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Triplet-sensitised di-π-methane rearrangement of *N*-substituted 2-azabarrelenones†

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When irradiated at λ = 366 nm or at λ = 420 nm in the presence of an appropriate sensitiser the title compounds underwent a di-π-methane rearrangement which led to the formation of tricyclic azasemibullvalenones (2*a*,2*a*^{1},2*b*,4*a*-tetrahydroazacyclopropa[*cd*]pentalenones) in yields of 63–87%.

2-Azabarrelenones (**1**)[1] represent a compound class in which one of the ethyne bridges in barrelene (**2**) is replaced by an amide (–NRCO–) fragment (Fig. 1). The photochemistry of barrelene and its substituted analogues was explored by Zimmerman and co-workers who discovered the di-π-methane rearrangement of barrelene to semibullvalene.[2] The reaction is typically performed in solvent mixtures containing acetone and was shown to occur by triplet sensitisation.[3,4] The first di-π-methane rearrangement of a benzo-2-azabarrelenone was reported for compound **3** by Paquette and Meisinger in 1970.[5] Additional work was performed on the reaction of related benzo-2-azabarrelenones which included variations of the substitution pattern at the arene and at the β,γ-unsaturated lactam.[6] However, the photochemistry of the parent 2-azabarrelenones has to the best of our knowledge not yet been studied and we disclose in this paper our preliminary work on the topic.

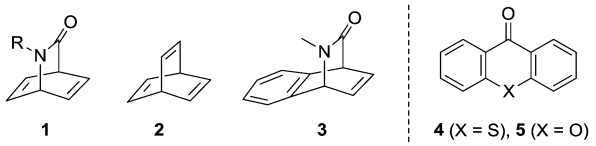

Fig. 1 Structures of 2-azabarrelenone (**1**), barrelene (**2**), benzo-2-azabarrelenone **3**, thioxanthone (**4**), and xanthone (**5**).

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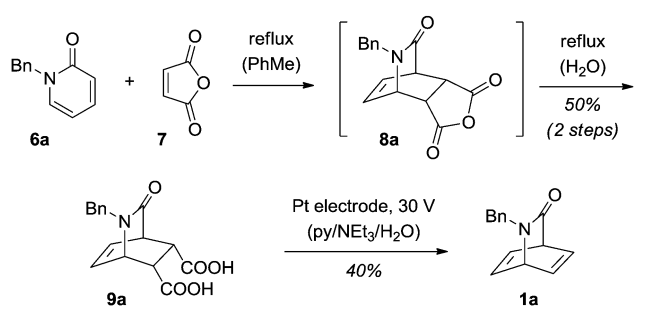
† Electronic supplementary information (ESI) available: Synthetic procedures and full characterization for all starting materials (**1**) and products (**10**, **11**, **16**). See DOI: 10.1039/c8cc08704k

It was found that catalytic amounts (50 mol%) of thioxanthone (**4**) or xanthone (**5**) trigger a high-yielding di-π-methane rearrangement reaction of compounds **1** that leads to otherwise inaccessible compounds with a unique tricyclic skeleton. The reaction can be performed with visible light (λ = 420 nm) or by UV-A irradiation (λ = 366 nm) depending on the sensitiser.

The synthesis of the starting materials was performed in analogy to a previously described method[1a] and is shown in Scheme 1 for the *N*-benzyl derivative **1a** (for the synthesis of other 2-azabarrelenones, see the ESI†). The Diels–Alder reaction of *N*-benzylpyridone (**6a**) and maleic anhydride (**7**) produced an intermediate **8a** (diastereomeric ratio d.r. = 93/7) to which water was added for hydrolysis. The mixture was refluxed for four hours which delivered the corresponding dicarboxylic acid **9a**. The latter compound was purified by recrystallization to yield exclusively a single diastereoisomer (presumably the *endo*-product[7]). In the synthesis of some other 2-azabarrelenones (*vide infra*) a mixture of diastereoisomers was taken into the final Kolbe decarboxylation step. The electrolysis was performed in an undivided cell (Winkler platinum electrode) at a constant voltage of 30 V (py = pyridine).[8]

