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İHSAN ERDEN

JENNY SABOL

ANA GUBELADZE

ANDREA RUIZ

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An expedient synthesis of 6-vinylfulvene

İhsan ERDEN,* Jenny SABOL, Ana GUBELADZE, Andrea RUIZ
Department of Chemistry and Biochemistry, San Francisco State University, San Francisco, CA, USA

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Abstract: 6-Vinylfulvenes constitute a class of fulvenes that are difficult to access due to the lack of a general method for their synthesis. In particular, the unsubstituted parent system has been very difficult to obtain by existing methods. In this communication we describe a convenient 3-step protocol for the synthesis of the title compound by way of sulfide oxidation and subsequent sulfoxide elimination.

Key words: Fulvene, vinylfulvene, sulfide, sulfoxide, desulfinylation

1. Introduction

Fulvenes have been known since their first synthesis by Thiele in 1900.[1] The classical Thiele fulvene synthesis features base-promoted condensation of cyclopentadiene with a carbonyl compound.[2] The original Thiele procedure employs sodium alkoxide as base in an alcohol solvent. In most cases, in particular with aliphatic aldehydes, yields are low due to competing aldol condensations. Improved procedures for the synthesis of simple fulvenes have been developed, the most notable being by Little and Stone,[3] utilizing at least stoichiometric amounts of pyrrolidine as base in methanol. Our most recent contribution to fulvene synthesis has recorded further improvements to the existing methods, featuring catalytic amounts of pyrrolidine in MeOH–H_2O solutions, with or without the addition of molecular sieves and/or NEt_3, depending on the nature and substitution pattern on the starting carbonyl compound.[4] The synthesis of 6-vinylfulvenes,[5] though, has remained problematic in spite of some improvements offered previously; however, the scope of these improvements has been limited.[6]

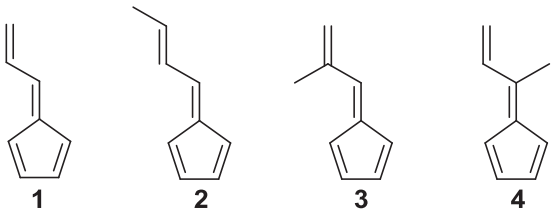

Figure 1. Yields on some 6-vinylfulvenes by the Thiele procedure.

While the previously reported yields on most 6-vinylfulvenes leave much to be desired[5] (Figure 1), Neuenschwander developed 2 additional, albeit indirect syntheses of 6-vinylfulvene:[7,8] (a) from 1-hydroxymethyl-spiro-

*Correspondence: ierden@sfsu.edu
Dedicated to the memory of Professor Ayhan S. Demir

[2,4]-hepta-4,6-diene with an alcoholic solution of concentrated HCl, followed by treatment with aqueous KOH in 10% yield along with considerable amounts of polymeric material; (b) from sodium cyclopentadienide and 3-acetoxy-3-chloro-1-propene by an S_N2 reaction followed by treatment of the alkylated product with NEt_3 to affect elimination of acetic acid from the alkylated product. However, under these conditions, the major product from this reaction was 3-(cyclopentadienyl)prop-1-ene-1-yl acetate along with 20% of the desired 6-vinylfulvene. Considering the fact that 3-acetoxy-3-chloro-1-propene is not commercially available and had to be synthesized in 55% yield from acrolein, the overall yield on 6-vinylfulvene was 11%.

Our interest in developing new syntheses for 6-vinylfulvenes stems from the diverse reactivity expected of these compounds in terms of their cycloadditions and photooxidation chemistry[9] and their potential role as synthetic building blocks. In view of the fact that competing Diels–Alder reaction with the α,β-unsaturated carbonyl compounds in favor of the condensation with the carbonyl group hamper, and in most cases preclude, 6-vinyl formation,[10] we recently developed a convenient synthesis of 6-methyl-6-vinylfulvene starting from fulvene **6** derived from the commercially available 4-hydroxy-2-butanone via the corresponding mesylate and elimination with DBU in a 62% overall yield, a remarkable improvement from the only previous method yielding merely 0.5% of the desired 6-methyl-6-vinylfulvene **4**.[11] (Figure 2). The efficacy of this protocol has now been improved to 86% by implementing our catalytic fulvene synthesis (method A) in the first step, raising the overall yield to 83%.[12]

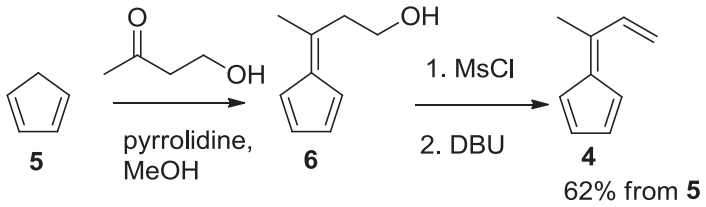

Figure 2. Efficient synthesis of **4** by a 3-step method.

