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1,2-Dihydropentalenes from Fulvenes by [6 + 2] Cycloadditions with 1-Isopropenylpyrrolidine

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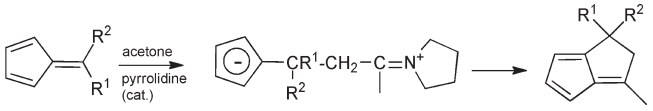
ABSTRACT



In situ generated acetone pyrrolidine enamine undergoes [6 + 2] cycloadditions with fulvenes to give 1,2-dihydropentalenes. This ring annulation method works particularly well with 6-monosubstituted fulvenes and is subject to steric hindrance at C-6 of the fulvene. On the basis of mechanistic studies, optimal conditions have been developed for a one-pot synthesis of 1,2-dihydropentalenes using catalytic amounts of pyrrolidine.

1,2-Dihydropentalenes (1,2-DHPs) are of considerable theoretical and synthetic interest and have served as versatile substrates in diverse modes of cycloadditions as well as complex ligands in organometallic chemistry.[1]

There are basically two routes to 1,2-dihydropentalenes; Hafner's method[2] appears to be most general and takes advantage of a thermal intramolecular cyclization of 6-(2′-aminovinyl)fulvenes to 3-*N*,*N*-dialkylamino-1,2-dihydropentalenes in boiling piperidine followed by regiospecific $LiAlH_4$ or RLi addition at C-3 and subsequent hydrolysis and amine elimination to give the parent system or 3-mono- or 1,3-disubstituted 1,2-dihydropentalenes. The other method, first reported by Nenitzescu et al.,[3] takes advantage of a Michael addition of the cyclopentadienide ion on chalcone and subsequent intramolecular condensation under Thiele conditions to give, among others, two isomeric diphenyl-1,2-dihydropentalenes. This latter method was more recently extended to β-phenylenones using the pyrrolidine method giving 1-phenyl-3-alkyl-substituted 1,2-dihydropentalenes in low to moderate yields.[4] Inspired by Hafner's intramolecular enamine cyclization method, Houk et al. reported formal intramolecular [6 + 2] enamine−fulvene cycloadditions to give linearly fused tricyclic 1,2-dihydropentalenes in low to moderate yields.[5,6] In our continued effort to extend the photooxygenation chemistry of fulvenes[7] to bicyclic analogues, we required a convenient synthesis of the only dihydropentalene isomers, 1,2-dihydropentalenes, that contain the fulvene moiety.

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(1) (a) Macomber, D. W.; Spink, W. C.; Rausch, M. D. *J. Organomet. Chem.* **1983**, *250*, 311–318. (b) Alves, N. P.; Maia, A. d. S.; de Oliveira, W. J. *Alloys Compd.* **2000**, *303–304*, 178–181and references cited therein. (c) Greger, I.; Kehr, G.; Fröhlich, R.; Erker, G. *Organometallics* **2010**, *29*, 3210–3221. (d) Boul, P. J.; Reutenauer, P.; Lehn, J.-M. *Org. Lett.* **2005**, *7*, 15–18. (e) Reutenauer, P.; Buhler, E.; Boul, P. J.; Candau, S. J.; Lehn, J.-M. *Chem.—Eur. J.* **2009**, *15*, 1893–1900.

(2) (a) Kaiser, R.; Hafner, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 892–893. (b) Hafner, K.; Kaiser, R. German Patent 2050404, 1972. (c) Hafner, K.; Kaiser, R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 335–337.

(3) Cioranescu, E.; Bucur, A.; Mihai, G.; Mateescu, G.; Nenitzescu, C. D. *Chem. Ber.* **1962**, 2325–2580.

(4) (a) Griesbeck, A. G. *J. Org. Chem.* **1989**, *54*, 4981–4982. (b) Griesbeck, A. G. *Chem. Ber.* **1991**, 403–405.

(5) Wu, T. C.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 5308–5309.

(6) Wang, Y.; Mukherjee, D.; Birney, D.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 4504–4506. (b) In two isolated cases, 1,2-dihydropentalenes were obtained from a 2-sulfur-substituted 6,6-dimethylfulvene and a cyclopentadienylphosphane, respectively: (a) Hartke, K.; Timpe, C. *Heterocycles* **1993**, *35*, 77–80. (b) Petrov, A. R.; Elfferding, M.; Möbus, J.; Harms, K.; Rufanov, K. A.; Sundermeyer, J. *Eur. J. Inorg. Chem.* **2010**, 4157–4165.

