Brief Communications

Synthesis of 2-substituted 3-iodo-4*H*-chromen-4-ones*

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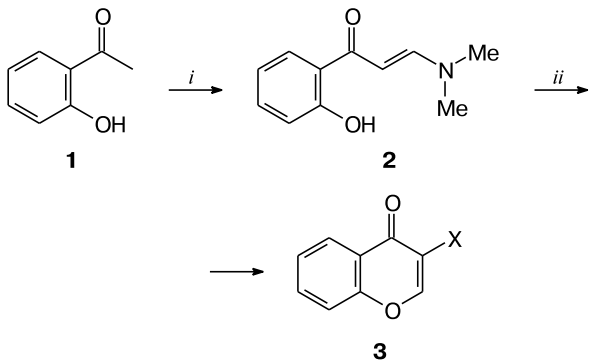
3-Iodochromones containing phenyl and furyl fragments at position 2 were synthesized by heterocyclization of β-ketoenamines.

Key words: iodochromones, β-ketoenamines, furans, heterocyclization reactions.

Chromone structure is a part of many natural and synthetic pharmaceutical agents possessing various biological activity.[1] Their halo derivatives are of significant interest as stimulants of the central nervous system, as well as the agents exhibiting high antiviral, antibacterial, antifungal, antiallergic, and neuroleptic activity.[2] Also note a high synthetic potential of these compounds,[2] especially iodo substituted derivatives,[3,4] which readily react with nucleophiles and can be involved in the cross-coupling reactions leading to the synthesis of a wide variety of benzopyrans.

Among existing approaches to the chromone halo derivatives, reactions of halogens with β-ketoenamines[4,5] **2** (obtained by the reaction of hydroxyacetophenones with dimethylformamide diacetal) is one of the most convenient methods (Scheme 1). It should be emphasized that in this case the heterocyclization involves the hydroxy group and leads to chromones **3** containing no substituents at position 2 (see Scheme 1).

Scheme 1



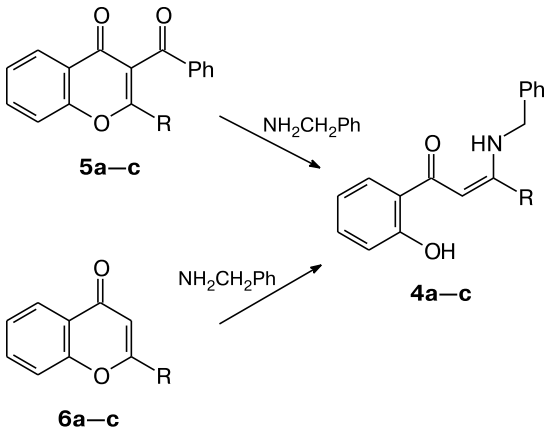
i. $Me_2NCH(OR)_2$; *ii*. X_2
X = Br, I

* On the occasion of the 80th anniversary of the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 0543—0545, February, 2014.
1066-5285/14/6302-0543

The approaches dealing with the syntheses of 3-halo chromones with substituents at position 2 based on β-ketoenamines are less developed. This method requires introduction of the corresponding substituent R into the β-ketoenamine fragment of compound **4** (Scheme 2). There are the literature data describing preparation of such enaminones with the limited set of substituents R (alkyl and phenyl groups)[6,7] and there is the only example of the transformation of the enaminone with the methyl group (R = Me) to the corresponding 3-bromo derivative upon treatment with bromine.

Scheme 2



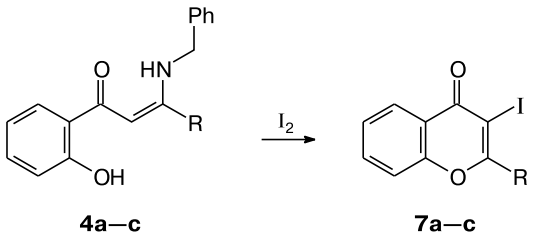
4—6: R = 2-Furyl (**a**), Ph (**b**), 4-Me-C_6H_4 (**c**)

In the present work, we suggest an approach to the synthesis of 2-substituted 4*H*-chromen-4-ones with the iodine atoms at position 3 (Schemes 2 and 3). The preparation of the intermediate products **4a—c** was carried out according to the Scheme 2 by the reaction of the primary amine with 3-acyl-2-hetarylchromones **5a—c** obtained by us earlier[8] or with benzopyrans **6a—c** with substituents at position 2 described in the literature.[9] The use in these processes of benzylamine in ethanol leads to the high yields of β-ketoenamines **4a—c**, which were within 85—89% (see Scheme 2). It should be noted that in the course of the reaction with 3-acyl-2-hetarylchromones, the formation of β-ketoenamines is accompanied by deacylation. The structures of compounds obtained were confirmed by ^{1}H and ^{13}C NMR spectroscopy. The signal for the NH group at δ 13 in the ^{1}H NMR spectrum is explained by the intramolecular interaction of the proton of the amino group with the keto group, that confirms the shown configuration of compounds.

