

2,3,4-Triphenyl-3-azabicyclo[3.2.0]hepta-1,4-diene – Facile Ring-Opening by Electrophiles and Novel Reactions with Dimethyl Acetylenedicarboxylate^[‡]

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A 3-azabicyclo[3.2.0]hepta-1,4-diene with no substituent in the cyclobutene moiety has been prepared for the first time; it undergoes extremely facile electrophilic attack at the β -position to give the ring-opened product, probably by a retro-Friedel–Crafts process. The title compound also undergoes a

novel reaction with dimethyl acetylenedicarboxylate to afford the azepine.

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Introduction

Benzocyclobutene and related compounds, including their heteroanalogues, represent a unique compromise between the thermodynamic stability associated with an aromatic system and the kinetic reactivity of a strained cyclobutene.^[1,2]

Although 3-thiabicyclo[3.2.0]hepta-1,4-diene and its derivatives are relatively well known,^[3,4] the sole example of the corresponding aza-analogue was reported by Garratt et al., who synthesised 6,7-di-*tert*-butyl-3-thiabicyclo[3.2.0]hepta-1,4-diene and its pyrrole and furan analogues through the base-catalysed rearrangement of the corresponding 4-heterohepta-1,6-dienes.^[5] We now report the first synthesis of the title compound with no substituent in the cyclobutene moiety along with the extremely facile ring-opening of **5a** by electrophiles and novel reactions of the title compound with dimethyl acetylenedicarboxylate (DMAD).

Results and Discussion

The 1,3-dipolar cycloaddition between *cis*-1,2,3-triphenylaziridine (*cis*-**1a**) and dimethylcyclobutene-1,2-dicarboxylate (**2**) took place smoothly and stereospecifically to produce the corresponding adduct **3a**,^[6] which was hydrolysed as described before^[7] to give *trans*-2,3,4-triphenyl-3-azabicyclo[3.2.0]heptane-1,5-dicarboxylic acid (*trans*-**4a**) in 69% yield. Hydrolysis was carried out with potassium hydroxide either in aqueous methanol or in aqueous dimethyl sulfoxide (Table 1). The latter conditions,^[7] which have been reported to be effective for hydrolysis of sterically hindered esters, proved to give better results for **3a**. The *trans*-**4a** was successfully subjected to oxidative decarboxylation with lead tetraacetate,^[8] affording the desired compound, 2,3,4-triphenyl-3-azabicyclo[3.2.0]hepta-1,4-diene (**5a**), in 50–60% yields. In our hands, however, this method was not amenable to production of the similar adducts **3b** or **3c**,^[6] from aziridines such as 1-benzyl-2,3-diphenyl-aziridine (**1b**) and 1-cyclohexyl-2-aryl-aziridines (**1c**). No dicarboxylic acid **4c** was obtained under the above conditions, for example, and neither did *cis*- or *trans*-**4b** smoothly undergo decarboxylation (Scheme 1). Furthermore, all attempts to decarboxylate *cis*- and *trans*-**4b** were unsuccessful under conditions either similar to those above or even more forced, presumably due to preferential attack at the benzylic position^[9] (Table 2).

Compound **5a** has an m.p. of 218–219 °C and is stable at room temperature. The methylene protons and carbons are observed at $\delta = 3.41$ (s, ¹H NMR) and $\delta = 27.50$ (¹³C NMR), and the coupling constant (*J*) in the cyclobutene moiety is 140 Hz. This value is comparable to those of

