2-Lithio-3-methoxy-1,3-dimethycyclopentene: A Synthetic Equivalent of 2-Lithio-1,3-dimethycyclopentadiene and Useful Synthon for 6-Alkyl-1,4-dimethylfulvenes and ansa-Metallocene Complexes

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Abstract: 2-Bromo-3-methoxy-1,3-dimethycyclopentene (3) is synthesized in 85% yield in 80 g scale by 1,2-addition of MeLi to 2-bromo-3-methyl-2-cyclopenten-1-one and subsequent in situ treatment of MeI. Addition of n-BuLi to the bromo-compound 3 in Et₂O affords 2-lithio-3-methoxy-1,3-dimethycyclopentene (1). Successive addition of RCHO (R=CH₃, (CH₂)₂CH₃, CH(CH₃)₂, C(CH₃)₃, Ph) and MeI to the lithium compound and aqueous acidic work-up provide cyclpentadiene compounds, 2-(CHR(OHMe))-1,3,6-trimethylfulvene (2), 1,4-dimethylfulvene, 6-isopropyl-1,4-dimethylfulvene, 6-tert-buty1-1,4-dimethylfulvene and 1,4-dimethylfulvene in 67–83% yields. Ligand for an ansa-metallocene complex, CH₂C(1,3,6-Me,C₅)₂ZrCl₂, can be shortly afforded in 64% yield by reacting the lithium compound 1 with the newly synthesized 1,4-dimethylfulvene.

Key words: fulvene synthesis, cyclopentadienes, metallocenes, lithiation, organometallic reagents

Fulvenes are versatile intermediates for metallocene complexes, which can be used as catalysts for polymerization of olefins, and also serve as substrates for cycloaddition reaction by which useful organic compounds can be provided. Most of fulvenes are prepared by coupling reaction of cyclopentadiene or substituted cyclopentadienes with aldehydes or ketones. 1,4-Disubstituted or 1,4,6-trisubstituted fulvenes cannot be afforded by the synthetic route. If a 1,3-disubstituted cyclopentadiene is reacted with an aldehyde or ketone aiming to prepare a 1,4,6-substituted fulvene, the substituents are situated mainly at 1,3-positions in the resulting fulvene due to steric reason. Other routes for synthesis of fulvene derivatives have been described but, in those cases, the products still have substituents on 1- and 3-positions. Syntheses of 1,2,3,4-tetramethylfulvene and 1,2,3,4,6-pentamethylfulvene and their use for preparation of useful metallocene complexes were reported.

Very recently, we have reported a synthetic route to obtain 1,4,6-substituted fulvenes (Scheme 1). The synthetic route contains protection/de-protection of carbonyl, which is not desirable for large-scale synthesis, and most intermediates were purified by column chromatography. In order for a metallocene complex to have commercial viability, scalable synthesis should be ensured. Herein, we report a more convenient and scaleable synthetic route for the fulvenes. A key intermediate of the synthetic route is 2-lithio-3-methoxy-1,3-dimethycyclopentene (1), which has potential to react with various electrophiles. Because the methoxy group can be easily eliminated by aqueous acidic work-up to furnish cyclopentadiene compounds, compound 1 is a synthetic equivalent of 2-lithio-1,3-dimethycyclopentadiene (Scheme 2).

Scheme 1 Previous synthetic route for 1,4,6-substituted fulvene

Scheme 2
added to the lithium alkoxide. This might be attributed to the presence of some proton donors in the reaction mixture, e.g., water in DMF. Complete ether formation was achieved by extra addition of NaH to the reaction mixture. The compound was easily purified by vacuum distillation.

![Scheme 3](image)

Addition of aldehydes to the lithium compound 1 and subsequent treatment of Mel and final aqueous 2 N HCl work-up furnished the desired cyclopentadiene compounds 4–8 in 60–84% yields (Scheme 4). Solvent change to DMF and an additional addition of NaH are required for the complete formation of methyl ethers. Elimination to DMF and an additional addition of NaH are required for isomers. Signals of vinyl proton and gish with the identical conditions. The fulvene pounds work-up furnished the desired cyclopentadiene compounds with the same reaction. The fulvene furnishes the desired cyclopentadiene compounds with the presence of some proton donors in the reaction mixture, e.g., water in DMF. Complete ether formation was achieved by extra addition of NaH to the reaction mixture. The compound was easily purified by vacuum distillation.

![Scheme 4](image)

Compound 8 can be prepared in one step from compound 2 (Scheme 5). The step is composed of successive treatments of five reagents but it can be conducted in one pot in 64% overall yield. 1,2-Addition of MeLi to 2 in THF afforded lithium tertiary alkoxide, which was directly lithiated by the addition of two equivalents of t-BuLi. Formaldehyde gas, which was generated by heating paraformaldehyde in the presence of catalytic amount of p-toluenesulfonic anhydride, was added and then the resulting dilithium salt was transformed to methyl ether by treatment of Mel in DMF. The same one-pot procedure did not give the desired compounds 4–6. Addition of the dilithium salts to the aldehydes containing α-protons might trigger some side reaction such as deprotonation reaction and subsequent the aldol condensation.

