

A NOVEL REGIOSELECTIVE SYNTHESIS OF 4-SUBSTITUTED TROPONES¹

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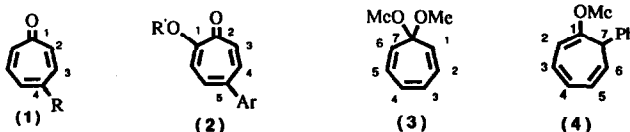
Summary: The preparation of 4-alkyl (or aryl) tropones has easily been accomplished by the anodic oxidation of 1-methoxy-4-alkyl (or aryl) cycloheptatrienes which were synthesized by the regioselective addition of alkyl or aryl lithium to 3-position of 7,7-dimethoxycycloheptatriene followed by the thermal 1,5-hydrogen shift of the resulting 3-methoxy-7-alkyl (or aryl) cycloheptatrienes.

The skeleton of 4-substituted tropone (**1**) is found widely in naturally occurring tropenoids and azulenoids,² and **1** (R=aryl group) is also the key intermediate for the preparation of 5-aryl-substituted tropolones⁴ (**2**) which have potent colchicine-type antimitotic activity.⁵⁻⁶

The hitherto known syntheses⁷ of **1**, however, require many troublesome steps since the simple and reliable method for the regioselective introduction of a substituent R (R=alkyl or aryl group) to the 4-position of tropone ring has not yet been generally established. Although the reaction of tropone with the Grignard reagent⁸ or alkyl (aryl) lithium⁹ may be one of the plausible methods of synthesizing **1**, the actual reaction site in these reactions is not the 4-position but mainly 2-position.

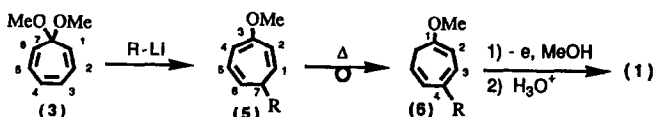
On the other hand, we have recently reported¹⁰ a new anodic method of synthesis of acetal of tropone, namely, 7,7-dimethoxycycloheptatriene (7,7-Di-MeO-CHT) (**3**).¹¹

Although we have already found that **3** is reactive to the Grignard reagent, the reaction was not regioselective and the product was a mixture of isomers.¹⁰ In addition, the reaction of **3** with PhMgBr in the presence of a catalytic amount of CuI showed different selectivity and 1-methoxy-7-phenyl-CHT (**4**) was obtained as the main product.



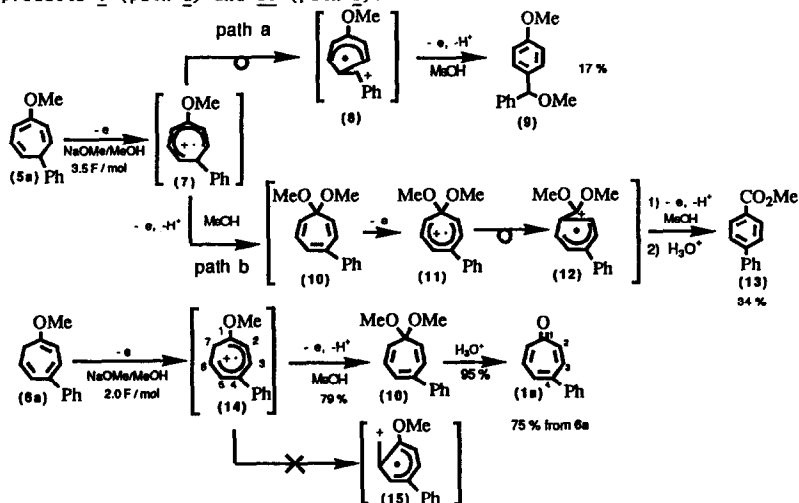
However, we have found in the present study that the remarkable difference of the reactivity of **3** from tropone was that the reaction of **3** with alkyl or aryl lithium (scheme 1) took place with high regioselectivity at the 3-position of **3** and formed 3-methoxy-7-alkyl (or aryl)-CHT (**5**). The product **5** was easily transformed to 1-methoxy-4-alkyl-CHT (**6**) by thermal rearrangement and the anodic oxidation of **6** gave **1** with high yield.

Scheme 1



Interestingly, the anodic oxidation (scheme 2) of 5a (R=Ph) in MeOH followed by hydrolysis did not give the corresponding tropone 1a (R=Ph) but yielded a mixture of rearranged products 9 (path a) and 13 (path b).¹³

Scheme 2



These results are explained by the difference of the oxidation potentials of 5a, 6a, and 10 ($E_p = \underline{5a}, 1.36; \underline{6a}, 1.14; \underline{10}, 1.40$ V vs.SCE).¹⁴ Namely, the anodic oxidation of 5a in methanol forms the first intermediate 7 which is followed by two competitive reaction pathways a and b. In the pathway a, a ring contracting rearrangement takes place to yield 9, while in the pathway b, the reaction of 7 with methanol gives the expected product 10 which is, however, not stable in this reaction since the oxidation potentials of 5a and 10 are almost the same and hence 10 is oxidized together with 5a to give 13 through a ring contracting rearrangement.


