

# STUDY ON SIMPLE METHYLATION OF 7-ISOPROPYL-4-METHYL-1-AZULENEMETHANOL AND PROPERTIES OF ITS ETHEREAL PRODUCTS\*



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**Abstract:** A novel compound, 7-isopropyl-1-methoxymethyl-4-methylazulene (**1**) was easily synthesized by direct etherification of 7-isopropyl-4-methyl-1-azulenemethanol (**2**) with methanol. The reaction occurred in several minutes in an ethereal solution at 0~5 °C (ice-water bath) catalyzed with sulfuric acid. There are some by-products including a dimer **5** and small amount of oligomers. The structures of **1** and **5** were elucidated from their spectroscopic data (<sup>1</sup>H NMR, FTIR, UV-vis and HR-MS).

**Key words:** 7-isopropyl-1-methoxymethyl-4-methylazulene; 7-isopropyl-4-methyl-1-azulenemethanol; methyl etherification

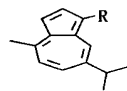
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When 7-isopropyl-4-methyl-1-azulenealdehyde (**3**) or methyl 7-isopropyl-4-methyl-1-azulenecarboxylate (**4**) is reduced with LiAlH<sub>4</sub>, the generally used acidic extraction could not result in the product 7-isopropyl-4-methyl-1-azulenemethanol (**2**). Subsequent study indicated that acidic conditions are not suitable for the reactions because compound **2** may be destroyed soon under strong acidic conditions. In 1994, the compound **2** was successfully synthesized from compounds **3** and **4** by an improved reaction method<sup>[1]</sup>. Therefore, more detailed study on the chemical properties and applications of **2** has become available.

On the basis of investigating the synthesis and properties of compound **2**, two convenient etherification methods were discovered. One was the direct ethylation of **2** with ethanol catalyzed by a mineral acid<sup>[2]</sup>; another was the reaction of **2** with gly-



1: R= CH<sub>2</sub>OMe

2: R= CH<sub>2</sub>OH

3: R= CHO

4: R= COOMe

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**Biography:** 赵振东(1960-), 男(白族), 云南昌宁人, 研究员, 博士, 主要从事萜类和类化学研究和利用、松树病虫害化学研究等方面的工作。

cidyl chloride catalyzed with a phase transfer catalyst<sup>[3,4]</sup>. The reactions are especially useful because they occurred in temperate conditions to supply azulenic ethereal compounds, which could not be prepared by generally known etherification methods.

For more understanding of the reactions and properties of the ethers, the etherification between **2** and alkyl (or aryl) alcohol or halide were further studied in detail.

As one of the serial studies and an application of direct ethyl etherification, compound **1** was synthesized successfully by the author's method<sup>[2]</sup> through the reaction between **2** and methanol as shown in Fig. 1.

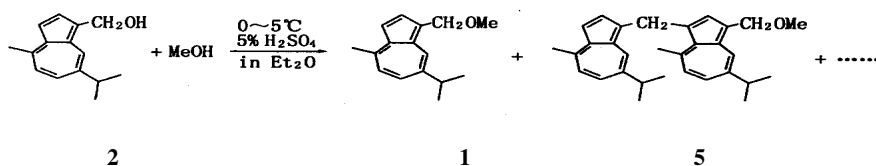


Fig. 1 Reaction of 7-isopropyl-4-methyl-1H-azulenemethanol with MeOH

## 1 Experimental

### 1.1 Reagents and equipments

Methanol, petroleum ether (60~ 90 °C), hexane, EtOAc are all analytical reagents. Silica gel used for the column chromatography is Wakogel G 300 made in Japan. Ultraviolet and visible spectra were obtained with Perkin-Elmer Lambda-6 spectroscopy. Infrared spectra were recorded by Nicolet 550 FTIR spectroscopy. High-resolution mass determinations were made with Nicolet FTMS-2000; <sup>1</sup>H NMR analysis was done with Bruker AF-300 Spectroscopy (300 MHz).

### 1.2 Preparation of **2**

Compound **2** was prepared by means of the method reported by Zhao et al.<sup>[1]</sup>. Its hexane or ethanol solution could only be stored temporarily at -20 °C because of the high reactivity. Freshly purified material was used preferably for the later reaction.

