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The Photochemistry of α-Azidocinnamates - A Reinvestigation#

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Abstract: α-Azidocinnamates have been reported elsewhere to yield one diastereomer of a trimer in a stepwise and efficient manner by photolysis using quartz equipment.[1] We find that use of pyrex filters or ketone sensitisation instead of quartz leads to high yields of the presumed intermediate diastereomeric pair of aziridinoimidazoline dimers, as does brief irradiation in quartz. These dimers have been characterised by spectral and crystallographic methods, and shown to oxidise with DDQ to give imidazoledicarboxylic esters, while the action of base on both dimer diastereomers leads to one rearranged dimer, a 1,2-dihydropyrimidine. Surprisingly, only a mixture of both diastereomeric dimers gives the trimer on further photolysis.

INTRODUCTION

The photolysis of α-azidoalkenes (e.g. **1**) have been thoroughly examined, and shown to yield azirines **2** and products therefrom[2]. In the case of α-azidocinnamates **1**, the reaction has been studied by Hickey, Moody and Rees[1] who showed that the reaction efficiently lead by way of the (presumed) dimers **3** to one diastereomer of the trimers **4**. They confirmed the structure and stereochemistry of the trimers by X-ray crystallography, unravelled the mechanism and showed that the reaction was quite general (Scheme 1).

The photolysis was conducted in quartz equipment in a 4-bulb Rayonet apparatus and we corroborated the process (although not always the yields) in several cases. The key steps are: (1) Azide **1** conversion into azirine **2**, a well documented reaction[2]; (2) photo-activated azirine ring-opening by C-C bond cleavage to give an azomethine ylide, also well documented[3]; (3) [4+2]cycloaddition of this 1,3-dipole to another molecule of azirine to give the non-isolated dimers **3**; (4) photo-ring-opening of the aziridine ring of the dimer to give another 1,3-dipole and finally (5) cycloaddition of a second molecule of azirine to this new dipole to yield the trimer **4**.

Dedicated to my friend, the tireless polymath, Alan R. Katritzky on his 70th birthday

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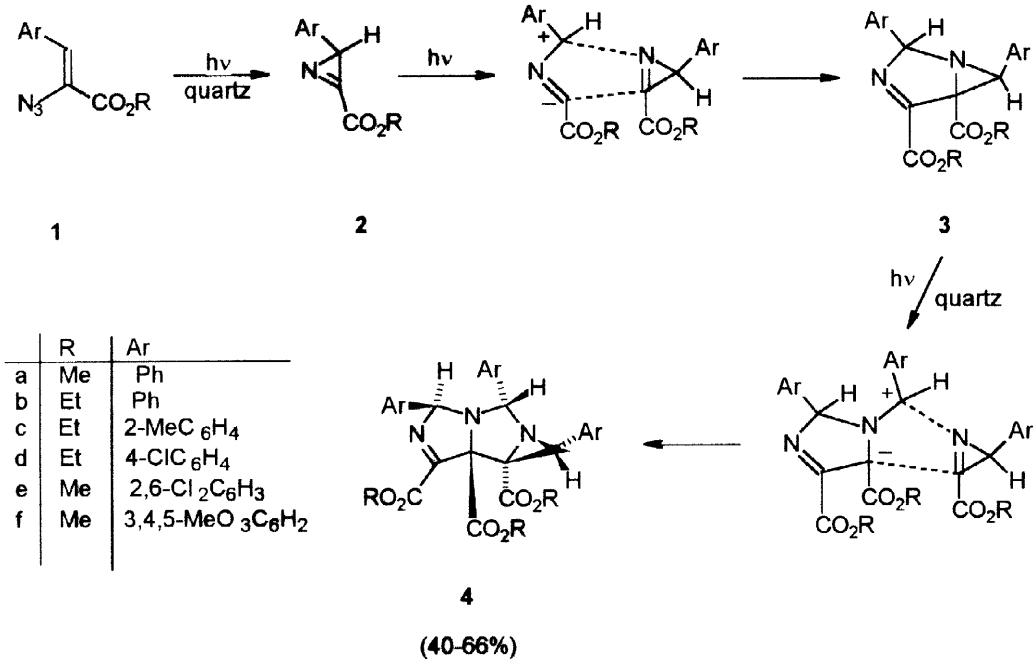


	R	Ar
a	Me	Ph
b	Et	Ph
c	Et	2-MeC $_6$H$_4$
d	Et	4-ClC $_6$H$_4$
e	Me	2,6-Cl $_2$C$_6$H$_3$
f	Me	3,4,5-MeO $_3$C$_6$H$_2$

Scheme 1

During studies of triplet-sensitised photolyses we re-examined the photolysis of various α–azidocinnamates in acetone solution with a view to observing alternative chemistry, mediated by radical pathways. This possibility was spurred particularly by the observation of Rees *et al* [4] that thermolysis of *o*-methylazidocinnamates in the presence of iodine (a 'heavy-atom' singlet-to-triplet nitrene converter) gave isoquinolines, presumably by triplet nitrene 'insertion' into the tolyl methyl group. (See Scheme 5 and later text).

