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ANGULAR ALKYLATION THROUGH A NOVEL INTRAMOLECULAR CATIONIC CYCLIZATION REACTION. A SIMPLE STEREOSPECIFIC ROUTE TO POLYCYCLIC BRIDGED-RING INTERMEDIATES TOWARDS SOME COMPLEX DITERPENOIDS

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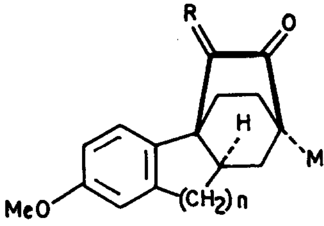
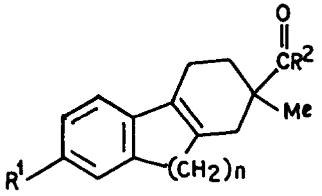
Although there are numerous examples[1] where the intermolecular alkylation of β-ketoesters and β-diketones have been realized through the corresponding enols in the presence of Lewis acids with tertiary and secondary carbocations generated from the appropriate alcohols, halides or the olefins, the intramolecular version of this reaction has been virtually non-existent[2]. As a part of our continuing interest in intramolecular alkylations[3] we have now developed a remarkably simple and potentially useful method of carbon-carbon bond formation involving a prototype of acid-catalyzed intramolecular Michael reaction. In this communication we wish to disclose for the first time, some applications of this reaction in the synthesis of two tetracyclic ketones 1a and 1b incorporating angularly bridged-bicyclo(2.2.2)octanone moiety, potential intermediates towards the synthesis of the complex carbocyclic ring systems present in the recently characterized diterpenoid antibiotic aphidicolin[4], and the antheridium-inducing factor A_{An}[5] respectively. We also report here transformation of the newly created oxo-ethano bridge for stereospecific generation of angular carboxyl group in these polycyclic systems.

The successful synthetic route was first established with a readily available monocyclic model 8[6]. Thus, the acid 8 (2 gm, 8 m mol) was transformed to the corresponding acyl chloride in the usual manner[6], and was condensed[7] in dry ether (50 ml) with $(OEt)MgCH(CO_2Et)_2$ and the crude product 9 was treated under N_2 with a mixture of AcOH (59 ml), H_2SO_4 (10.5 ml) and

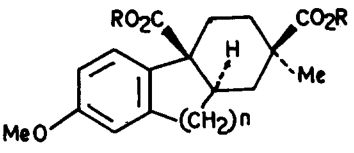
H_2O (14.6 ml) for 16 hr. at r.t. followed by refluxing for 7 hr. Chromatography on Al_2O_3, the product gave the bridged ketone 10[8], m.p. 87-88°C (78%). UV: λ_{max} 225 & 276 nm (log ε 4.18 & 3.31 respectively); IR: 1710 cm^{-1}; NMR: δ 1.0 (s, 3H), 1.26 (m, 2H), 1.60-2.10 (m, 6H), 2.50 (br s, 2H), 3.78 (s, 3H) and 6.75-7.28 (m, 4H).



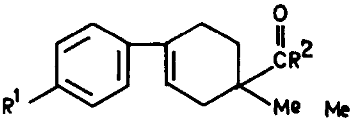
1, R = H_2
4, R = O
[1 - 7 : a; n = 2
b; n = 1]



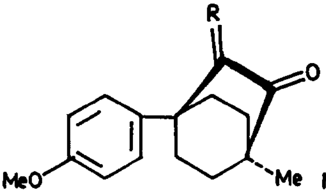
2, R^1=OMe; R^2=OH
3, R^1=OMe; R^2=$CH(CO_2Et)_2$
7, R^1=OMe; R^2=CH_3
15a, R^1=H; R^2=$CH(CO_2Et)_2$
17a, R^1=H; R^2=CH_3



