

**A CONVENIENT, ONE-POT AZULENE SYNTHESIS FROM CYCLOHEPTA-
[b]FURAN-2-ONES AND VINYL ETHER AND ITS ANALOGUES. (II).¹
ACETALS AS REAGENT²**

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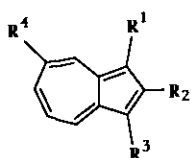
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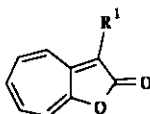
Abstract - Various functionalized azulene derivatives were synthesized in one-pot and by the reaction of cyclohepta[b]furan-2-ones with acetals of several aldehydes and ketones on heating at 160-190 °C in neat or aprotic solvent.

Recently, we have reported¹ that various functionalized azulene derivatives 1 and 2 were synthesized in one-pot and by the reaction of cyclohepta[b]furan-2-ones (3) and its 5-isopropyl derivatives 4 with vinyl ether, vinyl acetates, dihydrofurans, and dihydropyrans as reagent.

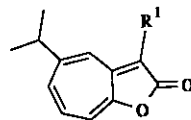


1: R⁴=H

2: R⁴=ipr



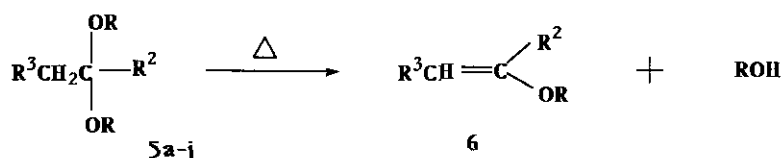
3a-c



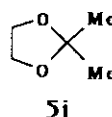
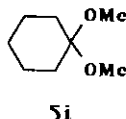
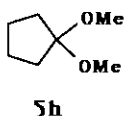
4a-c

In this communication we wish to report another convenient method to prepare similar azulenes 1 and 2 by the reaction of 3 and 4 with acetals 5 of some

aldehydes and ketones which are expected to afford corresponding vinyl ethers **6** at high reaction temperatures by elimination of one mole of alcohol.

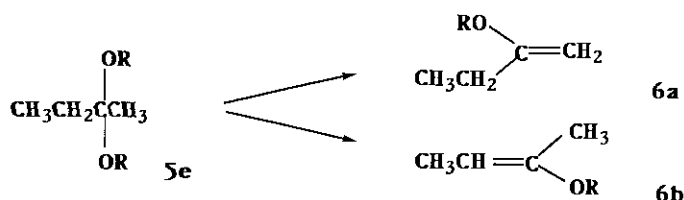


Acetals used in this study are those of acetaldehyde (**5a**), propionaldehyde (**5b**), isovaleraldehyde (**5c**), acetone (**5d**), methyl ethyl ketone (**5e**), diethyl ketone (**5f**), tert-butyl methyl ketone (**5g**), cyclopentanone (**5h**), cyclohexanone (**5i**), and 2,2-dimethyldioxolane (**5j**).



Generally, cyclohepta[b]furan-2-ones **3a-e** and **4a-e** having various functional groups (a: $\text{R}^1=\text{H}$, b: $\text{R}^1=\text{COOMe}$, c: $\text{R}^1=\text{COOEt}$, d: $\text{R}^1=\text{COMe}$, e: $\text{R}^1=\text{CN}$) at C-3 are heated neat or in aprotic solvent with an excess of acetals **5** at 160-190 °C in a Pyrex sealed tube. After removal of unreacted acetals in vacuo, azulenes produced are easily separated by silica gel column chromatography.

Asymmetrical acetal **5e** gives almost 1:3 ratio of 2-ethyl- (**1l**) and 2,3-dimethylazulenes (**1m**), because **5e** is decomposed into two isomeric vinyl ethers **6a** and **6b**.



The reaction of the present azulene synthesis is believed to proceed via [8+2]-cycloadducts of cyclohepta[b]furanones (**3** and **4**) with generated vinyl ethers **6**, as in the former case.¹ Cyclic acetals **5h** and **5i** give 1,2-annulated azulenes in good yields (see Tables 1 and 2), while 2,2-dimethyldioxalane **5j** gives azulene **1i** only in a low yield (12%). Structures, properties, and yield of azulenes obtained by this method are shown in Table 1.

Table. 1 Synthesis of Azulene Derivatives by the Reaction of 3 and 4 with 5.