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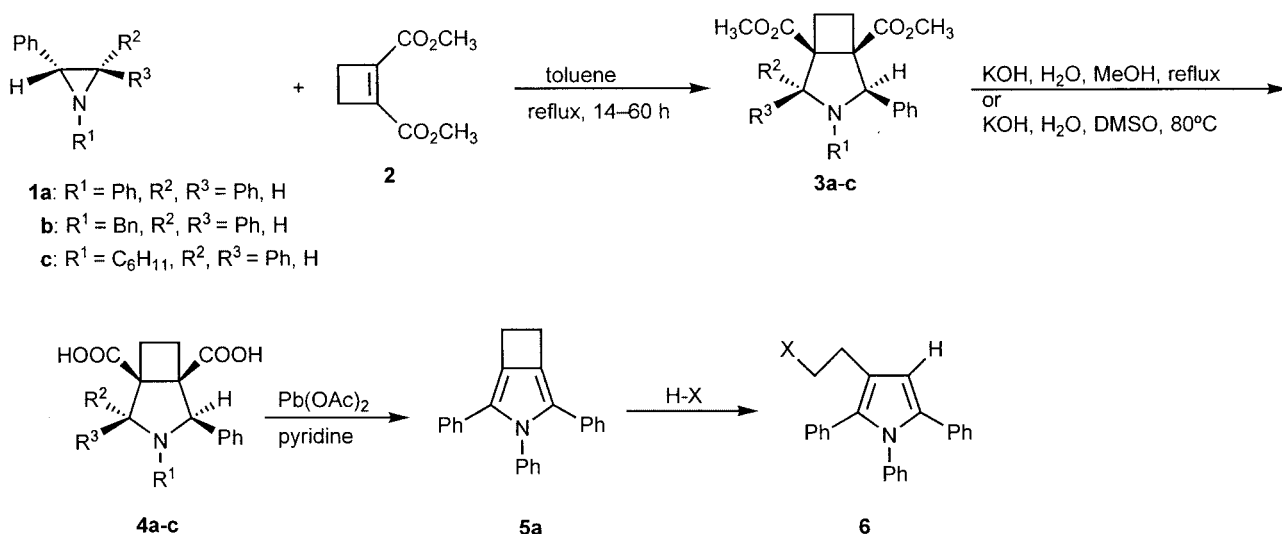
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Table 1. Hydrolysis of diesters **3a–3c**

Entry	Diester	R ¹	3 R ²	R ³	Method	Time (h)	4 Yield (%) ^[a]	4 m.p. (°C)
1	<i>trans</i> - 3a	Ph	Ph	H	A	60	69	221.5–224.0
2	<i>trans</i> - 3a				B	35	95	
3	<i>trans</i> - 3b	Bn	Ph	H	A	138	63	220.0–221.8
4	<i>trans</i> - 3b				B	17	69	
5	<i>cis</i> - 3b	Bn	H	Ph	A	29	0	
6	<i>cis</i> - 3b				B	49	65	239.3–243.0
7	<i>trans</i> - 3c	C ₆ H ₁₁	COPh	H	A	65	0	
8	<i>trans</i> - 3c				B	37	0	

[a] Isolated yields.

Scheme 1. Synthesis of **5a** and ring-opening by electrophilesTable 2. Oxidative decarboxylation of diacids **4** with Pb(OAc)₄

Entry	Diacids	4 R ¹ R ² R ³	Temp. (°C)	Time (h)	5a Yield (%) ^[a]
1	<i>trans</i> - 4a	Ph Ph H	room temp.	3	46
2	<i>trans</i> - 4a		70	3	55
3	<i>trans</i> - 4b	Bn Ph H	70	72	0
4	<i>cis</i> - 4b	Bn H Ph	70	5	0

[a] Isolated yield.

the parent cyclobutene (140 Hz),^[10] benzocyclobutene (138 Hz)^[11] and the heteroanalogues (137–140 Hz).^[3c] A crystal structure of this compound would thus be interesting, but unfortunately all attempts to obtain a crystal suitable for X-ray measurement failed in our hands.

