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UNEXPECTED FORMATION OF CHROMAN-4-ONES DURING THE SYNTHESIS OF 4-HYDROXYMETHYL-2H-CHROMENES FROM 4-ARYLOXYBUT-2-YN-1-OLS

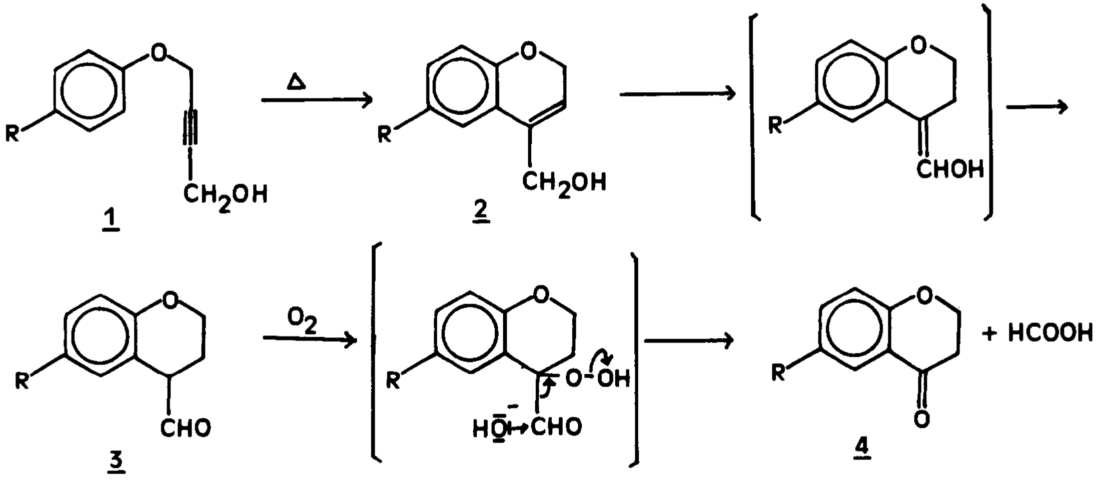
P. Camps,[a] M.A. Lluch,[b] M.J. Climent,[b] and M.A. Miranda[a]

[a]Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, Av. Blasco Ibañez 13, 46010-Valencia, Spain. [b]Departamento de Química, E.T.S. Ingenieros Industriales, Universidad Politécnica de Valencia, Spain

Abstract. The unexpected formation of chroman-4-ones by refluxing 4-aryloxybut-2-yn-1-ols in diethylaniline has been studied, 4-hydroxymethyl-2H-chromene and chroman-4-carboxaldehyde derivatives being established as intermediates.

In connection with the synthesis of 2H-chromene derivatives with potential precocene activity,[1] we attempted to prepare 4-hydroxymethyl-2H-chromenes, 2, from the corresponding 4-aryloxybut-2-yn-1-ols, 1, by the method of Besace and Marszak.[2] When the compounds 1 were heated in diethylaniline under reflux for 8 h in an open vessel, none of the expected chromenes 2 were observed; instead the corresponding chroman-4-one derivatives 4 were obtained (isolated yields: 4a, 68%; 4b, 61%; 4c, 40%). On one occasion, from the reaction of 1a, a small amount of 6-methoxychroman-4-carboxaldehyde, 3a, could be isolated, 4a being the major reaction product.

These unexpected results can be explained by assuming that compounds 1 cyclize to the corresponding chromenes 2, which are then oxidized by air to the chroman-4-ones 4, probably through the intermediacy of aldehydes 3, as shown in the scheme.



a, R = OCH_3 ; b, R = CH_3 ; c, R = OC_3H_7-n

To test this hypothesis, the following experiments were carried out: a) 4-(4-methoxyphenoxy)but-2-yn-1-ol, 1a, was heated under reflux in degassed diethylaniline under argon for 8 h, giving, in high yield, 4-hydroxymethyl-6-methoxy-2H-chromene, 2a, as the only observable (glc) reaction product; b) 2a in diethylaniline was heated under reflux in an open vessel for 4 h, and was transformed into the chromanone 4a as the major product (80% by glc); c) 2a was heated under reflux in degassed diethylaniline under argon in the presence of catalytic amounts of either azobisisobutyronitrile or benzoylperoxide, and was recovered unchanged after 2 h; d) 2a was heated under reflux for 20 h in degassed diethylaniline under argon in the presence of a trace of p-toluenesulfonic acid, and was converted nearly quantitatively (glc) into the aldehyde 3a; e) 2a was heated under reflux in diethylaniline in the presence of solid potassium carbonate (one equivalent) in an open vessel, and was recovered unchanged after 3 h; f) 3a was heated under reflux in diethylaniline in an open vessel, and was completely oxidized to the chromanone 4a after 8 h.

Experiments a) and b) show that compound 2a must be an intermediate in the conversion of 1a into 4a. Experiments c), d), and e) show that the isomerization of the allylic alcohol 2a to the aldehyde 3a takes place easily under very mild acidic catalysis (diethylanilinium p-toluenesulfonate) but not under the influence of radical generators. The results of experiment b) may be explained by assuming that an acid catalyst is initially formed by aerial oxidation of the reaction mixture. Its neutralization with added potassium carbonate would preclude the isomerization, as seems to be the case (experiment e)). Experiment f) shows that the aldehyde 3a can be an intermediate in the oxidation of 2a to 4a.

The acid catalyzed isomerization of 2a to 3a can be easily understood since protonation of 2a at C-3 would give a very stable cation whose transformation into the enol-form of 3a would be achieved by losing a proton from the hydroxymethyl group. Tautomeric equilibria between 4-alkyl-2H-chromenes and 4-alkylidenechromans have been observed by Baranton et al.[3] It is known[4] that enolates react with triplet oxygen to give α-hydroperoxycarbonyl compounds that can be easily degraded as shown in the scheme. Thus, it is quite reasonable to assume a similar mechanism for the aerial oxidation of the aldehyde 3a to the chroman-4-one 4a. Since this oxidation yields formic acid, diethylanilinium formate must also act as a catalyst in the isomerization of the chromene 2a to the aldehyde 3a.

In summary, the synthesis of 4-hydroxymethyl-2H-chromenes described by Besace and Marszak[2] requires an inert atmosphere, otherwise, chroman-4-ones are formed as major reaction products. In the presence of acid catalysts, 4-hydroxymethyl-2H-chromenes are quantitatively converted into chroman-4-carboxaldehydes, a type of compounds that only recently have been prepared from chroman-4-ones as direct precursors of anti-hypertensive and spasmolytic compounds.[5]

REFERENCES

1. "The Merck Index" tenth ed., Merck and Co. Inc., New Jersey, 1983, p. 1109
2. Y. Besace and I. Marszak, Bull. Soc. Chim. France, 2275(1971)
3. F. Baranton, G. Fontaine, and P. Maitte, Bull. Soc. Chim. France, 4203(1968)
4. "Houben-Weyl Methoden der Organischen Chemie", vol. IV/1a, George Thieme Verlag, Stuttgart, 1981, p. 149, and references therein cited.
5. A. Widdig, H.J. Kabbe, A. Knorr, and U. Benz, Ger. Offen. DE 3.300.004(1984), Chem. Abst., **102**, 6203q(1985). See also: M. Matsumoto and K. Kuroda, Koen Yoshishu-Tennen Yuki Kagobutsu Toronkai, 22nd, 347(1979), Chem. Abst., **93**, 46465d(1980)

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