RESULTS AND DISCUSSION

To our surprise, photolysis of the various α–azidocinnamates in acetone solution resulted in a rapid and clean reaction to give a mixture of two isomeric dimers, generally in good yield, which we herein show conclusively to be the intermediates **3** predicted by Rees and co-workers[1]. More surprisingly, the same products formed when a *non-sensitised* photolysis was conducted in *pyrex* equipment, either using the Rayonet reactor or more effectively using our novel simple, cheap and efficient reactor using a flat-topped pyrex flask with a water/air cooled jacket, illuminated with a 300 watt Osram ultra-vitalux lamp. Indeed even in quartz apparatus, the dimers **3** were easily isolated and only slowly transformed into the trimers **4** (Table 1).

The dimers were always isolated as a pair of separable diastereomers **3A** and **3B**, usually formed in similar amounts, the structures of which were easily assigned by difference n.O.e. showing the two aliphatic CH's interacting in **3A** but not in **3B**. Furthermore, their classification was easily achieved since the lower field aliphatic CH-resonance in **3A** was always in the range of 6.1-6.3 ppm while that of **3B** was at 6.8-7.1 ppm

Table 1 Products from the photolysis of azidocinnamates 1

Entry	Cpd	Solvent#	Filter*	Time (h)	Temp. °C	Products (%) 3A	3B	4	7	2
1	**1a**	P	Py	1	13	30	35	5	-	-
2	**1a**	A	Py	1	21	34	28	-	-	-
3	**1a**	P	Py	5.5@	28	28	42	5	-	-
4	**1a**	P	Q	1	29	20	27	27	-	-
5	**1a**	A	Q	0.5	28	43	26	11	6	-
6	**1a**	P/A-12:1	Q	1	30	34	41	19	-	-
7	**1a**	P/A-12:1	Q	2	30	30	30	30	-	-
8	**1a**	P/A-12:1	Q	3	30	25	13	50	-	-
9	**1a**	P/A-12:1	Q	4	30	20	0	60	-	-
10	**1b**	P	Py	1.25	20	32	54	5	-	-
11	**1b**	A	Py	1.25	20	51	36	-	-	-
12	**1b**	P	Q	0.6	45	21	42	21	-	-
13	**1b**	P/A-12:1	Q	1	30	25	38	36	-	-
14	**1b**	P/A-12:1	Q	2	30	11	21	62	-	-
15	**1b**	P/A-12:1	Q	3	30	-	1	87	-	-
16	**1b**	P/A-12:1	Q	4	30	-	87	-	-	-
17	**1c**	A	P	0.5	20	24	48	4	-	-
18	**1d**	P	P	1.5	20	25✪	14✪	-	-	-
19	**1d**	A	P	5.6	20	38	19	-	-	-
20	**1e**	P	P	1.5	20	-	37	-	-	42
21	**1f**	A	P	1	27	-	-	-	-	99

* P = light petroleum; A = acetone
\# P = pyrex; Q = quartz
@ reaction conducted on 10x scale
✪ also 34% of mixture of **3dA** and **3dB**

(Table 2). In one case (**3Aa**) when crystals formed we corroborated the structure by X-ray crystallography (Figure 1). The dimer **3Aa** shows molecules stacked in columns with no π interactions and only limited intermolecular interaction between H64 and O42. It has a localised double bond [1.275(3) Å] between N3 and C1, with an effectively planar five-membered ring incorporating N1, C2, N3, C1, and C5, with a maximum deviation from planarity of 0.0137Å. The two phenyl rings and the CO_2Me substituent are twisted out of plane by over 60^0, making for little conjugation.