(7) (a) Erden, I.; Gärtner, C. *Tetrahedron Lett.* **2009**, *50*, 2381–2383. (b) Erden, I.; Amputch, M. *Tetrahedron Lett.* **1987**, *28*, 3779–3782. (c) Erden, I.; Drummond, J.; Alstad, R.; Xu, F. *Tetrahedron Lett.* **1993**, *34*, 1255–1258. (d) Erden, I.; Drummond, J.; Alstad, R.; Xu, F. *J. Org. Chem.* **1993**, *58*, 3611–3612. (e) Erden, I.; Xu, F.; Cao, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1516–1518. (f) Erden, I.; Öcal, N.; Song, J.; Gleason, C.; Gärtner, C. *Tetrahedron* **2006**, *62*, 10676–10682.

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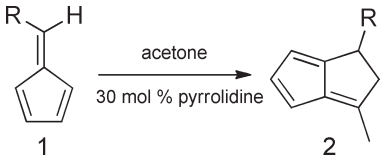
Herein we report a general and versatile synthesis of 1,2-dihydropentalenes based on intermolecular fulvene–enamine [6 + 2] cycloadditions.[8]

Treatment of 6-monosubstituted fulvenes with 30 mol % of pyrrolidine in acetone solution led cleanly to the formation of the corresponding 1,2-dihydropentalenes along with varying amounts of mesityl oxide, formed by base-catalyzed aldolization of acetone. The products were isolated after removal of solvent and mesityl oxide by rotary evaporation, purified by flash chromatography on silica gel, and characterized by NMR, UV, and high-resolution mass spectral analysis (Scheme 1, Table 1).

Scheme 1. Dihydropentalene Formation from Fulvenes



The optimal conditions for preparative purposes were established by a series of systematic studies involving the solvent effects and amount of catalyst by way of initial rate correlations.

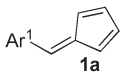
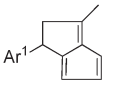
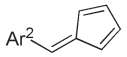
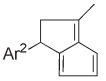
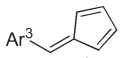
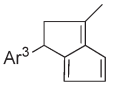
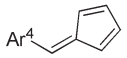
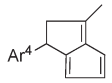
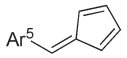
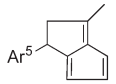
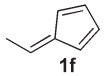
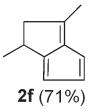
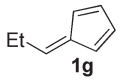
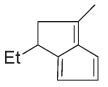
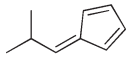
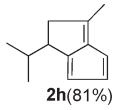
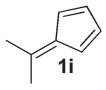
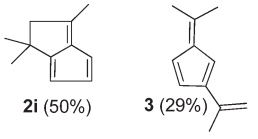
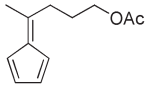
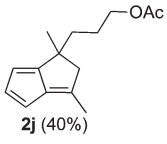
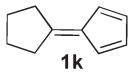
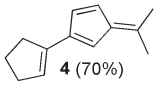
The rates were in the order DMSO > acetonitrile ≥ acetone > THF > toluene and correlate with solvent polarity index in a linear fashion pointing to polar intermediates in the reactions. We found that the solvents CH_3CN, DMSO, and acetone appear to be ideal for 1,2-DHP synthesis. The reported yields in Table 1 were obtained in acetone solvent.

In regard to the catalyst amount, the best ratio was determined to be 30 mol % of pyrrolidine since greater proportions of base only slightly accelerated the reactions at the expense of using larger amounts of a highly toxic and malodorous compound and a more tedious workup procedure.

Next, mechanistic details of these reactions were elucidated. The 1,2-dihydropentalene formation in acetonitrile solvent with 20 mol % of catalyst was determined to be bimolecular, as determined by a rate study: doubling the concentrations of either acetone or the fulvene doubled the rate, respectively. Similarly, lowering the concentration of acetone by 1/10 resulted in a 10-fold rate decelaration.