Initial irradiation experiments were performed with thioxanthone (**4**, triplet energy E_T = 272 kJ mol^{-1})[9] as sensitiser (Table 1, entry 1) at λ = 420 nm. The reaction in dichloromethane

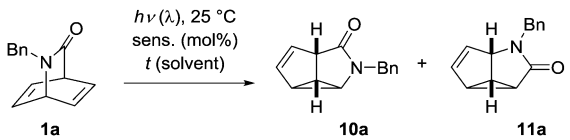


Scheme 1 Three-step synthesis of 2-azabarrelenone **1a** from pyridone **6a** and maleic anhydride (**7**).

remained incomplete and the products could not be obtained in sufficient purity to determine the reaction yield. The desired transformation was cleaner in acetonitrile and delivered the tricyclic lactams **10a** and **11a** with an azasemibullvalenone skeleton (entry 2). Compound **10a** prevailed and the regioisomeric ratio (r.r.) remained essentially constant throughout the optimization experiments (r.r. = **10a**/**11a** = 74/26 to 61/39). While it had been observed with benzo-2-azabarrelenone **3** that acidic conditions (70% HOAc in acetone) led to an improved regioselectivity[6a] there was no reaction under our conditions if HOAc was employed as a co-solvent (entry 3). Trifluorotoluene as solvent led to an improved chemoselectivity (72% combined yield) and a complete conversion was achieved after 11 hours (entry 4).

It was studied whether other sensitisers result in a higher turnover. A known iridium complex (E_T = 252 kJ mol^{-1})[11] failed to promote the desired reaction at λ = 420 nm (entry 5) while xanthone (E_T = 310 kJ mol^{-1})[12] turned out to be an efficient sensitiser at λ = 366 nm. At a loading of 50 mol%, the reaction was complete after five hours (entry 6, 83% yield). A further decrease of the sensitiser concentration resulted in longer reaction times (entries 7 and 8). As a control, it was probed whether the reaction proceeded under the conditions of entry 8 in the absence of a sensitiser but no reaction was observed (entry 9). The conversion of substrate **1a** was complete for entries 2, 4, 6–8 (Table 1) but a major by-product (*vide infra*) was isolated apart from the desired di-π-methane rearrangement products. The two diastereoisomers **10a** and **11a** could be readily separated and represent compound classes which have not yet been extensively investigated. Analogues of compound **11a** have been prepared previously by rearrangement reactions of Dewar benzene[13] and benzvalene[14] or by cyclopropanation.[15] Compounds with the tricyclic core skeleton

Table 1 Optimisation of the reaction conditions for the di-π-methane rearrangement of *N*-benzyl-2-azabarrelenone (**1a**)

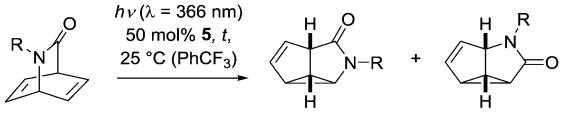


1a **10a** **11a**

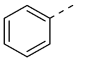
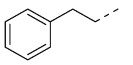
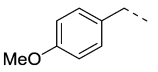
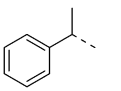
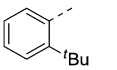
Entry[a]	λ [nm]	Sens. [mol%]	*t* [h]	Solvent	**10a**[b] [%]	**11a**[b] [%]
1	420	**4** (50)	20	CH_2Cl_2	n.d.[c]	n.d.[c]
2	420	**4** (50)	20	MeCN	48	17
3	420	**4** (50)	20	HOAc[d]	—[e]	—[e]
4	420	**4** (50)	11	$PhCF_3$	44	28
5	420	[Ir][f] (2)	20	MeCN	—[e]	—[e]
6	366	**5** (50)	5	$PhCF_3$	53	30
7	366	**5** (25)	7	$PhCF_3$	47	30
8	366	**5** (10)	12	$PhCF_3$	45	24
9	366	—	12	$PhCF_3$	—[e]	—[e]

[a] The reactions were performed under the indicated conditions in a merry-go-round apparatus[10] employing 16 fluorescent lamps as irradiation source. [b] Yield of isolated product. [c] The reaction was incomplete and a yield could not be determined (n.d.). [d] A 70% (v/v) solution of acetic acid in MeCN was used. [e] No reaction was observed. [f] [4,4′-Bis(*t*-butyl)-2,2′-bipyridine]bis{3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridin-yl]}phenyliridium hexafluorophosphate was used as the iridium catalyst [Ir].