As stated above, the existing syntheses of the parent 6-vinylfulvene suffer from either low yield (3%) or the fact that Neuenschwander's indirect synthesis, as stated above, yields 2 products from which the minor product, 6-vinylfulvene, needs to be separated by column chromatography. Herein, we describe the most efficient synthesis of 6-vinylfulvene to date by a 3-step sequence starting from commercially available starting materials where a single product is formed in each of the synthetic steps and lengthy chromatographic separations are not necessary.

2. Results and discussion

In our original survey of fulvene syntheses,[6] we reported the preparation of functionalized fulvenes from carbonyl compounds carrying diverse functional groups including the methyl or arylthio group.[5] Though the strategy employed in our synthesis of 6-methyl-6-vinylfulvene appeared to be the most promising route to 6-vinylfulvene as well, the requisite 3-hydroxypropanal is not commercially available and an OH-protected derivative needed to be prepared by a multistep synthesis; therefore, the aforementioned approach was not considered. Instead, a conceptually similar route was chosen in which the 3-hydroxypropanal was replaced by the commercially available 3-(methylthio)propanal. The Little and Stone procedure using stoichiometric amounts of pyrrolidine in methanol did not give satisfactory results (vide infra); however, our catalytic method using 10% pyrrolidine in a $MeOH/H_2O$ (4:1) mixture using a slight excess of cyclopentadiene at room temperature resulted in the

formation of the desired fulvene without any side products. The crude product was practically pure enough for further steps, yet a pure sample for analytical purposes was isolated by flash chromatography in 72% yield (Figure 3).

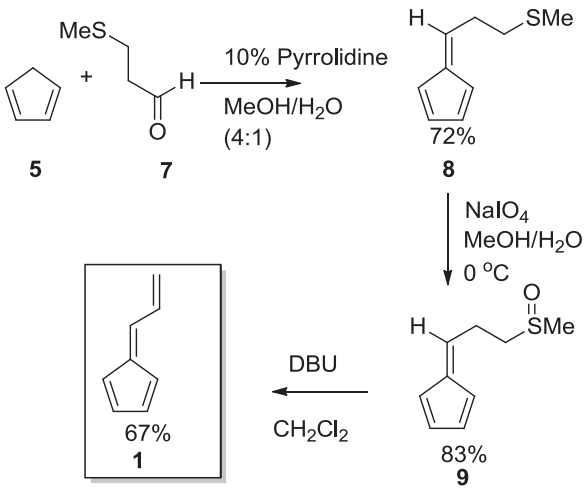

Figure 3. Synthesis of 6-vinylfulvene via sulfoxide elimination.

The bright yellow fulvene **8** exhibited multiplets at 6.57, 6.50, 6.47, and 6.21 (1H each, ring protons), as well as a triplet at 6.42 ppm for the olefinic proton on the exocyclic double bond. In the aliphatic region, the CH_2 groups absorbed at 2.83 (q) and 2.67 (t), respectively; the S-Me group gave a singlet at 2.14 ppm. The next step toward the eventual sulfoxide elimination entailed selective oxidation of the sulfide to the sulfoxide under mild conditions without causing an oxidative decomposition of the fulvene ring. Toward that end, a very mild, high-yield method proved to be oxidation in $MeOH/H_2O$ with excess $NaIO_4$ at 0 °C.[13] The resulting product was formed in nearly quantitative yield. An analytically pure sample was isolated in 83% yield after flash chromatography on silica gel. The product was then subjected to sulfoxide elimination with an equimolar amount of DBU in CH_2Cl_2 at room temperature. Initially the dropwise addition of DBU to the sulfoxide solution in CH_2Cl_2 was carried out at 0 °C, and, after complete addition, the ice-bath was removed. The color of the solution changed from bright yellow to red. The product, 6-vinylfulvene (**1**), was isolated after aqueous work-up as a red oil after flash chromatography in 67% yield. The NMR spectrum of **1** at 500 MHz is remarkably simpler than the counterpart previously reported by Neuenschwander et al.[7] in that at 500 MHz the spin systems are now first-order and peak assignments rendered exceptionally facile.

