Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

THE TRAPPING OF 6,6-DIMETHYLISOBENZOFULVENE BY ITS 1,3-DIPOLAR PRECURSOR: A RARE EXAMPLE OF A DIPOLAR [6+4] CYCLOADDITION

Ronald N. Warrener [a], Malcom L. A. Hammond [a] & Douglas N. Butler [a]

[a] Centre for Molecular Architecture, Central Queensland University, Rockhampton, Queensland, 4702, Australia

Published online: 09 Nov 2006.

To cite this article: Ronald N. Warrener, Malcom L. A. Hammond & Douglas N. Butler (2001) THE TRAPPING OF 6,6-DIMETHYLISOBENZOFULVENE BY ITS 1,3-DIPOLAR PRECURSOR: A RARE EXAMPLE OF A DIPOLAR [6+4] CYCLOADDITION, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:8, 1167-1175, DOI: 10.1081/SCC-100104000

To link to this article: http://dx.doi.org/10.1081/SCC-100104000

SYNTHETIC COMMUNICATIONS, 31(8), 1167–1175 (2001)

THE TRAPPING OF 6,6-DIMETHYLISOBENZOFULVENE BY ITS 1,3-DIPOLAR PRECURSOR: A RARE EXAMPLE OF A DIPOLAR [6 + 4] CYCLOADDITION

Ronald N. Warrener,* Malcom L. A. Hammond, and Douglas N. Butler

Centre for Molecular Architecture, Central Queensland University, Rockhampton, Queensland, 4702, Australia

ABSTRACT

A new route to isobenzofuran and isobenzofulvene is reported that is proposed to involve the 14e electrocyclic fragmentation of a transient 1,3-dipolar intermediate formed by ring-opening of a fused aziridinocyclobutane. 6,6-Dimethylisobenzofulvene generated in this way reacts with its 1,3-dipole precursor to form a $[10\pi + 4\pi]$ cycloadduct, the first of this type involving the participation of a 1,3-dipolar species.

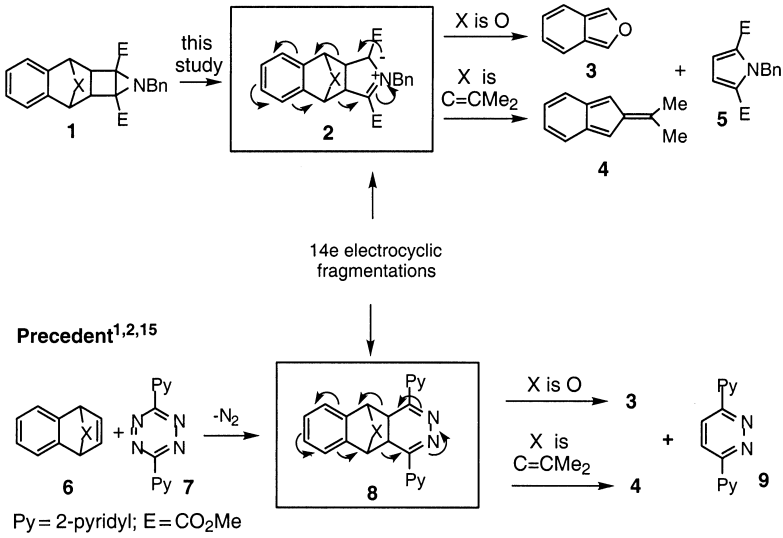
Isobenzofulvenes have been prepared by the 14e electrocyclic fragmentation of dihydropyridazine compounds formed by the treatment of benzonorbornadienes with s-tetrazines.[1,2] The reaction is general and has been used to prepare 6,6-dimethyl,[1] 6,6-diethyl,[2] 6,6-diphenyl,[3] and the parent isobenzofulvenes.[4] An alternative route involves a similar 14e electrocyclic

* Corresponding author. E-mail: r.warrener@cqu.edu.au

process from fused dihydrobenzenes generated in situ by the thermal decarbonylation of cyclone adducts of benzonorbornadiene.[2]