Table 2 Triplet sensitised di-π-methane rearrangement of various *N*-substituted 2-azabarrelenones **1**



1 **10** **11**

Entry[a]	Substrate	R	*t*[b] [h]	**10**[c] [%]	**11**[c] [%]
1	**1b**		8	33	32[d]
2	**1c**		4.5	46	19
3	**1d**		3	45	25
4	**1e**		6	49[e]	27[e]
5	**1f**		7	71[f]	16[g]

[a] The reactions were performed in a merry-go-round apparatus[10] employing 16 fluorescent lamps as irradiation source. [b] Reaction time required for full conversion. [c] Yield of isolated product. [d] Minor impurities could not be fully removed. [e] d.r. = 53/47. [f] d.r. = 78/22. [g] Single diastereoisomer.

of a 2*a*,2*a*^{1},2*b*,4*a*-tetrahydro-2-azacyclopropa[*cd*]pentalen-1(2*H*)-one (**10a**) have not been described. Although thioxanthone (**4**) allows for the di-π-methane rearrangement of **1a** to be conducted with visible light, it turned out that the reaction was slow with other 2-azabarrelenones and a full conversion could not be achieved within a reasonable period of time. A more rapid reaction was achieved with xanthone (**5**) which is why the conditions of entry 6 (Table 1) were used for the reaction of other substrates **1** (Table 2).

The *N*-substituted 2-azabarrelenones were prepared from the respective *N*-substituted pyridones as described in Scheme 1 for compound **1a**. The reaction of *N*-phenyl derivative **1b** (entry 1) was slower and less clean than the reaction of compound **1a**. The reaction mixture turned yellow upon irradiation and only regioisomer **10b** could be isolated in pure form. The other isomer **11b** was still contaminated by minor impurities. The reactions of *N*-phenylethyl and *N*-*para*-methoxybenzyl (PMB) 2-azabarrelenones **1c** (entry 2) and **1d** (entry 3) were slightly faster than the reaction of **1a** and equally chemoselective (65–70% yield). The r.r. remained in the region which had been earlier recorded for products **10a** and **11a**. The chiral substrate **1e** (entry 4) delivered products **10e** and **11e** as a mixture of two diastereoisomers (76% yield). While the diastereoselectivity remained low in this instance, the axially chiral compound **1f** (entry 5, 87% yield) exhibited a significant preference for a single diastereoisomer in its di-π-methane rearrangement reaction. The isolated major regioisomer **10f** showed a d.r. of 78/22, the minor regioisomer **11f** was isolated as a single diastereoisomer. However, there was evidence from analysis of the crude ^{1}H NMR spectrum that the other diastereoisomer was also formed and that the d.r. was similar to the d.r. of **10f**.

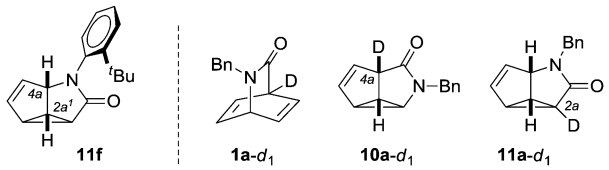


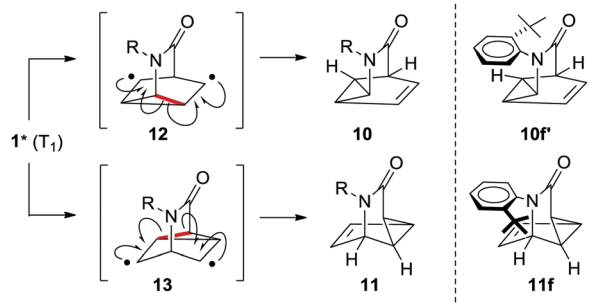
Fig. 2 Structure of product diastereoisomer **11f** and of the monodeuterated compounds **1a**-d_1, **10a**-d_1, and **11a**-d_1.

