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UMPOLUNG OF TROPONE: THE SYNTHESIS OF NOVEL 2-SUBSTITUTED TROPONES VIA 2-HALOCYCLOHEPTADIENONE ENOLATES

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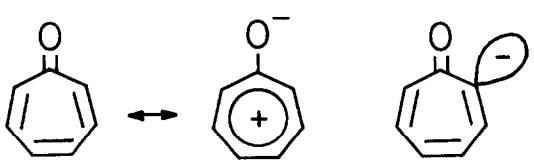
Summary: 2-Halocycloheptadienone enolates, which were generated by the reaction of 2-halotropones with hydride, Grignard, and organolithium reagents, reacted with cationic electrophiles including tropylium ion to give 2-substituted tropone derivatives.

Tropone 1 is easily attacked by nucleophiles as can be seen from its resonance structure 1a. Fairly extensive studies have already been made on the reactions of 1 and its derivatives with various nucleophiles,[1,2] and we have also studied the nucleophilic reaction of 2-halotropones with tricarbonyl(4-7-η-1H-1,2-diazepine)iron to provide the novel three isomers of 1-troponyl-1H-1,2-diazepine.[3] Several examples for the C-C bond forming reactions of 2-halotropones with carbanions,[1a] Grignard,[4,5] organolithium,[4,6] and organocopper reagents[7] have also been reported. Since the resistant nature of electrophilic attack onto the tropone nucleus is generally recognized,[1a,b] the study of a reverse polarity (umpolung) strategy for realizing a formal electrophilic reaction to 1 must be fruitful for the synthesis of a variety of substituted troponoids. Our synthetic approach to an equivalent for 2-troponide ion 2 involves 2-halocycloheptadienone enolates 4a-c and 8 generated in situ by the reaction of 2-halotropones 3a-c and hydride, Grignard, and organolithium reagents.

A typical procedure for the preparation of 4a-c involves a treatment of 3a-c (1 mmol) with $LiAlH_4$ (0.36 mmol) or $LiAlH(OBu^t)_3$[8] (1.3 mmol) at 0 °C or at ambient temperature in tetrahydrofuran (THF) (5 ml) for 10-20 min. The solution, which contains 4a-c, was then added dropwise to a stirred mixture of tropylium tetrafluoroborate (1.3 mmol) and triethylamine (1.3 mmol) in THF (5 ml) at 0 °C, and stirred for another 10 min at ambient temperature to result in the formation of 2-tropyltropone 7[9,10] in good yields (Scheme 1; Table 1, run 1-4). The ^1H NMR spectral studies[11] could reveal that both 4a and 4a(D), generated by the reaction of 3a with $LiAlH_4$ and $LiAlD_4$ in THF-d_8, respectively, are the mixtures of two enolates, the counter cations of which are presumably different from each



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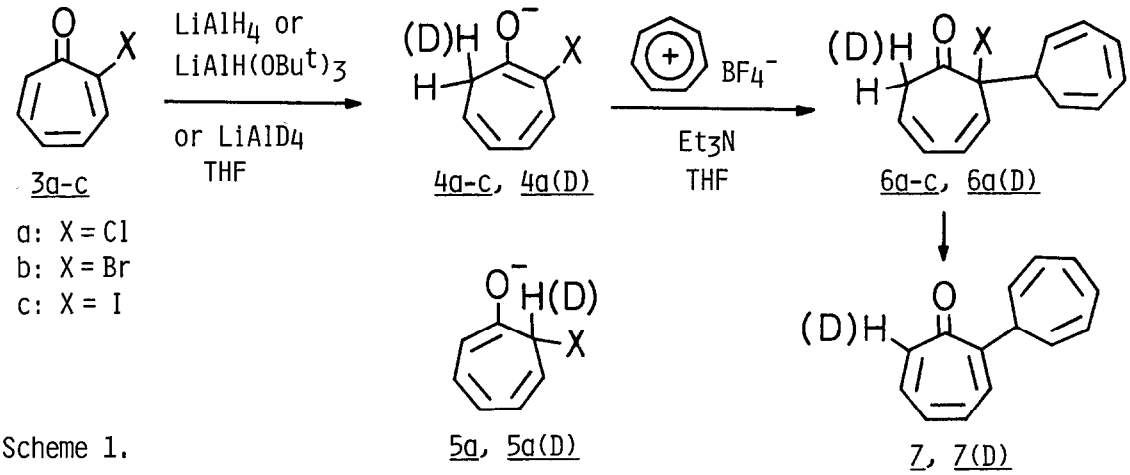
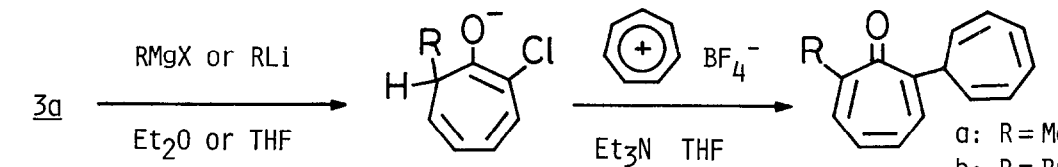


