



An Abnormal Reaction of Esters of 3-Hydroxy-3-methylbutan-2-one. A Rapid Synthesis of Bullatenone and Geiparvarin.

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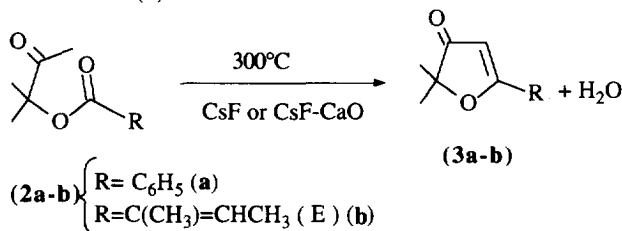
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Abstract: A new rapid and facile synthesis of two natural products with the structure of 3(2*H*)furanone is described by a cyclisation catalysed by cesium fluoride.

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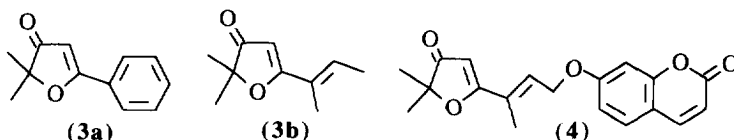
Generally the reaction of an enolate with an ester gives to a ketone (eg: Claisen reaction) with the elimination of an alkoxide¹. During our study of carbonyl compounds condensations with cesium fluoride as heterogeneous base², we observed an abnormal reaction with the esters of 3-hydroxy-3-methyl-2-butanone-2 (**1**). When the benzoate ester³ (**3a**, 5 mmol) was heated with cesium fluoride (3 g) at 300°C for 5 mn under a nitrogen atmosphere, the 3(2*H*)furanone (**3a**) (70%), benzoic acid (15%), 3-hydroxy-3-methyl-2-butanone-2 (**1**) (20%) and methylbutenone (3%) were formed with some coke.

Scheme 1: Cyclisation of esters of (**1**) on CsF or CsF on CaO



No trace of 4-hydroxy-4-methylphenylpentan-1,3-dione or its dehydrated product, coming from an intramolecular Dieckmann reaction was observed. The 3(2*H*)furanone (**3a**) results from a Knoevenagel type condensation on the carbonyl group, a reaction generally not observed with esters. The other products result from hydrolysis of the ester and some dehydration of the substrate (**1**). This abnormal reaction was attributed to the nature of ester and to the rather drastic conditions of temperature which allow activation of high demand energy processes.

Although the scope of this reaction seem to be limited, the resulting 2,2-dimethyl-3(2*H*) furanones have a substructure of natural product, the compound (**3a**) obtained as described above is bullatenone ^{4a,5}, a natural product. Analytical and spectroscopical data were identical to the literature ^{4a,4e,5}. A large number of synthetic methods for 3(2*H*)furanones have been reported in the literature: hydration of acetylene ⁴ or allene ⁶, diketone condensation ⁷, radical cyclisation ⁸, dipolar addition and hydrolysis ⁹. These methods were used for the synthesis of bullatenone but they generally involve many steps.



Our synthesis is more simple and convenient than others described. An other 3(2*H*)furanone of interest is geiparvarin (**4**) a natural product showing signifying tumor-inhibitor properties ^{7b}. Tiglate (**2b**), easily prepared ³ from (**1**), was heated with cesium fluoride at 300°C for 5 mn under a nitrogen flow, the 3(2*H*)furanone (**3b**) precursor of geiparvarin was obtained¹⁰. The precursor (**3b**) can easily be transformed in geiparvarin (**4**) by bromination by NBS followed by aryloxylation by commercially available 7-hydroxycoumarone according to Takeda et al ^{4f,5,11}.

The conversion depends on the nature of catalyst in the order CsF-CaF₂<<CsF<CsF-CaO. This order corresponds to the order of basicity of the catalyst ¹². A conversion of 80 and 85 % was obtained with (**3a**) on CsF and CsF-CaO¹³ respectively after 5 mn of contact. The catalyst CsF or CsF-CaO can be reused three times without apparent loss of activity.