### 1.3 Methylation of **2**

A mixture of **2** (6.4 mg, 0.156 mmol) and MeOH (1 mL) resolved in 10 mL Et<sub>2</sub>O was stirred in a 50-mL flask under 0~ 5 °C (ice-water bath) and catalyzed by 5% H<sub>2</sub>SO<sub>4</sub>. The reaction was stopped by 10% Na<sub>2</sub>CO<sub>3</sub> when raw material was consumed mostly (in several minutes), estimated with TLC. The ether solution was washed with water, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. An ultramarine paste (4.5 mg, yield = 66.2%) was obtained by removing ether with a rotary evaporator under reduced pressure.

The ethereal product was separated and refined into a main product MeOA<sub>1</sub> (**1**), two by-products MeOA<sub>2</sub> (**5**) and MeOA<sub>3</sub> (**6**) through silica gel columns (φ 1.5, L 10 cm, 100~ 200 mesh) eluted with petroleum ether/EtOAc (95 and 98). The structures of products **1** and **5** were elucidated by the spectroscopic data of their UV-vis, IR, <sup>1</sup>H NMR. The by-product **6** was few to be determined.

#### 1.3.1 7-Isopropyl-4-methyl-1-methoxymethylazulene (MeOA<sub>1</sub>, **1**: an ultramarine liquid)

*R<sub>f</sub>* = 0.32 (petroleum ether/EtOAc = 98);

UV-vis (hexane), λ<sub>max</sub>. nm (log ε): 205 (3.99), 243 (4.16), 283 (4.39), 288 (4.39), 303 (3.

91), 345(3.52), 362(3.47), 581(2.51), 625(sh, 2.45), 685(sh, 1.98);

IR (in MeOH,  $\text{cm}^{-1}$ ): 2947, 2835, 1659, 1450, 1412, 1122, 980, 879, 663;

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ),  $\delta$ : 1.373(d,  $J = 7.0\text{Hz}$ , 6H, iPr-7), 2.852(s, 3H, Me-4), 3.126(hept,  $J = 7.0\text{Hz}$ , methine-7), 3.364(s, 3H, OMe), 4.933(s, 2H, methylene-1), 7.187(d,  $J = 10.5\text{Hz}$ , 1H, H-5), 7.247(d,  $J = 3.9\text{Hz}$ , 1H, H-5), 7.247(d,  $J = 3.9\text{Hz}$ , 1H, H-3), 7.543(dd,  $J = 10.5; 1.8\text{Hz}$ , 1H, H-6), 7.746(d,  $J = 3.9\text{Hz}$ , 1H, H-2), 8.441(d,  $J = 1.8\text{Hz}$ , 1H, H-8);

ESI-MS,  $m/z$ : 229(7%,  $\text{M}^+ - 1$ ), 228( $\text{M}^+$ , 39), 198(15), 197(100), 182(4.7), 167(9.1), 155(4.5), 138(7.66), 121(7.5), 65(14);

HR-MS found: 228.15078, calc. for  $\text{C}_{16}\text{H}_{20}\text{O}$ :  $\text{M} = 228.15087$ ,  $\Delta = -0.09\text{mmu} (-0.38 \times 10^{-6})$ .

1.3.2 7-Isopropyl-4-methyl-3-[(7-isopropyl-4-methyl-1-azulenyl)methyl]-1-methoxymethylazulene (MeOA<sub>2</sub>, **5**: a blue paste)

$R_f = 0.23$  (petroleum ether/EtOAc = 982);

UV-vis (hexane),  $\lambda_{\text{max}}$ . nm (log  $\epsilon$ ): 217(4.11), 246(4.31), 290(4.53), 352(3.74), 369(3.74), 606(2.64), 650(sh, 2.58), 716(sh, 2.33);

IR (in MeOH,  $\text{cm}^{-1}$ ): 2947, 2835, 1654, 1450, 1412, 1122, 980, 883, 617;