Since chromones **6** are obtained from the same 1,3-diketones as chromones **5**, but require lesser number of steps, their use is preferable in the synthesis of β-ketoenamines.

The studies of the iodination reaction of β-ketoenamines obtained showed that the yields of the target products strongly depend on the presence of light and solvent. The reaction of β-ketoenamine with the furyl substituent **4a** with iodine in chloroform led to the formation of iodo derivative **7a** in 23% yield, whereas in methanol the yield of the product increased up to 33%. When the reaction was carried out in the dark in methanol, the corresponding iodo derivative **7a** was isolated in 66% yield, whereas the iodination of β-ketoenamines with phenyl and tolyl substituents **4b**,**c** gave 65—76% yields of the products (see Scheme 3).

Scheme 3



7: R = 2-Furyl (**a**), Ph (**b**), 4-Me-C_6H_4 (**c**)

It should be noted that attempted synthesis of compound **7a** using methods described earlier[10—12] was unsuccessful.

In conclusion, we suggested an approach to the synthesis of 3-iodochromones containing furyl (**7a**) and aryl (**7b**,**c**) fragments at position 2. Note that no synthesis of either β-ketoenamine **4a** or chromone 3-iodo derivative **7a** with furanyl moieties was described earlier. The latter can be a valuable starting compound in the preparation of photoactive benzopyrans.[13]

Experimental

^{1}H NMR spectra were recorded on Bruker AC-200 (200 MHz) and Bruker AM-300 (300 MHz) spectrometers in $CDCl_3$, ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (75 MHz) in $CDCl_3$, using signals for residual protons and carbon atoms of the solvent as the references. Melting points were determined on a Boetius heating stage and were not corrected. TLC on Merck Silica gel 60 F254 UV-254 plates was used to analyze all reaction mixtures and control purity of isolated compounds.

Synthesis of β-ketoenamines 4a—c (general procedure). A solution of 4*H*-chromen-4-one **5a—c** or **6a—c** (10 mmol) and benzylamine (30 mmol) in ethanol was refluxed for 48 h. Then, the reaction mixture was concentrated, a dry residue was dissolved in dichloromethane with some light petroleum. The products were isolated by column chromatography in the system CH_2Cl_2 : light petroleum (9 : 1).

3-Benzylamino-3-(furan-2-yl)-1-(2-hydroxyphenyl)propenone (4a). The yield was 85%, m.p. 122—123 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$)), δ: 13.34 (s, 1 H, NH); 11.32 (s, 1 H, OH); 7.73 (d, 1 H, H_{Ar}, J = 8 Hz); 7.61 (d, 1 H, H_{Fur}, J = 1.47 Hz);

7.45—7.30 (m, 6 H, H_{Ar+Fur}); 6.96 (d, 1 H, H_{Ar}, J = 7.3 Hz); 6.85 (m, 2 H, H_{Ar}); 6.54 (m, 1 H, H_{Fur}); 6.25 (s, 1 H, HC=C); 4.79 (d, 2 H, CH_2—Ph, J = 6.2 Hz). ^{13}C NMR (50.32 MHz, $CDCl_3$), δ: 191.44, 162.31, 154.55, 147.83, 144.78, 137.97 (2 C); 133.78, 129.01, 127.8 (2 C); 127.03 (2 C); 120.88 (2 C); 118.38, 114.66, 112.03, 89.99, 49.45. Found (%): C, 75.27; H, 5.24; N, 4.42. $C_{20}H_{17}NO_3$. Calculated (%): C, 75.22; H, 5.37; N, 4.39.

3-Benzylamino-1-(2-hydroxyphenyl)-3-phenylpropenone (4b). The yield was 86%, m.p. 97 °C (Ref. 14: m.p. 100 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 13.41 (s, 1 H, NH); 11.29 (s, 1 H, OH); 7.63 (d, 1 H, H_{Ar}, J = 8 Hz); 7.50—7.37 (m, 6 H, H_{Ar}); 7.37—7.26 (m, 3 H, H_{Ar}); 7.23 (d, 2 H, H_{Ar}, J = 7.1 Hz); 6.95 (d, 1 H, H_{Ar}, J = 8.3 Hz); 6.79 (t, 1 H, H_{Ar}, J = 7.4 Hz); 5.85 (s, 1 H, HC=C); 4.46 (d, 2 H, CH_2—Ph, J = 6.4 Hz). ^{13}C NMR (50.32 MHz, $CDCl_3$, δ: 191.47, 167.51, 162.44, 138.44, 135.36, 133.8 (2 C); 129.89, 128.93 (2 C); 128.76 (2 C); 127.92, 127.75 (3 C); 127.7, 126.92 (2 C); 120.68, 92.78, 48.82. Found (%): C, 80.3; H, 5.7; N, 4.1. $C_{22}H_{19}NO_2$. Calculated (%): C, 80.22; H, 5.81; N, 4.25.

