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A CONVENIENT SYNTHESIS OF 2-ACYL-6-AMINOFULVENES FROM CYCLOPENTADIENE

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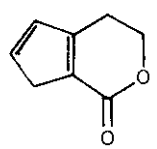
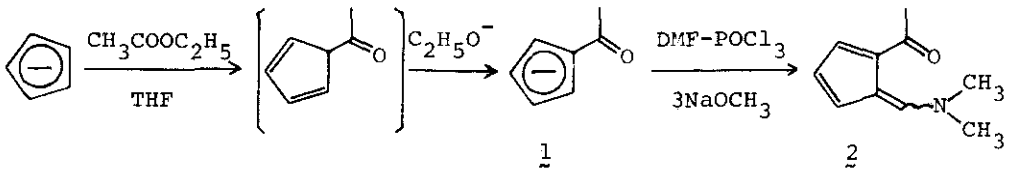
Several biologically active natural products have a structure with vicinally dialkylated five-membered carbocycles; prostaglandins,[1] pyrethroids,[2] brefeldin A,[3] jasmonoids,[4] and so on. Cyclopentadiene is the most simple and reactive five membered carbocyclic compound and is considered to be suitable as a starting material for them, but the selective method to introduce two alkyl chains into the vicinal position of the diene has not been studied much. Generally, alkylation of monosubstituted cyclopentadiene has a poor regioselectivity,[5] since the location of double bonds is not fixed in a cyclopentadiene ring.[6] Recently, the regiospecific method by the intramolecular steric control using a carbonate ester of cyclopentadienylethanols has been reported from our laboratory[7] to give cyclopentadienolactones. In the course of the study, the double bonds were found to be fixed in the cyclopentadiene ring when an acyl group is introduced on the ring. For example, the double bonds in cyclopentadienolactone(I) place to have the direction of the longest conjugation with the carbonyl group. By the use of this system, the second substituent would be introduced regioselectively. We now report here a novel method for the selective synthesis of 2-acyl-6-aminofulvenes from cyclopentadiene by one-pot procedure using a method by a resonance control of acylcyclopentadienes.



——— I

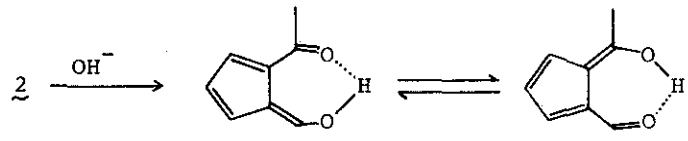
The Vilsmeier reaction was chosen as a second substitution reaction, because the Vilsmeier reagent, consisting of the adduct of dimethylformamide and phosphorus oxychloride, is reported to react easily with cyclopentadiene.[8] Acetylcyclopentadiene was easily obtained by the reaction of cyclopentadienyl anion with acetate ester by refluxing them in tetrahydrofurane for 15 hr. Because of the high acidity of the acetylated compound, it exists as a stable anionic form 1 in the solution by deprotonation with alkoxy anion formed.[9] When the Vilsmeier reagent prepared from 4 moles of N,N-dimethylformamide and one mole of phosphorus oxychloride[10] was added into the solution of the anion, no assignable product was obtained and the system gave only tarry substance. This is due to the decomposition of acid sensitive acylcyclopentadienyl derivatives by an acidic media liberated from the reaction system. On the other hand, 2-acyl-6-aminofulvenes were obtained in high yields when the sufficient amounts of alkoxide were present to neutralize the reaction system.

When the solution of the Vilsmeier reagnet was added into the solution of the anion 1 containing 3 equimolar of sodium methoxide, 2-acetyl-6-dimethylaminofulvene (2) was obtained in 93% yield as yellow crystals, mp 62-63°C; ms, m/e 163 (M^+).



