Pergamon

Tetrahedron Letters, Vol. 35, No. 36, pp. 6627-6630, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01407-8

Indenes *via* Fulvene Intermediates

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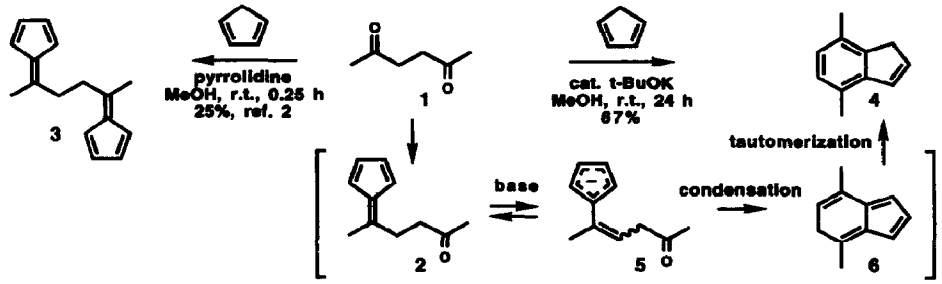
Abstract: Substituted indenes are prepared from 1,4-dicarbonyl compounds by treatment with base and cyclopentadiene.

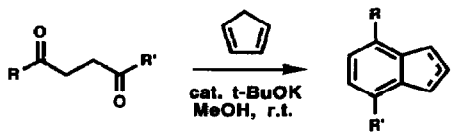
Indenes are typically prepared by cyclization reactions that annulate the five membered ring onto substituted aromatic systems.[1] We have found a novel cyclization reaction in which the aromatic system is annulated onto cyclopentadiene to generate a variety of substituted indenes and report herein results from our initial studies. Cyclopentadiene and hexane-2,5-dione (**1**) were condensed with the intent of preparing small quantities of mono-fulvene **2** (Scheme I). The pyrrolidine-catalyzed reaction of the same components has been reported to provide difulvene **3**.[2] Pyrrolidine catalysis produces rate enhancement in fulvene formation via iminium ion formation.[3] We hoped modest selectivity for the mono-fulvene could be achieved without resorting to protecting group strategies by use of alternative base catalysis. When cyclopentadiene and hexane-2,5-dione (**1**) were treated with 10 mol% of t-BuOK in methanol at room temperature, a yellow color was immediately observed, characteristic of fulvene formation.[4] Chromatographic analysis indicated the presence of two new materials: a yellow compound, later determined to be mono-fulvene **2** by GCMS and NMR analysis, and an unexpected, non-polar UV-active material. After 24 h, almost complete consumption of both hexane-2,5-dione (**1**) and fulvene **2** was observed. The non-polar product was isolated by column chromatography and determined to be 4,7-dimethylindene (**4**) by GCMS and NMR analysis.

Scheme I



Evidently alkoxide-catalyzed fulvene formation is sufficiently retarded that intramolecular cyclization competes, a result not observed in the iminium ion catalyzed reaction.[2] The first condensation of cyclopentadiene to form **2** is presumably followed by deprotonation of the mono-fulvene to form the vinylcyclopentadienyl anion **5**.[5] Subsequent intramolecular condensation to fulvene intermediate **6** and tautomerization gives indene **4**. When the reaction was interrupted after 1.5 h the fulvene **2** was isolated in 10% yield. Treatment of this material with t-BuOK (10 mol%) in methanol for 24 h provided **4**, supporting the mechanistic hypothesis proposed here. This transformation has features in common with the formation of isoindoles from 2,5-dialkylpyrroles,[6] isobenzothiophenes from 2,5-dialkyl thiophenes,[7] carbazoles from indoles,[8] dihydropentalenes from acyclic enones[9] and azulenes from pyridinium and pyrylium ions.[10]