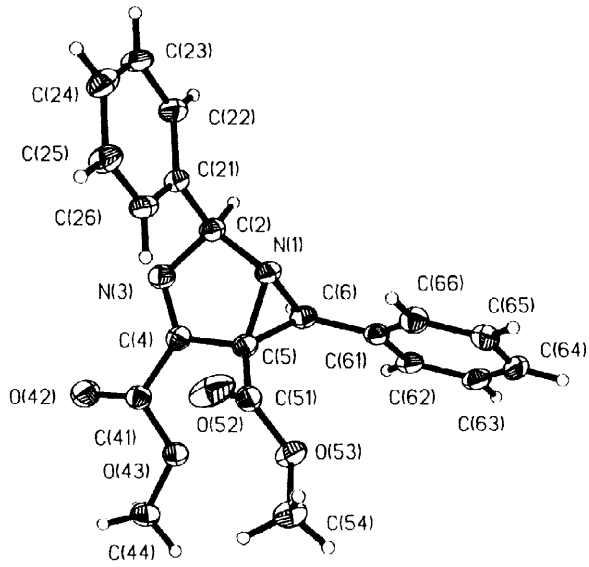
Several questions need addressing:

(1) What is the role of the solvent and the quartz/pyrex glassware?

(2) Can we learn anything from the subsequent chemistry of the dimers?

(3) Why is only one stereomer of the trimer isolated often in good yield, on quartz mediated photolysis, despite two dimers being precursors?

(4) How and why do both dimers give the one trimer?



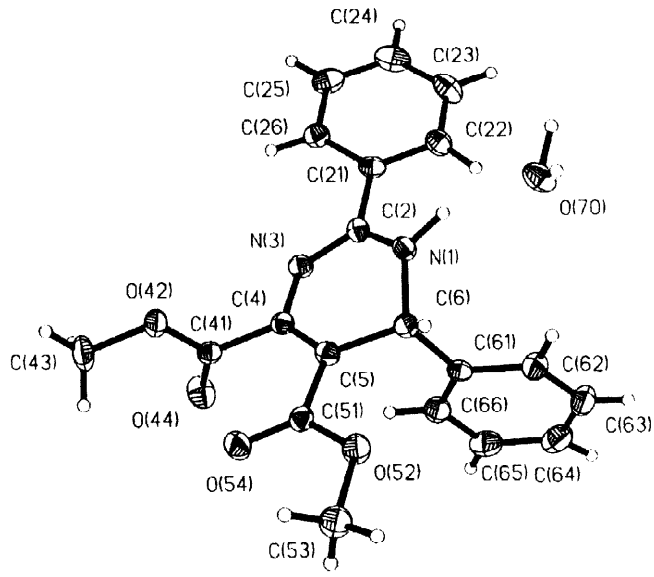
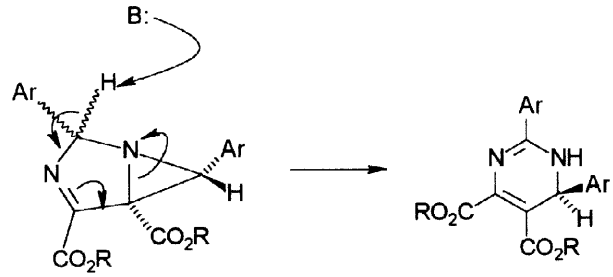


Figure 1 X-ray crystallography of compound 3Aa **Figure 2 X-ray crystallography of compound 5**

The first question is easily addressed. It is evident that ring-opening of an azirine occurs with lower energy (higher wavelength) light than that required for aziridine ring-opening[5]. This latter process therefore does not occur when acetone or pyrex filters are used in the photolysis. The fact that the azirine ring-opening may involve radical species in the sensitised cases appears not to alter the reaction pathway of subsequent cycloadditions. The similarity of dimer yields despite solvent and glassware changes suggest a common mechanism operates in all the photolyses.

The dimers show several novel aspects of further chemistry. They are not indefinitely stable but slowly change in solution even in the dark, the methyl esters reacting faster than the ethyl. The rate of this process is dramatically increased by added base but not by acid, suggesting that the basicity of the dimers cause autocatalytic rearrangement. Albeit, the mixture of diastereomers gave one rearranged isomer from this action, which proved to be the dihydropyrimidine **5** (Scheme 2).