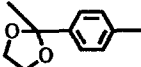
On the other hand, the difference of oxidation potential between 6a and 10 is sufficient enough for the selective oxidation¹⁵ of 6a with keeping 10 intact. The ring contracting rearrangement of the intermediate 14 is unlikely since the cation 15 formed by this rearrangement is much more unstable than 8 and 12.

The results summarized in Table 1 indicate that this reaction is extensively applicable¹⁶ for the preparation of a variety of 4-substituted tropones (1b-g). For instance, the anodic oxidation of 6f synthesized by the reaction of 3 with isopropyl lithium followed by the thermal rearrangement yielded nezukone (1f)¹⁷ in excellent yield and regioselectivity.

General procedure is as follows: 3 (10 mmol) was added dropwise into a solution of alkyl lithium (25 mmol) in pentane (60 ml) at room temperature under nitrogen atmosphere and reaction mixture was stirred for 3 hr at room temperature. After usual working-up, the product 5 was purified by silica gel column (eluent, hexane:AcOEt=20:1). Compound 6 was obtained by heating 5 at 170 °C for 2 hr under nitrogen atmosphere. Controlled

potential electrolysis of **6** (10 mmol) was carried out in an undivided cell equipped with platinum electrodes (2x2 cm). The applied anode potentials and supplied electricity are shown in table 1. Solvent was 30 mL of methanol containing NaOMe (20 mmol) as a supporting electrolyte. The usual working-up gave crude **10** and it was purified through alumina column (eluent, hexane:AcOEt=5:1). The hydrolysis of **10** in 2 N HCl at room temperature for 1 hr gave **1**. The structures of **5**, **6**, and **1** were determined by COSY, C^{13} -NMR, IR, and high resolution mass spectrometry.

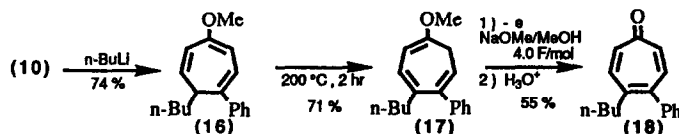
Table 1. Anodic Oxidation of CHTs^{a,b}

R =	Yield of 5 (%)	Yield of 6 (%)	Supplied electricity (F/mol)	Anode Potential (V vs. SCE)	Yield of 1 (%)
Ph	5a 94	6a 75	3.0	1.2	1a 75
p-MeOC ₆ H ₄	5b 90	6b 73	3.3	1.1	1b 71
	5c 90	6c 71	2.7	1.2	1c 89
p-BrC ₆ H ₄	5d 61	6d 78	4.0	1.2	1d 74
	5e 75	6e 73	2.4	1.3	1e 49
iso-Pr	5f 95	6f 99	2.2		1f 70 ^c
n-Bu	5g 94	6g 100	3.0		1g 65 ^c

a : Isolated yields. b : Unless otherwise stated controlled potential electrolysis was applied.
c : Constant current electrolysis.

It is also noteworthy that the reaction of **10** with n-butyl lithium (scheme 3) gave 1-phenyl-4-methoxy-7-butyl-CHT (**16**) and subsequent anodic oxidation of the thermally rearranged product (**17**) led to the regioselective formation of disubstituted tropone (**18**).

Scheme 3



Although the reasonable explanation for the regioselective formation of **5** by the reaction of **3** with RLi is not known at present,¹⁹ the method described in this paper is undoubtedly the most effective for the selective preparation of 4-substituted tropones.

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References and Notes

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11. The preparation of **3** by the other method¹² is rather troublesome. For example, **3** was synthesized by the treatment of tropone with the Meerwein reagent followed by the reaction of the resulting methoxytropylium salt with NaOMe.
12. R.W.Hoffmann, K.R.Eicken, H.J.Luthardt, and B.Dittrich, *Chem. Ber.* **103**, 1547 (1970).
13. We have previously reported the anodic ring contracting rearrangement of CHT to the benzenoid ring.¹⁰
14. Oxidation potentials (E_p) of **5a**, **6a**, and **10** (6.6 mM/l) were measured with platinum electrodes (1x2 cm) in MeCN (10ml) containing Et₄N⁺OTs⁻ (66 mM/l) as a supporting electrolyte (scanning rate= 200mv/sec).
15. Anodic oxidation of **6a** was carried out at +1.2V vs.SCE.
16. The reaction of **3** with MeLi was not regioselective and the yield of **5** (R=Me) was low.¹⁰
17. The C¹³-NMR of **1f** was completely the same as that of authentic sample.¹⁰
18. M.Cavazza, A.Guerriero, and F.Pietra, *J. Chem. Soc. Perkin Trans. I*, 2005 (1986).
19. It has been reported²⁰ that the reaction of alkyl lithium with 3,3,3-trimethoxy-1-propene (TMP) took place predominantly at 1-position of TMP, while that of the Grignard reagent with TMP is not regioselective.
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