None of the isobenzofulvenes has been isolated as monomers, but they can be trapped as $[4\pi + 2\pi]$ cycloadducts with a variety of electron-deficient alkenes,[1] heterocyclic dienophiles,[5] or higher order products with cyclic polyene reagents, e.g., $[8\pi + 6\pi]$ cycloaddition with tropone and 7,7-dicyanofulvalene,[6] and $[10\pi + 8\pi]$ cycloaddition with isobenzofurans.[7,8] In the absence of other cycloaddition partners, isobenzofulvenes undergo self-dimerization[8,9] with one molecule acting as the 10π reagent and another as its 8π partner. Accordingly, the credentials of isobenzofulvenes to act as cycloaddition reagents have been well-established. In spite of this, no reactions with 1,3-dipolar reagents have been reported, to the best of our knowledge, prior to the present study.[10]

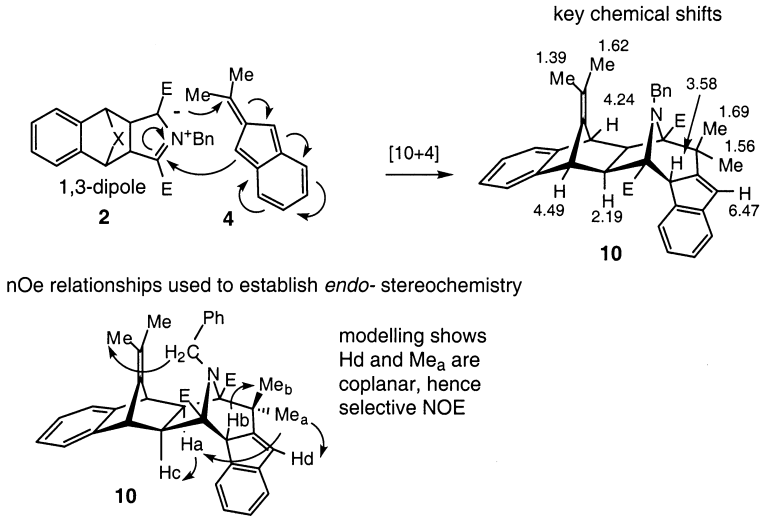
In the course of reactions involving the intermolecular trapping of



Scheme 1. Series a X is O Series b X is $C=CMe_2$ Series c X is CH_2

aziridinocyclobutanes with benzonorbornenes (*vide infra*),[11] we uncovered an unexpected fragmentation of **1a,b**,[12] which caused the yields of [4 + 2] products to drop in favor of the formation of pyrrole **5**, and other products derived from isobenzofuran **3** or 6,6-dimethylisobenzofulvene **4** (Schemes 1–3). In the case of the isopropylidene-bridged aziridinocyclobutene **1b**, a new minor compound ($m/z = 585.2881$, $C_{39}H_{39}NO_4$ requires 585.2879) was isolated, which has been assigned the structure **10** (Scheme 2) on the basis of

^{1}H NMR evidence (see Scheme 2 for chemical shift and nOe data). Dimers[4] of 6,6-dimethylisobenzofulvene **4** were also identified.[8,9]



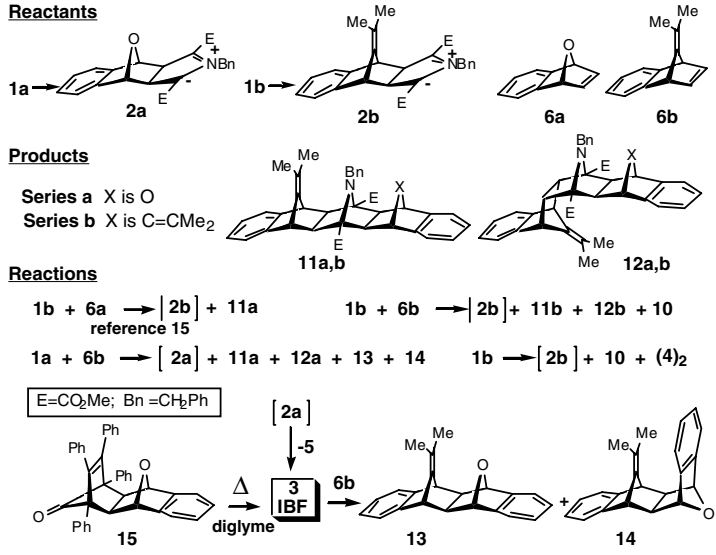
Scheme 2.