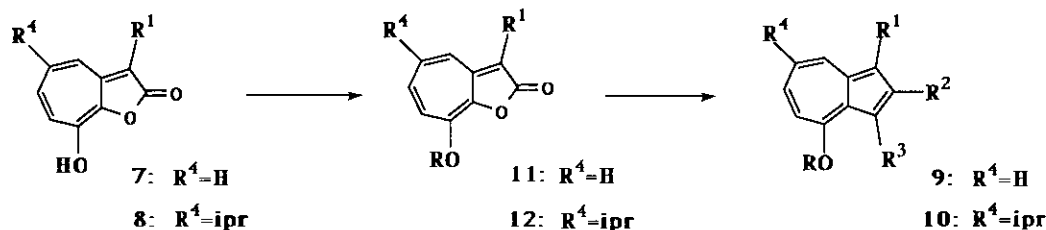
Reagent		Azulene Derivatives				Color / Form		mp	Yield
		R ¹	R ²	R ³				(°C)	(%)
3a	5a	1a	H	H	H	blue	needles	98-99	2
3c	5a	1b ¹	COOEt	H	H	violet	oil	---	64
3d	5a	1c	COMe	H	H	violet	oil	---	37
3e	5a	1d	CN	H	H	violet	prisms	51-52	75
3b	5b	1e ³	COOMe	H	Me	violet	needles	62-63	64
3d	5b	1f ⁷	COMe	H	Me	violet	oil	---	52
3e	5b	1g	CN	H	Me	violet	needles	97-98	48
3b	5c	1h	COOMe	H	ipr	violet	oil	---	20
3b	5d	1i	COOMe	Me	H	reddish violet	needles	42-43	92
3d	5d	1j	COMe	Me	H	violet	prisms	41-42	93
3e	5d	1k	CN	Me	H	violet	needles	109-110	85
3b	5e	1l ⁴	COOMe	Et	H	reddish violet	needles	40-41	20
		1m ⁴	COOMe	Me	Me	violet	needles	42-43	70
3b	5f	1n	COOMe	Et	Me	violet	oil	---	67
3d	5f	1o	COMe	Et	Me	violet	oil	---	55
3e	5f	1p ⁴	CN	Et	Me	violet	needles	52-53	91
3b	5g	1q	COOMe	t-Bu	H	violet	oil	---	7
3b	5h	1r ⁵	COOMe	-(CH ₂) ₃ -		violet	needles	97-98	30
3d	5h	1s	COMe	-(CH ₂) ₃ -		violet	plates	122-123	87
3e	5h	1t ⁵	CN	-(CH ₂) ₃ -		violet	needles	137-138	89
3c	5i	1u	COOEt	-(CH ₂) ₄ -		violet	oil	---	64
3d	5i	1v ⁸	COMe	-(CH ₂) ₄ -		violet	needles	115-116	28
3e	5i	1w ⁵	CN	-(CH ₂) ₄ -		violet	needles	82-83	95
3b	5j	1i	COOMe	Me	H	reddish violet	needles	42-43	12
4d	5a	2a	COMe	H	H	violet	oil	---	11
4e	5a	2b	CN	H	H	violet	oil	---	40
4b	5b	2c	COOMe	H	Me	violet	needles	60-61	48
4c	5b	2d	COOEt	H	Me	violet	needles	58-59	25
4d	5b	2e ⁹	COMe	H	Me	violet	needles	62-63	13
4e	5b	2f	CN	H	Me	violet	oil	---	63
4b	5d	2g	COOMe	Me	H	violet	oil	---	64
4d	5d	2h	COMe	Me	H	violet	oil	---	86
4e	5d	2i	CN	Me	H	violet	prisms	50-51	95
4d	5f	2j	COMe	Et	Me	violet	oil	---	30
4e	5f	2k	CN	Et	Me	violet	oil	---	77
4d	5h	2l ³	COMe	-(CH ₂) ₃ -		violet	needles	141-142	77
4e	5h	2m	CN	-(CH ₂) ₃ -		violet	needles	91-92	83
4d	5i	2n ³	COMe	-(CH ₂) ₄ -		violet	needles	85-86	54
4e	5i	2o	CN	-(CH ₂) ₄ -		violet	needles	76-77	81

Table. 2 Synthesis of Azulene Derivatives by the Reaction of 7 and 8 with 5.

