-1′), 126.0 (C-9), 128.5 (C-8), 129.9 (C-2′), 132.0 (C-7), 134.7 (C-6a), 146.4 (C-6), 160.3 (C-4′). **2-*endo*-isomer:** (0.04 g, 8%) isolated as a gum; δ_H (400 MHz, $CDCl_3$) 2.54−2.59 (m, 1H, H-1$_{endo}$), 2.97−2.99 (m, 1H, H-1$_{exo}$), 3.79 (s, 3H, OCH_3), 4.15 (dd, 1H, J = 8.8, 8.3, H-2), 4.54 (dd, 1H, H-10b), 6.90 (d, 1H, J = 8.8, H-10) 7.12−7.50 (m, 7H, H7 to H-9 and H-2′, H-3′), 7.75 (s, 1H, H-6).

Synthesis in Water. The reaction was carried out by stirring at 82 °C. For the work up the reaction was allowed to cool, and the products were extracted into dichloromethane (2 × 10 mL) and dried over $MgSO_4$. The purification step was identical to the reaction carried out in acetonitrile. Overall yield: 87% (2-*endo*:2-*exo* 1:8.6).

***exo*-2-(3-Fluorophenyl)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine and *endo*-2-(3-Fluorophenyl)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine (21).**[9c] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with 3-fluorostyrene (0.367 mL, 3.08 mmol) and stirred under reflux for 24 h. After this time the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed onto a flash column of silica gel (ASTM 230−400 mesh) packed with petroleum spirit (bp 40−60 °C)/dichloromethane in the ratio 1:1. The products were eluted with a mixture of petroleum spirit (bp 40−60 °C)/dichloromethane in the range 1:1 to 0:1 with a 2.5% (v/v) changing gradient. The products could not be separated by this chromatographic procedure, and the ratio of products, 5.1:1, was found by proton NMR. The main product, the *exo*-isomer (0.31 g, 56%), was purified by recrystalisation from ethanol, and the remaining mixture was composed of 1:1 of the 2-*exo* and 2-*endo*-isomers. **2-*exo*-isomer:** (0.38 g, 76%), mp 152−154 °C (ethanol); (Found C, 71.8; H, 4.1; N, 18.0; $C_{19}H_{13}N_4F$ requires C, 72.1; H, 4.1; N, 17.7%); ν_{max} (mull)/cm^{-1} 774 (*o*-disustituted benzene), 2146 (C≡N); δ_H (400 MHz, $CDCl_3$) 2.71−2.79 (m, 1H, H-1$_{exo}$), 2.82−2.90 (m, 1H, H-1$_{endo}$) 4.17 (dd, 1H, J = 11.2, 6.8, H-2), 4.54 (dd appearing as t, 1H, J = 8.8, 8.8, H-10b), 7.13−7.55 (m, 8H, H7 to H-10 and H-2′ and H-4′ to H-6′), 7.81 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 29.6 (C-1), 51.7 (C-2), 56.1 (C-10b), 63.0 (C-3), 110.6, 113.1 (C≡N), 115.7 (d, J_{F-C}= 22.5, C-2′ or C-4′), 116.5 (d, J_{F-C}= 18.2, C-2′ or C-4′), 123.1 (C-10a), 124.5 (C-10), 126.1 (C-6′), 128.7 (C-9 and C-5′), 130.9 (C-8), 132.0 (C-7), 136.0 (C-1′), 136.1 (C-6a), 146.6 (C-6), 163.0(d, J_{F-C}, 143.1, C-3′). **2-*endo*-isomer:** (0.07 g, 15%) gum; δ_H (400 MHz, $CDCl_3$) 2.49−2.53 (m, 1H, H-1$_{endo}$), 2.99−3.02 (m, 1H, H-1$_{exo}$), 7.03−7.67 (m, 8H, H7 to H-10 and H-2′ and H-4′, H-5′, H-6′), 7.71 (s, 1H, H-6). H-8a was masked by the H-8a of the main isomer. H-2 was masked by the H-2 of the main isomer in the mixture. This fraction was an inseperable 1:1 mixture of *endo*:*exo*-isomers

Synthesis in Water. The reaction was carried out by stirring at 82 °C. For the work up the reaction was allowed to cool, and the products were extracted into dichloromethane (2 × 10 mL) and dried over $MgSO_4$. The purification step was identical to the reaction carried out in acetonitrile. Overall yield: 82% (2-*endo*:2-*exo* 1:6.4)

