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Radical Reactions Leading to Substituted Coumarins

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Abstract: The reaction of 4-hydroxycoumarins with a series of quinonic chlorides under photostimulation was shown to provide an efficient approach to 3-alkylated coumarin derivatives. Alkylation reactions of this type proceeded via an electron transfer mechanism (S_{RN}1). © 1999 Published by Elsevier Science Ltd. All rights reserved.

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Coumarins are a class of naturally occurring lactones, which display a wide range of biological activities.¹ The dimeric coumarin dicoumarol is the hemorrhagic principle of fermented sweet clover and was once widely prescribed as an oral anticoagulant.² Condensation of 4-hydroxycoumarin and aldehydes was first described by Anschütz³ and thoroughly investigated by Link and co-workers.⁴ However, Appendino has reported that the synthesis of 3-alkylated-4-hydroxycoumarins by direct alkylation of 4-hydroxycoumarin and aliphatic aldehydes is hampered by polyalkylation problems, formation of significant amount of by-products and gave consistently low yields.⁵ In parallel, Kornblum has studied alkylation of 2-carbethoxycoumaran-3-one in nitrobenzylic system via radical chain process.⁶

In connection with our program directed toward the development of novel synthetic quinone congeners as anticancer agents via radical reactions,⁷ we report here a new preparative method for the alkylation of 4-hydroxycoumarin by chloroquinones, based on the displacement of a chloride by a $S_{RN}1$ process.⁸ This alkylation occurred with remarkable selectivity, affording exclusively the 3-substituted-4-hydroxycoumarins in good yield.

Starting substituted quinones 2 were easily prepared from the substituted benzaldehydes 1 by a few steps procedure (Scheme).⁷ Reduction of the aldehydic function of 1 with NaBH₄ in MeOH furnished the corresponding alcohols, which were converted into the intermediate chlorides by thionyl chloride in anhydrous CH₂Cl₂. Then, oxidation with cerium ammonium nitrate (CAN) in CH₃CN afforded the quinones 2 in overall yields of 67-85%. Finally, radical reduction⁹ of 2 with lithium salt of 4-hydroxycoumarin in degassed MeOH, under irradiation, gave very good yields (68-88%) of the 3-substituted-4-hydroxycoumarins 3, along with starting product 2. Results are summarized in the scheme.

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Scheme. *Reagents* : (a) NaBH₄, MeOH, 0° C \rightarrow r.t., 3 h; (b) SOCl₂, NE₃, CH₂Cl₂, 0°C \rightarrow r.t., 5h; (c) CAN, CH₃CN / H₂O, r.t., 1 h; (d) Li salt of 4-hydroxycoumarin (1.1 equiv.), MeOH degassed, hv, 24 h.

Study of the nature of the reaction in the presence of classical radical inhibitors¹⁰ and the fact that intermediate chlorides are recovered unchanged after 24 h when submitted to the standard experimental conditions for the radical reduction provide clear evidence that the C-alkylation product 3 is formed via a $S_{RN}1$ process. The conversion of compounds 2 into the 3-substituted-4-hydroxycoumarins 3 takes place by the heterolytic cleavage of the radical anion of 2 which looses a chloride anion. The intermediate "benzylic" radical is then alkylated by 4-hydroxycoumarin to form the corresponding products 3. Moreover, investigation of the nucleophilic addition of the 4-aminocoumarin salt to the quinone 2a, has allowed us to establish that best results are obtained when reactions are run in DMSO. Indeed, the alkylated product 3g was isolated in excellent yield (89%).

In summary, we describe a novel method for efficient preparation of 3-substituted coumarins is described. Experiments with different types of dinitroalkanes and chloronitroalkanes are actually underway in our laboratory in order to get a more complete understanding of this alkylation process.

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- 9. General procedure for the radical reaction. A degassed solution of chloro quinones (2.5 mmol), lithium salt of 4-hydroxycoumarin (2.5 mmol) in MeOH (20 ml) was irradiated with a 300 W sun lamp for 24 h at r.t. under an inert atmosphere. After evaporation of the MeOH and extraction with CH₂Cl₂, the crude product was purified by flash chromatography (CH₂Cl₂/Et₂O 9:1).
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