The relative configuration of compound **11f** was elucidated by NOESY experiments. Strong contacts between the *tert*-butyl protons and the protons at C4a and C2a[1] suggest a relative configuration (Fig. 2) in which the chirality axis between the nitrogen atom and the aryl ring has the configuration R_a* relative to the (2*aR**,2*a*[1]*S**,2*bR**,4*aS**)-configured tetrahydro-1-azacyclopropa[*cd*]pentalen-2(1*H*)-one skeleton.[16] Analogously, the major diastereoisomer **10f′** was shown to exhibit a S_a* configuration at the chirality axis relative to the configuration of the (2*aR**,2*a*[1]*R**,2*bR**,4*aS**)-tetrahydro-2-azacyclopropa[*cd*]-pentalen-1(2*H*)-one core. In this case, the other diastereoisomer **10f″** could also be analyzed spectroscopically and showed complementary NOESY signals to **10f′** (see ESI†).

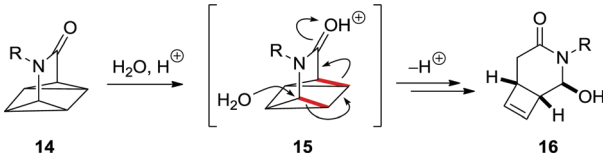
In order to obtain some information on the mechanistic course of the rearrangement the monodeuterated compound **1a**-d_1 was prepared from the 3-deuterated pyridone **6a**-d_1 (85% deuterium incorporation). Upon sensitised irradiation, the rearrangement products **10a**-d_1 and **11a**-d_1 were obtained in a similar ratio (77% yield, r.r. = 65/35) as the undeuterated compounds **10a** and **11a**. The degree of deuterium incorporation was unchanged and the deuterium atom was shown to be attached to carbon C4a in **10a**-d_1 and to C2a in **11a**-d_1 proving that the C–C bond in α-position to the carbonyl group was not cleaved in the rearrangement process. An oxadi-π-methane rearrangement pathway[3a,b] in which the carbonyl group undergoes 1,2-migration can consequently be ruled out.

Due to their low absorbance at $\lambda > 250$ nm it was not possible to obtain luminescence spectra of compounds **1**. Still, from the slow but successful reaction with thioxanthone the triplet energy of these compounds can be estimated to be in the range of *ca.* 260–275 kJ mol^{-1}. In analogy to the mechanism of the di-π-methane rearrangement of barrelene (**2**)[2,3] it is proposed that the excited triplet state **1*** decays to two regioisomeric 1,3-diradical intermediates **12** and **13** (Scheme 2). The subsequent cleavage of the marked cyclopropane bond (in red) determines the stereoselectivity. If there is no chiral information the indicated bond is broken at the same rate as its mirror carbon–carbon bond leading to the racemic products **10a–d** and **11a–d**. The α-phenylethyl group exerts little selectivity which is why the two diastereoisomers of **10e** and **11e** are formed in almost equal quantities.

A notable diastereoselectivity was observed with the axially chiral[17] *tert*-butylphenyl compound **1e**. In this case, assuming the chirality axis to be S_a* for **12f** and R_a* for **13f**, the preferential formation of products **10f′** and **11f** is linked to a selective bond cleavage at the indicated positions in intermediates **12f** and **13f**. The cleaved bond is always *trans* to the large *tert*-butyl group.



Scheme 2 Suggested reaction course for the triplet-sensitised di-π-methane rearrangement of 2-azabarrelenones (**1**).



Scheme 3 Mechanistic hypothesis for the formation of products **16** *via* 3-azatetracyclo[4.2.0.0^{2,8}.0^{5,7}]octan-4-one **14**.