After optimization of the conditions for 1,2-DHP synthesis, the substitutent effects were studied by conducting the experiments in acetone (fulvene/acetone ratio 1/65) with 30% catalyst with a series of 6-aryl-substituted fulvenes by initial rate measurements. The plot of $\log(r)_X$ versus the σ^+ constants produced a linear correlation ($R^2 = 0.996$) with

Table 1. Dihydropentalenes from Fulvenes

entry	fulvene[a]	product (yield)[b,c,d]
1 Ar^1 = Ph	 **1a**	 **2a** (60%)
2 Ar^2 = *p*-Tolyl	 **1b**	 **2b** (91%)
3 Ar^3 = *p*-Anisyl	 **1c**	 **2c** (78%)
4 Ar^5 = Vanillyl	 **1d**	 **2d** (71%)
5 Ar^6 = *p*-Chlorophenyl	 **1e**	 **2e** (71%)
6	 **1f**	 **2f** (71%)
7	 **1g**	 **2g** (78%)
8	 **1h**	 **2h**(81%)
9	 **1i**	 **2i** (50%) **3** (29%)
10	 **1j**	 **2j** (40%)
11	 **1k**	 **4** (70%)

[a] For the synthesis of fulvenes **1a**–**k**, see ref 9. [b] For spectral characterization of all new products, see the Supporting Information. [c] Isolated yields after chromatography on silica gel. [d] Fulvene (2 mmol), 20 mol % pyrrolidine, 10 mL of acetone, stirred overnight at rt; products isolated by flash chromatography on SiO_2.

ρ constant equal to 0.46 according to the equation $\log(r)_X = 0.46\sigma^+ - 0.77$.[10] The only product in each case after 1 h

(8) Although 6,6-dimethylfulvene was reported to react with enamines, the authors were not able to characterize the products because of their instability; see ref 5, footnote 6. In our hands, 6,6-dimethylfulvene undergoes clean reaction with in situ generated 1-isopropenylpyrrolidine **5** to give dihydropentalene **2i** and **3** (see entry 9, Table 1) both of which were stable under the reaction conditions and isolable by either chromatography or fractional distillation.

(9) (a) Coskun, N.; Erden, I. *Tetrahedron* **2011**, *67*, 8607–8614. (b) Erden, I.; Xu, F. P.; Sadoun, A.; Smith, W. A.; Sheff, G.; Ossun, M. *J. Org. Chem.* **1995**, *60*, 813–820.

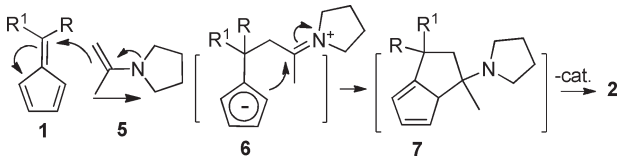
was the respective 1,2-DHP. The order of initial rates were 4-Cl > H > 4-Me > 3,4-dimethoxy ≅ 4-methoxy, indicating a trend wherein greater electron deficiency at the fulvene 6-position enhances attack by the nucleophile (vide infra). In the aliphatic series (6-alkyl or 6,6-dialkyl), a similar study revealed that steric factors affect the 1,2-DHP formation rates. Whereas after 1 h 6-methyl- and 6-ethylfulvenes were completely consumed to give the corresponding 1,2-DHPs, the conversion of 6-isopropyl derivative was only 25%. 6,6-Dimethylfulvene was reacted much more slowly than the 6-monosubstituted analogues and also gave rise to 2-isopropenyl-6,6-dimethylfulvene.

The 6-cyclopentylidene derivative **1k** did not give any 1,2-DHP; instead, product **4** was isolated from this reaction. The formation of **3**[11] and **4** presumably arises from initial base-catalyzed isomerization to alkenylcyclopentadienide followed by condensation with acetone, respectively. The tendencey of **1k** to undergo facile isomerization to cyclopent-1-enylcyclopentadiene has also been noted by Alder and Rühmann, as well as Nair et al.[12] On the basis of the studies described above, a plausible multistep mechanism emerges, consistent with our results. The 1,2-dihydropentalenes arise from a formal [6 + 2] cycloaddition of a fulvene with 1-isopropenylpyrrolidine **5**,[13] formed in situ from acetone and pyrrolidine. Nucleophilic attack at fulvene C-6 (the most electrophilic site in fulvenes, as documented in various examples)[14] gives rise to a zwitterionic intermediate incorporating a cyclopentadienyl anion and an iminium ion. The latter species cyclizes to a bicyclo[3.3.0]octadienyl derivative before eliminating pyrrolidine to give the final product (Scheme 2).