1 2

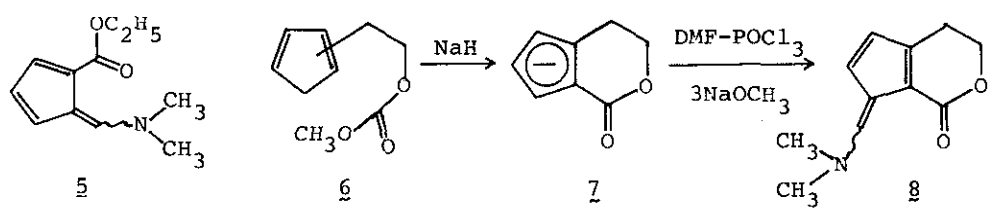
The structure of the vicinally substituted cyclopentadiene derivative was confirmed by the spectral data. The ir spectrum shows a strong broad peak at 1615 cm^{-1} due to the conjugated carbonyl group. The chemical shifts and coupling constants for adjacent three olefinic protons at δ 6.38(1H, dd, J=4.0 and 4.2 Hz), δ 6.87(1H, dd, J=2.0 and 4.2 Hz), and δ 7.12(1H, dd, J=2.0 and 4.0 Hz) along with the chemical shift for aminomethylene proton at δ 8.98(1H, s) show the existence of 2-acylfulvene structure. Further confirmation of the structure was achieved by hydrolysis of the amino group. Similarly to the hydrolysis of 6-aminofulvene-2-aldehyde,[8] the 2-acyl-6-aminofulvene 2 was easily hydrolyzed with dilute alkalin solution under mild conditions to give



3 4

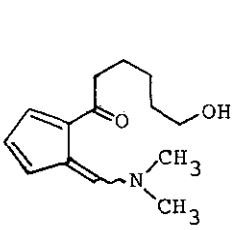
2-acetyl-6-hydroxyfulvene as a yellow oil in 87% yield: ms, m/e 136 (M^+). Although no peak attributable to hydroxy group was observed in the ir spectrum, it shows the existence of conjugated carbonyl group at 1630 and 1570 cm^{-1}. The chemical shift for hydroxy proton, however, observed at low field of δ 17.10, shows a remarkable characteristic of the enol structure of β-diketone. These observations strongly suggest that the hydroxyfulvene exists as a tautomeric pair of 3 and 4, which is a vinylogue of β-diketone.[11]

This convenient method thus appears to be of rather general applicability. For example, the use of diethyl carbonate in place of ethyl acetate gave a fulvenylcarboxylate, 2-ethoxycarbonyl-6-dimethylaminofulvene (5; mp 94°C)[12] in a yield of 39%. Similarly, the anion of cyclopentadienolactone(7),[7] which was obtained by an intramolecular cyclization of a carbonate ester of cyclopentadienylethanol(6) in the presence of a base, gave the fulvenolactone (8; mp 106-107°C)[12] in a 66% yield.



5 6 7 8

Lactone can be also used for the introduction of an acyl component. For example, ε-caprolactone gave 2-ω-hydroxyhexanoyl-6-dimethylaminofulvene(9)[12] as an oil in a yield of 54%. The acyl chain with a functional group can be prepared from the ester with the functional group when it is inert to the reaction conditions. For example, ethyl 3,3-ethylenedioxybutanoate and ethyl 3,3-ethylenedioxyoctanoate gave 2-(3,3-ethylenedioxyalkanoyl)-6-aminofulvenes (10a and 10b)[12] in 58 and 46% yields respectively. These 6-aminofulvenes also gave the corresponding 6-hydroxyfulvenes (e.g. 11 and 12)[12] by the alkalin hydrolysis as mentioned above.



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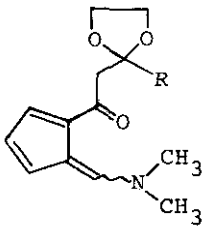
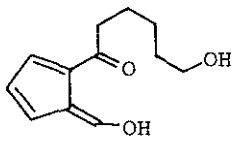


10a, R=CH_3
b, R=n-C_5H_{11}



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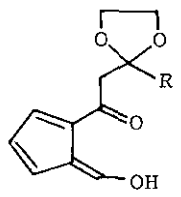

12a, R=CH_3
b, R=n-C_5H_{11}

An important feature in the novel acylfulvene synthesis is as follows. The aminomethylene group is regiospecifically introduced to the vicinal position of the acyl substituent. In addition, the reaction in the presence of alkoxide gave selectively only mono-aminomethylenated compound, different from the reaction of cyclopentadiene with the Vilsmeier reagent giving aminofulvene along with more substituted aminofulvenes.[8] Further, the acylfulvenes were synthesized by one pot procedure from cyclopentadiene as a starting material.

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