***exo*-2-(3-Nitrophenyl)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine and *endo*-2-(3-Nitroro-phenyl)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]-phthalazine (22).**[9c] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with 3-nitrostyrene (0.429 mL, 3.08 mmol) and stirred under reflux for 24 h. After this time the reaction was allowed cool, and the *exo*-2 isomer precipitated from solution and was collected by filtration (0.36 g, 68%). The solvent was removed from the filtrate under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed onto a flash column of silica gel (ASTM 230−400 mesh) packed with petroleum spirit (bp 40−60 °C)/dichloromethane in the ratio 1:1. The products were eluted with a mixture of petroleum spirit (bp 40−60 °C)/dichloromethane in the range 1:1 to 0:1 with a 2.5% (v/v) changing gradient to afford a inseperable mixture of the 2-*endo*- and 1-*endo*-isomers. Overall yield 79% (2-isomer) (2-*endo*:2-*exo* 1:6.2). **2-*exo*-isomer:** (0.36 g, 68%), mp 235−238 °C (ethanol); (Found C, 66.6; H, 3.9; N, 20.6; $C_{19}H_{13}N_5O_2$ requires C, 66.5; H, 3.8; N, 20.4%); ν_{max} (mull)/cm^{-1} 763 (*o*-disustituted benzene); δ_H (400 MHz, DMSO-d_6) 2.79−2.88 (m, 1H, H-1$_{endo}$), 2.96−3.03 (m, 1H, H-1$_{exo}$), 4.58(dd, 1H, J = 8.8, 8.3, H-10b), 4.86 (dd, 1H, J = 11.2, 5.8, H-2), 7.36 (d, 1H, J = 7.3, H-10), 7.49−7.64 (m, 3H, H7 to H-9), 7.86 (dd, 1H, J = 8.3, 7.8, H-5′), 8.07 (s, 1H, H-6), 8.14 (d, 1H, J = 7.8, H-6′), 8.35 (d, 1H, J = 8.3, H-4′), 8.50 (s, 1H, H-2′); δ_C (100 MHz, DMSO-d_6) 29.1 (C-1), 49.9 (C-2), 56.5 (C-10b), 63.0 (C-3), 111.4, 113.5 (C≡N), 123.8 (C-10), 124.2 (C-10a), 126.3 (C-9), 128.6 (C-8), 130.8 (C-7), 132.4 (C-6a), 124.6, 135.8, 137.2 (C-1′ to C-2′ and C-3′ to C-6′), 147.3 (C-6), 148.0 (C-3′). **2-*endo*-isomer:** (0.06 g, 11%); δ_H (400 MHz, $CDCl_3$) 2.54−2.61 (m, 1H, H-1$_{endo}$), 3.11−3.18 (m, 1H, H-1$_{exo}$), 4.32 (dd, 1H, J = 8.3, 8.3, H-2), 4.58 (dd, 1H, J = 9.3, 3.3, H-10b), 7.13−8.08 (m, 8H, H-7 to H-10 and H-2′ and H-4′, H-5′, H-6′), 8.23 (s, 1H, H-6). **1-*endo*-isomer:** (0.03 g, 6%); δ_H (400 MHz, $CDCl_3$) 2.82 (dd, 1H, J = 14.6, 2.9, H-2$_{endo}$), 3.51 (dd, 1H, J = 14.6, 9.3, H-2$_{exo}$), 4.12 (m, 1H, H-1), 4.90 (d, J = 6.3, H-10b), 6.48 (d, 1H, J = 7.8, H-10), 7.13−8.08 (m, 7H, H7 to H-9 and H-2′ and H-4′, H-5′, H-6′), 8.27 (s, 1H, H-6).

Synthesis in Water. The reaction was carried out by stirring at 82 °C. For the work up the reaction was allowed to cool, and the products were extracted into dichloromethane (2 × 10 mL) and dried

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over $MgSO_4$. The purification step was identical to the reaction carried out in acetonitrile. Overall yield: 82% (2-isomer) (2-*endo*:2-*exo* 1:7).