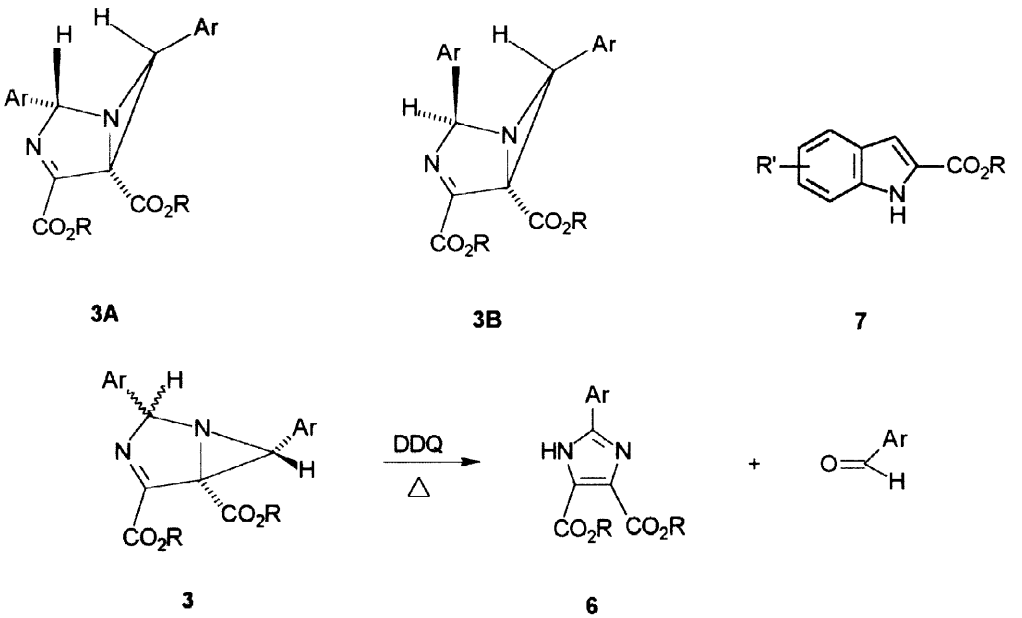


3 **5**

Scheme 2

This is a new type of rearrangement of such bicyclic systems and the structure of the rearranged dimer **5** was corroborated by X-ray crystallography (Figure 2). The structure contains co-crystallised H_2O, which interacts between O70···H1 (1.925Å), N3···H70A (2.084Å) and O54···H70B (1.837Å), creating layers of molecules.

We also studied the oxidative treatment of the isolated dimers **3A** and **3B** and of the mixture of both diastereomers. With DDQ, conversion of the dimers into a mixture of an aryl aldehyde and the imidazole **6** was observed. The structure of the imidazoles was confirmed by an alternative literature-based synthesis from tartaric acid[6] (Scheme 3).

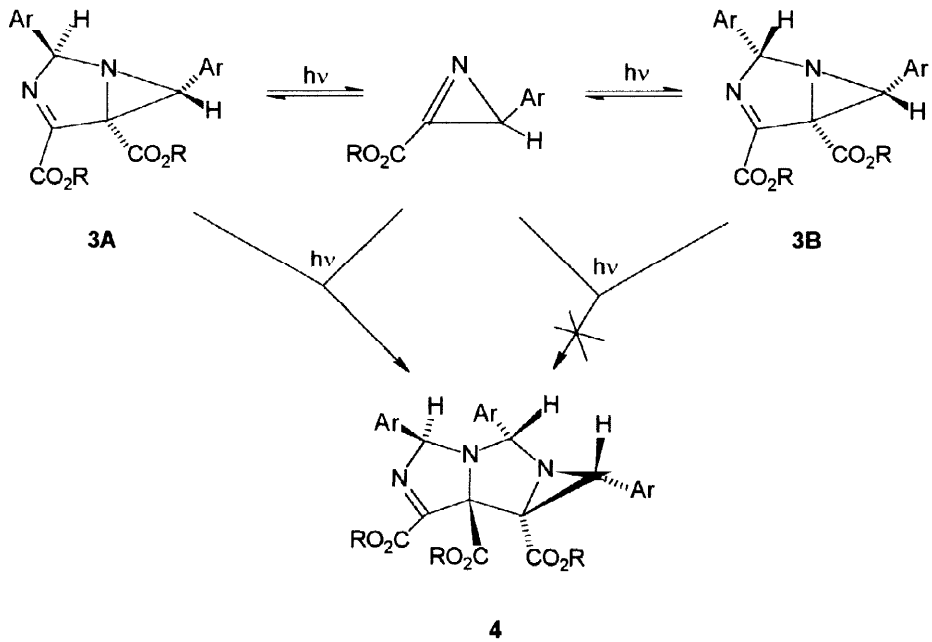


Scheme 3

In order to clarify further the mechanism of the photoreactions several experiments were conducted. Photolysis of various substituted α-azidocinnamates **1** proved instructive. Substituents in the phenyl ring which cause a bathochromic shift of the aryl UV absorption tend to allow the photolysis of the azide to be intercepted at the azirine stage. Thus the 3,4,5-trimethoxy- derivative **1f** gave solely the postulated intermediary azirine **2f** (Table 1, entry 21). Furthermore the 2,6-dichloro-derivative **1e** (Table 1, entry 20)could be taken through the whole process in a stepwise manner. Short photolysis in pyrex gave the azirine **2e** while longer reaction time gave the corresponding dimers **3Ae** and **3Be** in high overall yield. Clearly, in cases where the aryl chromophore absorbs most of the irradiation, chemistry at the azirine centre slows or stops.