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References :

1. March, J. *Advanced Organic Chemistry*, 4th Ed., J. Wiley and Sons, New York, **1992**, 491-493.
2. Clark, J.H. *Chem. Rev.*, **1980**, *80*, 429-452; Yakobson, G.G.; Akhmetova, N.E. *Synth.* **1983**, 169-184; *Encyclopedia of Reagents for Organic Chemistry*, Paquette, L.A., Ed., J. Wiley and Sons, New York, **1995**, 4220-4225.
3. Esters (**2a-b**) were prepared by the reaction of benzoyl or tiglyl chloride (20 mmol) on 3-hydroxy-3-methylbutan-2-one (**1**, 20 mmol) in triethylamine (15 ml) in the presence of 4-dimethylaminopyridine (2 mmol) under reflux for 3 h. Yield obtained : **2a** (85%), **2b** (70%).
4. a) Parker, W.; Raphael, R.A.; Wilkinson, D.I. *J. Chem. Soc.*, **1958**, 3871-3875; b) Saimoto, H.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.*, **1981**, *103*, 4975-4977; *Bull. Chem. Soc. Jpn.*, **1983**, *56*, 3078-3087; c) Jackson, R.F.W.; Raphael, R.A. *Tetrahedron Lett.*, **1983**, *24*, 2117-2120; d) Saimoto, H.; Shinoda, M.; Matsubara, S.; Oshima, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.*, **1983**, *56*, 3088-3092; e) Sakai, T.; Yamawaki, A.; Ito, H.; Utaka, M.; Takeda, J. *Heterocyclic Chem.*, **1986**, *23*, 1199-1201; f) Inoue, Y.; Ohuchi, K.; Imaizumi, K.S.; Hagiwara, H.; Uda, H. *Synth. Commun.*, **1990**, *20*, 3063-3068.
5. Brandt, C.W.; Taylor, W.I.; Thomas, B.R. *J. Chem. Soc.*, **1954**, 3245-3246.
6. Wolff S.; Agosta, W.C. *Tetrahedron Lett.*, **1985**, *26*, 703-704.
7. a) Dreyer, D.L.; Lee, A. *Phytochemistry*, **1972**, *11*, 763-767; b) Jerris, P.J.; Smith III, A.B. *J. Org. Chem.*, **1981**, *46*, 577-585.
8. Srikrishnan, A. *Ind. J. Chem.*, **1990**, *29B*, 479-480.
9. Curran, D.P.; Singleton, D. H. *Tetrahedron Lett.*, **1983**, *24*, 2079-2082.
10. 2,2-Dimethyl-5-(1-methyl-1-propenyl)-3(2*H*)furanone (**3b**) was purified by PTLC on silica (petrol ether/ether 1/1) R_f=0.4 ; C₁₀H₁₄O₂; PMR δ 1.39 (s, 6H, 2CH₃) 1.87 (d, ³J_{HH}= 7.3 Hz, 3H); 1.89 (d, ⁴J_{HH}=1.2 Hz, 3H); 5.48 (s, 1H); 6.7 (qq, ³J_{HH}= 7.3 Hz; ⁴J_{HH}= 1.2 Hz, 1H); CMR: δ 12.83, 14.38, 23.22, 76.20, 88.24, 98.70, 126.69, 199.20, 184.66; MS(m/e): 166 (M⁺, 100) 151 (14.2) 80 (94.6); IR: 1685 (νC=O), 1640, 1555.
11. Sakai, T.; Ito, H.; Yamawaki, A.; Takeda, A. *Tetrahedron Lett.*, **1984**, *25*, 2987-2985.
12. Villemin, D.; Hachemi, M. *React. Kin. Cat. Lett.*, **1994**, *53*, 147-153; Hachemi, M.; Puciova-Sebova, M.; Toma, S.; Villemin, D. *Phosphorous and Sulfur*, **1996**, *113*, 131-136.
13. CsF-CaF₂ (1/1) was obtained by evaporation of an aqueous solution of CsF in presence of CaF₂, followed by activation at 300°C. CsF-CaO (1/1) was obtained by grinding CaO and CsF together followed by activation at 300°C.

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