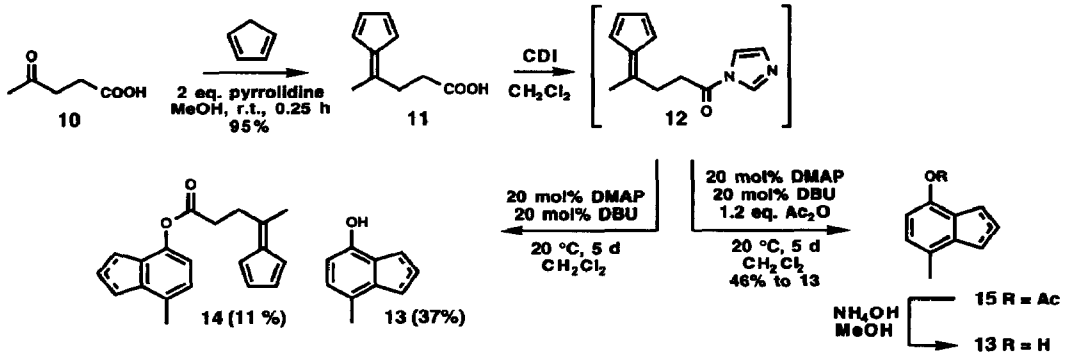
We have explored the steric demands of the reaction as indicated in the table below. The reaction rate is decreased by phenyl or isopropyl substitution (examples 7 and 8). t-Butyl methyl ketone 9 reacts to form the monofulvene which can be isolated. After prolonged exposure to alkoxide, ketone 9 cyclizes to form the t-butyl methyl indene which was detected by GCMS but not isolated (<15% GC yield after 96 h). This method represents a facile and practical synthesis of 4,7-disubstituted indenes from primary or secondary alkyl and aryl substituted diones.[11,12]



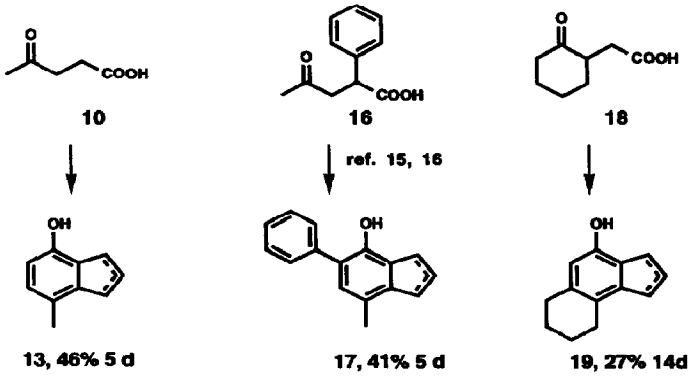
dione	R	R'	t-BuOK mol%	reaction time (h)	isolated yield %
1	CH_3	CH_3	20	24	67
7[13]	Ph	Ph	100	96	69
8[14]	CH_3	i-Pr	10	90	26
9[14]	CH_3	t-Bu	10	96	0

Trapping of the fulvene-derived vinylcyclopentadienyl anion intermediate (such as 5) by other electrophiles offers the possibility of introducing other functional groups. We have found that acylimidazolides similarly react intramolecularly with vinylcyclopentadienyl anion to produce 4(7)-hydroxyindenes. Levulinic acid 10 was converted to 6-(3-propionyl)-6-methylfulvene (11).[3] Treatment with 1,1'-carbonyldiimidazole[15] in methylene chloride presumably generated the acylimidazole 12 which was treated with 20 mol% each of 4-dimethylaminopyridine (DMAP) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Two major non-polar products were observed by TLC; after 5 days at room temperature standard work-up and chromatography provided 13 and 14.[16,17] All attempts to increase the rate of the cyclization (solvent, temperature, acyl activating groups) either stop the reaction altogether or accelerate fulvene and indene decomposition, generating intractable mixtures. In an effort to avoid non-productive acylation by 12, acetic anhydride was added to generate 15: this process effectively competes for the newly formed phenol under these conditions and allowed more efficient conversion of 12 to 13.

Scheme II



This cyclocondensation reaction has been examined with substituted levulinic acids and found to be a general and facile synthesis of substituted indenes. Biphenyl (**16** to **17**) and fused (**18** to **19**) systems not easily accessed by other means are formed in two steps.[16,17] The ease of preparation of the fulvene intermediates and the catalytic nature of the cyclization process make this a valuable method for the preparation of a variety of indenes, despite the moderate yields and prolonged reaction times.