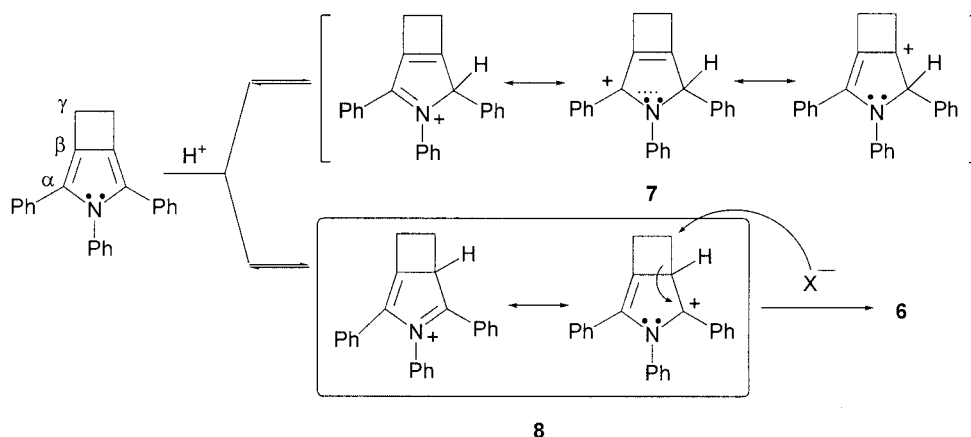
During the workup after decarboxylation of *trans*-2,3,4-triphenyl-3-azabicyclo[3.2.0]heptane-1,5-dicarboxylic acid (**4a**), we found an extremely facile ring-opening of **5a** by electrophiles in the cyclobutene moiety. Thus, treatment of **5a** with 1 N nitric acid in benzene at room temperature afforded the corresponding ester **6a** in quantitative yield. Such conversion took place even in methanol, albeit after 2 weeks at reflux and in only moderate yield. The results

Table 3. Treatment of 2,3,4-triphenyl-3-azabicyclo[3.2.0]hepta-1,4-diene (**5a**) with electrophiles

Entry	Y–X	Temp (°C)	Time	6 Yield (%) ^[a]
1 ^[b]	H–ONO ₂	room temp.	a few min	(6a) quant.
2 ^[b]	H–Cl	room temp.	2.5 h	(6b) quant.
3 ^[b]	H–OAc	room temp.	76 h	(6c) 73
4 ^[c]	H–OCH ₃	reflux	14 d	(6d) 36
5 ^[d]	H–OCH ₃	room temp.	16 h	(6d) quant.
6 ^[e]	Br–Br	room temp.	a few min	(9) quant.

[a] Isolated yields. [b] A suitable amount of 1 N aqueous HX solution in benzene was used. [c] HX was used as solvent. [d] A catalytic amount of 1 N HNO₃ was used. [e] In chloroform.

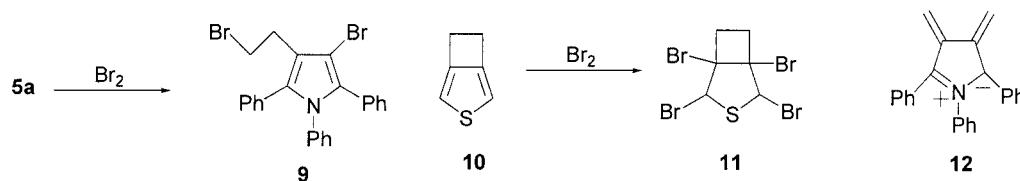
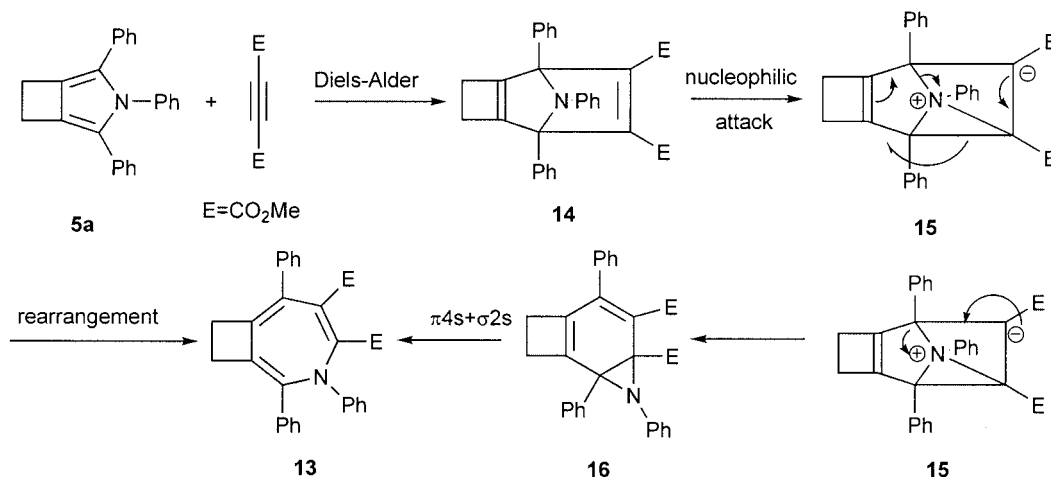
are summarized in Table 3. The reaction can readily be explained in terms of an initial electrophilic addition of a proton to form a nitrogen-stabilized carbocation, which undergoes nucleophilic attack at the γ -position, giving the product **6**. The reaction can formally be regarded as a retro-Friedel–Crafts reaction. The driving force of the reaction must be not only strain of the cyclobutene ring but also the stabilization of the carbocation by the nitrogen atom and the phenyl groups. The higher strain in **7** relative to **8** is apparent from the number of sp²-hybridised carbon atoms