Scheme 1.

other. However, the cationic moieties are uncertain here. Furthermore, hydride and deuteride attack to 3a were proved to take place onto C7 to give 4a and 4a(D), and not onto C2 to give 5a and 5a(D).[11] The enolate 4a(D) was reasonably reacted with tropylium cation to give a mixture of 7 and 7(D),[9,12] probably via the intermediate 6a(D). Thus, the reaction pathways of 3a-c to give 7 and 7(D) (Table 1, run 1-5) elucidated as shown in Scheme 1. Although the cycloheptadienone enolate has been suggested in the reaction of 1 with



Scheme 2.

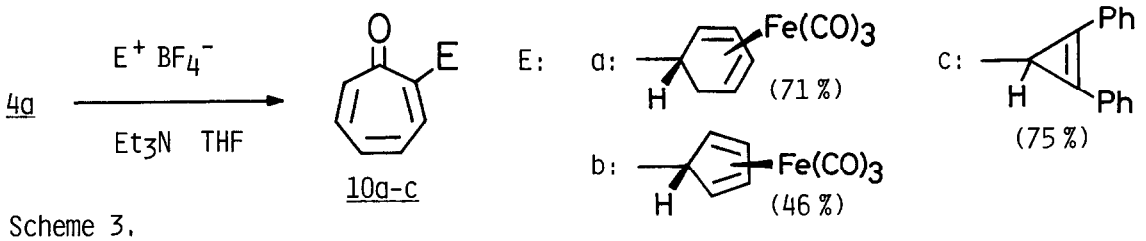
Table 1. The reactions of tropylium tetrafluoroborate with 4a-c, 4a(D), and 8.

Run	2-Halotropone	Nucleophile	Product/ yield (%)	
1	3a	$LiAlH_4$	7	(74)
2	3a	$LiAlH(OBu^t)_3$	7	(87)
3	3b	$LiAlH(OBu^t)_3$	7	(83)
4	3c	$LiAlH(OBu^t)_3$	7	(74)
5	3a	$LiAlD_4$	7+7(D)	(70)[a]
6	3a	MeMgI	9a	(89)
7	3a	MeLi	9a	(88)
8	3a	BuLi	9b	(79)
9	3a	PhMgBr	9c	(90)

a) A mixture of 7 and 7(D) in a ratio of 27 : 73.

$LiAlH_4$ followed by protonation to give 3,5-cycloheptadienone,[13] the present studies clarified the structural features and the C-C bond forming reaction of the enolates 4a-c and 4a(D).

In a similar way, 7-substituted 2-chlorocycloheptadienone enolate 8 was generated by the reaction of 3a with Grignard reagents in ether or organolithium reagents in THF, and subsequently reacted with tropylium cation to give 7-substituted 2-tropyltropones

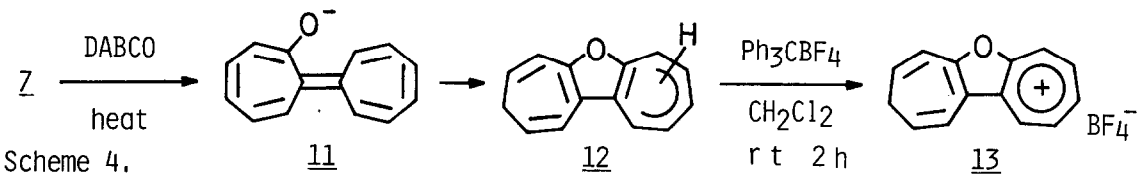


Scheme 3.

9a-c in good yields (Scheme 2; Table 1, run 6-9). Since the nucleophilic attack to 3a and its related compound has been reported to take place onto C7,[6,14] the intermediacy of 8 is reasonably accepted.

The enolate 4a reacted with other cationic electrophiles, such as tricarbonyl(cyclohexadienylium)iron, tricarbonyl(cyclopentadienylium)iron, and diphenylcyclopropenylium tetrafluoroborates to give the corresponding 2-substituted tropones 10a-c in moderate yields (Scheme 3).