Analysis of the cycloaddition step proposed for the formation of **10** in Scheme 2 indicated a dual role for the 1,3-dipole **2b**, in which it acted as both the source of 6,6-dimethylisobenzofulvene **4** and also as its trapping reagent. The generation of the isobenzofulvene **4** by the 14e electrocyclic fragmentation of the dipolar intermediate **2b** found good analogy in the isoelectronic fragmentation of the dihydropyridazines **8a,b** (Scheme 1)[1,2,14] but the reaction of **4** with a 1,3-dipole was without precedent. This reaction was also noteworthy since it involved the reaction of two transient species, neither of which could be characterized definitively. The color developed by heating **1c** in toluene (reversed on cooling) provided support for 1,3-dipole **2c**, whereas Wentrup et al. showed that very low temperature spectroscopy was required to provide evidence for the existence of monomeric isobenzofulvene.[16]

The success of the intermolecular reaction of **4** with **2b** leading to the [10 + 4] adduct **10** depended very much on the high reactivity and electrocyclic compatibility of each species and the short but real lifetime of the 1,3-dipolar species **2b**. The fact that dimers of **4** were also obtained in this reaction indicated that the reactivity of 1,3-dipole **2b** with **4** must be comparable with the rate of dimerization of **4**, which is known too fast at

room temperature to afford ^{1}H NMR evidence of monomeric isobenzofulvene **4**.

Other experiments confirmed the special features that were necessary for the observed formation of **10**. When aziridine **1b** was heated in the presence of a powerful dipolarophilic reagent such as 7-oxabenzonorbornadiene **6a**, the intermediate 1,3-dipole **2b** was trapped exclusively to form the [4 + 2] adduct **11a** in 94% yield (Scheme 3),[17] i.e., trapping was faster than fragmentation.



Scheme 3.

In the related reaction in which aziridine **1b** was heated with the less reactive dipolarophile **6b**, direct [4 + 2] dipolar cycloaddition of **2b** with **6b** occurred to form adducts **11b** and **12b**, but this reaction competed with the [10 + 8] electrocyclic fragmentation of intermediate 1,3-dipole **2b** to form pyrrole **5** and isobenzofulvene **4** and trapping of **2b** with **4** to give adduct **10**. Thermolysis of **2b** in the absence of **6b** raised the yield of **10** to 8%, however formation of the *syn*- and *anti*-dimers of 6,6-dimethylisobenzofulvene dominated.

Heating the oxa-bridged aziridinocyclobutene **1a** in the presence of 7-isopropylidenebenzonorbornadiene **6b** produced the 1,3-dipolar adducts **11a** (12%) and **12a** (18%) by addition to 1,3-dipole **2a**. In this case, no evidence for the reaction of isobenzofuran (IBF) **3** with 1,3-dipolar intermediate **2a** was observed (only a [4 + 2]reaction is symmetry allowed). Instead, addition of IBF **3** with the 7-isopropylidenebenzonorbornadiene **6b** (acting as dieno-

phile) occurred to form the Diels-Alder adducts **13** and **14**. These structures were confirmed by spectroscopy and separate synthesis from the addition of IBF, generated by the Fieser method[18] from **15**,[19] with **6b**.

This study has uncovered a new fragmentation route to 6,6-dimethyl isobenzofulvene **4** and isobenzofuran **3**. The reaction of **4** with the 1,3-dipolar species **2b** is an exceptional example of serendipitous timing, as breakdown of the intermediate **2b** (too fast to observe by ^{1}H NMR) is still slow enough to allow its offspring **4** (itself a transient species) time to attack its forebear. This reaction is a rare example of a symmetry-allowed [6 + 4] cycloaddition involving a 1,3-dipolar species; the only earlier examples of which we are aware[10] are the dipolar addition to diazomethane[22] or benzonitrile oxide[23] to fulvenes, and the addition of diphenylnitrileimine to tropone.[24] A [6 + 4] reaction has also been implicated in the reaction of carbethoxyformonitrileoxide with dihydrocyclopenta[c]pyran.[25]