Scheme 2. Mechanism of ring-opening of **5a** by electrophiles

in the four-membered ring (i.e., two such atoms in **7** and only one in **8**), together with i-strain. Although pyrroles usually undergo electrophilic attack at their α -positions, this was not the case here, attack taking place at the β -position, probably because of the unfavourable resonance structure (strained cyclobutene) derived from electrophilic attack at the α -position. Indeed, from semiempirical molecular orbital calculations, the heat of formation of **7** is higher than that of **8**.^[12] In a similar fashion, **5a** readily reacted with bromine to give **9**, whereas the parent 3-thiabicyclo[3.2.0]hepta-1,4-diene **10** was reported to react with bromine to afford the tetrabromide **11** (Scheme 3).^[3b]

Treatment with DMAD was next performed, since we hoped the compound **5a** would serve either as a diene or an azomethine ylide or as both, as shown in structure **12**.

Treatment of **5a** with 1 equiv. of DMAD in 1,2-dichlorobenzene at reflux for 3 h afforded a 1:1 adduct as orange needles in 54% yield. Inspection of the ^1H and ^{13}C NMR spectra confirmed that the compound had retained its cyclobutene ring, but that it was unsymmetrically substituted. An X-ray analysis of this compound established that the compound had the structure **13**, which is also consistent with the NMR spectroscopic data. Photochemical^[13a] and thermal^[13b] formation of analogous but isomeric azepine diesters had been reported from pyrrole and DMAD, and from 3-azaquadricyclane. No thermal formation of an azepine from pyrroles has been reported,^[14,15] although treatment of 1-methylindole with DMAD gave the azepine.^[16] The formation of **13** can be explained in terms of an initial Diels–Alder reaction between **5a** and DMAD to

Scheme 3. Reaction of bromine with **5a** compared with **10**Scheme 4. Plausible mechanism for the formation of the azepine **13** on treatment of **5a** with DMAD

give the adduct **14**, which undergoes an intramolecular nucleophilic attack to form the zwitterionic intermediate **15**, followed by rearrangement. The driving force for this intramolecular nucleophilic attack and subsequent novel rearrangement might be the highly sterically congested nature of the initial adduct.^[17] As a passing note, we initially proposed intervention of a bicyclic aziridine **16** from **15**, but **16** would also be highly energetically (i.e., sterically) unfavourable according to semiempirical molecular orbital calculations.^[17] The calculated values of the kinetic energies of the transition states should in principle be more important, but unfortunately it was not possible, in our hands, to find reasonable transition state structures by the AM1 and PM3 methods (Scheme 4).

Conclusion

In conclusion, since a wide variety of mesoionic compounds^[18] and non-stabilized azomethine ylides^[19] are available, it may be anticipated that this strategy might provide a route to 3-azabicyclo[3.2.0]hepta-1,4-diene systems, which may in turn serve as useful building blocks in organic synthesis.

Experimental Section

Melting points were taken on a Yanagimoto micro melting point apparatus and were uncorrected. The ¹H NMR spectra were measured either on a JEOL JNM-EX270 (270 MHz) or on a JNM-ALPHA500 (500 MHz) instrument. The ¹³C NMR spectra were recorded either on a JNM-EX270 or on a JNM-ALPHA500 pulsed Fourier-transform spectrometer, operating at 67.80 Hz or at 125.65 Hz, respectively. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Either partial proton decoupling or the DEPT method was used to distinguish between individual carbon atoms. Preparative medium-pressure liquid chromatography was carried out on a column (25 × 310 mm) prepacked with silica gel (Lobar, LiChroprep Si60, Merck).

