SPECIAL ISSUE | COMMUNICATION
https://doi.org/10.1071/CH22139
AUSTRALIAN JOURNAL OF CHEMISTRY

Photochemical generation of the 2-azabicyclo[4.2.0]octa-4,7-diene skeleton

Tyler Fahrenhorst-Jones[A], G. Paul Savage[B] and Craig M. Williams[A,*]

For full list of author affiliations and declarations see end of paper

*Correspondence to:
Craig M. Williams
School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, Qld 4072, Australia
Email: c.williams3@uq.edu.au

Handling Editor:
Curt Wentrup

Received: 16 June 2022
Accepted: 19 July 2022
Published: 31 August 2022

Cite this:
Fahrenhorst-Jones T *et al.* (2022)
Australian Journal of Chemistry
75(11), 884–887. doi:10.1071/CH22139

ABSTRACT

A 2-azabicyclo[4.2.0]octa-4,7-diene derivative was unexpectedly isolated from the photochemical irradiation of 2-vinyl-1,2-dihydropyridine. A cascading 6π–8π–4π electrocyclic rearrangement has been proposed as a possible mechanistic pathway.

Keywords: azabicyclo[4.2.0], azaoctadiene, cascade, dihydropyridine, electrocyclisation.

Introduction

The 2-azabicyclo[4.2.0]octadiene system has seldom been described in the literature. In 1971, Acheson and Wright reported the first example of the 2-azabicyclo[4.2.0]octa-3,7-diene skeleton (i.e. **1**), utilising a cycloaddition involving a 1,4-dihydropyridine (**2**) and dimethyl acetylenedicarboxylate (Scheme 1).[1] A year later, Lehman reported a benzo derivative of the 2-azabicyclo[4.2.0]octa-3,7-diene system (i.e. **3**) using the same protocol.[2] However, beyond later work by Acheson *et al.* in the intervening years,[3,4] further contributions to this area have not been forthcoming.

In the course of investigating synthetic routes towards highly strained cage bicyclic systems that contain nitrogen (e.g. **4** and **5**),[5] a functionalised 1,2-dihydropyridine (**6**) was viewed as a logical starting point, because they readily undergo photochemically mediated cyclisation to afford the 2-azabicyclo[2.2.0]hex-5-ene ring system (**7**) (Scheme 1).[6,7] However, introducing extended unsaturation lead to unexpected behaviour, results of which are now disclosed herein.

Results and discussion

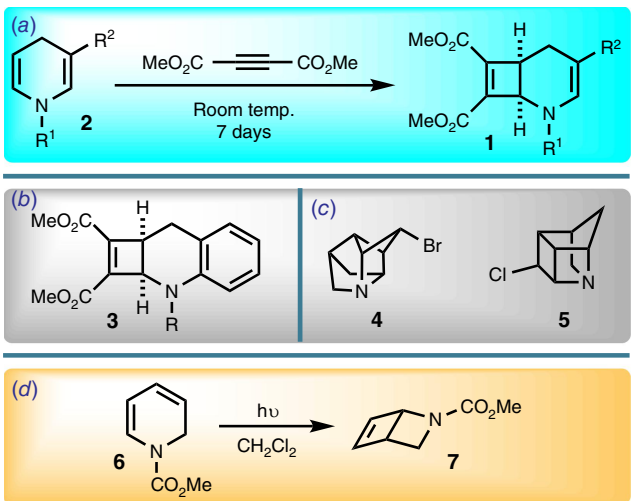
The investigation was initiated by synthesising the known 2-vinyl-1,2-dihydropyridine carbamate **10** (Scheme 2). Following Yamaguchi's procedure,[8] vinyl magnesium bromide (**8**) reacted regioselectively with pyridine (**9**) upon ring activation by an alkyl chloroformate. The 2-vinyl-1,2-dihydropyridine methyl carbamate (**10**) was isolated in 79% yield as a foul-smelling colourless oil, which degraded at room temperature within a day (Scheme 2). It was later discovered that both the methyl- (**10**) and ethyl- (**11**) carbamates, derived from the same procedure, were not stable as neat oils, but could instead be stored as dilute solutions at −20°C for a number of days.