***exo*-8a,9,10,11,12,12a-Hexahydro-9,12-methanoisoindolo-[1,2-*a*]phthalazine-8,8(12b*H*)-dicarbonitrile and *endo*-8a,9,10,11,12,12a-Hexahydro-9,12-methanoisoindolo[1,2-*a*]-phthalazine-8,8(12b*H*)-dicarbonitrile (23).** A suspension of compound **1** (0.100 g, 0.512 mmol) in acetonitrile (6.4 mL) was treated with an excess of norbornene (0.48 g, 5.12 mmol) and stirred at ambient temperature for 16 h to give a pale yellow solution. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed on a flash column of silica gel (230−400 mesh ASTM) and eluted with a gradient mixture of dichloromethane and petroleum spirit (bp 40−60 °C) in the range 30:70 to 100:0. The *endo*/*exo*-isomers proved difficult to isolate separately. The characterization given is for the mixture of the *endo*- and *exo*-isomers, and the ratio of *endo*/*exo*-isomers was determined through integration of the H-10b signals. ***endo*- and *exo*-isomers:** (0.135 g, 92%, *endo*:*exo* 1:1.8), off-white solid; HRMS (ESI) calcd for $C_{18}H_{17}N_4$ $(M + H)^+$ 289.1454, found 289.1465; δ_H (500 MHz, $CDCl_3$) 1.13 (d, 2H endo, J = 10.6), 1.28−1.48 (m, 5H exo, 4H endo), 1.75−1.77 (m, 2H exo), 1.91−1.94 (m, 1H exo, 1H endo), 2.41 (s, 1H endo), 2.63−2.66 (app t, 1H exo, 1H endo), 2.69 (s, 1H exo), 2.85 (app t, 1H exo, 1H endo), 3.86 (d, 1H, J = 8.6, H-10b exo), 4.51 (d, 1H, J = 6.7, H-10b endo), 7.19 (d, 1H, J = 7.5, H-10 endo), 7.24 (d, 1H, J = 7.8, H-10 exo), 7.27−7.30 (m, 1H exo, 1H endo), 7.35−7.42 (m, 1H exo, 1H endo), 7.45−7.58 (m, 1H exo, 1H endo), 7.61 (s, 1H, H-6 endo), 7.71 (s, 1H, H-6 exo); δ_C (125 MHz, $CDCl_3$) 27.5 (endo), 27.8 (exo), 28.6 (exo), 29.3 (endo), 34.5 (exo), 34.5 (endo), 36.2 (endo), 37.6 (exo), 38.6 (exo), 40.2 (endo), 45.0 (endo), 50.2 (exo), 54.5 (endo), 55.2 (exo), 59.1 (exo), 59.2 (endo), 59.6 (exo), 60.2 (endo), 112.2, 114.8 (C≡N exo) 112.4, 113.3 (C≡N endo), 123.0 (exo), 125.0 (exo), 125.2 (endo), 125.9 (exo), 126.6 (exo), 128.5 (exo), 131.4 (endo), 131.9 (exo), 133.1 (endo), 134.5 (exo), 145.6 (C-6 endo), 146.2 (C-6 exo).

The terms *endo* and *exo* refer to the isomers to which the signal belongs. Some of the *exo*-isomer peaks are missing in the ^{13}C NMR due to overlap with the major *endo*-isomer.

Synthesis in Water. The reaction stirred at room temperature for 48 h; however, no product was observed by TLC. The reaction was heated to 82 °C for 24 h where the reaction went to completion. Yield 91% (*endo*:*exo* 1:2.3).