![Scheme 5](image)

The fulvenes were afforded by treatment of NaH to the cyclopentadiene compounds 4–6 and 8 in pentane or hexane at room temperature in 69–83% yield (Scheme 4). The yellow color appeared as the reaction proceeded. In the case of bulky t-butyl compound 7, the reaction was sluggish with the identical conditions. The fulvene 12 was successfully generated by treatment of more reactive KH at 35–40 °C for 2 days in 67% yield. Fulvenes 9–12 were simply purified by passing the residue through short pad of silica gel eluting with pentane or hexane. Fulvene 13 was so volatile that it was isolated by bulb-to-bulb distillation under the vacuum after pentane was removed by vacuum at low temperature (~30 °C). Polymerization of 13 to a viscous residue is frequently observed during the distillation but it can be avoided when the pentane solution is thoroughly washed with water before distillation. A cyclopentadienyl anion formed in the presence of NaH might initiate the polymerization. The 1H NMR, 13C NMR spectra, and the high-resolution mass data were in agreement with the fulvene structures.
complex was prepared in five steps from 1,4-pentadiyne with low overall yield (6.8%). The starting material, 1,4-pentadiyne, was not readily available and the intermediates were purified mainly by column chromatography. By using the lithium compound 1 and newly synthesized fulvene 13, compound 14 was prepared in one step in 64% yield (Scheme 6). The compound 14 was easily purified by passing the crude residue through short pad of alumina eluting with hexane.

**Scheme 6**

In conclusion, short and scalable synthesis of 6-alkyl-1,4-dimethylfulvenes (alkyl = methyl, n-propyl, isopropyl, r-butyl) is achieved in two steps in overall 47–59% yields from 2-bromo-3-methoxy-1,3-dimethylcyclopentadiene (3), which can be easily synthesized in 80 g scale from 2-bromo-3-methyl-2-cyclopenten-1-one (2). 1,4-Dimethylfulvene (13) was synthesized from 2 in two steps in 53% overall yield. Key intermediate of the synthetic route, 2-lithio-3-methoxy-1,3-dimethylcyclopentene (1), can react with newly synthesized 1,4-dimethylfulvene (13) to give a bicyclopentadiene compound 14, which can be used for the synthesis of a useful ansa-metalloocene complex, CH2C(1,3-Me2Cp)2ZrCl2 (15).

All manipulations were performed under an inert atmosphere using standard glove box and Schlenk techniques. Pentane, hexane, THF, and Et2O were distilled from benzophenone keyl. DMF was purified by vacuum distillation and subsequent contacting with molecular sieves. NMR spectra were recorded on a Varian Mercury plus 400. Mass spectra were obtained on a Micromass VG Autospec.

### 2-Bromo-3-methoxy-1,3-dimethylcyclopentene (3)

Mel as complex with LiBr (300 mL, 1.5 M in Et2O 456 mmol) was added to a flask (1 L) and Et2O was removed by vacuum. THF (200 mL) was added at –78 °C and compound 2 (80.g, 456 mmol) dissolved in THF (200 mL) was added with syringe pump for 1 h. The solution was stirred for 1 h at –78 °C. The solvent was removed by vacuum. Anhyd DMF (400 mL) and Mel (64.8 g, 456 mmol) were added successively. The solution was stirred for 2 h. NaH (11.0 g, 450 mmol) and Mel (64.8 g, 456 mmol) were additionally added and the solution was stirred overnight at 40 °C. Water (800 mL) and hexane (1600 mL) were added. Organic phase was collected and washed with brine (3 × 400 mL). The organic phase was dried with anhyd Na2CO3 and solvent was removed with rotary evaporator. Anhyd MgSO4 should not be used as a drying agent because it causes the elimination reaction. The product was isolated and purified by vacuum distillation (50 °C/0.5 torr); yield: 85% (80 g).

1H NMR (CDCl3): δ = 3.11 (s, 3 H, OCH3), 2.42–2.24 (m, 2 H, CH2), 2.18 (ddd, J = 14.0, 9.2, 4.0 Hz, 1 H, CH2). 1.92 (ddd, J = 14.4, 9.2, 5.6 Hz, 1 H, CH2), 1.82 (s, 3 H, CH3), 1.36 (s, 3 H, CH3).

13C{1H} NMR (CDCl3): δ = 141.50, 121.79, 88.36, 50.30, 34.83, 31.40, 26.35, 16.37.