Interestingly, Tsuchiya *et al.* also encountered stability problems with several *N*-alkoxycarbonyl-1,2-dihydropyridine derivatives, and found it was best to handle this system without isolation prior to further transformations.[9] Adopting this method, crude **11** was irradiated at 300 nm in dichloromethane, which afforded the desired 2-azabicyclo[2.2.0]hex-5-ene (**12**), but only in 2% isolated yield. The major product, isolated in 32% yield, was elucidated as the 2-azabicyclo[4.2.0]octa-4,7-diene **13** (Scheme 2).

The unexpected isolation of 2-azabicyclo[4.2.0]octa-4,7-diene (**13**) indicated that introduction of the vinyl group on the dihydropyridine skeleton was promoting a more favourable competing photochemical pathway to that of the desired 2-azabicyclo[2.2.0]hex-5-ene (**12**). Given that 1,2-dihydropyridine carbamates are reported to undergo

6π-electrocyclic ring-opening to 1-azahexatrienes,[10,11] it was reasonable to envisage that the 2-vinyl-1,2-dihydropyridine (**11**) initially formed the corresponding 1-azaoctatetraene (**14**) via a 6π-electrocyclic ring-opening. *E*- to *Z*-isomerisation of the double bond at position 4 (i.e. to give **15**) would then enable an 8π-electrocyclisation to give azacyclooctatriene **16**, which is perfectly placed to undergo a final 4π-electrocyclisation leading to the product (i.e. **13**) (Scheme 3). Such a mechanistic proposition has analogies with the corresponding hydrocarbon octatetraene, which was observed to undergo 8π-electrocyclic ring closure to cyclooctatriene,[12,13] and subsequently proceeded to give bicyclo[4.2.0]octadiene via a 4π electrocyclic ring closure.[12,14]

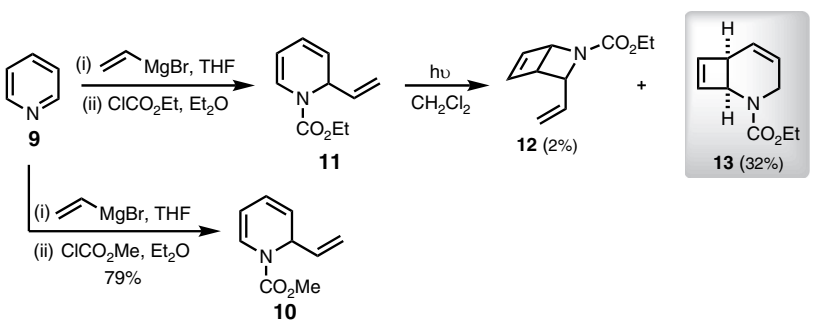
To eliminate the notion of an alternate pathway potentially involving the 3-vinyl-2-azabicyclo[2.2.0]hex-5-ene (**12**), as an intermediate *en route* to **13**, **12** was subjected to repeat photochemical conditions. However, several attempts in a variety of solvents (acetonitrile, toluene, benzene, dichloromethane, and acetone) with and without a photosensitiser (acetone) and at 254 nm, mostly resulted in decomposition. The exception being the isolation of an unstable chlorocyclobutene (**17**) in 8% yield, which was identified subsequent to irradiation of **12** at 254 nm in dichloromethane (Scheme 4). This observation is in line with the reported exposure of 2-azabicyclo[2.2.0]hex-5-ene carbamates to either hydrochloric acid or chloronium ion, which mediates ring-opening to chlorocyclobutenes via heterolysis of the C–N bond.[7,15] That is, during photolysis dichloromethane degraded producing trace amounts of hydrochloric acid leading to protonation of the carbamate (i.e. **18**), and subsequent carbocation formation (i.e. **19**), which is trapped by chloride. Considering that the 4π-electrocyclisation involving 1,2-dihydropyridine has been described as *endo* specific,[16,17] and NOE correlations between the vinyl protons and cyclobutene sp^2 protons confirmed the *endo*-configuration of **12**, the resulting relative stereochemistry of **17** is therefore proposed as shown in Scheme 4.



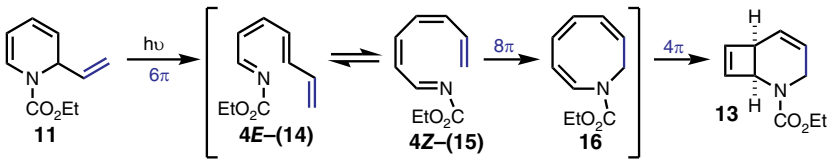
Scheme 1. (*a*, *b*, *d*) Reactions involving dihydropyridines, and (*c*) strained azabicyclic systems.