Circumstantial evidence for the intermediacy of 1,3-diradicals **12** and **13** is based on the isolation of the above-mentioned side products to which structure **16** was assigned (Scheme 3). The bicyclic lactams were obtained in varying amounts of 5–20% in the course of the sensitised di-π-methane rearrangement reactions (Table 2). A straightforward explanation for their formation rests of the intermediacy of strained 3-azatetracyclo[4.2.0.0^{2,8}.0^{5,7}]octan-4-ones[18] **14**, which result from carbon–carbon bond formation in 1,3-diradicals **12** and **13**. They represent intramolecular [2+2] photocycloaddition[19,20] products with a high ring strain, and a facile fragmentation might occur under slightly acidic conditions. A possible reaction pathway includes intermediate **15**, which is attacked by water to form products **16**. Although the reaction is depicted as a formal S_N2 type reaction, it can also be conceived to proceed *via* an acyliminium ion which provides product **16** along an S_N1 type pathway.[21] Epimerization *via* the respective aldehyde should be possible[22] and compound **16** represents the more stable diastereoisomer.

In summary, it has been shown that parent 2-azabarrelenones **1** undergo a di-π-methane rearrangement that leads to the yet unexplored tricyclic lactams **10** and **11**. The factors that govern the regioselectivity and diastereoselectivity of the reaction are not completely understood and require additional experiments. Further transformations of the products are currently studied in particular with regard to a cleavage of the bond between carbon atoms 2*a*[1] and 2*b*.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) R. Gompper and A. Schmidt, *Angew. Chem., Int. Ed.*, 1980, **19**, 463; (*b*) K. Somekawa, R. Imai, R. Furukido and S. Kumamoto, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1112; (*c*) K. Matsumoto, K. Hamada, T. Uchida and H. Yoshida, *Heterocycles*, 1989, **29**, 21.

2 (*a*) H. E. Zimmerman and G. L. Grunewald, *J. Am. Chem. Soc.*, 1966, **88**, 183; (*b*) H. E. Zimmerman, R. W. Binkley, R. S. Givens, G. L. Grunewald and M. A. Sherwin, *J. Am. Chem. Soc.*, 1969, **91**, 3316.

3 Reviews: (*a*) M. G. Banwell and D. J.-Y. D. Bon in *Molecular Rearrangements in Organic Synthesis*, ed. C. M. Rojas, Wiley, Hoboken, 2015, p. 261; (*b*) E. Riguet and N. Hoffmann in *Comprehensive Organic Synthesis*, ed. P. Knochel and G. A. Molander, Elsevier, Amsterdam, 2nd edn, 2014, vol. 5, p. 200; (*c*) T. Tsuno in *Handbook of Synthetic Photochemistry*, ed. A. Albini and M. Fagnoni, Wiley-VCH, Weinheim, 2010, p. 95; (*d*) H. E. Zimmerman and D. Armesto, *Chem. Rev.*, 1996, **96**, 3065; (*e*) S. S. Hixson, P. S. Mariano and H. E. Zimmerman, *Chem. Rev.*, 1973, **73**, 531.

4 For recent synthetic and theoretical studies on the di-π-methane rearrangement, see: (*a*) O. Yahiaoui, L. F. Pašteka, B. Judeel and T. Fallon, *Angew. Chem., Int. Ed.*, 2018, **57**, 2570; (*b*) X. Li, T. Liao and L. W. Chung, *J. Am. Chem. Soc.*, 2017, **139**, 16438; (*c*) H. Ihmels and J. Luo, *Z. Phys. Chem.*, 2014, **228**, 229.

5 L. A. Paquette and R. H. Meisinger, *Tetrahedron Lett.*, 1970, **11**, 1479.

6 (*a*) M. Kuzuya, M. Ishikawa, T. Okuda and H. Hart, *Tetrahedron Lett.*, 1979, **20**, 523; (*b*) M. Kuzuya, E. Mano, M. Ishikawa, T. Okuda and H. Hart, *Tetrahedron Lett.*, 1981, **22**, 1613.

7 (*a*) H. Tomisawa and H. Hongo, *Chem. Pharm. Bull.*, 1970, **18**, 925; (*b*) H. Hongo, *Chem. Pharm. Bull.*, 1972, **20**, 226; (*c*) H. Tomisawa, H. Hongo, H. Kato, K. Sato and R. Fujita, *Heterocycles*, 1981, **16**, 1947.