Dimethyl 3-azabicyclo[3.2.0]heptane-1,5-dicarboxylates **3** were previously reported in our paper.^[6]

General Procedure for Hydrolysis of Dimethyl 3-Azabicyclo[3.2.0]heptane-1,5-dicarboxylates (3). **Method A:** A mixture of **3** (2.3 mmol), potassium hydroxide (9.00 mmol, 0.60 g), methanol (15 mL) and water (8 mL) was heated at reflux for 60 h. After the system had cooled, water (6 mL) was added to the solution, which was made acidic with 6 N sulfuric acid. The colourless precipitates were filtered and dried in vacuo, to give almost pure **4**.

Method B: A mixture of **3** (0.29 mmol), potassium hydroxide (1.22 mmol, 0.076 g), DMSO (20 mL) and water (2 mL) was kept at 80 °C in an oil bath for 17 h. The cooled solution was poured into water (500 mL), acidified with 6 N sulfuric acid and extracted with diethyl ether. The organic layer was dried with anhydrous MgSO₄. After evaporation of solvent, the residue was recrystallised from diethyl ether/hexane to give **4** as colourless crystals.

trans-2,3,4-Triphenyl-3-azabicyclo[3.2.0]heptane-1,5-dicarboxylic Acid (trans-4a): M.p. 222–224 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.55–2.19 (m, 4 H), 5.47 (s, 1 H), 5.92 (s, 1 H), 6.43–7.34 (m, 15 H) ppm. ¹³C NMR (67.8 MHz, [D₆]DMSO): δ = 20.0, 28.7, 58.5, 61.0, 68.3, 74.5, 118.1, 119.4, 126.8, 127.0, 127.2, 127.8,

128.1, 129.1, 138.7, 139.1, 145.7, 172.3, 173.8 ppm. C₂₆H₂₃NO₄ (413.5): calcd. C 75.53, H 5.61, N 3.39; found C 75.31, H 5.46, N 3.35.

trans-3-Benzyl-2,4-diphenyl-3-azabicyclo[3.2.0]heptane-1,5-dicarboxylic Acid (trans-4b): M.p. 220–222 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.95–2.60 (4 H), 2.72, 3.70 (dd, *J* = 15.7 Hz, 2 H), 4.23 (s, 1 H), 5.14 (s, 1 H), 7.23–7.94 (m, 15 H) ppm. ¹³C NMR (67.8 MHz, [D₆]DMSO): δ = 18.1, 28.3, 50.1, 56.4, 59.8, 70.5, 71.7, 126.7, 127.3, 127.4, 127.6, 127.9, 128.4, 137.0, 137.5, 138.7, 172.6, 173.5 ppm. C₂₇H₂₅NO₄ (427.5): calcd. C 75.86, H 5.89, N 3.28; found C 75.56, H 6.02, N 3.25.

cis-3-Benzyl-2,4-diphenyl-3-azabicyclo[3.2.0]heptane-1,5-dicarboxylic Acid (cis-4b): M.p. 239–243 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.95–2.60 (m, 4 H), 2.72, 3.70 (dd, *J* = 15.7 Hz, 2 H), 4.23 (s, 1 H), 5.14 (s, 1 H), 7.23–7.94 (m, 15 H) ppm. ¹³C NMR (67.8 MHz, [D₆]DMSO): δ = 18.1, 28.9, 50.1, 56.4, 59.8, 70.5, 71.7, 126.7, 127.3, 127.4, 127.6, 127.9, 128.4, 137.0, 137.5, 138.7, 172.6, 173.5 ppm. C₂₇H₂₅NO₄ (427.5): calcd. C 75.86, H 5.89, N 3.28; found C 75.56, H 6.02, N 3.25.