Conclusion

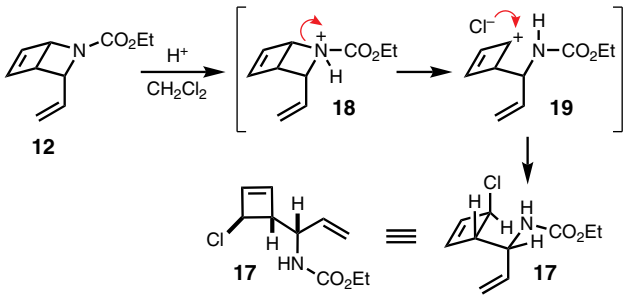
In summary, photolysis of 2-vinyl-1,2-dihydropyridine has afforded the first example of a 2-azabicyclo[4.2.0]octa-4,7-diene, the skeleton of which having only been described previously as a potential reaction intermediate over 40 years ago.[18] At this stage, the proposed mechanism is consistent with the observed products, and literature precedents, but nevertheless remains speculative until further experimentation can rigorously exclude alternative pathways.



Scheme 2. Photochemical synthesis of the cyclobutenes **12** and **13**.



Scheme 3. Proposed electrocyclic mechanism for the formation of **13**.



Scheme 4. Cyclobutene **12** ring opening to **17**.

Experimental

General experimental

Glassware was oven dried (160°C) before use with anhydrous solvents and reagents. Acetonitrile, dichloromethane, benzene, and toluene were freshly distilled to dryness over calcium hydride under an argon atmosphere. Diethyl ether was freshly distilled from elemental sodium/benzophenone under an argon atmosphere. Unless stated otherwise commercially available chemicals were used without further purification. Rayonet (Srinivasen–Griffin) reactors (254 nm or 300 nm) were used for photochemical reactions. NMR spectra were recorded using a Bruker AS500 or AV500 (500, 125 MHz) instruments. Chemical shifts (δ) are reported in parts per million (ppm) and referenced internally according to solvent: DMSO-d_6 (^{1}H δ: 2.50 ppm, ^{13}C δ: 39.5 ppm). The following abbreviations are used to report multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution electrospray mass spectrometry (HRMS-ESI) measurements were obtained on Bruker MicroOTOF-Q spectrometer or Orbitrap Elite mass spectrometer instruments. Flash column chromatography was undertaken using basic ~150 mesh Brockmann I activated aluminium oxide. TLC was performed with neutral aluminium oxide plates (alumina oxide 60 F_{254}). Fractions were initially visualised using UV irradiation and subsequently by heating TLC plates exposed to phosphomolybdic acid stain.

Experimental procedures

Methyl 2-vinylpyridine-1-(2*H*)-carboxylate (10)

Following the procedure of Yamaguchi *et al.*[8]: anhydrous pyridine (**9**) (135 µL, 1.68 mmol) was cooled to −15°C and a tetrahydrofuran solution of vinyl magnesium bromide (**8**) (1.0 M, 3.3 mL) was added to the stirring solution under an argon atmosphere. Methyl chloroformate (170 µL, 1.75 mmol) was then added slowly such that the reaction temperature did not exceed 0°C. The mixture was stirred for 5 h at −5°C, and at room temperature for 20 min. The solution was subsequently added to an ice cooled aqueous solution of ammonium chloride (1.0 M, 20 mL) in a separatory funnel and shaken vigorously. After extracting with diethyl ether (4 × 10 mL), the combined organic phases were washed with water (4 × 10 mL), and brine (1 × 10 mL), before being dried over sodium sulfate. The solvent was removed *in vacuo* and the crude oil was purified using basic alumina column chromatography (dichloromethane) to give **10** (219 mg, 79%) as a foul-smelling colourless oil. [**Note**: Product may be stored at −20°C for 48 h in diethyl ether before degradation starts to occur.] **^{1}H-NMR** (300 MHz, DMSO-d_6) δ: 6.70–6.68 (m, 1H), 6.00–5.94 (m, 1H), 5.78–5.67 (m, 1H), 5.63–5.58 (m, 1H), 5.29 (br, 1H), 5.15 (br, 1H), 5.09–4.99 (m, 2H), 3.71 (s, 3H). Data reported are consistent with that of Yamaguchi *et al.*[8]

