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New Synthesis of 2,4-Dimethylfuro[3,2-*c*]quinolines

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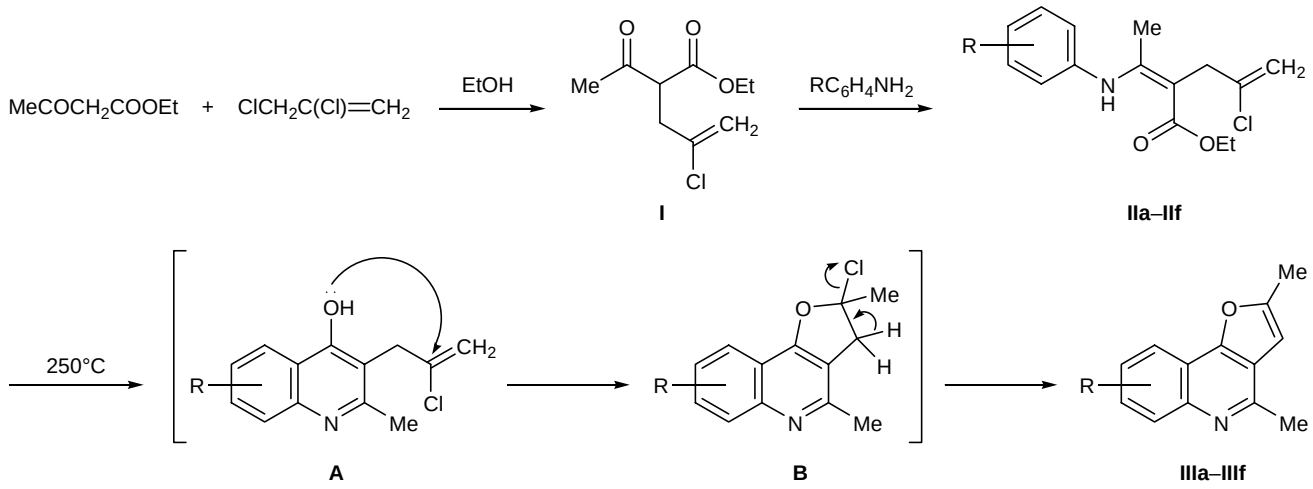
Abstract—Thermal cyclization of ethyl α-(2-chloro-2-propenyl)-β-arylaminocrotonates in mineral oil afforded the corresponding substituted 2,4-dimethylfuro[3,2-*c*]quinolines instead of the expected 4-hydroxy-2-methyl-3-(2-chloro-2-propenyl)quinolines.

Development of the quinoline chemistry has been stimulated mainly by the isolation and studying of furoquinoline alkaloids. These compounds attract interest from both theoretical and practical viewpoints due to wide spectrum of their biological activity [1, 2]. Among the most widely known furoquinoline alkaloids, dictamnine (4-methoxyfuro[2,3-*b*]quinoline), fagarine (8-methoxydictamnine), and skimmianine (7,8-dimethoxydictamnine) [1, 2] should be noted.

The present communication reports on a new convenient method for the synthesis of 2,4-dimethylfuro-[3,2-*c*]quinolines **IIIa**–**IIIf** by thermal cyclization of ethyl 2-[1-(arylamino)ethylidene]-4-chloro-4-pentenoates **IIa**–**IIf**. The latter were prepared by reaction of ethyl 2-acetyl-4-chloro-4-pentenoate (**I**) [3] with substituted anilines and were subjected to cyclization on heating to 250°C in mineral oil. Previously, the cyclization of α-allyl-, α-(3,3-dichloroallyl)-, and α-(3-chloro-2-butenyl)-β-arylaminocrotonic acids afforded the corresponding 3-allyl-, 3-(3,3-dichloroallyl)-, and 3-(3-chloro-2-butenyl)-4-hydroxy-2-methylquinolines [4, 5]. The unusual reaction path leading to substituted furoquinolines **III** (which were identical to those reported in [4]) may be interpreted as follows. The primary thermal cyclization products are likely to be 4-hydroxy-3-(2-chloro-2-propenyl)-2-methylquinolines **A** which are then converted into the corresponding 2-chloro-2,4-dimethyl-2,3-dihydrofuro[3,2-*c*]-quinolines **B**, and the subsequent aromatization of the latter via elimination of hydrogen chloride yields 2,4-dimethylfuro[3,2-*c*]quinolines **IIIa**–**IIIf** as shown in Scheme 1. The proposed scheme is supported by the fact that treatment of 4-hydroxyquinolines having an allyl group in position *3* with pyridine hydro-

Scheme 1.



