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

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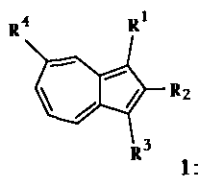
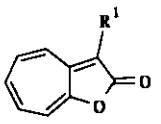
Abstract - Variously functionalized azulene derivatives were synthesized in one-pot and by the reaction of cyclohepta[b]-furan-2-ones with acetals of several aldehydes and ketones on heating at 160-190 °C in neat or aprotic solvent.

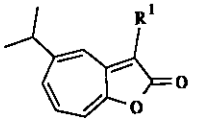
Recently, we have reported[1] that variously functionalized azulene derivatives **1** and **2** were synthesized in one-pot and by the reaction of cylohepta[b]furan-2-ones (**3**) and its 5-isopropyl derivatives **4** with vinyl ether, vinyl acetates, dihydrofurans, and dihydropyrans as reagent.



1: R^4=H
2: R^4=ipr



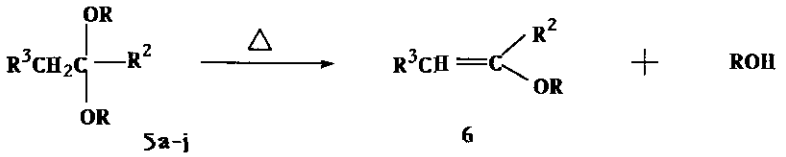
3a-e



4a-e

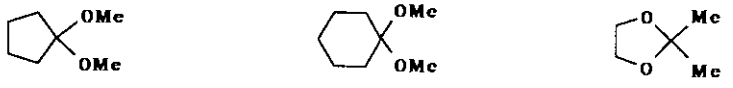
In this communication we wish to report another convenient method to prepare similar azulenes **1** and **2** by the reaction of **3** and **4** with acetals **5** of some

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



5a-j **6**

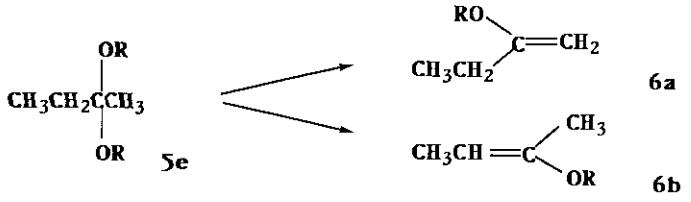
Acetals used in this study are those of acetaldehyde (**5a**), propionaldehyde (**5b**), isovaleraldehyde (**5c**), acetone (**5d**), methyl ethyl ketone (**5e**), diethyl ketone (**5f**), tert-butyl methyl ketone (**5g**), cyclopentanone (**5h**), cyclohexanone (**5i**), and 2,2-dimethyldioxolane (**5j**).



5h **5i** **5j**

Generally, cyclohepta[b]furan-2-ones **3a-e** and **4a-e** having various functional groups (a: R^1=H, b: R^1=COOMe, c: R^1=COOEt, d: R^1=COMe, e: R^1=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-dimethyl-azulenes (**1m**), because **5e** is decomposed into two isomeric vinyl ethers **6a** and **6b**.



5e **6a** **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**.

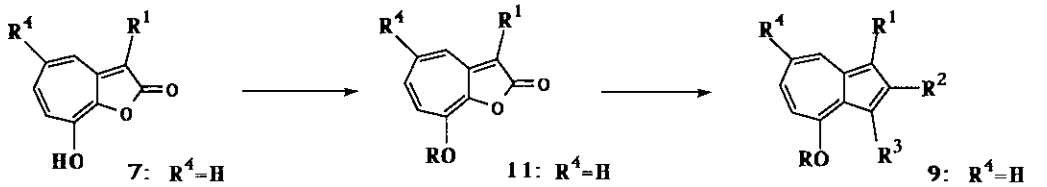
Reagent		Azulene Derivatives				Color / Form		mp	Yield
			R^1	R^2	R^3			(°C)	(%)
3a	**5a**	**1a**	H	H	H	blue	needles	98-99	2
3c	**5a**	**1b**[1]	COOEt	H	H	violet	oil	---	64
3d	**5a**	**1c**	COMe	H	H	violet	oil	---	37
3e	**5a**	**1d**	CN	H	H	violet	prisms	51-52	75
3b	**5b**	**1e**[3]	COOMe	H	Me	violet	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	R^1	R^2	R^3	OR	Color / Form	mp (°C)	Yield (%)
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 smothly 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.



7: R^4=H
8: R^4=ipr
11: R^4=H
12: R^4=ipr
9: R^4=H
10: R^4=ipr

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7) **1f**: ^{1}H 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**: ^{1}H Nmr (300 MHz, $CDCl_3$) δ=1.95 (4H, q, J=3.0 Hz, $(CH_2)_2$), 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**: ^{1}H 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**: ^{1}H 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, $OC\underline{H}_2Me$), 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, $CDCl_3$) δ =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, $CDCl_3$) δ =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, $CDCl_3$) δ =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, $CDCl_3$) δ =1.38 (6H, d, J=6.9 Hz, $CH\underline{Me}_2$), 1.44 (3H, t, J=7.2 Hz, $OCH_2\underline{Me}$), 1.56 (3H, t, J=6.9 Hz, $OCH_2\underline{Me}$), 3.14 (1H, m, J=6.9 Hz, $C\underline{H}Me_2$), 4.34 (2H, q, J=6.9 Hz, $OC\underline{H}_2Me$), 4.40 (2H, q, J=7.2 Hz, $OC\underline{H}_2Me$), 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, $CDCl_3$) δ =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, $CDCl_3$) δ =1.34 (6H, d, J=6.9 Hz, $CH\underline{Me}_2$), 1.56 (3H, t, J=6.9 Hz, $OCH_2\underline{Me}$), 2.64 (3H, s, Me), 2.73 (3H, s, COMe), 3.09 (1H, m, J=6.9 Hz, $C\underline{H}Me_2$), 4.28 (2H, q, J=6.9 Hz, $OC\underline{H}_2Me$), 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, $CDCl_3$) δ =1.32 (6H, d, J=6.9 Hz, $CH\underline{Me}_2$), 1.56 (3H, t, J=6.9 Hz, $OCH_2\underline{Me}$), 2.69 (3H, s, Me), 3.05 (1H, m, J=6.9 Hz, $C\underline{H}Me_2$), 4.31 (2H, q, J=6.9 Hz, $OC\underline{H}_2Me$), 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, $CDCl_3$) δ =1.35 (6H, d, J=6.9 Hz, $CH\underline{Me}_2$), 2.65 (3H, s, Me), 3.10 (1H, m, J=6.9 Hz, $C\underline{H}Me_2$), 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, $CDCl_3$) δ =1.34 (6H, d, J=6.9 Hz, $CH\underline{Me}_2$), 2.45 (2H, q, J=7.4 Hz, CH_2), 2.57 (3H, s, COMe), 3.08 (1H, m, J=6.9 Hz, $C\underline{H}Me_2$), 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, $CDCl_3$) δ =1.34 (6H, d, J=6.9 Hz, $CH\underline{Me}_2$), 1.56 (3H, t, J=7.0 Hz, $OCH_2\underline{Me}$), 1.86 (4H, t, J=3.0 Hz, $(CH_2)_2$), 3.06 (1H, m, J=6.9 Hz, $C\underline{H}Me_2$), 3.08 (2H, br, CH_2), 3.29 (2H, br, CH_2), 4.30 (2H, q, J=7.0 Hz, $OC\underline{H}_2Me$), 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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