Ethyl *endo*-3-vinyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (12) and ethyl 2-azabicyclo[4.2.0]octa-4,7-diene-2-carboxylate (13)

Adapted from the procedure of Kurita *et al.*[9]: anhydrous pyridine (**9**) (5.37 mL, 66.6 mmol) was chilled to −15°C and a tetrahydrofuran solution of vinyl magnesium bromide (**8**) (1.0 M, 72 mL) was added to the stirring solution under an argon atmosphere. A diethyl ether solution (7 mL) of ethyl chloroformate (6.36 mL, 66.8 mmol) was then added dropwise such that the reaction temperature did not exceed 0°C. The mixture was then stirred for 5 h at −5°C and at room temperature for 20 min. The solution was subsequently added to an ice cooled aqueous solution of ammonium chloride (1.0 M, 200 mL) in a separatory funnel and shaken vigorously. Following extraction with diethyl ether (4 × 60 mL), the combined organic layers were washed with water (4 × 60 mL), and brine (1 × 60 mL), before being dried over sodium sulfate and concentrated *in vacuo* to approximately a 20 mL solution. The crude solution was added to anhydrous dichloromethane (80 mL) in a pyrex vessel flushed with argon, and irradiated in a Rayonet (Srinivasen–Griffin) photochemical reactor equipped with 300 nm lamps for 46 h. The solution was then concentrated *in vacuo* and purified via basic alumina column chromatography (50% diethyl ether/hexanes v/v) to give **12** (253 mg, 2%) and **13** (3.85 g, 32%) as yellow oils. **12** – **^{1}H-NMR** (500 MHz, DMSO-d_6) δ: 6.54 (t, J = 2.4 Hz, 1H), 6.37 (t, J = 2.8 Hz, 1H), 5.81 (ddd, J = 17.0, 10.5, 6.6 Hz, 1H), 5.16–5.12 (m, 2H), 4.73 (br, 1H), 4.60 (br, 1H), 4.00–3.96 (m, 2H), 3.64–3.62 (m, 1H), 1.16–1.10 (m, 3H); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ (only one rotamer reported): 155.9, 141.7, 141.5, 135.4, 117.0, 63.3, 60.8, 60.1, 43.1, 14.7; **HRMS-ESI** calcd for $C_{10}H_{13}NO_2H^+$ $([M + H])^+$: 180.1020; found: 180.1021. **13** – **^{1}H-NMR** (500 MHz, DMSO-d_6) δ: 6.20–6.19 (m, 1H), 6.13 (br, 1H), 5.97–5.94 (m, 1H), 5.78 (br, 1H), 4.97–4.93 (m, 1H), 4.18–4.13 (m, 1H), 4.05 (q, J = 6.6 Hz, 2H), 3.57–3.55 (m, 1H), 3.51–3.39 (m, 1H), 1.19 (t, J = 6.8 Hz, 3H); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ: 154.5, 139.4, 136.9, 126.8, 123.8, 60.9, 53.2, 43.0, 39.1, 14.6; **HRMS-ESI** calcd for $C_{10}H_{13}NO_2H^+$ $([M + H])^+$: 180.1020; found: 180.1019.

Ethyl (1-(4-chlorocyclobut-2-en-1-yl)allyl) carbamate (17)

Ethyl *endo*-3-vinyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**12**) (20 mg, 110 μmol) was dissolved in dichloromethane (20 mL) in a quartz vessel flushed with argon and irradiated in a Rayonet (Srinivasen–Griffin) photochemical reactor equipped with 254 nm lamps for 16 h. Following concentration under a stream of nitrogen the residue was purified by basic alumina column chromatography (50% diethyl ether/hexanes v/v) to give **17** (1.9 mg, 8%) as white crystals. **^{1}H-NMR** (500 MHz, DMSO-d_6) δ: 7.36–7.16 (m, 1H), 6.27–6.25 (m, 2H), 5.91–5.78 (m, 1H), 5.17–5.05 (m, 3H), 4.19–3.94 (m, 3H), 3.20–3.17 (m, 1H), 1.17–1.13 (m, 3H); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ: 155.7, 140.7, 138.7, 137.3, 114.8, 59.7, 58.3, 53.4, 55.2, 14.6; **HRMS-ESI** calcd for $C_{10}H_{14}ClNO_2H^+$ $([M + H])^+$: 216.0786, 218.0757; found: 216.0778, 218.0748.