R = H (**a**), 6-CH_3 (**b**), 8-CH_3 (**c**), 6-OCH_3 (**d**), 8-OCH_3 (**e**), 6-Cl (**f**).

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chloride on heating or with sulfuric acid or bromine at room temperature leads to formation of the corresponding furoquinolines [6–8]. It was also found that furoquinolines containing a halogen atom in the α-position of the furan ring readily undergo aromatization as a result of elimination of hydrogen halide even by the action of a weak base [6].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz) from solutions in DMSO-d_6. The purity of the products was checked by thin-layer chromatography on Silufol UV-254 plates using chloroform–hexane (1:2) as eluent and iodine vapor as developer.

Ethyl 2-acetyl-4-chloro-4-pentenoate (I) was synthesized by the procedure described in [3] from ethyl acetoacetate and 2,3-dichloropropene. Yield 153.4 g (71%), bp 84–86°C (5 mm) , n_D^{20} = 1.4625.

Ethyl 2-(1-arylaminoethylidene)-4-chloro-4-pentenoates IIa–IIf (*general procedure***).** A mixture of 20.45 g (0.1 mol) of compound **I**, 0.1 mol of the corresponding substituted aniline, and 2–3 drops of hydrochloric acid in 200 ml of benzene was heated at the boiling point with simultaneous removal of water as azeotrope with benzene. When the required amount of water separated (1.8 ml), the solvent was distilled off, and the residue was subjected to heterocyclization without additional purification.

2,4-Dimethylfuro[3,2-*c*]quinolines IIIa–IIIf (*general procedure***).** Compound **IIa**–**IIf**, was added in a stream of nitrogen under vigorous stirring to 300 ml of mineral oil heated to 250°C. The mixture was cooled, the precipitate was filtered off and dissolved in 5% hydrochloric acid, the solution was treated with charcoal and filtered, and the filtrate was made alkaline (pH 8–8.5) by adding a solution of sodium hydroxide. The precipitate was filtered off and recrystallized from aqueous alcohol (1:1).

2,4-Dimethylfuro[3,2-*c*]quinoline (IIIa). Yield 78%, mp 63°C, R_f 0.62. ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH_3), 2.52 s (3H, $NCCH_3$), 6.65 s (1H, 4-H), 7.37–7.78 m (4H, H_{arom}). Found, %: C 79.10; H 5.70; N 7.16. $C_{13}H_{11}NO$. Calculated, %: C 79.19; H 5.58; N 7.10.

2,4,6-Trimethylfuro[3,2-*c*]quinoline (IIIb). Yield 74%, mp 72–73°C, R_f 0.67. Found, %: C 79.49; H 6.33; N 6.76. $C_{14}H_{13}NO$. Calculated, %: C 79.62; H 6.16; N 6.64.

2,4,8-Trimethylfuro[3,2-*c*]quinoline (IIIc). Yield 75%, mp 80–81°C, R_f 0.60. Found, %: C 79.75; H 6.20; N 6.51. $C_{14}H_{13}NO$. Calculated, %: C 79.62; H 6.16; N 6.64.

6-Methoxy-2,4-dimethylfuro[3,2-*c*]quinoline (IIId). Yield 76%, mp 115°C, R_f 0.59. ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 2.67 s (3H, $NCCH_3$), 3.9 s (3H, OCH_3), 6.62 s (1H, 4-H), 7.40–7.80 m (4H, H_{arom}). Found, %: C 73.80; H 5.90; N 6.10. $C_{14}H_{13}NO_2$. Calculated, %: C 73.99; H 5.77; N 6.17.

8-Methoxy-2,4-dimethylfuro[3,2-*c*]quinoline (IIIe). Yield 79%, mp 95–96°C, R_f 0.54. Found, %: C 74.06; H 5.86; N 6.21. $C_{14}H_{13}NO_2$. Calculated, %: C 73.99; H 5.77; N 6.17.

6-Chloro-2,4-dimethylfuro[3,2-*c*]quinoline (IIIf). Yield 68%, mp 118°C, R_f 0.64. Found, %: C 67.48; H 4.20; Cl 15.19; N 6.17. $C_{13}H_{10}ClNO$. Calculated,%: C 67.36; H 4.32; Cl 15.33; N 6.05.

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