Tetrahedron Letters, Vol. 33, No. 30, pp. 4337-4340, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

REGIOSELECTIVE SYNTHESIS OF SUBSTITUTED TROPONES AND AZULENES USING ANODIC OXIDATION OF CYCLOHEPTATRIENE SYSTEMS AS THE KEY REACTION[1]

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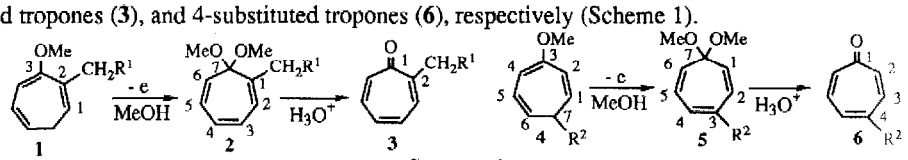
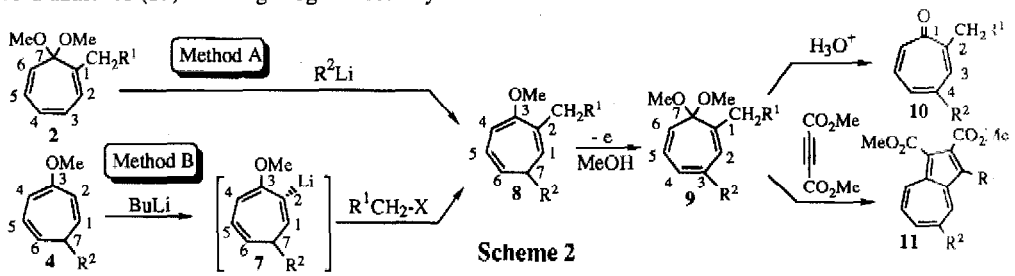
Abstract : Regioselective synthesis of di- and trisubstituted tropones has been attained by utilizing anodic oxidation of cycloheptatriene systems as the key reaction. This anodic oxidation has also been found to be useful for the regioselective synthesis of mono- and disubstituted azulenes.

In our recent studies on the anodic oxidation of cycloheptatriene systems, simple and efficient methods for the regioselective synthesis of monosubstituted tropones and tropolones have already been explored.[2-4] Namely, the anodic oxidation of 2-alkyl-3-methoxycycloheptatrienes (**1**), and 3-methoxy-7-alkylcycloheptatrienes (**4**) in MeOH afforded 1-alkyl-7,7-dimethoxycycloheptatrienens (**2**), and 3-alkyl-7,7-dimethoxycycloheptatrienens (**5**), respectively. The hydrolysis of **2** and **5** led to the regioselective formation of 2-substituted tropones (**3**), and 4-substituted tropones (**6**), respectively (Scheme 1).



Scheme 1

It has been found in this study that reaction of **2** with alkyl(aryl) lithium (R^2Li) took place regioselectively at position-3 of **2** yielding 2,7-disubstituted cycloheptatrienes (**8**) (Method A, Scheme 2), anodic oxidation of **8** in MeOH afforded 1,3-disubstituted-7,7-dimethoxycycloheptatrienens (**9**), and the hydrolysis of **9** led to the regioselective formation of 2,4-disubstituted tropones (**10**). It has also been found that reaction of **4** with n-BuLi formed the anionic species **7** and its reaction with alkyl halides (R^1CH_2-X) afforded also **8** (Method B, Scheme 2). Moreover, reaction of **9** with dimethyl acetylenedicarboxylate (DMAC) has been found to afford azulenes (**11**) with high regioselectivity.