It is noteworthy that the Little–Stone method using stoichiometric pyrrolidine, in contrast to our catalytic method, did not yield the desired fulvene as the only product; rather, a mixture of 3 products was obtained in low yield in which the fulvene was a minor component. To our surprise, 2 products were formed in a ratio of 1:2.5. The minor product in the mixture was fulvene **8**, whereas the major product was a mixture of the regioisomeric cyclopentadienes **11** and **12** (almost 1:1 ratio). As to the mechanism of their formation, the only satisfactory rationalization is, at this time, a base-promoted equilibrium being established between the β-sulfidoaldehyde and the sulfide/aldehyde mixture, i.e. a partial delsulfenylation via a retro-conjugate addition. With excess pyrrolidine in MeOH, desulfenylation results in the formation of acrolein and methyl thiolate. The latter, being a strong nucleophile, attacks the fulvene formed during the reaction at the 6-position, as fulvenes are prone to attack by nucleophiles at the exocyclic double bond[6,14] (Figure 4).

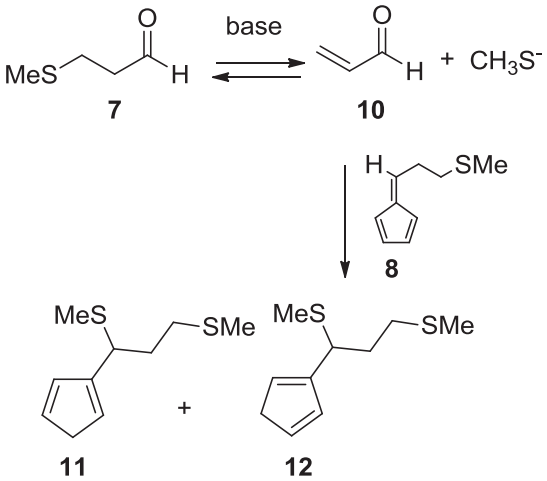

Figure 4. Side reactions with stoichiometric pyrrolidine.

The mixture of cyclopentadienes **11** and **12** was also oxidized with $NaIO_4$ to the corresponding bis-sulfoxides; the latter were treated with DBU in CH_2Cl_2 without purification to give the 6-vinylfulvene by way of a 2-fold desulfinylation; however, the formation of the mixture of **8**, **11**, and **12** by the Little–Stone procedure proceeded in ca. 17% yield. This route, therefore, was not further pursued as a viable alternative to our first method employing our catalytic fulvene synthesis.

In summary, we have developed the most efficient 6-vinylfulvene synthesis to date in an overall yield of 37% from commercially available starting materials. With **1** now available in preparatively useful quantities, its cycloadditions, singlet oxygenation, and reagent-induced transformations are currently being studied, and the results from these reactions will be reported in due course.

3. Experimental section

General. ^1H and ^{13}C NMR spectra were recorded on a 500-MHz NMR spectrometer, using $CDCl_3$ as solvent and TMS as internal standard, unless specified otherwise. Most column chromatographic separations were carried out on a flash chromatography system using 40–60 mm silica gel columns using ethyl acetate/*n*-hexane solvent mixtures. For preparative TLC, Merck silica gel (grade 60 PF_{254}) was used. All reactions were conducted under an atmosphere of dry nitrogen or argon. Nondeuterated solvents were dried and distilled prior to use. Pyrrolidine is an exceptionally foul-smelling and toxic compound and should be handled with care in a well-ventilated hood. Fulvenes are oxygen- and heat-sensitive compounds; all reactions should be carried out under a nitrogen or argon atmosphere. Exact masses of all new products by high resolution mass spectra (HRMS) were determined at the Mass Spectrometry facilities at San Francisco State University.

6-[2-(Methylthio)ethyl]fulvene (**8**). To an ice-cold solution of 0.52 g (5 mmol) of 3-(methylthio)propanal and 0.66 g (1.0 mmol) of freshly distilled cyclopentadiene in $MeOH/H_2O$ (5 mL, 4/1) was added 0.036 g (0.5 mmol) of pyrrolidine. After stirring the reaction mixture at 0 °C for 5 min, the ice-bath was removed and the stirring continued for another 30 min. TLC analysis showed that the starting aldehyde was consumed and a bright yellow product spot was formed. The mixture was transferred to a separatory funnel containing 20 mL of brine and 10 mol% (0.03 g) of AcOH. The mixture was extracted twice with 15 mL of ether each; the combined ether layers washed successively with 15 mL of a saturated $NaHCO_3$ solution, followed by 15 mL of brine, dried over $MgSO_4$, and the solvent rotovapped. The ^1H NMR spectrum of the crude product showed

the presence of the desired fulvene along with a small amount of cyclopentadiene dimer. Flash chromatography (10% EtOAc/n-hexane) yielded 540 mg (72%) of a bright-yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.57 (m, 1H), 6.50 (m, 1H), 6.47 (m, 1H); 6.44 (t, J = 7.6 Hz, 1H), 6.21 (dt, J = 5.2 Hz, 1.7 Hz, 1H); 2.83 (q, J = 7.6 Hz, 2H); 2.67 (t, J = 7.6 Hz, 2H); 2.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$)δ: 146.9, 139.5, 133.6, 131.3, 125.6, 118.9, 34.5, 30.6, 15.5 ppm; HRMS: calcd. for $C_9H_{12}S$: 152.0660. Found: 152.0457.