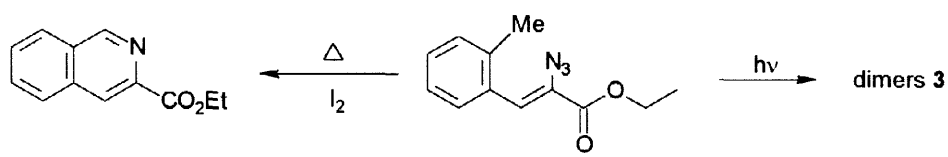
As mentioned earlier, when an ethyl or methyl azidocinnamate is photolysed in quartz equipment and monitored continually by NMR spectroscopy, firstly both dimers **3** are formed, to be slowly and totally replaced by the one trimer, **4**. When the mixture of dimers **3a** is further photolysed using *quartz* equipment a slow conversion into the trimer **4a** is observed, with complete consumption of the major dimer **3B** but only

partial utilisation of the isomer **3A**. The ratio of the two dimers and trimer [**3Aa:3Ba:4a**] after 1, 2, 3 and 4 hours changes from 34:41:19 to 30:30:30, 25:13:50 and finally to 20:0:60 (Table 1, entries 6-9). Again, only one stereomer of the trimer forms. Indeed, irradiation of either pure dimer gives no trimer, but slowly leads to decomposition of the dimer. *Only a mixture of both dimers gives the trimer*. A similar process is observed with the ethyl ester **1b**, which after 3 hours irradiation is essentially completely converted to trimer **4b** in 87% yield with virtually complete consumption of both dimers (Table 1, entries 13-16). While both dimers will be in photoequilibrium with the parent azirine **2** it appears that one of the dimers ring-opens considerably more readily than the other, and that the other or more likely, both are a source of the azirine **2** (Scheme 4). The stereochemistry of the resulting trimer indicates that the least congested dimer **3A** ring opens to give the new 1,3-dipole that is trapped by the regenerated azirine **2**.



Scheme 4

The 2-methylphenyl-derivative **1c** gave solely the expected dimers **3c** with no sign of triplet nitrene attack of the methyl group which would give an isoquinoline, a reaction observed during the thermolysis of the same azide in the presence of iodine, a 'heavy-atom-triplet' forming system (Scheme 5)[4]. This again suggests that the acetone used as solvent in our photolyses is acting more as a filter of short wavelength light than as a triplet sensistiser/radical mediator and that ionic dipoles are involved in the subsequent cycloaddition chemistry.



Scheme 5

To summarise, we conclude that the photolysis of α-azidocinnamates **1** is wavelength dependent even in a triplet sensitising solvent such as acetone. All wavelengths transform the azides into the azirines **2** which form dimers (aziridino[1,2-b]imidazolines) **3** at any wavelength of irradiation. These dimers are in photo-equilibrium with the precursor azirines **2** and when low wavelength light is utilised the aziridine ring of the dimers **3** ring opens by C-C bond breakage. One isomer, probably **3A**, ring opens faster than the other and the resultant 1,3-dipole cycloadds to the azirine **2** uniquely to give one trimer **4**. The dimers **3** yield imidazoles **6** with DDQ and a 3,4-dihydropyrimidine **5** with base.