3-Benzylamino-1-(2-hydroxyphenyl)-3-(4-tolyl)propenone (4c). The yield was 89%, m.p. 115—116 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 13.45 (s, 1 H, NH); 11.29 (s, 1 H, OH); 7.65 (d, 1 H, H_{Ar}, J = 7.9 Hz); 7.50—7.20 (m, 10 H, H_{Ar}); 6.95 (d, 1 H, H_{Ar}, J = 8.2 Hz); 6.79 (t, 1 H, H_{Ar}, J = 7.4 Hz); 5.84 (s, 1 H, HC=C); 4.48 (d, 2 H, CH_2—Ph, J = 6.3 Hz); 2.43 (s, 3 H, CH_3). ^{13}C NMR (50.32 MHz, $CDCl_3$), δ: 191.25, 167.76, 162.42, 140.13, 138.23, 133.7, 132.46; 129.41 (2 C); 128.91 (2 C); 127.87, 127.72, 127.66 (2 C); 126.90 (2 C); 120.73, 118.33, 118.28, 92.71, 48.82, 21.45. Found (%): C, 80.3; H, 6.0; N, 4.1. $C_{23}H_{21}NO_2$. Calculated (%): C, 80.44; H, 6,16; N, 4.08.

Synthesis of 2-substituted 3-iodo-4*H*-chromen-4-ones (7a—c) (general procedure). β-Ketoenamine **4a—c** (1 mmol) was dissolved in methanol (10—15 mL), followed by addition of iodine (2 mmol). The reaction mixture was stirred for 16 h. After the reaction reached completion, the solvent was evaporated *in vacuo*, dichlomethane was added, and the mixture was twice washed with saturated aqueous sodium thiosulfate and water. The organic layer was separated and dried with anhydrous sodium sulfate. The products was isolated by column chromatography in dichloromethane.

2-(Furan-2-yl)-3-iodochromen-4-one (7a). The yield was 66%, m.p. 128—130 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 8.26 (d, 1 H, H_{Ar}, J = 7.7 Hz); 7.78 (m, 2 H, H_{Fur}); 7.71 (t, 1 H, H_{Ar}, J = 6.9 Hz); 7.55 (d, 1 H, H_{Ar}, J = 8.4 Hz); 7.45 (t, 1 H, H_{Ar}, J = 6.4 Hz); 6.70 (m, 1 H, H_{Fur}). ^{13}C NMR (50.32 MHz, $CDCl_3$), δ: 174.28, 155.49, 154.09, 146.38, 145.83, 134.25, 126.9, 125.81, 119.97, 118.47, 117.53, 112.30, 84.03. Found (%): C, 46.5; H, 2.09. $C_{13}H_7IO_3$. Calculated (%): C, 46.18; H, 2.09.

3-Iodo-2-phenylchromen-4-one (7b). The yield was 65%, m.p. 120—121 °C (Ref. 15: m.p. 121—123 °C). ^{1}H NMR ($CDCl_3$, 300.13 MHz): 8.28 (dd, 1 H, H_{Ar}, J = 8.0 Hz, J = 1.6 Hz); 7.72 (ddd, 1 H, H_{Ar}, J = 8.3 Hz, J = 7.1 Hz, J = 1.6 Hz); 7.60—7.57 (m, 2 H, H_{Ar}); 7.56—7.42 (m, 5 H, Ph). ^{13}C NMR (50.32 MHz, $CDCl_3$), δ: 174.8, 164.0, 155.9, 135.4, 134.5, 131.4, 129.9 (2 C); 128.4 (2 C); 127.2, 125.9, 120.3, 117.9, 88.4. Found (%): C, 52.01; H, 2.62. $C_{15}H_9IO_2$. Calculated (%): C, 51.75; H, 2.61.

3-Iodo-2-(*p*-tolyl)chromen-4-one (7c). The yield was 76%, m.p. 127—129 °C (Ref. 16: m.p. 126 °C). ^{1}H NMR ($CDCl_3$, 300.13 MHz): 8.30 (d, 1 H, H_{Ar}, J = 7.7 Hz); 7.84 (d, 1 H, H_{Ar}, J = 8 Hz); 7.72 (d, 2 H, Tol, J = 8.1 Hz); 7.57—7.44 (m, 2 H, H_{Ar}); 7.34 (d, 2 H, Tol, J = 7.9 Hz); 2.48 (s, 3 H, CH_3). ^{13}C NMR (50.32 MHz, $CDCl_3$), δ: 174.92, 165.11, 156.03, 142.15, 141.75, 134.34, 129.59 (2 C); 125.96, 125.11, 120.03, 118.09, 117.73 (2 C); 87.92, 21.7. Found (%): C, 53.01; H, 3.00. $C_{16}H_{11}IO_2$. Calculated (%): C, 53.06; H, 3.06.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 13-03-01054-a).

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Received November 27, 2013;
in revised form December 27, 2013