Reagent		Azulene Derivatives				Color / Form		mp	Yield
		R ¹	R ²	R ³	OR			(°C)	(%)
7c	5a	9a ⁶	COOEt	H	H	OEt	reddish violet needles	82-83	33
7d	5a	9b	COMe	H	H	OEt	reddish violet needles	49-50	9
7e	5a	9c	CN	H	H	OEt	reddish violet needles	102-103	50
7c	5b	9d ⁶	COOEt	H	Me	OMe	violet needles	85-87	51
7d	5b'	9e ¹⁰	COMe	H	Me	OEt	violet needles	53-54	15
7e	5b'	9f	CN	H	Me	OEt	violet needles	145-146	61
7c	5d	9g	COOEt	Me	H	OMe	reddish violet needles	87-88	49
7d	5d	9h ¹¹	COMe	Me	H	OMe	reddish violet needles	90-91	18
7e	5d	9i	CN	Me	H	OMe	reddish violet needles	130-131	50
7c	5f	9j	COOEt	Et	Me	OEt	reddish violet needles	49-59	58
7e	5f	9k	CN	Et	Me	OEt	reddish violet needles	91-92	59
7d	5h	9l	COOMe	-(CH ₂) ₃ -		OMe	reddish violet needles	109-110	47
7d	5h	9m ³	COMe	-(CH ₂) ₃ -		OMe	reddish violet needles	152-153	19
7e	5h	9n ¹²	CN	-(CH ₂) ₃ -		OMe	reddish violet needles	170-171	38
7c	5i	9o ³	COOEt	-(CH ₂) ₄ -		OEt	reddish violet needles	78-79	47
7e	5i	9p	CN	-(CH ₂) ₄ -		OEt	violet prisms	167-168	53
8c	5a	10a ¹³	COOEt	H	H	OEt	reddish violet oil	---	24
8d	5a	10b	COMe	H	H	OEt	reddish violet oil	---	7
8e	5a	10c	CN	H	H	OEt	reddish violet needles	97-98	42
8c	5b'	10d ⁶	COOEt	H	Me	OEt	violet oil	---	58
8d	5b'	10e ¹⁴	COMe	H	Me	OEt	violet needles	72-73	16
8e	5b'	10f ¹⁵	CN	H	Me	OEt	violet prisms	142-143	50
8d	5d	10g	COMe	Me	H	OMe	reddish violet needles	82-83	38
8e	5d	10h ¹⁶	CN	Me	H	OMe	reddish violet prisms	128-129	39
8c	5f	10i	COOEt	Et	Me	OEt	reddish violet oil	---	51
8e	5f	10j	CN	Et	Me	OEt	violet needles	108-109	60
8d	5h	10k ¹⁷	COMe	-(CH ₂) ₃ -		OMe	reddish violet needles	107-108	11
8e	5h	10l	CN	-(CH ₂) ₃ -		OMe	reddish violet needles	164-165	45
8c	5i	10m	COOEt	-(CH ₂) ₄ -		OEt	reddish violet needles	138-139	42
8e	5i	10n ¹⁸	CN	-(CH ₂) ₄ -		OEt	violet needles	196-197	54

Similarly, 8-hydroxycyclohepta[b]furan-2-ones (7 and 8) were smoothly converted to 8-alkoxyazulenes (9 and 10) via 8-alkoxyl derivatives (11 and 12). Addition of trialkyl orthoformate as alkylating agents to the reaction mixture results in an almost quantitative yield of 8-alkoxylazulenes.

Structures and yields of 8-alkoxyazulenes 9 and 10 are shown in Table 2.