***endo*-1-Propanoyl-3,3-dicyano-1,2,3,8a-tetrahydropyrrolo-[1,2-*b*]pyridazine and *exo*-1-Propanoyl-3,3-dicyano-1,2,3,8a-tetrahydropyrrolo[1,2-*b*]pyridazine (24).**[31] A solution of compound **1A** (0.30 g, 2.08 mmol) in acetonitrile (15 mL) was treated with ethyl vinyl ketone (1.03 mL, 10.4 mmol) and stirred at 60 °C for 24 h. After this time the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed onto a flash column of silica gel (ASTM 230−400 mesh) packed with petroleum spirit (bp 40−60 °C)/dichloromethane in the ratio 1:1. The products were eluted with a mixture of petroleum spirit (bp 40−60 °C)/dichloromethane in the range 1:1 to 0:1 with a 2.5% (v/v) changing gradient. **1-*endo*-isomer:** (0.38 g, 80%) mp 110−112 °C (ethanol); (Found C, 63.4; H, 4.9; N, 25.0; $C_{12}H_{12}N_4O$ requires C, 63.2; H, 5.3; N, 24.6%); ν_{max} (mull)/cm^{-1} 1712 (C═O); δ_H (400 MHz, $CDCl_3$) 1.07 (t, 3H, J = 7.3, CH_3), 2.51−2.67 (m, 2H, CH_2), 2.78 (dd, 1H, J = 13.9, 8.8, H-2_{endo}), 3.03 (dd, 1H, J = 13.9, 4.4, H-2_{exo}), 3.43−3.48 (m, 1H, H-1), 4.26 (d, 1H, J = 7.3, H-8a), 5.97 (d, 1H, J = 9.7, H-7), 6.12 (d, 1H, J = 9.7, H-8), 7.15 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 7.07 (CH_3), 36.7 (CH_2), 37.0 (C-2), 47.2 (C-1), 53.6 (C-3), 55.7 (C-8a), 113.2 and 113.3 (C≡N), 119.9 (C-7), 127.9 (C-8), 142.2 (C-6), 207.7 (C═O). **1-*exo*-isomer:** (0.03 g, 6%) gum; δ_H (400 MHz, $CDCl_3$) 1.12 (t, 3H, J = 7.3), 2.43−2.74 (m, 2H, CH_2), 2.87 (dd, 1H, J = 13.9, 9.9, H-2_{exo}), 2.99 (dd, 1H, J, 13.9, 7.8, H-2_{endo}), 3.31−3.38 (m, 1H, H-1), 4.03 (d, 1H, J = 9.7, H-8a), 5.99 (d, 1H, J = 9.5, H-7), 6.18 (d, 1H, J = 9.5, H-8), 7.21 (s, 1H, H-6).

Synthesis in Water. The reaction was carried out under identical conditions to the reaction in acetonitrile. For the work up the reaction was allowed to cool, and the products were extracted into dichloromethane (2 × 10 mL) and dried over $MgSO_4$. The purification step was identical to the reaction carried out in acetonitrile. Overall yield: 92% (1-*endo*:1-*exo* 22:1).

***endo*-1-Methoxycarbonyl-3,3-dicyano-1,2,3,8a-tetrahydropyrrolo[1,2-*b*]pyridazine and *exo*-1-Methoxycarbonyl-3,3-dicyano-1,2,3,8a-tetrahydropyrrolo[1,2-*b*]-pyridazine (25).**[31] A solution of compound **1A** (0.30 g, 2.08 mmol) in acetonitrile (15 mL) was treated with methyl acrylate (0.94 mL, 10.4 mmol) and stirred at 60 °C for 24 h. After this time the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed onto a flash column of silica gel (ASTM 230−400 mesh) packed with petroleum spirit (bp 40−60 °C)/dichloromethane in the ratio 1:1. The products were eluted with a mixture of petroleum spirit (bp 40−60 °C)/dichloromethane in the range 1:1 to 0:1 with a 2.5% (v/v) changing gradient. **1-*endo*-isomer:** (0.38 g, 86%), red gum; HRMS (ESI) calcd for $C_{11}H_{10}N_4O_2$ $(M + H)^+$ 231.0883, found 231.0888; ν_{max} (mull)/cm^{-1} 1738 (C═O); δ_H (400 MHz, $CDCl_3$) 2.85 (dd, 1H, J = 14.4, 8.3, H-2_{endo}), 3.24 (dd, 1H, J = 14.4, 2.9, H-2_{exo}), 3.29−3.36 (m, 1H, H-1), 3.69 (s, 3H, CH_3), 4.24 (d, 1H, J = 6.8, H-8a), 5.96 (d, 1H, J = 9.7, H-7), 6.28 (d, 1H, J = 9.7, H-8), 7.16 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 37.5 (C-2), 42.0 (C-1), 52.7 (CH_3) 53.4 (C-3), 56.1 (C-8a), 113.5 and 113.6 (C≡N), 119.8 (C-7), 128.6 (C-8), 142.8 (C-6), 170.4 (C═O). **1-*exo*-isomer:** (0.03 g, 6%) gum; δ_H (400 MHz, $CDCl_3$) 2.95 (dd, 1H, J = 14.1, 10.2, H-2_{exo}), 3.07 (dd, 1H, J = 14.1, 7.8, H-2_{endo}), 3.24−3.28 (m, 1H, H-1), 3.80 (CH_3), 4.02 (d, 1H, J = 9.7, H-8a), 5.98 (d, 1H, J = 9.7, H-7), 6.25 (d, 1H, J = 9.7, H-8), 7.22 (s, 1H, H-6).