Scheme 2

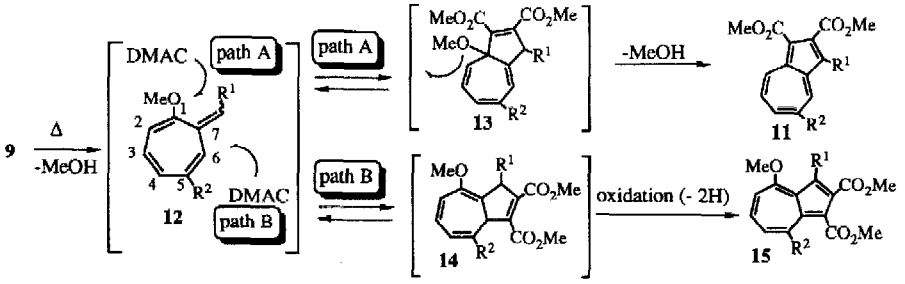
General procedures for the preparation of **8**, **9**, and **10** are as follows: The starting materials **2** and **4** were synthesized by our previously reported methods.[4] Method A: A solution of **2** (10 mmol) in dry THF (5 mL) was added dropwise into a solution of alkyl(aryl) lithium (R^2Li, 25 mmol) in pentane (60 mL) at -20°C under nitrogen atmosphere and the reaction mixture was stirred for 30 minutes at room temperature. Method B: A solution of n-BuLi (12 mmol, 1.6 M in hexane) was added dropwise into a solution of **4** (10 mmol) in dry THF (30 mL) at -78°C under nitrogen atmosphere. Into this solution was added a solution of alkyl halide (R^1CH_2-X, 20 mmol) in THF (5 mL), and the reaction mixture was stirred for 30 minutes at room temperature. After the usual working up, the product **8** was purified by silica gel column (hexane:AcOEt=150:1). Anodic oxidation of **8** (3 mmol) was carried out in an undivided cell equipped with platinum electrodes (2x2cm). Solvent was 20 ml of MeOH containing NaOMe (0.1g) and Et_4NOTs (0.1g) as supporting electrolytes. The usual working up gave **9** which was subsequently hydrolyzed without further purification in aqueous H_2SO_4 (20 %) at room temperature to give **10**. The structure of the product was determined by NMR, IR, and high resolution mass spectrometry (HRMS).[5] As the results are summarized in Table 1, this new method is generally applicable to the synthesis of 2,4-disubstituted tropones **10**.[6]

Table 1. Preparation of 2,4-Disubstitued Tropones.

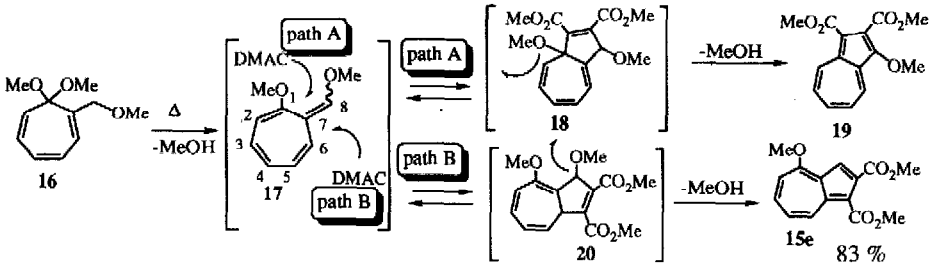
Starting Material				Method	Alkylating Agent		Yield of 8[a]	Anodic oxidation of 8 to 9	Product 10		Yield of 10[a]
2	R^1	4	R^2		R^1	R^2	(%)	Supplied Electricity (F/mol)	R^1	R^2	(%)
2a	H			A		*iso*-Pro	**8a** 54	2.5	H	*iso*-Pro	**10a** 62
2b	Me			A		n-Bu	**8b** 58	3.0	Me	n-Bu	**10b** 65
		4a	n-Bu	B	H		**8c** 87	3.0	H	n-Bu	**10c** 50
		4b	Ph	B	Me		**8d** 89	3.5[b]	Me	Ph	**10d** 63

a) Isolated yields. b) Anodic oxidation of **8d** to **9d** was carried out after **8d** was thermally rearranged to 1-methoxy-2-ethyl -4-phenylcycloheptatriene. See ref. 3.

Since 1-methoxy-5-substituted heptafulvene (**12**) should be formed from **9** by thermal elimination of one molecule of MeOH, the reaction of **9** with dimethyl acetylenedicarboxylate (DMAC) was carried out in refluxing toluene, and azulenes (**11**)[8] were obtained along with a small amount of methoxylated azulenes (**15**) through the [2+8] cycloaddition of **12** with DMAC (Scheme 3 and Table 2). These results are interesting since the addition of DMAC to **12** takes place at the *hindered* site of **12** (path A) rather than the *less hindered* site (path B). The formation of **13** and **14** by the reaction of **12** and DMAC is a reversible [2+8] cycloaddition, whereas the formation of **11** from **13** and that of **15** from **14** are both irreversible reaction. Although the formation of **14**, namely path B, seems to be more favorable than the formation of **13** due to a steric effect, the oxidation of **14** yielding **15** is highly limited because of the nonoxidative atmosphere of the reaction system. Hence, the entire reaction proceeds according to the path A. Then, the steric effect on the [2+8] cycloaddition was examined with respect to the reaction of **16** with DMAC, and it was found that the [2+8] cycloaddition of DMAC with 1,8-dimethoxyheptafulvene (**17**) generated from **16** took place at the *less hindered* site (path B) exclusively rather than at the *hindered* site (path A), since the formation of **19** from **18** (path A) and that of **15e** from **20** (path B) are both achieved by elimination of MeOH and hence, both paths are not limited by the nonoxidative atmosphere of the reaction system. Therefore, the entire reaction proceeds according to the path B[9] (Scheme 4).