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ),  $\delta$ : 1.285(d,  $J = 6.8\text{Hz}$ , 6H, iPr-7'), 1.360(d,  $J = 7.0\text{Hz}$ , 6H, iPr-7), 2.803(s, 3H, Me-4), 2.879(s, 3H, Me-7'), 3.038(hept,  $J = 6.8\text{Hz}$ , 1H, methine-7'), 3.060(hept,  $J = 7.0\text{Hz}$ , 1H, methine-7), 3.364(s, 3H, OMe), 4.880(s, 2H, methylene-3, 1'), 4.996(s, 2H, methylene-1), 6.952(d,  $J = 10.8\text{Hz}$ , 1H, H-5), 7.064(d,  $J = 10.7\text{Hz}$ , 1H, H-5'), 7.131(d,  $J = 4.0\text{Hz}$ , 1H, H-3'), 7.141(d,  $J = 4.0\text{Hz}$ , 1H, H-2'), 7.376(dd,  $J = 10.8; 2.0\text{Hz}$ , 1H, H-6), 7.463(dd,  $J = 10.7; 1.7\text{Hz}$ , 1H, H-6'), 7.482(s, 1H, H-2), 8.294(d,  $J = 1.7\text{Hz}$ , 1H, H-8'), 8.341(d,  $J = 2.0\text{Hz}$ , 1H, H-8);

ESI-MS,  $m/z$ : 425(9%,  $\text{M}^+ - 1$ ), 424(26,  $\text{M}^+$ ), 380(4), 379(12), 335(4), 321(4), 321(4), 321(4), 293(6), 292(4), 291(5), 289(6), 279(5), 278(4), 277(5), 276(6), 240(13), 210(16), 209(100), 198(5), 197(19), 195(5), 194(7), 193(8), 184(11), 183(4), 179(8), 178(7), 169(7), 167(13), 166(6), 165(21), 155(6), 154(5), 153(10), 152(11), 149(5), 141(6), 138(4), 128(5), 121(6), 115(6), 97(4), 95(5), 65(4);

HR-MS found: 424.27424, calc. for  $\text{C}_{31}\text{H}_{36}\text{O}$ :  $\text{M} = 424.27607$ ,  $\Delta = -1.8\text{mmu} (-4.3 \times 10^{-6})$ .

## 2 Results and discussion

### 2.1 Methyl etherification of **2**

Mixture of compound **2** and methanol resolved in diethyl ether could not have any reaction without catalyst. Etherification took place immediately in an ice-water bath with small amount of sulfuric acid to produce a main product MeOA<sub>1</sub>(**1**), a dimmer MeOA<sub>2</sub>(**5**), and a trimer MeOA<sub>3</sub>(**6**) accompanied with some azulenic oligomers.

The reaction was affected by amount of catalyst, temperature and solvent. For example, no expected product except green azulenic oligomers were obtained in methanol solution catalyzed by 10% sulfuric

acid under room temperature. Sulfuric acid is better than nitric acid as a catalyst, while hydrochloric acid can not be used because it may completely destroy the material and the products. The yield of total ethereal compounds achieved to 66% under the best conditions, namely in ethyl ether solvent, ice-water bath, 5% sulfuric acid catalyst, 3 minutes, and the reaction was stopped immediately with 10% sodium bicarbonate when alcohol **2** was consumed mostly traced with TLC.

In comparison with ethylation, methyl etherification produced less ethereal compound and more azulenic hydrocarbon by-products according to the TLC analysis.

## 2.2 Separation and purification of the reaction products

The reaction product is a mixture that can be separated to azulenic hydrocarbons, ethereal compounds and polar compounds with a silica gel column eluted by petroleum ether/EtOAc (955). Pure MeOA<sub>1</sub>(**1**), MeOA<sub>2</sub>(**5**) and a small amount of MeOA<sub>3</sub>(**6**) were obtained through repeated silica gel column chromatography eluted by petroleum ether/EtOAc(982).

These ethereal compounds are so reactive that they become less and less while separated and purified through a silica gel column. This may be due to the weak acidity of silica gel, high air temperature, oxygen in air, etc.