Synthesis in Water. The reaction was carried out under identical conditions to the reaction in acetonitrile. For the work up, the reaction was allowed to cool, and the products were extracted into dichloromethane (2 × 10 mL) and dried over $MgSO_4$. The purification step was identical to the reaction carried out in acetonitrile. Overall yield: 94% (1-*endo*:1-*exo* 1:0). None of the *exo*-isomer was observed.

Synthesis of *endo*-1,3,3-Tricyano-1,2,3,8a-tetrahydropyrrolo[1,2-*b*]pyridazine and *exo*-1,3,3-Tricyano-1,2,3,8a-tetrahydropyrrolo[1,2-*b*]pyridazine (26). A solution of compound **1A** (0.30 g, 2.08 mmol) in acetonitrile (15 mL) was treated with acrylonitrile (0.685 mL, 10.4 mmol) and stirred at 60 °C for 48 h. After this time the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed onto a flash column of silica gel (ASTM 230−400 mesh) packed with petroleum spirit (bp 40−60 °C)/dichloromethane in the ratio 1:1. The products were eluted with a mixture of petroleum spirit (bp 40−60 °C)/dichloromethane in the range 1:1 to 0:1 with a 2.5% (v/v) changing gradient. The column was flushed with methanol, and only intractable resins were present. **1-*endo*-isomer:** (0.22 g, 54%), white solid. mp 152−153 °C (ethanol); (Found C, 60.9; H, 3.45; N, 35.6; $C_{10}H_7N_5$ requires C, 60.9; H, 3.6; N, 35.5%); ν_{max} (mull)/cm^{-1} 2240, 2341, 2360 (C≡N); δ_H (500 MHz, $CDCl_3$) 3.03 (dd, 1H, J = 14.1, 3.9, H-2_{exo}), 3.12 (dd, 1H, J = 14.1, 8.8, H-2_{endo}), 3.47−3.52 (m, 1H, H-1), 4.20 (d, 1H, J = 6.3, H-8a), 6.16 (d, 1H, J = 9.7, H-7), 6.31 (d, 1H, J = 9.7, H-8), 7.26 (s, 1H, H-6); δ_C (125 MHz, $CDCl_3$) 31.5 (C-2), 40.5 (C-1), 54.8 (C-3), 57.6 (C-8a), 115.9 (C≡N), 120.2 (C≡N), 122.6 (C-7), 130.4 (C-8), 145.8 (C-6). **1-*exo*-isomer:** (0.04 g, 10%) gum; δ_H (400 MHz, $CDCl_3$) 2.95 (dd, 1H, J = 14.0, 8.3, H-2_{endo}), 3.15 (dd, 1H, J = 14.0, 9.9, H-2_{exo}), 3.27−3.34 (m, 1H, H-1), 4.27 (d, 1H, J = 9.7, H-8a), 6.09 (d, 1H, J = 9.7, H-7), 6.26 (d, 1H, J, 9.7, H-8), 7.24 (s, 1H, H-6); δ_C (100 MHz, $CDCl_3$) 28.8 (C-2), 38.4 (C-1), 50.0 (C-3), 56.9 (C-8a), 115.9 (C≡N), 120.7 (C-7), 126.9 (C-8), 143.0 (C-6).

Synthesis in Water. The reaction was carried out under identical conditions to the reaction in acetonitrile. For the work up, the reaction was allowed to cool, and the product was precipitated from solution and isolated by filtration. Overall yield: 71% (1-*endo*:1-*exo* 1:0). None of the *exo*-isomer was observed.

***endo*-1,2-(Dicarboxy-*N*-methylimido)-3,3-dicyano-1,2,3,8a-tetrahydropyrrolo[1,2-*b*]pyridazine and *exo*-1,2-(Dicarboxy-*N*-methylimido)-3,3-dicyano-17,2,3,8a-tetrahydropyrrolo[1,2-*b*]-pyridazine (27).** A solution of compound **1A** (0.30 g, 2.08 mmol) in acetonitrile (15 mL) was treated with *N*-methylmaleimide (0.254 g, 2.31 mmol) and stirred under reflux for 24 h. After this time the