EXPERIMENTAL

Reaction of Aziridinocyclobutanes 1a,b with Benzonorbornadienes

Generation and Trapping of 6,6-Dimethylisobenzofulvene

A layer of aziridine **1b** (57 mg, 0.13 mmol) was deposited inside a flask from chloroform by evaporation and heated at 120°C for 20 m. The residue was chromatographed on silica gel (gradient elution light petroleum b.p. 40°–60°/ethyl acetate) to afford the pyrrole **5** (17 mg, 49%), a mixture of 6,6-dimethylisobenzofulvene dimers (4 mg, 19%; 1:4 exo:endo), and the [10 + 8] adduct **10** (3 mg, 8%).

Dimethyl N-benzylpyrrole-2,6-dicarboxylate **(5)**

M.p. 98°–99°C; ^{1}H NMR (400 MHz, $CDC1_3$) δ 3.80 (6H, s), 6.17 (2H, s), 6.97 (2H, s), 7.00 (2H, d, J=7.2 Hz), 7.18 (1H, d, J=7.2 Hz), 7.25 (2H, m). ^{13}C NMR δ 49.21, 51.60, 117.04, 126.14, 126.88, 127.67, 128.37, 138.71, 160.99; HRMS m/z found 273.1003, $C_{15}H_{15}O_4N$ requires 273.1001.

Dimethyl (1α,11α,12α,13β,14α,21α,22β)-23-benzyl-24-isopropylidene-23-aza-heptacyclo[10.10.1.1^{4,21}.0^{3,11}.0^{5,10}.0^{13,22}.0^{15,25}] tetracosa-3,5,7,9,15,17,19-heptaene-1,12-dicarboxylate **(10)**

M.p. 227°–228°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (1H, d J = 7.3 Hz), 1.39 (3H, s), 1.56 (3H, s), 1.62 (3H, s), 1.69 (3H, s), 2.19 (1H,

d $J = 7.3$ Hz), 3.02 (3H, s), 3.58 (1H, s), 3.85 (3H, s) 4.24 (1H, s), 4.34 (1H, d $J = 15.65$ Hz), 4.49 (1H, s), 4.74 (1H, d $J = 15.65$ Hz), 6.47 (1H, s), 6.85 (2H, m) 6.95 (1H, t $J = 7.3$ Hz), 7.06 (2H, t $J = 7.3$ Hz), 7.18 (3H, m), 7.28 (3H, t $J = 7.3$ Hz), 7.45 (2H, d $J = 7.3$ Hz), ^{13}C NMR δ 20.99 (2 lines), 26.40, 28.54, 46.45, 47.43, 47.55, 47.75, 48.79, 51.47, 51.69, 53.14, 54.00, 73.18, 78.33, 112.10, 119.44, 120.56 (2 lines), 120.90, 124.18, 124.66, 125.34 (2 lines), 126.82, 127.51, 126.02, 128.05, 141.50, 143.40, 145.84, 146.70, 148.32, 149.08, 154.44, 170.92, 172.27 HRMS m/z found 585.2881, $C_{39}H_{39}O_4N$ requires 585.2879.

Generation and Trapping of Isobenzofuran

Aziridine **1a** (180 mg, 0.46 mmol) and 7-isopropyliden-benzonorbornadiene **6a** were heated under reflux in benzene (1.5 mL) for 30 h. The reaction mixture was evaporated to dryness and the products separated by radial chromatography (silica, gradient elution light petroleum/methanol).

(1α,2β,3α,10α,11β,12α,13β,14α,21α,22β) Dimethyl 23-benzyl-23-aza-25-isopropylidene-2-oxadecacyclo[10.10.1.1^{14,21} .0^{2,11} .0^{4,9}.0^{13,22} .0^{15,20}]pentaconta-4,6,8,15,17,19-hexaene-1,12, dicarboxylate **(11)**

M.p. 145°–146°C. ^{1}H NMR δ: 1.40 (6H, s, CH_3); 1.90 (2H, s, H13,22); 2.29 (2H, s, H2,11); 3.57 (2H, s, H14,21); 3.79 (6H, s, OCH_3); 3.93 (2H, s, HCH_2Ph); 5.49 (2H, s, H3,10); 6.92–7.43 (13H, m). ^{13}C NMR δ 20.33; 46.44; 50.62; 54.00; 57.57; 58.06; 76.39; 79.25; 111.29; 119.36; 119.84; 125.42; 125.61; 126.73; 127.15; 128.82; 142.80; 143.35; 146.82; 147.79; 171.25. M/z found 573.2524, $C_{37}H_{35}O_5N$ requires 573.2515.