### 2-(1-Methoxyethyl)-1,3-dimethyl-1,3-cyclopentadiene (4)

Compound 3 (10.0 g, 48.8 mmol) was dissolved in Et2O (60 mL) and the solution was cooled to –30 °C. n-BuLi (19.5 mL, 2.5 M in hexane, 48.8 mmol) was added dropwise and the solution was allowed to warm to r.t. The solution was stirred for 20 min at –30 °C. The volatile was removed by vacuum. Anhyd DMF (50 mL) and NaH (11.7 g, 48.8 mmol) were added and the solution was stirred for 30 min at r.t. Mel (13.9 g, 97.6 mmol) was added and the resulting mixture was stirred overnight. Water (100 mL) and hexane (100 mL) were added and the organic phase was collected which was washed with brine (150 mL). Solvent was removed with rotary evaporator and the residue was dissolved in EtOAc (10 mL). Aqueous HCl (2N, 30 mL) was added and the two-phase mixture was shaken vigorously for 2 min. Water phase was removed and the organic phase was washed with sat aq NaHCO3 (40 mL). The organic phase was dried with anhyd MgSO4 and solvent was removed with rotary evaporator. Analysis of the 1H and 13C NMR spectra indicated that the crude residue was fairly clean and it was used for the next reaction without further purification; yield: 60% (45.0 g).

1H NMR (CDCl3): δ = 5.78 (d, J = 2.0 Hz, 1 H, sCH), 4.31 (q, J = 6.4 Hz, 1 H, CHOCH3), 3.17 (s, 3 H, OCH3), 2.77 (s, 2 H, CH2), 2.00 (q, J = 2.0 Hz, 3 H, CH2), 1.98 (s, 3 H, CH3), 1.35 (d, J = 6.4 Hz, 3 H, CHCH3).

13C{1H} NMR (CDCl3): δ = 142.63, 140.07, 139.64, 124.83, 73.37, 55.95, 44.28, 21.01, 15.43, 13.78.

HRMS (EI): m/z calcd for C10H18O: 152.1201; found: 152.1203.

### 2-(1-Methoxybutyl)-1,3-dimethyl-1,3-cyclopentadiene (5)

The compound was synthesized according to the method and conditions used for 4 by using 3 (2.00 g, 9.75 mmol) and butanal (0.773 g)
g. 10.7 mmol). The crude residue was used for the next reaction without further purification; yield: 68% (1.19 g).

1H NMR (CDCl3): δ = 5.83 (d, J = 1.6 Hz, 1 H, =CH), 4.17 (t, J = 7.2 Hz, 1 H, CHOCH3), 3.21 (s, 3 H, OCH3), 2.84 (quintet, J = 6.2 Hz, 2 H, CH2), 2.03 (q, J = 1.6 Hz, 3 H, CH3), 1.87–1.78 (m, 1 H, CH(CH3)CH2), 1.65–1.55 (m, 1 H, CH2CH2CH3), 1.46–1.34 (m, 2 H, CH2CH3), 0.94 (t, J = 7.6 Hz, 3 H, CH2CH3).

13C{1H} NMR (CDCl3): δ = 142.67, 140.79, 138.61, 124.67, 77.55, 55.89, 44.14, 37.35, 19.56, 14.13, 13.82.

HRMS (EI): m/z calcd for C13H22O: 180.1514; found: 180.1512.

2-(1-Methoxy-2-methylpropyl)-1,3-dimethyl-1,3-cyclopentadiene (6)

The compound was synthesized according to the method and conditions used for 4 by using 3 (5.00 g, 24.4 mmol) and isobutylaldehyde (1.94 g, 26.9 mmol). The crude residue was used for the next reaction without further purification; yield: 73% (3.19 g).

HRMS (EI): m/z calcd for C13H22O: 180.1514; found: 180.1512.

2-(1-Methoxy-2,2-dimethylpropyl)-1,3-dimethyl-1,3-cyclopentadiene (7)

The compound was synthesized according to the method and conditions used for 4 by using 3 (1.00 g, 4.88 mmol) and trimethylaldehyde (0.462 g, 5.37 mmol). The crude residue was used for the next reaction without further purification; yield: 84% (0.796 g). Signals of two sets of isomers were observed in the 1H NMR spectrum in a 3:2 ratio. The signals for the minor isomer are marked by italic character.

1H NMR (CDCl3): δ = 5.82 (s, 1 H, =CH), 3.87, 3.74 (s, 1 H, CHOCH3), 3.20, 3.19 (s, 2 H, OCH3), 2.86, 2.80 (br s, 2 H, CH2), 2.11, 2.07 (s, 3 H, CH3), 1.96, 1.92 (s, 3 H, CH3), 0.96 (s, 9 H, CH3).

13C{1H} NMR (CDCl3): δ = 141.99, 141.88, 137.90, 124.57, 83.96, 57.69, 44.37, 14.11, 13.90.