EXPERIMENTAL

Melting points, which are uncorrected, were determined using a Reichert Kofler hot-stage apparatus. Infrared spectra were obtained on a Unicam Research Series 1 FTIR instrument as KBr discs or liquid films. NMR spectra were recorded in $CDCl_3$ or d_6-DMSO solution with $SiMe_4$ as internal standard on a JEOL spectrometer. Chemical shifts are reported in ppm while the coupling constant J values are in Hz. Mass spectra were measured on a Kratos MS8ORF mass spectrometer (using EI) and microanalyses were carried out at Newcastle University. Single-crystal X-ray diffraction experiments on compounds **3Aa** and **5** were carried out at room temperature on a Siemens SMART CCD diffractometer (graphite-monochromated Mo-Kα Xradiation λ = 0.71073 Å). The structures were solved by direct methods (SHELXS-93 programs)[7] and refined by full-matrix least squares against F^2 of all reflections (SHELXL-93).[8] Non-hydrogen atoms were refined with anisotropic normal parameters; all H atoms were refined in an isotropic approximation and treated as "riding". Crystal data for **3Aa**: Monoclinic, Space Group $P2_1/c$, a = 9.545 (2), b = 18.187 (2), c = 10.449 (4) Å, β = 105.93(3)^0, D_c = 1.334 mg/m^{-3}, μ(Mo-Kα) = 0.094 mm^{-1}, θ (range) 2.22 to 28.32 deg., F(000) = 736, R_{int} = 0.13, ω$R(F^2)$ = 0.206 for all data and R(F) = 0.0713 for I>2σ(I), Goof = 1.166, difference Fourier, max +0.37, min -0.35 e.Å^{-3}, extinction coef. = 0.004 (2). Crystal data for **5**: Monoclinic, Space Group Cc, a = 13.892 (3), b = 17.649 > (4), c = 8.227 (2), β = 115.21(3), D_c = 1.341 mg/m^{-3}, μ(Mo-Kα) = 0.097 mm^{-1}, θ (range) 1.99 to 25.36^0 F(000) = 776, R_{int} = 0.0435, ω$R(F^2)$ = 0.129 for all data and R(F) = 0.0445 for > I>2σ(I), Goof = 1.071 difference Fourier, max +0.19, min -0.17 e.Å^{-3}, extinction coef. = 0.003 (2).

Thin layer chromatography (TLC) was performed with Merck silica $60F_{254}$ plates and Janssen silica (35-70 μm) was used for flash chromatography. Petrol refers to light petroleum of b.p. 60-80 °C. Azidocinnamates were made according to literature methods.[2] Photolyses were conducted under nitrogen using either the 'flathead' flask as described above with water cooling or in a Rayonet apparatus as described by Rees and co-workers[1]. In both cases the progress of the reaction was monitored by TLC.

General method for the photolyses of α-azidocinnamates

The photolyses were performed under conditions of solvent, time, temperature and wavelength as shown in Table 1 and the solvent then removed on a rotary evaporator. The yellow oil remaining was examined by 1-H NMR spectroscopy and if necessary, purified by flash chromatography, to give the products shown in Table 1, the properties of which are recorded in Table 2. The presence of small amounts of the trimers **4** were inferred by reference to the 1-H NMR spectral details in comparison with the literature data, and with material isolated by use of the conditions reported by Rees and co-workers[1].

Methyl 3-(3,4,5-trimethoxyphenyl)azirin-2-carboxylate (Found: C, 59.0 , H, 5.6, N, 5.3. $C_{20}H_{18}N_2O_4$ requires C, 58.9; H, 5.7; N, 5.3%).

Dimethyl 1,3-diaza-2,6-diphenylbicyclo[3,1,0]hex-3-en-4,5-dicarboxylate 3Aa (Found: C, 68.3 , H, 4.9, N, 7.8. $C_{20}H_{18}N_2O_4$ requires C, 68.55; H, 5.2; N, 8.0%).

General method for the oxidation of the dimers 3 with DDQ

To a solution of the isolated or mixed dimers **3** (0.41 mmol) in dry dioxane (1.5 cm^{-1}) was added DDQ (1.20 g, 0.45 mmol) and the mixture heated to reflux for 18h. The cooled solution was filtered and the solid washed with chloroform. The combined filtrate was evaporated and flash chromatographed using ethyl acetate and dichloromethane to give the following products:

Dimethyl 2-phenylimidazole-4,5-dicarboxylate 6a (40%) as colourless needles from aqueous ethanol, m.p. 157-158 °C (lit.[9] m.p. 157-160 °C) ν_{max} (KBr) 3270, 1725, 1685cm^{-1}; δ_H ($CDCl_3$) 3.95 (6H, s,