(1α,2α,3β,10β,11α,12α,13β,14α,21α,21α,22β) Dimethyl 23-benzyl-25-isopropylidene-23-aza-oxadecacyclo[10.10.1.1^{3,10} .1^{14,21} .0^{2,11} .0^{4,9} .0^{13,22} .0^{15,20}] pentaconta-4,6,8,15,17, 19-hexaene-1,12-dicarboxylate **(12)**

M.p. 208°–209°C ^{1}H NMR δ: 1.05 (6H, s, CH_3); 2.11 (2H, s, H13,22); 2.75 (2H, s, H2,11); 3.57 (6H, s, OCH_3); 3.71 (2H, s, H3,10); 3.82 (2H, s, NCH_2Ph); 5.38 (2H, s, H14,21); 7.00–7.50 (13H, m) ^{13}CNMR δ 20.07; 45.08; 48.63; 49.15; 51.79; 54.50; 74.82; 80.47; 113.84; 118.85; 120.22;

125.58; 125.76; 126.68; 127.55; 127.60; 141.65; 146.17; 147.62; 149.38; 171.75. *M/z* found = 573.2512 $C_{37}H_{25}O_5N$ requires 573.2515.

Reaction of Isobenzofuran **(3)** with 7-Isopropylidene Benzonorbornadiene **(6b)**

A solution of the Fieser adduct **15** [18] (1.1 g, 2.08 mmol) in chloroform (2 mL) and diglyme (5 mL) was added dropwise over 15 m to a refluxing solution of **6b** (0.4 g, 2.2 mmol) in diglyme (3 mL). After a further 5 m at reflux, the mixture was poured into water and extracted with ether. The white solid obtained from the ether extract was separated by preparative thick layer chromatography on silica by development with 50% methylene chloride in hexane (adduct **14** was more mobile than its isomer 13). Tetraphenylbenzene was also identified but not quantified.

(1α,2β,3α,6α,7β,8α) 20-isopropylidene-19-oxahexacyclo [10.6.1.1 ^{3,10}*.0*^{2,11}*.0*^{4,9}*.0*^{13,18}*]eicosa-4,6,8,13,14,17-hexaene* **(13)**.

M.p. 241°–242°C. ^{1}H NMR δ 1.69 (6H, s, CH_3); 1.88 (2H, s, H2,11); 3.86 (2H, s, H3,10); 5.19 (2H, s, H1,12); 6.96 (2H, m, H6,7); 7.04 (2H, m, H15,16); 7.09 (2H, m, H5,8); 7.16 (2H, m, H14,17). ^{13}C NMR δ 20.33, 47.30, 51.89, 82.00, 112.49, 118.80, 120.09, 125.48, 126.28, 145.51, 146.79, 148.17. *M/z* Found 300.1514 calc. for $C_{22}H_{20}O$ 300.1514. Found C 87.66, H 6.57 requires C 87.96, H 6.71%.

(1α,2α,3β,6α,7α,8β) 20-isopropylidene-19-oxahexacyclo[10.6.1.1^{3,10} *.0*^{2,11} *.0*^{4,9} *.0*^{13,18}*]eicosa-4,6,8,13,14,17-hexaene* **(14)**

M.p. 226°–227°C. ^{1}H NMR δ 1.03 (6H, s, CH_3); 2.63–2.70 (2H, m, H2,11); 3.36 (2H, s, H3,10); 5.17–5.24 (2H, m, H1,12); 6.96–7.24 (8H, m, ArH). Found C 87.92, H 6.79, $C_{22}H_{20}O$ requires C 87.96, H 6.71%.

ACKNOWLEDGMENT

M.L.A.H. thanks the Center for Molecular Architecture for the award of an honors scholarship. This project was supported by funds from the

CQU Merit Research Program. We thank Dr. Ian Pitt for performing the experiment involving the addition of isobenzofuran to 7-isopropylidene-benzonorbornadiene well ahead of its time (ANU, 14/9/82).