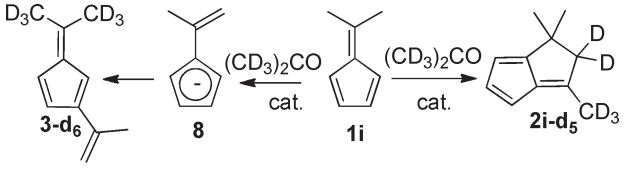
In order to exclude the possibility of a 1-isopropenylfulvene formation followed by an 8π-electrocyclization to give the 1,2-DHP, we conducted the reaction of **1i** in acetone-d_6 with catalytic base.

The ^{1}H NMR spectrum of the reaction mixture clearly showed that the signal for the C-2 protons (dihydropentalene numbering) in **2i** at 2.9 ppm, now a CD_2 group, had disappeared (Scheme 3); likewise, the C-6 methyl groups

Scheme 2. Mechanism of Fulvene−enamine [6 + 2] Cycloaddition



Scheme 3. Condensation of **1j** with Acetone-d_6 and Pyrrolidine

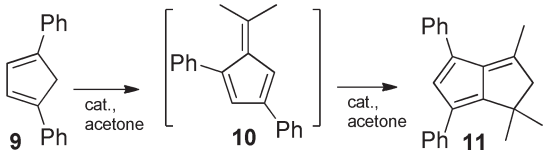


in **3** were also not visible, confirming the mechanism proposed in Scheme 2.

On an interesting note, 1,4-diphenylcyclopentadiene under the same conditions (acetone solvent/pyrrolidine catalyst) underwent a tandem condensation with acetone and subsequent dihydropentalene formation to give **11** (Scheme 4).

Obviously, the condensation with acetone did not take place at the position between the phenyl groups. The intermediate fulvene **10** was not isolated; under the conditions, it underwent attack by **5** to give the 1,2-DHP derivative **11**. Similarly, the direct condensation of 1,3-cyclopentadiene in acetone solution in the presence of catalytic pyrrolidine led to the same mixture as obtained from **1i** by way of a domino condensation with acetone.

Scheme 4. One-Pot Fulvene−1,2-DHP Formation from **9**



The scope and limitations of the 1,2-DHP synthesis were also studied. The use of methyl isopropyl ketone, acetophenone, and cyclopentanone in the presence of pyrrolidine did not result in 1,2-DHP formation. Likewise, increased steric bulk at C-6 in the starting fulvene impeded fulvene formation, e.g., fulvenes derived from cyclopropyl methyl ketone or *p*-methylacetophenone were also unreactive toward acetone/pyrrolidine. However, the use of a preformed enamine, i.e., 1-pyrrolidino-1-cyclopentene with **1c** gave a mixture of the corresponding [6 + 2] cycloadducts **12a** and **b**; pyrrolidine did not eliminate spontaneously in these cases. Preliminary results show that treatment of **1c**

(10) (a) Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191–261. (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195. (c) March, J. *Advanced Organic Chemistry Reactions Mechanism and Structure*, 3rd ed.; Wiley & Sons: New York, 1985; p 244.

(11) (a) Fenton, D. M.; Hurwitz, M. J. *J. Org. Chem.* **1963**, *28*, 1646–1651. (b) Weyschardt, H.; Plenio, H. *Organometallics* **2008**, *27*, 1479–1485. (c) Smith, W. B.; Gonzales, C. *J. Org. Chem.* **1963**, *28*, 3541–3542.

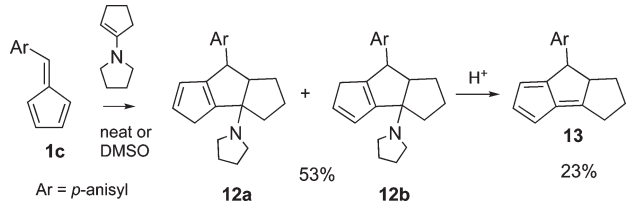
(12) (a) Alder, K.; Ruhmann, R. *Justus Liebigs Ann.* **1950**, *566*, 1–27. (b) Nair, V.; Nair, J. S.; Kumar, S.; Rath, N. P.; Williard, P. G.; Eigendorf, G. K. *Tetrahedron Lett.* **1998**, *39*, 460–4606.