6-[2-(Methylsulfinyl)ethyl]fulvene (9). To 7 mL (3.5 mmol) of a 0.5 M solution of $NaIO_4$ in H_2O was added 0.5 g (3.28 mmol) of **8** in 10 mL of MeOH at 0 °C. The mixture was stirred in an ice-bath for 4 h while the progress of the reaction was monitored by TLC. The precipitate was removed by vacuum filtration and the product extracted twice with each 50 mL of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and the solvent rotovapped. According to the crude ^{1}H NMR, the product was better than 95% pure. Purification was carried out by flash chromatography on silica gel eluting with 30% EtOAc/n-hexane to give 457 mg (83%) of a bright-yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$)δ: 6.57 (m, 2H); 6.51 (m, 2H); 6.47 (m, 1H), 6.37 (t, J = 7.7 Hz, 1H); 6.19 (dt, J = 5.2 Hz, 1.7 Hz, 1H); 3.0 (m, 2H); 2.87 (m, 2H); 2.61 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$)δ: 147.8, 136.9, 134.5, 132.1, 125.6, 118.9, 53.5, 38.8, 24.2 ppm; HRMS calcd. for $C_9H_{12}OS$: 168.0609. Found: 168.0612.

6-Vinylfulvene (**1**). Sulfoxide **11** (400 mg, 2.37 mmol) was dissolved in 10 mL of CH_2Cl_2, the solution cooled in an ice-bath, and 0.36 g (2.37 mmol) of DBU dissolved in 5 mL of CH_2Cl_2 was added dropwise while stirring. The color of the solution promptly changed from bright-yellow to red. TLC analysis of the reaction mixture after 5 min confirmed that all starting material was converted to product. Another 10-mL portion of CH_2Cl_2 was added, followed by dropwise addition of 142 mg (2.37 mmol) of acetic acid. The mixture was transferred to a separatory funnel and washed with 2 mL of H_2O, then dried over $MgSO_4$, and the solvent carefully rotovapped at 0 °C in order to avoid losses of the relatively volatile 6-vinylfulvene. The ^{1}H NMR spectrum of the crude product was devoid of any impurities. A pure sample of **1** was obtained by flash chromatography (n-pentane) as a red oil (163 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.55 (d, J = 10.0 Hz, 1H), 5.65 (d, J = 16.5 Hz, 1H), 6.24 (m, 1H), 6.50 (m, 1H), 6.57 (m, 2H), 6.78 (d, J = 11.4 Hz, 1H), 6.97 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 119.0, 125.2, 125.7, 132.4, 133.6, 134.4, 137.3, 146.5 ppm. HRMS (M+H): Calcd. 105.0704. Found 105.0702.

Attempted formation of 8 by the stoichiometric pyrrolidine method. To a solution of 0.52 g (5 mmol) of 3-(methylthio)propanal and 0.8 g (6.1 mmol) of freshly distilled cyclopentadiene in 10 mL of MeOH was added dropwise 0.36 g (5 mmol) of pyrrolidine at 0 °C. After the addition, the ice-bath was removed and the mixture stirred at room temperature for 30 min. Then the mixture was cooled in an ice-bath and 300 mg (5 mmol) of AcOH was added, followed by 20 mL of H_2O. The mixture was extracted with 2 × 20 mL of ether, the combined ether layers washed with 15 mL of a saturated solution of $NaHCO_3$, then with 15 mL of brine, the organic layer dried over anhydrous $MgSO_4$, and the solvent rotovapped. Flash chromatography on silica gel with 15% EtOAc/n-hexane yielded 130 mg of a 2.5/1 mixture of (**11** + **12**)/**8** (combined yield 14.2%).

Disulfide **11** (in the mixture of **11** + **12** + **8**): ^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.56 (m, 1H); 6.46 (m, 1H); 6.12 (m, 1H); 3.7 (t, J = 7.5 Hz, 1H); 3.04 (m, 2H), 2.56 (m, 2H); 2.09 (s, 3H); 2.04 (m, 2H); 1.9 (s, 3H); isomer **12**, δ: 6.38 (m, 1H), 6.35 (m, 1H); 6.31 (m, 1H); 3.75 (t, J = 7.5 Hz, 1H); 3.03 (m, 2H); 2.56 (m, 2H); 2.09 (s, 3H); 2.04 (m, 2H); 1.90 (s, 3H) ppm. Due to expected complexity, no ^{13}C NMR was taken of the 3-component mixture. LC-MS analysis: minor component **8**: m/e 152.5; disulfides **11** + **12**; m/e 200.5.

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