Preparation of 2,3,4-Triphenyl-3-azabicyclo[3.2.0]hepta-1,4-diene (5a): Lead tetraacetate (0.123 g, 0.250 mmol) was added portionwise under argon, with stirring, to a solution of *trans*-2,3,4-triphenyl-3-azabicyclo[3.2.0]heptane-1,5-dicarboxylic acid (0.050 g, 0.121 mmol) in dry pyridine (2 mL). The mixture was heated to 70 °C for 3 h. After evaporation of the solvent under vacuum, the residue was chromatographed on alumina, eluting with benzene, giving **5a** as white powder in 55% yield (0.021 g, 0.066 mmol). M.p. 218.0–219.0 °C. ¹H NMR (270 MHz, CDCl₃): δ = 3.41 (s, 4 H), 6.92–7.32 (m, 15 H) ppm. ¹³C NMR (68 MHz, CDCl₃): δ = 27.50, 125.45, 126.42, 127.78, 127.92, 128.92, 129.55, 132.54, 140.22 ppm. C₂₄H₁₉N (321.4): calcd. C 89.68, H 5.96, N 4.36; found C 89.65, H 5.87, N 4.33.

Reactions between 5a and Electrophiles

With Nitric Acid: Nitric acid (1 N, 0.1 mL) was added with stirring, at room temp., to a solution of **5a** (0.13 mmol) in dichloromethane (1 mL) for a few min. After evaporation of solvent, pure 2-(1', 2', 5'-triphenyl-3'-pyrrolyl)ethyl nitrate (**6a**) was obtained in quantitative yield. M.p. 156.7–157.1 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.94 (t, *J* = 7.3 Hz 2 H), 4.61 (t, *J* = 7.3 Hz 2 H), 6.42 (s, 1 H), 6.43–7.23 (m, 15 H) ppm. ¹³C NMR (67.8 MHz, CDCl₃): δ = 24.23, 73.59, 110.03, 116.50, 126.29, 126.93, 127.10, 127.92, 128.43, 128.50, 128.73, 130.76, 131.95, 132.81, 133.71, 134.46, 138.74 ppm. C₂₄H₂₀N₂O₃ (384.4): calcd. C 74.98, H 5.24, N 7.28; found C 74.98, H 5.16, N 7.24. MS (*m/z*): 384 [*M*⁺].

With Hydrogen Chloride: Hydrogen chloride (1 N, 0.1 mL) was added at room temp. with stirring to a solution of **5a** (50 mg, 0.13 mmol) in dichloromethane (1 mL). After evaporation of solvent in vacuo, pure 2-(1', 2', 5'-triphenyl-3'-pyrrolyl)ethyl chloride (**6b**) was obtained in quantitative yield as a colourless powder. M.p. 145.2–147.8 °C. ¹H NMR (270 MHz, CDCl₃): δ = 3.00 (t, *J* = 7.6 Hz, 2 H), 3.69 (t, *J* = 7.6 Hz 2 H), 6.43 (s, 1 H), 6.90–7.23 (m, 15 H) ppm. ¹³C NMR (67.8 MHz, CDCl₃): δ = 30.26, 44.93, 110.05, 118.85, 126.16, 126.85, 126.92, 127.84, 127.91, 128.39, 128.46, 128.72, 130.73, 132.11, 132.90, 133.41, 134.18, 138.78 ppm. C₂₄H₂₀ClN (357.9): calcd. C 80.55, H 5.63, N 3.91; found C 80.26, H 5.40, N 3.93.

With Acetic Acid: Acetic acid (0.5 mL) was added with stirring at room temp to a solution of **5a** (23 mg, 0.072 mmol) in dichloromethane (2 mL). After evaporation of solvent under vacuum, pure

2-(1',2',5'-triphenyl-3'-pyrrolyl)ethyl acetate (**6c**) was obtained in 73% yield as a colourless powder. M.p. 165.8–166.5 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.03 (s, 3 H), 2.86 (t, *J* = 7.3 Hz, 2 H), 4.27 (t, *J* = 7.3 Hz, 2 H), 6.43 (1 H, s), 6.92–7.21 (m, 15 H) ppm. ¹³C NMR (67.8 MHz, CDCl₃): δ = 21.04, 25.84, 65.27, 110.30, 118.29, 126.11, 126.77, 127.75, 127.87, 128.41, 128.75, 130.80, 132.29, 133.03, 133.39, 134.16, 138.89, 171.09 ppm. C₂₅H₂₁NO₂ (367.4): calcd. C 81.72, H 5.76, N 3.81; found C 81.55, H 5.69, N 3.90.