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solvent was removed under reduced pressure to yield an oily residue, which quickly crystallized. The crude solid was recrystalised from ethanol to yield the title compound. ***endo*-isomer:** (0.41 g, 75%), mp 190−191 °C (ethanol); (Found C, 56.45; H, 3.4; N, 27.3; $C_{12}H_9N_5O_2$ requires C, 56.5; H, 3.55; N, 27.4%); ν_{max} (mull)/cm^{-1} 1693 (C═O), 2195 (C≡N); δ_H (500 MHz, $CDCl_3$) 3.06 (s, 3H, CH_3), 3.49 (dd, 1H, *J* = 7.8, 7.8, H-1), 3.80 (d, 1H, *J* = 7.8, H-2), 4.16 (d, 1H, *J* = 7.8, H-8a), 6.01 (d, 1H, *J* = 9.7, H-7), 6.69 (d, 1H, *J* = 9.7, H-8), 7.30 (s, 1H, H-6); δ_C (125 MHz, DMSO-d_6) 25.3 (CH_3), 41.8 (C-1), 49.0 (C-2), 54.2 (C-8a), 57.1 (C-3), 110.7 and 111.5 (C≡N), 119.4 (C-7), 130.6 (C-8), 146.4 (C-6), 171.3 and 174.0 (C═O). ***exo*-isomer:** (0.04 g, 10%) obtained as a gum by removal of the ethanol under reduced pressure from the filtrate; δ_H (400 MHz, $CDCl_3$) 3.08 (s, 3H, CH_3), 3.58 (dd, 1H, *J* = 9.7, 8.3, H-1), 3.97 (d, 1H, *J* = 8.3, H-2), 4.06 (d, 1H, *J* = 9.7, H-8a), 6.06 (d, 1H, *J* = 9.7, H-7), 6.43 (d, 1H, *J* = 9.7, H-8), 7.27 (s, 1H, H-6).

Synthesis in Water. The reaction was carried out by stirring the reaction at 20 °C for 96 h. Once the reaction was finished, the reaction precipitated from solution and was collected by filtration. Overall yield: 85% (*endo*:*exo* 1:0). None of the *exo*-isomer was observed.

***exo*-2-Phenyl-3,3-dicyano-1,2,3,8a-tetrahydropyrrolo[1,2-*b*]pyridazine and *endo*-1-Phenyl-3,3-dicyano-1,2,3,8a-tetrahydropyrrolo[1,2-*b*]pyridazine (28).** A solution of compound **1A** (0.30 g, 2.08 mmol) in acetonitrile (15 mL) was treated with styrene (2.38 mL, 20.8 mmol) and stirred at 60 °C for 7 days. After which time the solvent was removed under reduced pressure, and the residue was placed onto a flash column of silica gel. The products were eluted with a mixture of petroleum spirit (bp 40−60 °C)/dichloromethane in the range 1:1 to 0:1 with a 2.5% (v/v) changing gradient. The products coeluted from the column together. **2-*exo*-isomer:** (0.38 g, 73%) precipitated out of solution, mp 160−161 °C (ethanol); (Found C, 72.7; H, 4.5; N, 23.1; $C_{15}H_{12}N_4$ requires C, 72.6; H, 4.8; N, 22.7%); ν_{max} (mull)/cm^{-1} 706 (-Ph), 2199 (C≡N); δ_H (500 MHz, $CDCl_3$) 2.46−2.58 (m, 2H, H-1), 4.07 (dd, 1H, *J* = 10.2, 7.3, H-2$_{endo}$), 4.14 (dd, 1H, *J* = 8.7, 8.7, H-8a), 5.98 (d, 1H, *J* = 9.7, H-7), 6.22 (d, 1H, *J* = 9.7, H-8), 7.26 (s, 1H, H-6), 7.45 (s, 5H, C_6H_5); δ_C (125 MHz, $CDCl_3$) 31.2 (C-1), 51.9 (C-2), 52.9 (C-8a), 62.9 (C-3), 110.6 and 113.0 (C≡N), 119.2 (C-7), 128.5 (C-2′), 129.0 (C-3′), 129.2 (C-4′), 131.6 (C-8), 133.5 (C-1′) 143.5 (C-6). The solvent of the filtrate was removed under reduced pressure to yield the **2-*endo*-isomer:** (0.11 g, 21%) which was isolated as a gum; δ_H (400 MHz, $CDCl_3$) 2.36−2.44 (m, 1H, H-1$_{endo}$), 2.61−2.68 (m, 1H, H-1$_{exo}$), 3.97 (dd, 1H, *J* = 9.7, 7.3, H-2$_{exo}$), 4.25 (m, 1H, H-8a), 5.92 (d, 1H, *J* = 9.7, H-7), 6.04 (d, 1H, *J* = 9.7, H-8), 7.17 (s, 1H, H-6), 7.41 (s, 5H, Ph).