Table 2 Properties of the azirines 2 and dimers 3A and 3B

Cpd	M.p. ^0C	Infrared ν_{max} cm^{-1}	δ_H ($CDCl_3$)	δ_C ($CDCl_3$)	m/z calc	m/z found
2f	66-68	1749, 1712	3.42 (1H, s, CH), 3.83 (3H, s, Me), 3.84 (6H, s, Me), 4.03 (3H, s, Me), 6.33 (2H, s, Ar H's)	30.9, 39.0, 53.7, 56.1, 60.8, 103.4, 133.8, 138.2, 153.4, 159.1, 163.2		
3Aa	88-90	1739, 1721	3.15 (1H, s, CH), 3.58 (3H, s, Me), 3.96 (3H, s, Me), 6.20 (1H, s, CH), 7.29-7.59 (10H, m, Ar H's)	52.5, 53.2, 54.6, 98.1, 126.3, 126.9, 127.8, 129.0, 133.5, 138.5, 161.6, 162.1, 165.1		
3Ba	oil	1740, 1729	3.01 (1H, s, CH), 3.55 (3H, s, Me), 4.01 (3H, s, Me), 6.91 (1H, s, CH), 7.21-7.61 (10H, m, Ar H's)		350.1276	350.1278
3Ab	oil	1739, 1721	0.98 (3H, t, J 7.3, Me), 1.40 (3H, t, J 7.3, Me), 3.15 (1H, s, CH), 4.03 (2H, m, CH_2), 4.42 (2H, m, CH_2), 6.19 (1H, s, CH), 7.31-7.59 (10H, m, Ar H's)		378.1580	378.1582
3Bb	oil	1740, 1729	0.96 (3H, t, J 7.3, Me), 1.44 (3H, t, J 7.3, Me), 3.03 (1H, s, CH), 4.02 (2H, m, CH_2), 4.99 (2H, m, CH_2), 6.91 (1H, s, CH), 7.89-7.50 (10H, m, Ar H's)		378.1580	378.1578
3Ac	oil	1752, 1722	0.91 (3H, t, J 6.8, Me), 1.45 (3H, t, J 7.3, Me), 2.43 (3H, s, Me),), 2.60 (3H, s, Me), 3.19 (1H, s, CH), 3.96 (2H, m, CH_2), 4.45 (2H, m, CH_2), 6.32 (1H, s, CH), 7.17-7.59 (8H, m, Ar H's)		406.1893	406.1893
3Bc	oil	1754, 1724	0.91 (3H, t, J 7.0, Me), 1.45 (3H, t, J 7.0, Me), 2.32 (3H, s, Me),), 2.75 (3H, s, Me), 2.96 (1H, s, CH), 3.98 (2H, m, CH_2), 4.43 (2H, m, CH_2), 6.91 (1H, s, CH), 6.95-7.40 (8H, m, Ar H's)		406.1893	406.1891
3Ad	oil	1743, 1727	1.01 (3H, t, J 7.3, Me), 1.38 (3H, t, J 7.3, Me), 3.09 (1H, s, CH), 4.04 (2H, q, J 7.3, CH_2), 4.41 (2H, q, J 7.3, CH_2), 6.14 (1H, s, CH), 7.29-7.51 (8H, m, Ar H's)		446.0800	446.0803
3Bd	oil	1743, 1727	1.03 (3H, t, J 7.3, Me), 1.44 (3H, t, J 7.3, Me), 2.88 (1H, s, CH), 4.06 (2H, m, CH_2), 4.47 (2H, m, CH_2), 6.84 (1H, s, CH), 7.26-7.46 (8H, m, Ar H's)		446.0800	446.0799
3Ae	oil	1745, 1727	3.10 (1H, s, CH), 3.59 (3H, s, Me), 3.96 (3H, s, Me), 6.17 (1H, s, CH), 7.25-7.75 (6H, m, Ar H's)		485.9708	485.9709
3Be	125-127	1746, 1725	3.34 (1H, s, CH), 3.60 (3H, s, Me), 4.04 (3H, s, Me), 7.09 (1H, s, CH), 7.23-7.30 (6H, m, Ar H's)	48.8, 52.7, 53.3, 65.6, 95.6, 128.3, 128.5, 129.0, 129.3, 131.3, 134.3, 134.4, 134.5, 161.7, 163.95, 164.7	485.9708	485.9709

Me's), 7.46 (3H, m, Ar H's), 7.97 (2H, m, Ar H's), 10.90 (1H, b, NH); δ_C ($CDCl_3$) 52.5, 77.3, 126.3, 128.0, 128.9, 130.4, 148.9, 160.7, 163.2; m/z 260 (M^+).

Also isolated was benzaldehyde (25%).

Diethyl 2-phenylimidazole-4,5-dicarboxylate 6b (40%) as colourless needles from aqueous ethanol, m.p. 190 ^{0}C. (Lit[10] m.p. 190 ^{0}C) ν_{max} (KBr) 3424, 1737, 1718cm^{-1}; δ_H ($CDCl_3$) 1.39 (6H, t, J 7.3, Me's), 4.42 (4H, m, CH_2's), 7.44 (3H, m, Ar H's), 7.97 (2H, m, Ar H's), 10.48 (1H, b, NH); δ_C ($CDCl_3$) 14.2, 61.8, 77.2, 126.3, 128.1, 128.9, 130.3, 147.9, 159.4, 162.5. m/z 288 (M^+).

