Bis(5-alkyl-2-furyl)(2-carboxyphenyl)-methanes for the Synthesis of Tetracyclic Isochromone Derivatives

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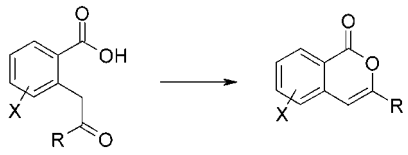
Introduction

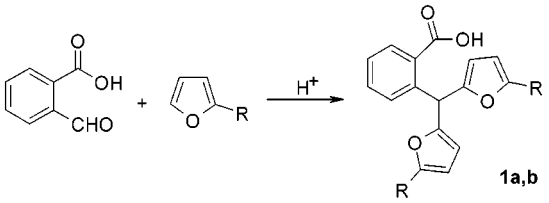
Isochromone (isocoumarin) derivatives constitute a class of heterocyclic compounds that is widespread in nature, and there are plenty of examples for biological activity of different kinds.[1] The main synthetic approach toward isochromone still involves utilizing the cyclization of 2-(2-oxoethyl)benzoic acids (Scheme 1), the carbonyl group of which can be both in apparent[2] and in latent form (acetylenes,[3] preoxidized ethylenes,[4] enol ethers,[5] vinyl bromides[6]).

It is a well-known fact that alkylfurans in acidic media are able to act as a source of 1,4-dicarbonyl compounds, and this property of furan derivatives is extensively used in organic synthesis.[7] Our previous investigations have shown that a number of ortho-substituted benzylfurans in acidic media undergo the recyclization reaction of furan ring with formation of new heterocycles such as benzo[*b*]furans,[8] indoles,[9] and isoquinolones.[10] Herein, we report a new approach to the synthesis of isochromone

Scheme 1



Scheme 2



1a R = CH_3; **1b** R = CH_2CH_3

(isocoumarin) derivatives, and in this case, the furan cycle also provides a carbonyl function for heterorecyclization.

Results and Discussion

First of all, bis(5-alkyl-2-furyl)(2-carboxyphenyl)methanes **1a**,**b** have been obtained by condensation of 2-alkylfurans and 2-formylbenzoic acid in dioxane in the presence of $HClO_4$ (Scheme 2).

The following treatment of the benzoic acids **1a**,**b** with anhydrous methanolic HCl solution affords the isochromones **2a**,**b** with high yields (Scheme 3).

Apparently the reaction begins with the protonation of one of two furan rings, followed by the intramolecular attack of the hydroxy group of 2-carboxyphenyl residue on the furanyl cation. The intermediate spiro compound then transforms into 4-(5-alkyl-2-furyl)-3-(3-oxobutyl)-1*H*-1-isochromenone **3**. Unfortunately, all attempts have failed to isolate this compound because it easily undergoes intramolecular cyclization of the carbonyl group to the 3-position of the furyl moiety affording the tetracyclic isochromones **2a**,**b**. This result is consistent with those obtained previously, as 3-(5-methyl-2-furyl)-3-(3-oxobutyl)benzo[*b*]furans also easily underwent intramolecular cyclization into tetracyclic benzofuran derivatives,[8b] and also the recyclization of *N*-benzyl-2-bis(5-methyl-2-furyl)-methylbenzamide into isoquinolone derivative was accompanied with secondary cyclization into similar tetracyclic compound.[10]

It has been also found possible to obtain the tetracycles **2a**,**b** directly from 2-alkylfurans and 2-formylbenzoic acid by a one-pot procedure with moderate yields.

In conclusion, a simple and convenient synthesis of novel tetracyclic system of 1,11-dialkyl-3,5-dihydrofuro-[2′,3′:3,4]cyclohepta[*c*]isochromen-5-one has been developed starting from easily available materials.

Experimental Section

General Methods. All ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, using $CDCl_3$ as a solvent; chemical shifts are in ppm downfield from tetramethylsilane as internal standard; IR spectra were taken in Nujol, and the most intense or representative bands are reported

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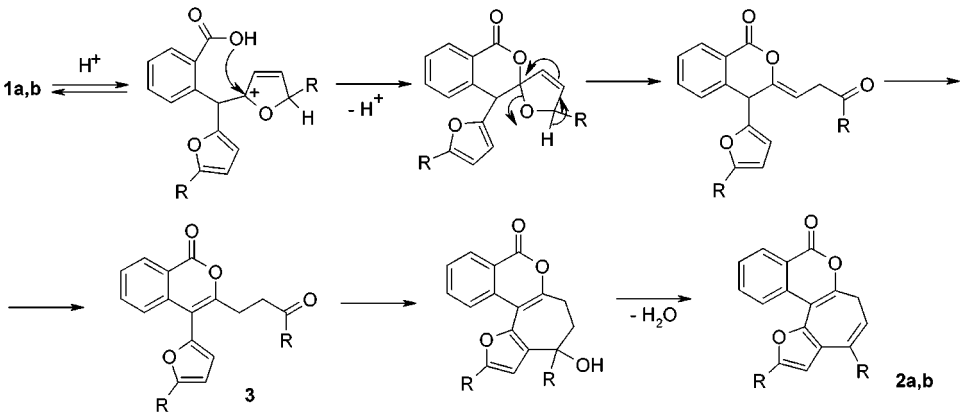
Scheme 3



(in cm^{-1}). Melting points are uncorrected. 2-Formylbenzoic acid obtained from Aldrich; freshly distilled 2-methylfuran and 2-ethylfuran were taken for each synthesis.