REFERENCES

1. Watson, P.L.; Warrener, R.N. Aust. J. Chem. **1973**, *26*,1725.
2. Tanida, H.; Irie, T.; Torie, K. Bull. Chem. Soc., Japan **1972**, *45*, 1999.
3. Gell, K.I.; Warrener, R.N. unpublished results.
4. Warrener, R.N.; Russell, R.A.; Collin, G.J. Tetrahedron Lett. **1978**, 4447.
5. Warrener, R.N.; Harrison, P.A.; Russell, R.A. Electronic Conference on Heterocyclic Chemistry ′98, 1998, Rzepa, H.S.; Kappe, O.: Eds; Imperial College Press: 081. (http://www.ch.ic.ac.uk/ectoc/echet98/pub/081/index.htm)
6. Paddon-Row, M.N.; Warrener, R.N. Tetrahedron Lett. **1974**, 382.
7. Warrener, R.N.; Evans, D.A.C.; Paddon-Row, M.N.; Russell, R.A. Aust. J. Chem. **1982**, *35*, 757.
8. Russell, R.A.; Longmore, R.W.; Warrener, R.N. J. Chem. Ed. **1992**, *34*, 403.
9. Warrener, R.N.; Paddon-Row, M.N.; Russell, R.A.; Watson, P.L. Aust. J. Chem. **1981**, *34*, 397.
10. A SciFinder Scholar search on isobenzofulvenes plus 1,3-dipoles registered no hits (March, 2000).
11. Butler, D.N.; Malpass, J.R.; Margetic, D.; Russell, R.A.; Sun, G.; Warrener, R.N. Synlett **1998**, 588–589.
12. The ruthenium-catalyzed $[2\pi + 2\pi]$ addition of dimethyl acetylene dicarboxylate to 7-oxabenzonorbornadiene **6a** has been described.[13] The resultant cyclobutene was treated with benzyl azide (benzene, RT, 48 h) and the triazolidine adduct so formed, deazetised by ultraviolet irradiation (300 nm, benzene) to give **1a**. Aziridine **1b** was prepared in a similar way from **6b**.[17]
13. Mitsudo, T.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Wantanabe, Y.; Takegami, Y. J. Org. Chem. 1979, *44*, 4492–4496.
14. Isobenzofulvenes are conveniently prepared using our s-tetrazine route outlined in Scheme 1. This 14e electrocyclic fragmentation approach was first described[15] for the preparation of isobenzofuran **3** (Scheme 1) and later used for the production of isobenzofulvenes **4**.[1]
15. Warrener, R.N. J. Am. Chem. Soc. **1971**, *93*, 2346.
16. Gross, G.; Schulz, R.; Scheig, A; Wentrup, C. Angew. Chem. **1981**, *93*, 1078.

17. Butler, D.N.; Hammond, M.L.A.; Johnston, M.R.; Sun, G.; Malpass, J.R.; Fawcett, J.; Warrener, R.N. Org. Letters **2000**, *2*, 721–724.
18. Fieser, L.F.; Haddadin, M.J. Can. J. Chem. **1965**, *43*, 1599.
19. The structure of this adduct has been recently been established by x-ray crystallography.[20] The structure was in no doubt, having been assigned by a long-range CO-H coupling method reported by us in 1979.[21]
20. Packe-Wirth, R.; Enkelmann, V. J. Mol. Structure **1998**, *448*, 1.
21. Tan, R.Y.S.; Russel, R.A.; Warrener, R.N. Tetrahedron Lett. **1979**, 5031.
22. Houk, K.N.; Luskus, L.J. Tetrahedron Lett. **1970**, *46*, 4029.
23. Caramella, P.; Frattini, P.; Gruenanger, P. Tetrahedron Lett. **1971**, *41*, 3817.
24. Houk, K.N.; Watts, C.R. Tetrahedron Lett. 1970, 46, 4025.
25. Alazard, J.P.; Leboff, A.; Thal, C. Tetrahedron **1986**, *42*, 1407.

Received April 26, 2000