HRMS (EI): m/z calcd for C13H22O: 180.1514; found: 180.1512.

1,4,6-Trimeptylfulvene (9)

Compound 2.89 g, 19.2 mmol) was dissolved in pentane (20 mL) and NaH (0.534 g, 22.3 mmol) was added under nitrogen. The mixture was stirred overnight at r.t. The solution turned to yellow and the by-product of NaOCH3 precipitated. The evolved hydrogen gas was removed by venting. The mixture was filtered and washed with pentane until the filtrate is colorless. The solution was passed through short pad of silica gel (5.0 g). The solvent was removed by vacuum.

1H NMR (CDCl3): δ = 6.44 (q, J = 7.6 Hz, 1 H, C=CHCH3), 6.06 (s, 1 H, =CH), 5.96 (s, 1 H, =CH), 2.25 (s, 3 H, CH3), 2.20 (d, J = 7.6 Hz, 3 H, C=CHCH3), 2.05 (s, 3 H, CH3).

13C{1H} NMR (CDCl3): δ = 145.71, 133.07, 132.73, 130.24, 129.98, 125.27, 17.44, 15.16, 12.57.

HRMS (EI): m/z calcd for C13H22: 120.0939; found: 120.0938.

6-Propyl-1,4-dimethylfulvene (10)

The compound was synthesized according to the method and conditions used for 9 by using 5 (0.973 g, 5.40 mmol) and NaH (0.154 g, 6.48 mmol); yield: 69% (0.554 g).

1H NMR (CDCl3): δ = 6.32 (t, J = 7.6 Hz, 1 H, C=CHCH2), 6.05 (s, 1 H, =CH), 5.95 (s, 1 H, =CH), 2.60 (q, J = 7.6 Hz, 2 H, C=CHCH2), 2.22 (s, 3 H, CH3), 2.04 (s, 3 H, CH3), 1.61 (sextet, J = 7.6 Hz, 2 H, CH2CH3), 1.04 (t, J = 7.6 Hz, 3 H, CH2CH3).

13C{1H} NMR (CDCl3): δ = 144.73, 138.89, 132.98, 130.24, 130.13, 125.33, 90.27, 23.06, 17.34, 14.12, 12.66.


6-Isopropyl-1,4-dimethylfulvene (11)

The compound was synthesized according to the method and conditions used for 9 by using 6 (1.19 g, 6.57 mmol) and NaH (0.189 g, 7.89 mmol); yield: 81% (0.788 g).

1H NMR (CDCl3): δ = 6.10 (d, J = 10.4 Hz, 1 H, C=CHCH2), 6.05 (s, 1 H, =CH), 5.95 (s, 1 H, =CH), 3.30 [d septet, J = 10.4, 6.4 Hz, 1 H, CH(CH3)2], 2.24 (s, 3 H, CH3), 2.04 (s, 3 H, CH3), 1.16 (d, J = 6.4 Hz, 6 H, CH2CH3).

13C{1H} NMR (CDCl3): δ = 145.54, 142.18, 133.45, 130.34, 130.09, 125.36, 27.70, 23.03, 17.03, 12.68.


6-tert-Butyl-1,4-dimethylfulvene (12)

The compound was synthesized according to the method and conditions used for 9 by using 7 (0.119 g, 0.610 mmol) and KH (0.29 g, 0.73 mmol). The reaction was so sluggish at r.t. that the mixture was heated to 35–40 °C for 2 d; yield: 67% (0.066 g).

1H NMR (CDCl3): δ = 6.46 (s, 1 H, =CH), 6.17 (s, 1 H, =CH), 5.95 (s, 1 H, CH), 2.32 (s, 3 H, CH3), 2.04 (s, 3 H, CH3), 1.38 [d, J = 0.8 Hz, 9 H, C(CH3)3].

HRMS (EI): m/z calcd for C19H26: 270.1734; found: 270.1742.
The compound was synthesized according to the method and conditions used for 9 by using 8 (14.2 g, 103 mmol) and NaH (2.47 g, 103 mmol) in pentane (100 mL). The reaction time was reduced to 3 h. Thus, the reaction mixture was filtered and washed with pentane.

The volatile product was isolated by following the work-up procedure. Thus, the reaction mixture was filtered and washed with pentane until the filtrate is colorless. The filtrate was washed thoroughly with water and dried over anhyd MgSO4. Pentane was removed under vacuum at –30 °C. The compound was isolated by bulb-to-bulb distillation at r.t. under vacuum; yield: 83% (9.07 g).

HRMS (EI): m/z calcld for C12H18: 162.1408; found: 162.1410.

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References


(8) Related acylvinyl and vinylogous synthons were comprehensively reviewed. See: Chinchilla, R.; Nájera, C. Chem. Rev. 2000, 100, 1891.