Synthesis in Water. A suspension of compound **1A** (0.30 g, 2.08 mmol) in water (15 mL) was treated with styrene (2.38 mL, 20.8 mmol) and stirred at 60 °C for 4 days. The reaction was allowed to cool, and the products were extracted into dichloromethane (2 × 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the reaction was worked up as with the reaction in acetonitrile. Overall yield 95% (2-*endo*:2-*exo* 1:12)

2-Phenyl-3-cyanopyrollo[2,1-*a*]phthalazine (29).[34b] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with an excess of phenylacetylene (1.69 mL, 15.4 mmol), stirred under reflux in an anhydrous atmosphere for 24 h, cooled to ambient temperature, and filtered to give the title compound (0.34 g, 82%): white needles, mp 210−212 °C (acetonitrile); (Found C, 80.0; H, 4.0; N, 15.4. $C_{18}H_{11}N_3$ requires C, 80.2; H, 4.1; N, 15.6%); ν_{max} (mull)/cm^{-1} 2214 (C≡N); δ_H (400 MHz, DMSO-d_6, 60 °C) 7.41−7.45 (m, 1H, H-4′), 7.51−7.57 (m, 2H, H-3′), 7.57 (s, 1H, H-1), 7.71−7.75 (m, 1H, H-9), 7.85−7.87 (m, 2H, H-2′), 7.90−7.92 (m, 1H, H-8), 8.06 (d, 1H, *J* = 7.7, H-10), 8.31 (d, 1H, *J* = 8.1, H-7), 8.90 (s, 1H, H-6); δ_C (100 MHz, DMSO-d_6, 60 °C) 99.2 (C-1), 113.5 (C≡N), 120.6 (C-2), 122.5 (Ph C-4′), 125.9 (C-3), 127.7 (C-10b),128.4, 128.6, 128.9, 129.0 (C-8 to C-10 and C-2′ and C-3′), 131.8 (C-1′) 133.5 (C-7),133.9 (C-6a) 146.2(C-6).

Synthesis in Water. The product was prepared by heating in water at 82 °C as described and isolated by direct filtration. Yield 78%.

1-Deuterio-2-phenyl-3-cyano-pyrrolo[2,1-*a*]phthalazine (30).[34b] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with an excess of phenylacetylene-d_1 (1.69 mL, 15.4 mmol), stirred under reflux in an anhydrous atmosphere for 24 h, cooled to ambient temperature, and filtered to give the title compound (0.36 g, 86%): white needles, mp 213−214 °C (acetonitrile); HRMS (ESI) calcd for $C_{18}H_{10}DN_3$ (M + H)$^+$ 271.1095, found 271.1113; ν_{max} (mull)/cm^{-1} 2215 (C≡N); δ_H (400 MHz, DMSO-d_6 60 °C) 7.43 (t, 1H, *J* = 6.3, Ph H-4′), 7.51−7.57 (m, 2H, Ph H-3′), 7.71−7.75 (m, 1H, H-9), 7.85−7.87 (m, 2H, Ph H-2′), 7.90−7.92 (m, 1H, H-8), 8.06 (d, 1H, *J* = 7.7, H-10), 8.31 (d, 1H, *J* = 8.1, H-7), 8.90 (s, 1H, H-6), the H-1 signal at 7.57 was absent; δ_C (100 MHz, DMSO-d_6 60 °C) 113.5 (C≡N), 120.6 (C-2), 122.5 (C-4′), 125.9 (C-3), 127.7 (C-10b),128.4, 128.6, 128.9, 129.0 (C-8 to C-10 and C-2′ and C-3′), 131.8 (C-1′) 133.5 (C-7),133.9 (C-6a) 146.2(C-6), the C-1 signal at 99.2 ppm was reduced almost to zero.

Synthesis in Water. The product was prepared by heating in water at 82 °C as described and isolated by direct filtration. Yield 87%.