Scheme 3



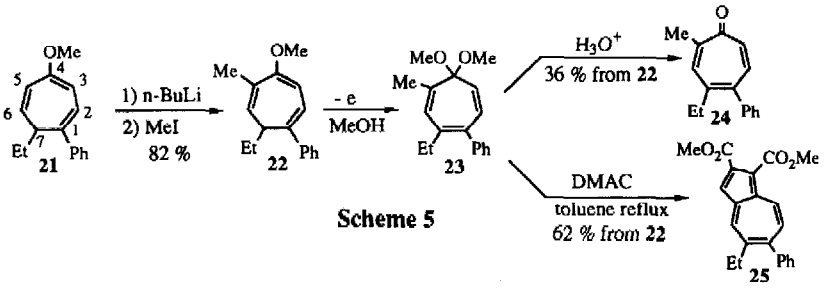
Scheme 4

Table 2. Preparation of Azulenes **11** and **15**.

Starting Material **9**[a]			Yield[b]	
R^1	R^2		**11** (%)	**15** (%)
H	iso-Pro	**9a**	**11a** 60	**15a** 13
H	n-Bu	**9b**	**11b** 69	**15b** 6
H	H	**9e**	**11e** 63	**15e** 10
Me	H	**9f**	**11f** 34	**15f** 13

a) Starting materials **9** were prepared by the anodic oxidation of **8** and used without further purification. b) Isolated yields.

As shown in Scheme 5, this new method was also applicable to the regioselective synthesis of a trisubstituted tropone (**24**) and a disubstituted azulene (**25**). The alkylation of 1-phenyl-3-methoxy-7-ethylcycloheptatriene (**21**)[10] using n-BuLi as a base, for example, formed the regioselectively alkylated product **22**. The anodic oxidation of **22** in MeOH gave **23** and its hydrolysis with aq. H_2SO_4 afforded **24**.[11] On the other hand, the reaction of **23** with DMAC in refluxing toluene gave **25**.[12]