Bitropones, which have a skeleton similar to 7, have attracted considerable interest because of its potential use for the synthesis of novel π-electron systems.[15] The 2-tropyltropones which have become available through the methodology described here can also be very useful in further synthesis. For example, the compound 7 was reactive to 1,4-diazabicyclo[2.2.2]octane (DABCO) in 1,2-dimethylbenzene under reflux for 30 min to give a mixture of three isomers of dihydrodicyclohepta[b,d]furan, 12,[9,16] in 85% yield, probably via the enolate 11. Although the mixture 12 was not separable by column chromatography, the subsequent hydride abstraction of 12 with trityl tetrafluoroborate in dichloromethane gave the cation 13,[9,17] in 96% yield as a single product (Scheme 4).



Scheme 4.

We believe that the foregoing methodology has considerable potential for the synthesis of a variety of substituted troponoids. The reaction of 2-halocycloheptadienone enolates with other electrophiles and the synthetic applications of the products are now underway.

References and Notes

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9) Elemental analyses and high resolution mass spectral data are satisfactory for all new compounds described in this paper.
10) For 7: pale yellow oil; ^{1}H NMR ($CDCl_3$), δ=3.47 (1H, broad t, J=6.0 Hz), 5.37 (2H, dddd, J=8.9, 6.0, 0.9, 0.7 Hz), 6.25 (2H, dddd, J=8.9, 3.9, 2.7, 0.9 Hz), 6.60 (2H, dddd, J=3.9, 2.7, 0.9, 0.7 Hz), 6.89-7.21 (4H, m), 7.25-7.42 (1H, m); ^{13}C NMR ($CDCl_3$), δ=185.9 (s), 153.7 (s), 140.3 (d), 134.8 (d), 134.1 (d), 133.1 (d), 132.8 (d), 130.0 (2C, d), 124.8 (2C, d), 124.7 (2C, d), 43.7 (d); IR ($CHCl_3$), 2990, 1627, 1577, 1514, 1466, 837, 686 cm^{-1}; λ_{max} (EtOH) (log ε), 229 (4.29), 307 (3.86).
11) ^{1}H NMR (THF-d_8), for 4a: δ=2.50-2.78 (2H, m), 5.24 (0.56H, broad dt, J=9.7, 6.7 Hz), 5.59 (0.44H, dt, J=10.8, 6.2 Hz), 5.80-6.72 (3H, m), on irradiation at δ2.62, the signals at δ5.24 and δ5.59 became doublets, respectively; for 4a(D): δ=2.48-2.76 (1H, m), 5.25 (0.7H, broad dd, J=7.9, 7.7 Hz), 5.59 (0.3H, dd, J=9.7, 5.9 Hz), 5.80-6.72 (3H, m), on irradiation at δ2.58, the signals at δ5.25 and δ5.59 became doublets, respectively.
12) For 7 + 7(D): ^{1}H NMR ($CDCl_3$), δ=3.45 (1H, broad t, J=6.0 Hz), 5.36 (2H, broad dd, J=8.8, 6.0 Hz), 6.23 (2H, broad dt, J=8.8, 3.0 Hz), 6.59 (2H, broad t, J=3.0 Hz), 6.84-7.15 (3.27H, m), 7.18-7.42 (1H, m); ^{13}C NMR ($CDCl_3$), δ=186.2 (s), 154.0 (s), 140.6 (d, weak), 134.8 (d), 134.2 (d), 133.3 (d), 132.9 (d), 130.2 (2C, d), 125.0 (4C, d), 43.9 (d).
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16) ^{1}H NMR ($CDCl_3$), δ=2.28-2.57 (m), 3.05 (d, J=5.9 Hz), 3.28 (d, J=6.2 Hz), 5.05-5.56 (m), 5.80-6.73 (m); IR ($CHCl_3$), 2992, 2863, 1640, 1563, 1409, 1147, 909 cm^{-1}.
17) Mp 127-129 °C (decomp); ^{1}H NMR (CD_3CN), δ=2.88 (2H, broad t, J=6.7 Hz), 5.92 (1H, dt, J=9.9, 6.6 Hz), 6.47 (1H, dt, J=10.2, 6.8 Hz), 7.12 (1H, d, J=10.2 Hz), 7.14 (1H, d, J=9.9 Hz), 8.68-9.06 (3H, m), 9.10-9.43 (2H, m); ^{13}C NMR (CD_3CN), δ=166.9 (s), 165.0 (s), 148.9 (d), 148.5 (s), 144.6 (d), 144.0 (d), 142.1 (d), 140.3 (d), 135.7 (d), 127.0 (d), 124.8 (s), 119.2 (d), 117.9 (d), 28.1 (t); IR (KBr), 2926, 1478, 1445, 1083, 1037 cm^{-1}; λ_{max} (EtOH) (log ε), 235 (4.45), 288 (4.06), 322 (sh, 3.89), 430 (3.94), 445 (sh, 3.91).

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