8 (*a*) H. Westberg and H. Dauben, *Tetrahedron Lett.*, 1968, **9**, 5123; (*b*) A. P. Marchand and R. W. Allen, *J. Org. Chem.*, 1975, **40**, 2551; (*c*) R. Gompper and K. H. Etzbach, *Angew. Chem., Int. Ed.*, 1978, **17**, 603; (*d*) P. Camps, T. Gómez, A. Otermin, M. Font-Bardia, C. Estarellas and F. J. Luque, *Chem. – Eur. J.*, 2015, **21**, 14036.

9 A. Ilyer, A. Clay, S. Jokusch and J. Sivaguru, *J. Phys. Org. Chem.*, 2017, **30**, e3738.

10 S. Poplata and T. Bach, *J. Am. Chem. Soc.*, 2018, **140**, 3228.

11 A. Singh, K. Teegardin, M. Kelly, K. S. Prasad, S. Krishnan and J. D. Weaver, *J. Organomet. Chem.*, 2015, **776**, 51.

12 S. L. Murov, I. Carmichael and G. L. Hug, *Handbook of Photochemistry*, 2nd edn, Dekker, New York, 1993, p. 91.

13 (*a*) L. A. Paquette, *Tetrahedron Lett.*, 1968, **9**, 2133; (*b*) L. A. Paquette and G. R. Krow, *J. Am. Chem. Soc.*, 1969, **91**, 6107.

14 M. Christl, E. Brunn and F. Lanzendörfer, *J. Am. Chem. Soc.*, 1984, **106**, 373.

15 Y. Ohfune, T. Demura, S. Iwama, H. Matsuda, K. Namba, K. Shimamoto and T. Shinada, *Tetrahedron Lett.*, 2003, **44**, 5431.

16 All compounds were obtained as racemic mixtures. The relative configuration is indicated by the *R**/*S** nomenclature: E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 1206.

17 For recent work on photochemical atropselective reactions, see: (*a*) E. Kumarasamy, A. J.-L. Ayitou, N. Vallavoju, R. Raghunathan, A. Iyer, A. Clay, S. K. Kandappa and J. Sivaguru, *Acc. Chem. Res.*, 2016, **49**, 2713; (*b*) E. Kumarasamy, R. Raghunathan, M. P. Sibi and J. Sivaguru, *Chem. Rev.*, 2015, **115**, 11239.

18 A. I. Meyers and P. Singh, *J. Org. Chem.*, 1970, **35**, 3022.

19 Review: S. Poplata, A. Tröster, Y.-Q. Zou and T. Bach, *Chem. Rev.*, 2016, **116**, 9748.

20 For related [2+2] photocycloaddition reactions of dihydrobarrelenes, see: (*a*) H. Prinzbach, W. Eberbach and G. Philippossian, *Angew. Chem., Int. Ed.*, 1968, **7**, 888; (*b*) R. S. H. Liu, *Tetrahedron Lett.*, 1969, 1409; (*c*) S. F. Nelsen and J. P. Gillespie, *Tetrahedron Lett.*, 1969, 5059; (*d*) H. Prinzbach, H. Fritz, H. Hagemann, D. Hunkler, S. Kagabu and G. Philippossian, *Chem. Ber.*, 1974, **107**, 1971; (*e*) P. G. Gassman and T. H. Johnson, *J. Am. Chem. Soc.*, 1975, **98**, 861; (*f*) R. Gleiter and F. Ohlbach, *J. Org. Chem.*, 1996, **61**, 4929.

21 For acid-catalyzed ring opening reactions of donor–acceptor substituted cyclopropanes, see: (*a*) J. W. Herndon and S. U. Tumer, *J. Org. Chem.*, 1991, **56**, 286; (*b*) L. K. A. Pilsl, T. Ertl and O. Reiser, *Org. Lett.*, 2017, **19**, 2754.

22 M. Isobe, N. Fukami and T. Goto, *Chem. Lett.*, 1985, 71.