1,2-Diphenyl-3-cyanopyrrolo[2,1-*a*]phthalazine (31).[32] A suspension of compound **1** (0.30 g, 1.54 mmol) in acetonitrile (20 mL) was treated with diphenylacetylene (2.74 g, 15.4 mmol) and stirred under reflux for 24 h, after which time the product precipitated from solution and was filtered to give the title compound (0.32 g, 60%): mp 213−214 °C (acetonitrile); HRMS (ESI) calcd for $C_{24}H_{15}N_3$ (M + H)$^+$ 346.1345, found 346.1349; ν_{max} cm^{-1} (nujol mull) 2216 (C≡N); δ_H (400 MHz, DMSO-d_6 60 °C) 7.31−7.64 (m, 13H, H-7 to H-9, H-2′ to H-4′ and H-2″ to H-4″), 8.06 (d, 1H, *J* = 7.3, H-10), 8.95 (s, 1H, H-6); δ_C (100 MHz, DMSO-d_6, 60 °C) 112.5 (C≡N), 116.3 (C-3), 120.9 (C-2), 121.2 (C-10), 123.1 (C-1), 126.0 (C-10b), 127.6, 127.9, 128.6, 128.7, 129.0, 130.6, 130.8, 132.1 (C-7 to C-9, C-1′ to C-4′ and C-1″ to C-4″ some overlap of signals), 146.1 (C-6).

Synthesis in Water. The product was prepared at 82 °C in water as described for acetonitrile and isolated by direct filtration. Yield 71%.

1,2-Dimethoxycarbonyl-3-cyano-pyrrolo[1,2-*b*]pyridazine (32).[37] A solution of compound **1A** (0.30 g, 2.08 mmol) in acetonitrile (15 mL) was treated with DMAD (1.23 mL, 10.4 mmol) and stirred under reflux for 5 h. After this time the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (4 mL). This was placed onto a flash column of silica gel (ASTM 230−400 mesh) packed with petroleum spirit (bp 40−60 °C)/dichloromethane in the ratio 1:4. The products were eluted with a mixture of petroleum spirit (bp 40−60 °C)/dichloromethane in the ratio of 1:4 up to 19:1 dichloromethane/diethylether with a 2.5% (v/v) changing gradient (0.51 g, 95%): mp 134−136 °C (ethanol); (Found C, 55.4; H, 3.2; N, 15.9; $C_{12}H_9N_3O_4$ requires C, 55.6; H, 3.5; N, 16.2%); ν_{max} (mull)/cm^{-1} 1734, 1693 (C═O), 2232 (C≡N); δ_H (400 MHz, $CDCl_3$) 3.94 (s, 3H, CH_3), 4.03 (s, 3H, CH_3), 7.21 (dd, 1H, *J* = 9.3, 4.4, H-7), 8.53 (dd, 1H, *J* = 4.4, 1.9, H-6), 8.57 (dd, 1H, *J* = 9.3, 1.9, H-8); δ_C (100 MHz, $CDCl_3$) 52.0, 53.0 (CH_3), 102.6 (C-3), 104.7 (C-1), 109.8 (C≡N), 118.5 (C-7), 128.9 (C-8), 145.8 (C-6), 161.8, 162.0 (C═O).

Synthesis in Water. The reaction using water as the reaction medium was stirred at 82 °C for 5 h. The reaction was cooled, and the compound precipitated from solution and was collected by suction filtration. Yield: 89%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Examples of the typical NOEDS enhancements observed for both *endo*- and *exo*-isomers. ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: r.debuitleir@nuigalway.ie; agc40@cam.ac.uk.

Notes

The authors declare no competing financial interest.

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(30) (a) A referee has suggested that this comment is unwarranted because when there is an excess of insoluble methyl vinyl ketone it will dissolve in the cyclopentadiene layer and give a neat reaction for which no catalysis is required. The reaction would be highly exothermic, and indeed the temperature of this neat reaction mixture has been measured approaching 90 °C, and higher temperatures tend to favour the thermodynamic *exo*-isomer.[30b] We are happy to state the referees point of view. Our view is that once the excess of water insoluble methyl vinyl ketone dissolves in the cyclopentadiene, which *is in contact with a water layer*, the conditions for an on-water reaction are present, and on-water catalysis will occur irrespective of whether it is necessary or not, and all the more because methyl vinyl ketone is a strong H-bond acceptor. (b) Windmon, N.; Dragojlovic, V. *Green Chem. Lett.* **2008**, *1*, 155−163.
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