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- 2) Presented at the 57th National Meeting of the Chemical Society of Japan, Sendai, 1988, Abstr. No. E214.
- 3) (a) P.-W. Yang, M. Yasunami, and K. Takase, *Tetrahedron Lett.*, 1971, 4275; (b) K. Takase, and M. Yasunami, *Yuki Gosei Kagaku Kaishi*, 1981, **39**, 1172.
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- 6) T. Yanagisawa, S. Wakabayashi, T. Tominaga, M. Yasunami, and K. Takase, *Chem. Pharm. Bull.*, 1988, **36**, 641.
- 7) **1f**: ^1H Nmr (300 MHz, CDCl_3) δ =2.53 (3H, s, Me), 2.63 (3H, s, COMe), 7.27 (1H, t, J =10 Hz, H-5), 7.41 (1H, t, J =10 Hz, H-7), 7.66 (1H, t, J =10 Hz, H-6), 8.01 (1H, s, H-2), 8.23 (1H, d, J =10 Hz, H-4), and 9.72 (1H, d, J =10 Hz, H-8); ^{13}C Nmr (75.5 MHz, CDCl_3) δ =12.4 (q), 29.0 (q), 123.0 (s), 125.3 (s), 125.9 (d), 128.5 (d), 135.2 (d), 138.6 (d), 139.0 (d), 130.2 (s), 141.2 (d), 141.6 (s), and 195.0 (s).
- 8) **1v**: ^1H Nmr (300 MHz, CDCl_3) δ =1.95 (4H, q, J =3.0 Hz, $(\text{CH}_2)_2$), 2.66 (3H, s, COMe), 3.00 (2H, br, CH_2), 3.26 (2H, br, CH_2), 7.34 (1H, t, J =10 Hz, H-5), 7.43 (1H, t, J =10 Hz, H-7), 7.64 (1H, t, J =10 Hz, H-6), 8.18 (1H, d, J =10 Hz, H-4), and 9.44 (1H, d, J =10 Hz, H-8); ^{13}C Nmr (75.5 MHz, CDCl_3) δ =22.7 (t), 22.9 (t), 23.7 (t), 28.6 (q), 32.4 (t), 123.5 (s), 126.1 (d), 116.8 (s), 128.3 (d), 132.6 (d), 136.3 (d), 137.5 (d), 139.7 (s), 140.9 (s), 151.5 (s), and 196.3 (s).
- 9) **2e**: ^1H Nmr (300 MHz, CDCl_3) δ =1.22 (6H, d, J =6.9 Hz, CHMe_2), 2.57 (3H, s, Me), 2.66 (3H, s, COMe), 3.19 (1H, m, J =6.9 Hz, CHMe_2), 7.36 (1H, t, J =10 Hz, H-5), 7.69 (1H, dd, J =10 and 1.8 Hz, H-6), 8.06 (1H, s, H-2), 8.22 (1H, d, J =10 Hz, H-4), and 9.91 (1H, d, J =1.8 Hz, H-8); ^{13}C Nmr (75.5 MHz, CDCl_3) δ =12.4 (q), 24.6 (q), 29.1 (q), 39.1 (d), 122.2 (s), 124.3 (s), 125.9 (d), 133.7 (d), 137.9 (d), 139.0 (d), 140.4 (s), 141.5 (d), 141.8 (s), 150.2 (s), and 194.9 (s).
- 10) **9e**: ^1H Nmr (300 MHz, CDCl_3) δ =1.56 (3H, t, J =6.9 Hz, OCH_2Me), 2.63 (3H, s,