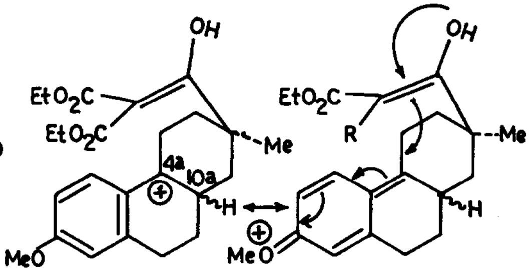
5, R = H
6, R = Me



8, R^1=OMe; R^2=OH
9, R^1=OMe; R^2=$CH(CO_2Et)_2$
14, R^1=H; R^2=$CH(CO_2Et)_2$
16, R^1=H; R^2=CH_3



10, R = H_2
11, R = O



12a, α-10aH,R=H or CO_2Et
13a, β-10aH,R=H or CO_2Et

The intermediate β-oxo-diester 3a prepared through the corresponding known acid 2a[9] and cyclization exactly under the aforementioned conditions provided a single epimeric bridged-ketone 1a, m.p. 137°C (81%), IR: 1710 cm^{-1}; NMR: δ 0.91 (s, 3H), 1.1-2.03 (m, 9H) 2.06-2.43 (partially resolved pair of doublets centered at 2.23 and 2.28, J_{AB} = 9Hz, 2H), 2.65-2.90 (m, 2H), 3.70 (s, 3H), 6.53-7.25 (complex m, 3H); m/e 270 (M^+). Similarly, 3b prepared from 2b[10] again gave a single epimeric bridged-ketone 1b, m.p. 112°C (77%);

IR: 1710 cm^{-1}; NMR: δ 1.0 (s, 3H), 1.30-3.13 (m 11H), 3.73 (s, 3H), 6.56-7.10 (m, 3H); m/e 254 (M^+). Although detailed ^{13}C NMR of these ketones[11] using Yb $(DPM)_3$ shift reagent failed to draw conclusive evidence regarding the stereochemical assignment of the C-10a chiral centre but from the mechanistic considerations[12] we have tentatively assigned the depicted stereochemistry of these ketones.

The cyclization reactions of β-oxo-diesters 3a, 3b are highly sensitive on the reaction conditions and by changing the concentration of the acidic mixture or reaction temperature the competitive direct hydrolytic decarboxylation process becomes the major path leading to the respective methyl ketones 7a & 7b. It seems that the first step in the cyclization of the β-oxo-diesters, eg. 3a is the formation of C-10a epimeric cations 12a & 13a possibly in equilibrium. In the absence of a p-methoxy stabilizing group, such cations are not generated as evidenced by persistent failures in attempted cyclization of the des-methoxy β-oxo-esters such as 14 & 15a. In each case the corresponding methyl ketone 16 or 17a was the only isolable product. The most notable feature in the cyclization of 3a & 3b leading to single diastereoisomer in each case can be rationalized by considering the geometry of the intermediate stages[12] 12a & 13a. Examinations of the molecular models of these intermediate cations with C-10a α-H and C-10a β-H respectively suggest[12] that only in the former case can the π-orbital of the sp^2-hybridized C-4a reactive carbon overlap with the enolate orbital. Such overlapping is sterically impossible in 13a. Similar explanation is also valid for 3b.

The structures of the bridged ketones 10, 1a & 1b were further proved by their oxidation[13] with SeO_2 in Ac_2O to the respective diketones (90-95%); 11, m.p. 160°C; IR: 1740 (sh), 1720(s), 1600(m) cm^{-1}; NMR: δ 1.15 (s, 3H), 1.8-2.53 (m, 8H), 3.76 (s, 3H), 6.76-7.23 (m, 4H); 4a, m.p. 182°C; IR: 1740(m), 1720(s), 1600(m) cm^{-1}; NMR: δ 1.18 (s, 3H), 1.33-2.50 (m, 9H), 2.70-2.96 (m, 2H), 3.77 (s, 3H), 6.63-7.03 (m, 3H); 4b, m.p. 160°C; NMR: δ 1.16 (s, 3H), 1.50-2.70 (m, 7H), 2.73-3.00 (m, 2H), two partially resolved ABX systems at 2.85 (J_{AB} = 10 Hz, J_{BX} = 14 Hz) and 3.07 (J_{AB} = 10 Hz,

J_{AX} = 3 Hz), 6.7-7.12 (m, 3H). Finally, oxidative cleavage[14] of 4a & 4b with alkaline H_2O_2 (30%) in Bu^tOH-H_2O gave 5a, m.p. 212°C & 5b, 230°C (90%). The dimethyl esters (diazomethane) 6a, m.p. 114°C; IR: 1725 cm^{-1}; NMR δ 1.22 (s, 3H), 1.4-2.2 (m, 9H), 2.6-3.0 (m, 2H), 3.55 (s, 3H), 3.62 (s, 3H), 3.70 (s, 3H), 6.5-7.33 (m, 3H) and 6b, m.p. 71°C; IR: 1700-1710 (br, s); NMR: δ 1.27 (s, 3H), 1.57-3.30 (m, 9H), 3.53 (s, 3H), 3.67 (s, 3H), 3.71 (s, 3H), 6.43-7.10 (m, 3H).

Thus, besides the construction of the bridged-bicyclo(2.2.2)octanone intermediates this reaction provides with a simple route to a stereospecific introduction of the C-2 and C-4a- cis-dicarboxylic acid functionalities in hydrophenanthrene and hydrofluorene moieties. Additional studies on this new reaction are in progress.

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