The mechanism of this catalytic conversion mimics the dione examples, although it is necessary to avoid hydroxylic base. To this end, acylimidazolides provide a reasonable balance between leaving group ability and auto catalysis. The pKa of the fulvene allylic proton in **2** and **12** is 22.7.[18] Amidine base (DBU) initiates cyclization *via* fulvene deprotonation, which after intramolecular cyclization generates imidazole anion (pKa, 14.5) to continue the catalytic cycle. Although DMAP used as the sole base promotes cyclization, these conditions are particularly sluggish, requiring weeks for substantial reaction to proceed. DBU by itself causes decomposition. The combination of DMAP as acyl transfer agent and DBU as cyclization initiator has thus far provided the best results.[19]

References and Notes

1. For a review see, *Chemistry of Carbon Compounds*, Vol. III; Rodd, E. H., Ed.; Elsevier: Ansterdam, 1954. For a few examples see a) Macleod, J. K.; Monahan, L. C. *Tetrahedron Lett.* **1988**, *29*, 391. b) Yamashita. A. *Tetrahedron Lett.* **1986**, *27*, 5915. c) Jones, M. Jr.; Hendrick, M. E.; Gilbert, J. C.; Butler, J. R. *Tetrahedron Lett.* **1970**, 845.

2. Erickson, M. S.; Cronan, J. M. Jr.; Garcia, G. J.; McLaughlin, M. L. *J. Org. Chem.* **1992**, *57*, 2504.

3. Stone, K. J.; Little, R. D. *J. Org. Chem.* **1984**, *49*, 1849.

4. For recent reviews see, Neuenschwander, M. Fulvenes. In *The Chemistry of Double-bonded Functional Groups*; Patai, S., Ed.; John Wiley: New York, 1989; pp 1131-1268. Zeller, K. P. Pentafulvenes. In *Methoden Der Organischen Chemie*; 1985; Vol. 5/2C, pp 504-684.

5. An alternative course of events was suggested by a reviewer, whereby methoxide addition to fulvene **2** generates a cyclopentadienyl anion, however the reaction proceeds in t-BuOH with t-BuOK as catalyst. See Hine, J.; Knight, D. B. *J. Org. Chem.* **1980**, *45*, 991. Also, for a related trapping of cyclopentadienyl anion by an intramolecularly tethered ketone, see Büchi, G.; Berthet, D.; Decorzant, R.; Grieder, A.; Hauser, A. *J. Org. Chem.* **1976**, *41*, 3208.

6. Bender, C. O.; Bonnett, R. *J. Chem. Soc. (C)*, **1968**, 3036. Also see Dalton. L. K.; Teitei. T. *Aust. J. Chem.* **1968**, *21*, 2053.

7. Dann, O.; Kokorudz, M.; Gropper, R. *Chem. Ber.* **1954**, *87*, 140.

8. Dalton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan, J. M.; Teitei, T. *Aust. J. Chem.* **1967**, *20*, 2715.

9. Griesbeck, A. G. *Chem. Ber.* **1990**, *123*, 549.

10. Hafner, K. *Angew. Chem.* **1958**, *70*, 419 and Hafner, K.; Kaiser, H. in *Organic Synthesis*,; Baumgarten, H. E., Ed.; John Wiley: New York, 1970; Vol. V, pp. 1088-1091.

11. Typical experimental conditions for the preparation of **4**: To a stirred solution of t-BuOK (7.58 g, 67.6 mmol) in reagent grade methanol (150 mL) was added cyclopentadiene (22.3 g, 338 mmol) under N_2 atmosphere. After 2 min hexane-2,5-dione **2** (38.5 g, 338 mmol) was introduced. An initial exotherm and gradual darkening of the mixture was observed. The reaction was stirred for 24 h then poured into saturated $NaHCO_3$ solution (200 mL) and product was extracted with pet. ether (bp. 40 - 60 °C, 3 x 100 mL). After drying ($MgSO_4$) and concentration, the resulting oil was filtered through a 2 x 7 inch silica gel pad eluting with pet. ether to provide **4**, (32.8 g, 67%). R_f 0.51 (hexane); ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.98 (m, 2H), 6.91 (m, 1H), 6.56 (m, 1H) 3.28 (s, 2H), 2.41 (s, 3H), 2.33 (s, 3H); GCMS (M^+) 144.

