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LETTERS

Radical Reactions Leading to Substituted Coumarins

Anne Giraud,[1] Patrice Vanelle,[2] Luc Giraud[1*]

[1] *Université de Fribourg, Institut de Chimie Organique, Pérolles, CH-1700 Fribourg, Switzerland*
[2] *Laboratoire de Chimie Organique, Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille Cedex 05, France*

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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 ($S_{RN}1$).

Keywords : coumarins; quinones; radical reactions; electron transfer; alkylation

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 Anschütz[3] 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 $NaBH_4$ in MeOH furnished the corresponding alcohols, which were converted into the intermediate chlorides by thionyl chloride in anhydrous CH_2Cl_2. Then, oxidation with cerium ammonium nitrate (CAN) in CH_3CN afforded the quinones **2** in overall yields of 67-85%. Finally, radical reduction[9] 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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[*] Current address: Firmenich SA, Route de la Plaine 45, CH-1283 La Plaine-Genève, Suisse. Fax ++41 (0) 22 780 14 73; E-mail luc.giraud@firmenich.com

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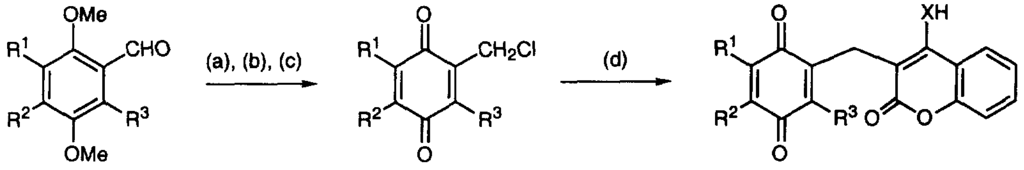

1 **2** **3**

1a : $R^1 = R^2 = R^3 = Me$	**2a** : 79%	X = O	**3a** : 84 %
1b : $R^1 = R^2 = Me, R^3 = H$	**2b** : 72 %	X = O	**3b** : 72 %
1c : $R^1 = Me, R^2 = R^3 = H$	**2c** : 67 %	X = O	**3c** : 68 %
1d : $R^1 = R^2 = R^3 = OMe$	**2d** : 84 %	X = O	**3d** : 87 %
1e : $R^1 = R^2 = OMe, R^3 = H$	**2e** : 79 %	X = O	**3e** : 77 %
1 f : $R^1 = R^2 = Me, R^3 = Br$	**2 f** : 85 %	X = O	**3 f** : 88 %
1a : $R^1 = R^2 = R^3 = Me$	**2a**	X = NH	**3g** : 89%

Scheme. *Reagents* : (a) $NaBH_4$, MeOH, 0° C → r.t., 3 h; (b) $SOCl_2$, NEt_3, CH_2Cl_2, 0°C → r.t., 5h; (c) CAN, CH_3CN / H_2O, r.t., 1 h; (d) Li salt of 4-hydroxycoumarin (1.1 equiv.), MeOH degassed, hν, 24 h.

Study of the nature of the reaction in the presence of classical radical inhibitors[10] 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.

References and notes

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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 CH_2Cl_2, the crude product was purified by flash chromatography (CH_2Cl_2/Et_2O 9:1).
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