## 2.3 Properties and identification of **1**

The main product **1** is a bright ultramarine paste that is very reactive to decompose into less polar azulenic hydrocarbons and more polar polymers during separation and purification.

In UV-vis spectrum, **1** has absorption at  $\lambda_{\max}$  581 nm which is very similar to the pattern of its raw material **2**. IR spectrum showed a strong absorption at  $1\ 122\ \text{cm}^{-1}$  that means an ethereal bond. Its high-resolution mass spectrum described a formula of C<sub>16</sub>H<sub>20</sub>O that satisfied with the calculation for 7-isopropyl-1-methoxymethyl-4-methylazulene. MS showed a molecular ion peak  $m/z$  228 and a base peak  $m/z$  197. <sup>1</sup>H NMR spectrum showed a singlet at  $\delta$  3.364 attributed to methoxy protons, a singlet at  $\delta$  4.993 to methylene-1 protons and others(see 1.3.1). These data elucidated that the structure of **1** is 7-isopropyl-1-methoxymethyl-4-methylazulene.

## 2.4 Ethereal by-products

The major by-product compound **5** is an ultramarine paste. UV-vis indicated  $\lambda_{\max}$  606 nm that had a red shift for 25 nm than that of compound **1**. It also showed a strong absorption at  $1\ 122\ \text{cm}^{-1}$  due to the ethereal bond. <sup>1</sup>H NMR showed a singlet at  $\delta$  3.364 attributed to the methoxy group, two singlets at  $\delta$  4.996 and 4.880 to the methylene-1 and methylene-3, 1', respectively. The MS gave the molecular ion peak of  $m/z$  424, a base peak of  $m/z$  209. HR-MS gave a formula of C<sub>31</sub>H<sub>36</sub>O. Analytic data elucidated the structure of MeOA<sub>2</sub> to be 7-isopropyl-4-methyl[(7-isopropyl-4-methyl-1-azulenyl)methyl-1-methoxymethyl-4-methylazulene which has one more guaiazulene unit than MeOA<sub>1</sub>.

## 2.5 Azulenic hydrocarbon by-products

It is confirmed that there are 7, 7'-diisopropyl-4, 4'-dimethyl-1, 1'-methylenediazulene, 7-isopropyl-4-methyl-1, 3-bis[(7-isopropyl-4-methyl-1-azulenyl)-methyl] azulene, in the less polar hydrocarbons, identified<sup>[1,2]</sup> by silica gel TLC. The polar hydrocarbon is a mixture of polymerized azulenoids that is necessary to be investigated in detail. Polymers increase during over-reacted methylation or repeated

column chromatography due to the high reactivity of the ethers.

### 3 Conclusion

7-Isopropyl-4-methyl-1-azulenemethanol has no reaction with methanol in ether without catalyst. Methyl etherification finished easily in several minutes while about 5% sulfuric acid was added into the mixture, to produce 7-isopropyl-1-methoxymethyl-4-methylazulene, accompanied with other ethereal compounds and azulene oligomers. Yield of the total ethereal compounds was about 60%. Ethers **1**, **5** and **6** are so reactive to transfer into azulene oligomers during the separation and purification, especially in warm seasons.

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## 7-异丙基-4-甲基-1-甲醇的简单甲基化反应及其产物性质研究

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**摘要:** 研究了新化合物 7-异丙基-1-甲氧甲基-4-甲基-1-甲醇 (**1**) 的合成方法及其物理化学性质。通过 7-异丙基-4-甲基-1-甲醇 (**2**) 与甲醇之间的简单醚化反应即可以制得化合物 **1**, 比常规醚化的反应条件温和而简单易行, 仅用乙醚溶剂、无机酸催化剂和 0~5 °C 的反应温度, 在数分钟内即可完成反应。反应还生成二聚体化合物 (**5**) 及其它少量多聚体副产物。经过 <sup>1</sup>H NMR, FTIR, UV-vis, HR-MS 等波谱分析证实了新化合物 **1** 和 **5** 的化学结构。

**关键词:** 7-异丙基-1-甲氧甲基-4-甲基-1-甲醇; 7-异丙基-4-甲基-1-甲醇; 甲基醚化