Supplementary material

Copies of ^{1}H, ^{13}C and 2D NMR spectral data (PDF). Supplementary material is available online.

References

[1] Acheson RM, Wright ND. *J Chem Soc D* 1971; 1421–2. doi:10.1039/C29710001421

[2] Lehman PG. *Tetrahedron Lett* 1972; 4863.

[3] Acheson RM, Wright ND, Tasker PA. *J Chem Comm Perkin Trans 1* 1972; 2918. doi:10.1039/P19720002918

[4] Acheson RM, Paglietti G. *J Chem Comm Perkin Trans 1* 1979; 591. doi:10.1039/P19790000591

[5] Fahrenhorst-Jones T, Bernhardt PV, Savage GP, Williams CM. *Org Lett* 2022; 24: 903–6. doi:10.1021/acs.orglett.1c04240

[6] Fowler FW. *J Org Chem* 1972; 37: 1321–3. doi:10.1021/jo00974a009

[7] Beeken P, Bonfiglio JN, Hasan I, Piwinski JJ, Weinstein B, Zollo KA, Fowler FW. *J Am Chem Soc* 1979; 101: 6677–82. doi:10.1021/ja00516a032

[8] Yamaguchi R, Nakazono Y, Matsuki T, Hata E, Kawanisi M. *Bull Chem Soc Jpn* 1987; 60: 215–22. doi:10.1246/bcsj.60.215

[9] Kurita J, Iwata K, Sakai H, Tsuchiya T. *Chem Pharm Bull* 1985; 33: 4572–80. doi:10.1248/cpb.33.4572

[10] Kumagai T, Saito S, Ehara T. *Tetrahedron Lett* 1991; 32: 6895–8. doi:10.1016/0040-4039(91)80437-B

[11] Maynard DF, Okamura WH. *J Org Chem* 1995; 60: 1763–71. doi:10.1021/jo00111a039

[12] Chapman OL, Borden GW, King RW, Winkler B. *J Am Chem Soc* 1964; 86: 2660–3. doi:10.1021/ja01067a029

[13] Thomas BE, Evanseck JD, Houk KN. *J Am Chem Soc* 1993; 115: 4165–9. doi:10.1021/ja00063a039

[14] Grange RL, Gallen MJ, Schill H, Johns JP, Dong L, Parsons PG, Reddell PW, Gordon VA, Bernhardt PV, Williams CM. *Chem Eur J* 2010; 16: 8894–903. doi:10.1002/chem.200903454

[15] Krow GR, Cannon GC. 2-Azabicyclo[2.2.0]hex-5-enes and 2-Azabicyclo[2.2.0]hexanes. A Review. *Heterocycles* 2004; 64: 577. doi:10.3987/REV-04-SR(P)2

[16] Krow GR, Lee YB, Lester WS, Liu N, Yuan J, Duo J, Herzon SB, Nguyen Y, Zacharias D. *J Org Chem* 2001; 66: 1805–10. doi:10.1021/jo0015570

[17] Krow GR, Lin G, Yu F. *J Org Chem* 2005; 70: 590–5. doi:10.1021/jo0484171

[18] (a) Acheson RM, Paglietti G, Tasker PA. *J Chem Soc Perkin Trans 1* 1974; 2496–500. doi:10.1039/P19740002496
(b) Weinstein B, Lin L-CC, Fowler FW. *J Org Chem* 1980; 45: 1657–61. doi:10.1021/jo01297a025

Data availability. The data that support this study are available in the article and accompanying online supplementary material.

Conflicts of interest. The authors declare no conflicts of interest.

Declaration of funding. The Australian Research Council (DP180103004, FT110100851), the University of Queensland (UQ), and the Commonwealth Scientific and Industrial Research Organisation (CSIRO), are gratefully acknowledged for financial support. T. F.-J gratefully acknowledges the Australian Government and UQ for Research Training Program (RTP) and Tuition Fee Offset Scholarships.

Author affiliations

[A]School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, Qld 4072, Australia.

[B]CSIRO Manufacturing, Ian Wark Laboratory, Melbourne, Vic. 3168, Australia.