With Methanol: A solution of **5a** (20 mg, 0.062 mmol) in methanol (2 mL) was heated at reflux for 2 weeks. After evaporation of solvent, the residue was recrystallised from dichloromethane/hexane to afford 3-(2-methoxyethyl)-1,2,5-triphenylpyrrole (**6d**) as a white powder in 36% yield (10 mg, 0.028 mmol). M.p. 165.5–166.5 °C. ¹H NMR (270 MHz, CDCl₃): δ = 2.82 (t, *J* = 7.3 Hz, 2 H), 3.25 (s, 3 H), 3.63 (t, *J* = 7.3 Hz, 2 H), 6.44 (s, 1 H), 6.91–7.20 (m, 15 H). ¹³C NMR (67.8 MHz, CDCl₃): δ = 26.72, 58.51, 73.57, 110.35, 119.19, 125.97, 126.58, 126.67, 127.66, 127.82, 128.39, 128.75, 130.78, 132.44, 133.15, 134.02, 138.99. C₂₅H₂₃NO (353.5): calcd. C 84.95, H 6.56, N 3.96; found C 84.84, H 6.42, N 4.03.

When the same reaction was performed at room temp. with a catalytic amount of 1 N HNO₃, **6d** was obtained in quantitative yield (see Table 3).

Treatment of 5a with Bromine: A solution of bromine (0.1 mL) in chloroform (1 mL) was added dropwise to a stirred solution of **5a** (30 mg, 0.093 mmol) in chloroform (2.5 mL). Evaporation of the solvent in vacuo gave 2-(1',2',5'-triphenyl-3'-pyrrolyl)ethyl acetate 2-(4'-bromo-1',2',5'-triphenyl-3'-pyrrolyl)ethyl bromide as a white powder. M.p. 196.0–197.0 °C (dec). ¹H NMR (270 MHz, CDCl₃): δ = 3.11 (t, *J* = 7.8 Hz, 2 H), 3.54 (t, *J* = 7.8 Hz, 2 H), 6.84–7.25 (m, 15 H) ppm. ¹³C NMR (67.8 MHz, CDCl₃): δ = 30.01, 31.57, 99.66, 118.99, 127.04, 127.30, 127.53, 127.75, 128.07, 128.41, 128.61, 130.64, 130.89, 131.41, 132.74, 138.20 ppm. C₂₄H₁₉Br₂N (481.2): calcd. C 59.63, H 4.08, N 2.75; found C 59.90, H 3.98, N 2.91.

Treatment of 5a with DMAD: A solution of **5a** (0.034 g, 0.11 mmol) and DMAD (0.12 cm³, 1 mmol) in 1,2-dichlorobenzene (3 mL) was heated at reflux under argon for 3 h. After evaporation of solvent, the residue was chromatographed on silica gel with hexane/ethyl acetate as eluent to give the product, which was recrystallised from ethanol to produce the azepine **13** as orange needles. M.p. 258.3–263.0 °C (dec.). ¹H NMR (270 MHz, CDCl₃): δ = 2.97–3.41 (m, 4 H), 3.55 (s, 3 H), 3.71 (s, 3 H), 6.75–7.87 (m, 15 H) ppm. ¹³C NMR (67.8 MHz, CDCl₃): δ = 29.22, 29.47, 52.31, 52.42, 112.71, 119.01, 119.68, 127.64, 128.05, 128.27, 128.39, 128.63, 128.68, 129.18, 132.29, 134.20, 134.63, 135.98, 142.05, 145.23, 146.51, 151.11, 165.25, 167.30 ppm. C₃₀H₂₅NO₄ (463.5): calcd. C 77.74, H 5.44, N 3.02; found C 77.80, H 5.08, N 2.99.

Crystal Structure Determination for Compound 13: The results were already reported in a preliminary communication.^[1] CCDC-207/142 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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