Also isolated was benzaldehyde (14%).

Diethyl 2-(4-chlorophenyl)imidazole-4,5-dicarboxylate 6d This reaction was conducted on the separated dimers **3Ad** and **3Bd** to give respectively 4-chlorobenzaldehyde (21% and 57%), and the *title product* (35 and 41%) as colourless needles from aqueous ethanol, m.p. 128-131 ^{0}C. (Found: C, 55.8 , H, 4.4, N, 8.5. $C_{15}H_{16}N_2O_4$ requires C, 55.8; H, 4.7; N, 8.7%). ν_{max} (KBr) 3297, 1749, 1691cm^{-1}; δ_H ($CDCl_3$) 1.40 (6H, t, J 6.9, Me's), 4.43 (4H, m, CH_2's), 7.43 (2H, d, J 8.1, Ar H's), 7.91 (2H, d, J 8.1, Ar H's), 10.7 (1H, b, NH); 14.2, 61.6, 62.0, 76.3, 76.5, 126.7, 127.5, 129.3, 136.6, 137.6, 145.7 and 159.3; m\z 324/322 (M^+).

The formation of dimethyl 1,6-dihydro-2,4-diphenylpyrimidin-5,6-dicarboxylate 5

The dimers **3a** (separately or as a mixture) on long storage (8 months) slowly crystallised over the storage period. This process could be conducted within 24h by treating a solution of the dimers in methanol with a few drops of triethylamine followed by evaporation. In both cases the residue was recrystallised from aqueous methanol to give the *title product as a monohydrate* as colourless, chunky needles m.p. 112-113.5 ^{0}C. (Found: C, 65.1, H, 5.5, N, 7.5. $C_{20}H_{20}N_2O_5$ requires C, 65.2; H, 5.5; N, 7.6%). ν_{max} (KBr) 3351, 1724, 1706, 1610, 1498, 1236cm^{-1}; δ_H ($CDCl_3$) 3.64 (3H, s, Me), 3.91(3H, s, Me), 5.65 (1H, s, CH), 6.38 (2H, s, H_2O), 7.29-53 (8H, m, Ar H's), 7.74 (4H, m, Ar H's), 10.90 (1H, b, NH); m/z 350 (M^+).

The synthesis of dimethyl 2-phenylimidazole-4,5-dicarboxylate 6a

The literature method[6] for the synthesis of 2-phenylimidazole-4,5-dicarboxylic acid and its methyl ester from tartaric acid was adapted as follows, giving the title product identical (m.p., mixed m.p. and infrared spectrum) to that described above:

To tartaric acid (3.00g, 20 mmol) was added concentrated nitric acid (69%, 3.5 cm^3) and fuming nitric acid (90%, 9.5 cm^3). The suspension was stirred at ambient temperature while concentrated sulfuric acid ((95-97%, 13 cm^3) was added rapidly dropwise, with a cooling bath to maintain a temperature of about 40 ^{0}C. After completion of the addition the mixture was cooled in an ice-bath, filtered through a cintered Buchner funnel and the precipitate sucked as dry as possible to give crude tartaric acid dinitrate. This solid was added to crushed ice (~40-50g) and cooled to -10 ^{0}C with stirring and neutralised by dropwise addition of ammonium hydroxide (d 0.880, ~10 cm^3) ensuring the temperature was maintained below -5 ^{0}C. A further portion of ammonium hydroxide (6 cm^3) was added followed by freshly distilled benzaldehyde (20 mmol, 2.0 cm^3). The resulting solution was stirred overnight at 0 ^{0}C, carefully neutralised with hydrochloric acid (35%) and the product, 2-phenylimidazole-4,5-dicarboxylic acid, was filtered, washed with water and then ether and dried (2.9g, 53%).

This acid was dissolved in dry methanol (100 cm^3) and hydrogen chloride gas was bubbled into the solution until saturated. The solution was stoppered and set aside in the dark for 21 days, after which the solvent was removed, ice-water (~50 cm^3) added and the clear solution neutralised to pH 9 with aqueous sodium hydroxide keeping the material below 10 ^{0}C in an ice-bath. The product was extracted with dichloromethane, the extract dried ($MgSO_4$) and evaporated to give dimethyl 2-phenylimidazole-4,5-dicarboxylate as a solid product which was recrystallised from aqueous ethanol as colourless needles, m.p. 157-8 ^{0}C (lit. m.p. 156-8 ^{0}C).

In a similar manner the diethyl ester was made using ethanol instead of methanol.

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