General Procedure for the Synthesis of Bis(5-alkyl-2-furyl)(2-carboxyphenyl)methanes. To the solution of 2-formylbenzoic acid (1.5 g, 0.01 mol) and 2-alkylfuran (0.022 mol) in 5 mL of dioxane 0.2 mL of 70% $HClO_4$ was added, and the mixture left overnight at room temperature. It was then poured into 30 mL of water, and the precipitated solid was filtered 3 h later.

Bis(5-methyl-2-furyl)(2-carboxyphenyl)methane 1a: yield 55%; mp 145−146 °C (benzene); ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 6H, CH_3), 5.86 (d, J = 3.2 Hz, 2H, 3-H_{Fur}), 5.89 (d, J = 3.2 Hz, 2H, 4-H_{Fur}), 6.68 (s, 1H, CH), 7.30−7.39 (m, 2H, H_{Ar}), 7.47−7.58 (m, 1H, H_{Ar}), 8.03−8.12 (m, 1H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.6 (2C), 40.6, 106.1 (2C), 108.6 (2C), 127.0, 127.9, 130.2, 131.7, 133.1, 142.2, 151.4, 152.7, 173.4; IR (Nujol) 2900, 1690 cm^{-1}; m/z 296 (M^+). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.03; H, 5.41.

Bis(5-ethyl-2-furyl)(2-carboxyphenyl)methane 1b: yield 67%; mp 114−115 °C (benzene); ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7.5 Hz, 6H, CH_2CH_3), 2.59 (q, J = 7.5 Hz, 4H, CH_2CH_3), 5.85 (d, J = 3.2 Hz, 2H, 3-H_{Fur}), 5.88 (d, J = 3.2 Hz, 2H, 4-H_{Fur}), 6.68 (s, 1H, CH), 7.28−7.39 (m, 2H, H_{Ar}), 7.45−7.56 (m, 1H, H_{Ar}), 8.04−8.11 (m, 1H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 12.2 (2C), 21.4 (2C), 40.8, 104.4 (2C), 108.4 (2C), 126.9, 128.0, 130.2, 131.7, 133.0, 142.4, 152.6 (2C), 157.2 (2C), 173.3; IR (Nujol) 2900, 1690 cm^{-1}; m/z 324 (M^+). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.81; H, 6.35.

General Procedure for the Synthesis of 1,11-Alkyl-3,5-dihydrofuro[2′,3′:3,4]cyclohepta[*c*]isochromen-5-ones. To a solution of compound **1a,b** (0.01 mol) in 10 mL of methanol 10 mL of dry saturated methanolic HCl solution was added in one portion, and the reaction mixture stirred under reflux for 30 min. Then it was cooled and diluted with 100 mL of H_2O. The liberated thick oil was washed by decantation, dissolved in 20 mL of ethanol, and left overnight to crystallize.

1,11-Methyl-3,5-dihydrofuro[2′,3′:3,4]cyclohepta[*c*]isochromen-5-one 2a: yield 86%; mp 146−147 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 2.03 (d, J = 1.2 Hz, 3H, CH_3), 2.48 (d, J = 1.0 Hz, 3H, CH_3), 2.98 (d, J = 6.8 Hz, 2H, CH_2), 5.37 (t.q, J = 1.2, 6.8 Hz, 1H, =CH), 6.29 (q, J = 1.0 Hz, 1H, H_{Fur}), 7.45−7.54 (m, 1H, H_{Ar}), 7.72−7.81 (m, 1H, H_{Ar}), 8.31−8.40 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 13.8, 20.3, 31.6, 105.4, 105.7, 115.5, 119.7, 124.4, 127.0, 127.4, 129.8, 137.6, 134.8, 135.4, 145.5,146.8, 151.3, 162.3; IR (Nujol) 1740 cm^{-1}; m/z 278 (M^+). Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.24; H, 5.05.

1,11-Ethyl-3,5-dihydrofuro[2′,3′:3,4]cyclohepta[*c*]isochromen-5-one 2b: yield 89%; mp 168−169 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.48 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.40 (q. d, J = 1.2, 7.5 Hz, 2H, CH_2CH_3), 2.83 (q. d, J = 1.0, 7.5 Hz, 2H, CH_2CH_3), 2.99 (d, J = 6.8 Hz, 2H, CH_2), 5.38 (t.t, J = 1.2, 6.8 Hz, 1H, =CH), 6.29 (t, J = 1.0 Hz, 1H, H_{Fur}), 7.45−7.56 (m, 1H, H_{Ar}), 7.72−7.81 (m, 1H, H_{Ar}), 8.31−8.41 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 12.1, 13.2, 21.5, 27.2, 31.5, 103.8, 105.4, 114.0, 119.8, 124.4, 126.2, 127.4, 129.8, 134.8, 135.6, 137.6, 145.8, 147.2, 156.8, 162.3; IR (Nujol) 1740 cm^{-1}; m/z 306 (M^+). Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.27; H, 5.69.

One-Pot Procedure for the Synthesis of 1,11-Alkyl-3,5-dihydrofuro[2′,3′:3,4]cyclohepta[*c*]isochromen-5-ones 2a,b. To the solution of 2-formylbenzoic acid (1.5 g, 0.01 mol) and 2-alkylfuran (0.022 mol) in 10 mL of methanol was added 2 mL of dry saturated methanolic HCl solution in one portion, and the reaction mixture was stirred for 5 min. Then 8 mL of CH_3-OH/HCl was added, and the darkened mixture was stirred under reflux within 30 min. Then it was cooled and diluted with 100 mL of H_2O. The liberated thick dark oil was washed by decantation, dissolved in 20 mL of ethanol, and left overnight. Double recrystallization of the precipitated crystalline solid from ethanol gave 37% and 41% yields of **2a** and **2b**. Main analytical data are the same as for those mentioned above.

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