12. During the preparation of this manuscript similar results were disclosed in the patent literature. See Erker, G.; Nolte, R.; Aulbach, M.; Weiss, A.; Reuschling, D.; Rohrmann, J. Pat. No. DE 4104931, **1992**.

13. Vankar, Y. D.; Kumarevel, G.; Mukherjee, N.; Rao, C. T. *Synth. Commun.* **1987**, *17*, 181.

14. These diones were prepared by alkylation of the corresponding β-ketoesters with methallyl chloride (Brandstrom, A. *Acta Chem. Scand.* **1959**, *13*, 607), saponification (KOH, MeOH) and oxidative cleavage ($OsO_4/NaIO_4$, THF/H_2O).

15. Staab, H. A.; Lüking, M.; Dürr, F. H. *Chem. Ber.* **1962**, *95*, 1275.

16. Typical conditions for the preparation of 4-hydroxyindenes from levulinic acids. Levulinic acid (1 mmol) and cyclopentadiene (1.5 mmol) were dissolved in methanol (5 mL) at 0 °C and treated with pyrrolidine (2 mmol).[3] After complete conversion to the fulvene (TLC, 15 min at 0°C to 24 h at ambient temperature) the reaction was poured into H_2O and extracted with Et_2O. The pH was adjusted to 1 - 2 by addition of 1*N* HCl then the fulvene-acid extracted with Et_2O washed with H_2O and saturated sodium chloride solution. The solution was dried ($MgSO_4$), filtered and concentrated to a yellow oil. This crude material was dissolved in CH_2Cl_2 (5 mL) and treated with 1',1-carbonyldiimidazole (1.1 mmol) and stirred 1 h. Ac_2O (1.5 mmol), DMAP and DBU (0.2 mmol each) were introduced and the mixture stirred then put aside for 5 - 10 days. The acetates so produced could be isolated, or more typically, methanol (5 mL) and 30% ammonium hydroxide (2 mL) were added and stirred 3 h. The crude mixture was poured into Et_2O and extracted with 1*N* HCl solution. The Et_2O layer was dried ($MgSO_4$), filtered and concentrated to an oil which was chromatographed on Silica gel to isolate the least polar material. Yield and reaction time for **13** (46%, 5 days), **17** (41%, 5 days), and **19** (27%, 10 days). All products were mixtures of olefin isomers (~45-50%).

17. The following data was acquired for the indanes produced by hydrogenation of the indene isomeric mixtures (H_2 @ 40 psi, 10% Pd/C, MeOH, 2 h). Data for indane from **13**: R_f 0.55 (50% CH_2Cl_2/hexane); ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.85 (d, 1H), 6.56 (d, 1H), 4.41 (s, OH), 2.87 (m, 4H), 2.19 (s, 3H), 2.10 (m, 2H); GCMS (M^+), 148. Data for indane from **17**: R_f 0.53 (50% CH_2Cl_2/hexane); ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.42-7.30 (5H), 6.95 (s, 1H), 4.95 (s, OH), 2.88 (t, 2H), 2.82 (t, 2H), 2.05 (m, 2H), 2.03 (s, 3H); GCMS (M^+), 224. Data for indane from **19**: R_f 0.15 (50% CH_2Cl_2/hexane); ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1H), 4.29 (s, OH), 2.81 (t, 2H), 2.72 (t, 2H), 2.65 (t, 2H), 2.49 (t, 2H), 2.05 (m, 2H),1.75 (m, 4H); GCMS (M^+), 188.

18. Knight, D,. B.; Harrelson, J. H. *J. Chem. Soc. Chem. Commun.* **1987**, 116.

19. For a recent account of acylation of cyclopentadiene to generate 6-oxyfulvenes see: McLoughlin J. I.; Little, R. D. *J. Org. Chem.* **1988**, *53*, 3624.

(*Received in USA* 3 *June* 1994; *revised* 15 *July* 1994; *accepted* 20 *July* 1994)