Scheme 5

References and Notes

1. Electroorganic Chemistry. 137.
2. Shono,T.; Nozoe,T.; Maekawa,H.; Kashimura,S. *Tetrahedron Lett.* **1988**, *29*, 555.
3. Shono,T.; Maekawa,H.; Nozoe,T.; Kashimura,S.*Tetrahedron Lett.* **1990**, *31*, 895.
4. Shono,T.;Nozoe,T.;Maekawa,H.; Yamaguchi,Y.; Kanetaka,S.; Masuda,H.; Okada,T.; Kashimura,S. *Tetrahedron*, **1991**, *47*, 593.
5. The spectroscopic values of typical compounds (**8a**,**8c**,**10a**,and **10c** in the Table 1) are as follows:
   8a ;^{1}H-NMR ($CDCl_3$) δ 1.00 (d, 6H, J = 6.6Hz), 1.29-1.41 (m, 1H), 1.78-1.92 (m, 1H), 1.91 (s, 3H), 3.69 (s, 3H), 5.19 (d, 1H, J = 5.5Hz), 5.21 (dd, 1H, J = 5.2 and 5.5Hz), 5.79 (d, 1H, J = 6.3Hz), 6.04-6.09 (m, 1H). IR (neat) 2950, 1630, 1540, 1220 cm^{-1}. HRMS. Calcd for $C_{12}H_{18}O$: 178.1358; Found:178.1359
   8c; ^{1}H-NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 7.0Hz), 1.20-1.50 (m, 4H), 1.55-1.75 (m, 2H), 1.89 (s, 3H), 3.68 (s, 3H), 5.06- 5.15 (m, 2H), 5.65 (d, 1H, J = 6.3Hz), 6.04 (dd, 1H, J = 6.3 and 9.2Hz). IR (neat) 2920, 1630, 1540, 1220 cm^{-1}. HRMS. Calcd for $C_{13}H_{20}O$: 192.1515; Found: 192.1495.
   10a; ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 6H, J = 6.9H), 2.31 (s, 3H), 2.71-2.85 (m, 1H), 6.78-7.31 (m, 4H). IR (neat) 2970, 1630, 1580, 830 cm^{-1}. HRMS. Calcd for $C_{11}H_{14}O$: 162.1045; Found: 162.1045.
   10c; ^{1}H-NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.2Hz), 1.25-1.70 (m, 4H), 2.29 (s, 3H), 2.51 (t, 2H, J = 7.3Hz), 6.75 (m, 4H). IR (neat) 2950, 1650, 1580 cm^{-1}. HRMS. Calcd for $C_{12}H_{16}O$: 176.1202; Found: 176.1208.
6. The regioselective synthesis of di- and trisubstituted tropones usually requires many steps.[7]
7. Kessler, H " *Methoden der Organische Chemie*," ed by Houben-Weil-Müller, Gerog Thieme Verlag, Stuttgart (1972), Bd. 5/1d, p. 301; Asao, T.; Oda, M. (1985), bd. 5/2c, p. 49 and 710.
8. The spectroscopic values of typical compounds (**11a** and **11b** in the Table 2) are as follows:
   11a; ^{1}H-NMR ($CDCl_3$) δ 1.39 (d, 6H, J = 6.9Hz), 3.05-3.28 (m, 1H),3.94 (s, 3 H), 3.98 (s, 3H), 7.38 (s, 1H), 7.54 (t, 1H, J= 10.1Hz) , 7.81 (d, 1H, J = 10.1Hz), 8.45 (s, 1H), 9.36 (d, 1H, J = 10.1Hz). IR (neat) 3040, 2980, 1740, 1450, 1380, 1050 cm^{-1}. HRMS. Calcd for $C_{17}H_{18}O_4$: 286.1200; Found:286.1202.
   11b ;^{1}H-NMR ($CDCl_3$) δ 0.96 (t,3H, J = 7.2Hz), 1.25-1.80 (m, 4H), 2.90 (t, 2H, J = 7.3Hz), 3.94 (s, 3H), 3.98 (s, 3H), 7.36 (s, 1H), 7.50 (t, 1H, J = 10.2Hz), 7.77 (d, 1H, J = 10.2Hz), 8.41 (s, 1H), 9.35 (d, 1H, J = 10.2 Hz). IR (neat) 2940, 1720, 1690, 1440, 1200 cm^{-1}. HRMS. Calcd for $C_{18}H_{20}O_4$: 300.1356; Found: 300.1362.
9. The compound **15e** shows following spectroscopic data, and they are reasonable for the assigned structure. **15e**;^{1}H-NMR ($CDCl_3$) δ 3.94 (s, 3H), 3.96 (s, 3H), 4.20 (s, 3H) , 7.18 (d, 1H, J=10.6 Hz), 7.31 (d, 1H, J=10.6 Hz), 7.71 (s, 1H), 7.82 (t, 1H, J=10.6 Hz), 9.32 (d, 1H, J = 10.6 Hz). IR (KBr) 2950, 1720, 1600, 1220cm^{-1}. Anal Calcd for $C_{15}H_{14}O_5$: C,65.69; H,5.15. Found: C,65.95; H, 5.40.
10. We have already reported the synthesis of 1-phenyl-3-methoxy-7-alkylcycloheptatrienes.[3]
11. **24**; ^{1}H-NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.6 Hz), 2.35 (s, 3 H), 2.38 (q, 2H, J=7.6 Hz), 6.88-7.50 (m, 8H). IR (neat) 2970, 1620, 1570 cm^{-1}. HRMS. Calcd for $C_{16}H_{16}O$: 224.1202; Found: 224.1184.
12. **25**; ^{1}H-NMR ($CDCl_3$) δ 1.15 (t, 3H, J = 12.5 Hz), 2.69 (q, 2H, J = 12.5 Hz), 3.91 (s, 3H), 3.96 (s,3H),7.05-7.55 (m,7H), 8.51 (s, 1 H), 9.03 (d,1H,J=10.5Hz). IR (neat) 2950, 1720, 1690, 1440, 1200 cm^{-1}. HRMS. Calcd for $C_{22}H_{20}O_4$: 348.1362; Found:348.1350.

(Received in Japan 6 March 1992)