- Me), 2.75 (3H, s, COMe), 4.29 (2H, q, $J=6.9$ Hz, OCH_2Me), 6.93 (1H, d, $J=11$ Hz, H-5), 7.13 (1H, t, $J=10$ Hz, H-7), 7.54 (1H, ddd, $J=11$, 10, and 0.9 Hz, H-6), 7.79 (1H, s, H-2), and 9.42 (1H, dd, $J=10$ and 0.9 Hz, H-8); ^{13}C Nmr (75.5 MHz, CDCl_3) $\delta=14.6$ (q), 18.2 (q), 29.2 (q), 65.2 (t), 111.6 (d), 123.0 (d), 123.5 (s), 126.2 (s), 129.9 (s), 137.8 (d), 138.9 (s), 139.8 (d), 140.1 (d), 166.0 (s), and 195.3 (s).
- 11) **9h**: ^1H Nmr (300 MHz, CDCl_3) $\delta=2.26$ (3H, s, Me), 2.81 (3H, s, COMe), 4.13 (3H, s, OMe), 7.10 (1H, d, $J=11$ Hz, H-5), 7.27 (1H, t, $J=10$ Hz, H-7), 7.29 (1H, s, H-3), 7.62 (1H, t, $J=10$ Hz, H-6), and 9.45 (1H, d, $J=10$ Hz, H-8).
- 12) **9n**: ^1H Nmr (200 MHz, CDCl_3) $\delta=2.48$ (2H, q, $J=7.3$ Hz, CH_2), 3.10 (2H, q, $J=7.3$ Hz, CH_2), 3.25 (2H, t, $J=7.3$ Hz, CH_2), 4.09 (3H, s, OMe), 6.95 (1H, d, $J=10$ Hz, H-5), 7.07 (1H, t, $J=10$ Hz, H-7), 7.57 (1H, t, $J=10$ Hz, H-6), and 8.28 (1H, d, $J=10$ Hz, H-8).
- 13) **10a**: ^1H Nmr (300 MHz, CDCl_3) $\delta=1.38$ (6H, d, $J=6.9$ Hz, CHMe_2), 1.44 (3H, t, $J=7.2$ Hz, OCH_2Me), 1.56 (3H, t, $J=6.9$ Hz, OCH_2Me), 3.14 (1H, m, $J=6.9$ Hz, CHMe_2), 4.34 (2H, q, $J=6.9$ Hz, OCH_2Me), 4.40 (2H, q, $J=7.2$ Hz, OCH_2Me), 7.07 (1H, d, $J=11.2$ Hz, H-5), 7.40 (1H, d, $J=4.1$ Hz, H-3), 7.63 (1H, dd, $J=11.2$ and 1.5 Hz, H-6), 8.13 (1H, d, $J=4.1$ Hz, H-2), and 9.72 (1H, d, $J=1.5$ Hz, H-8); ^{13}C Nmr (75.5 MHz, CDCl_3) $\delta=14.6$ (q), 14.8 (q), 24.6 (q), 38.5 (d), 59.3 (t), 64.9 (t), 111.6 (d), 112.1 (d), 116.0 (s), 132.8 (s), 136.5 (d), 136.7 (d), 137.7 (d), 139.2 (s), 143.2 (s), 162.1 (s), and 165.9 (s).
- 14) **10e**: ^1H Nmr (300 MHz, CDCl_3) $\delta=1.34$ (6H, d, $J=6.9$ Hz, CHMe_2), 1.56 (3H, t, $J=6.9$ Hz, OCH_2Me), 2.64 (3H, s, Me), 2.73 (3H, s, COMe), 3.09 (1H, m, $J=6.9$ Hz, CHMe_2), 4.28 (2H, q, $J=6.9$ Hz, OCH_2Me), 6.95 (1H, d, $J=11.4$ Hz, H-5), 7.52 (1H, dd, $J=11.4$ and 1.8 Hz, H-6), 7.77 (1H, s, H-2), and 9.85 (1H, d, $J=1.8$ Hz, H-8).
- 15) **10f**: ^1H Nmr (300 MHz, CDCl_3) $\delta=1.32$ (6H, d, $J=6.9$ Hz, CHMe_2), 1.56 (3H, t, $J=6.9$ Hz, OCH_2Me), 2.69 (3H, s, Me), 3.05 (1H, m, $J=6.9$ Hz, CHMe_2), 4.31 (2H, q, $J=6.9$ Hz, OCH_2Me), 6.95 (1H, d, $J=11.7$ Hz, H-5), 7.51 (1H, s, H-2), 7.55 (1H, dd, $J=11.7$ and 1.8 Hz, H-6), and 8.33 (1H, d, $J=1.8$ Hz, H-8).
- 16) **10h**: ^1H Nmr (300 MHz, CDCl_3) $\delta=1.35$ (6H, d, $J=6.9$ Hz, CHMe_2), 2.65 (3H, s, Me), 3.10 (1H, m, $J=6.9$ Hz, CHMe_2), 4.13 (3H, s, OMe), 7.09 (1H, d, $J=11.5$ Hz, H-5), 7.17 (1H, s, H-3), 7.62 (1H, d, $J=11.5$ Hz, H-6), and 8.35 (1H, s, H-8).
- 17) **10k**: ^1H Nmr (300 MHz, CDCl_3) $\delta=1.34$ (6H, d, $J=6.9$ Hz, CHMe_2), 2.45 (2H, q, $J=7.4$ Hz, CH_2), 2.57 (3H, s, COMe), 3.08 (1H, m, $J=6.9$ Hz, CHMe_2), 3.20 (2H, t, $J=7.4$ Hz, CH_2), 3.24 (2H, t, $J=7.4$ Hz, CH_2), 4.02 (3H, s, OMe), 6.89 (1H, d, $J=11.1$ Hz, H-5), 7.45 (1H, t, $J=11.1$ Hz, H-6), and 9.75 (1H, s, H-8).
- 18) **10n**: ^1H Nmr (200 MHz, CDCl_3) $\delta=1.34$ (6H, d, $J=6.9$ Hz, CHMe_2), 1.56 (3H, t, $J=7.0$ Hz, OCH_2Me), 1.86 (4H, t, $J=3.0$ Hz, $(\text{CH}_2)_2$), 3.06 (1H, m, $J=6.9$ Hz, CHMe_2), 3.08 (2H, br, CH_2), 3.29 (2H, br, CH_2), 4.30 (2H, q, $J=7.0$ Hz, OCH_2Me), 6.94 (1H, d, $J=11.6$ Hz, H-5), 7.48 (1H, d, $J=11.6$ Hz, H-6), and 8.28 (1H, s, H-8).

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