(13) The progress of the reactions was monitored by ^{1}H NMR; in each case, the presence of in situ formed enamine **5** was detected, as confirmed by comparison of its ^{1}H NMR signals ($CDCl_3$) with those of a sample formed in situ from acetone and pyrrolidine. The vinyl protons have characteristic peaks (narrow multiplets) at δ 4.74 and 4.62 ppm in the ^{1}H NMR spectra of the crude reaction mixtures as well as a mixture of pyrrolidine and acetone which we ascribe to the methylene protons in **5**.

(14) (a) Yates, P. Fulvenes. In *Advanced Alicyclic Chemistry*; Academic Press: New York, 1968; Vol. 2, pp 59−184. (b) Zeller, K. P. Pentafulvenes. *Methoden Org. Chem. (Houben-Weyl)* **1985**, *5/2C*, 504–684. (c) Neuenschwander, M. Fulvenes. In *The Chemistry of Double-Bonded Functional Groups, Supplement A*; Patai, S., Ed.; Wiley: New York, 1989, pp 1131−1268. (d) Buchi, G.; Decorzant, D. B. R.; Grieder, A.; Hauser, A. *J. Org. Chem.* **1976**, *41*, 3208–3209.

with malonic acid in the presence of NaOAc in ether/H_2O delivers the tricyclic 1,2-dihydropentalene **13**, albeit in low yield (Scheme 5).

Scheme 5. Dihydropentalene with a Preformed Enamine

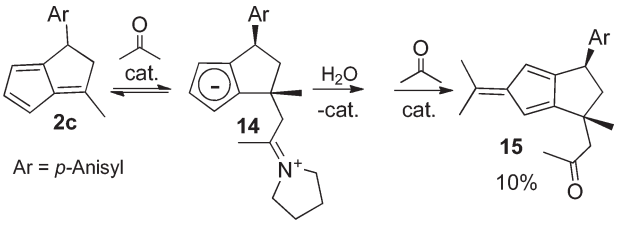


In order to test the dipolar nature of the [6 + 2] cycloaddition, and in hopes of trapping an intermediate proposed in Scheme 2, we conducted the reaction of **1c** with in situ-generated acetone pyrrolidine enamine in DMSO containing 2% H_2O. Under the conditions, in addition to the dihydropentalene **2c**, a small amount of a product was isolated that was identified as fulvene **15** (Scheme 6). Its formation can be rationalized in terms of a second enamine addition to **2c**; the resulting iminium ion **14** is hydrolyzed to give the corresponding ketone. The resulting cyclopentadiene undergoes pyrrolidine-catalyzed condensation with acetone to give **15**. Since no 1,2-DHP-enamine cycloaddition was observed previously in the absence of H_2O, the second enamine attack is reversible since the cyclization of the intermediate is geometrically not feasible and the alternative four membered ring formation would also be unfavorable. Thus, when no H_2O is present, **14** reverts to **2c**.

(15) This work was presented at the 43rd IUPAC World Congress in San Juan, Puerto Rico, paper no. 589, Aug 1, 2011.

(16) Erden, I.; Gärtner, C. Inter- and Intramolecular Trapping of Cyclopropanone Intermediates in the Photooxygenation of 1,2-Dihydropentalenes. Presented at the Pacifichem conference in Honolulu, HW, Symposium No. 1 (Reactive Intermediates and Unusual Molecules), paper no. 1354, Dec 18, 2010.

Scheme 6. Enamine–fulvene Reaction in the Presence of H_2O



In conclusion, we have developed a convenient general synthesis of 1,2-dihydropentalenes from fulvenes involving a formal stepwise [6 + 2] cycloaddition with an in situ generated enamine.[15] By way of mechanistic studies, we elucidated the mechanism of the reaction and optimized the reaction conditions. With a variety of 1,2-dihydropentalenes now readily accessible, we plan to explore various aspects of the chemistry of these interesting bicyclic fulvenes, including cycloadditions, singlet oxygenation,[16] as well as applications to natural product synthesis.

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Supporting Information Available. General experimental procedures, spectral data, and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.