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Synthesis of 3-(5-Aryl-1,3,4-oxadiazol-2-yl)chromones

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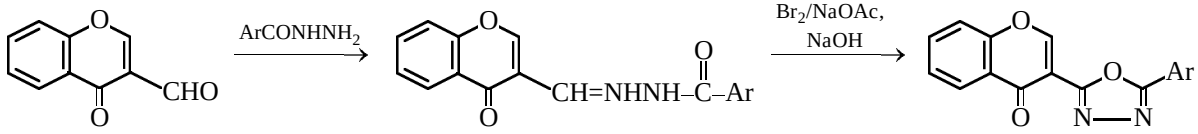
Abstract—A general procedure was proposed for the synthesis of 3-(5-aryl-1,3,4-oxadiazol-2-yl)chromones by reaction of 3-formylchromone with aroylhydrazines, transformation of the corresponding acylhydrazones into 1,3-dipoles by the action of bromine in the presence of sodium acetate, and intramolecular ring closure.

3-Heteryl-substituted chromones are known to exhibit biological activity over a wide range. They show high antiallergic, anticholesteric, hypolipidemic, antimicrobial, fingicide, and antiblastic properties and stimulate central nervous system [1]. Therefore, synthesis of new compounds of this series has attracted much attention in the recent years. Methods of synthesis of 3-heterylchromones were reviewed in [1]. Two main approaches were noted. According to the first of these, the chromone system is built up from substituted α-heteryl-2-hydroxyacetophenones using appropriate reagents; the second approach involves introduction of a heterocyclic group into already completed chromone system. In the present work we used the latter approach to synthesize hitherto unknown (but promising from various viewpoints) 3-(5-aryl-1,3,4-oxadiazol-2-yl)chromones **III** on the basis of accessible 3-formylchromone (**I**) [2]. By reaction of **I** with aroylhydrazines we obtained the corresponding aroylhydrazones **IIa**–**IIg** which were treated with molecular bromine in the presence of sodium acetate to generate intermediate nitrilimines [3]. Intramolecular cyclization of the latter gave the target products, 3-(5-aryl-1,3,4-oxadiazol-2-yl)chromones **IIIa**–**IIIi**.



I **IIa**–**IIi** **IIIa**–**IIIi**

Ar = C_6H_5 (**a**), *o*-ClC_6H_4 (**b**), *o*-$NO_2C_6H_4$ (**c**), *p*-$NO_2C_6H_4$ (**d**), 2-phenyl-1,2,3-triazol-4-yl (**e**), 2-trifluoromethyl-1-benzimidazolylmethyl (**f**), 1-benzotriazolylmethyl (**g**), 3-pyridyl (**h**), and 5-methyl-1-phenyl-1,2,3-triazol-4-yl (**i**).

The IR spectra of aroylhydrazones **IIa**–**IIi** contain characteristic absorption bands at 3100–3200 (NH) and 1630–1650 cm^{-1} (C=O). In the ^1H NMR spectra of **IIa**–**IIi** we observed a signal at δ 8.2–8.9 ppm, belonging to proton in position 2 of the pyran ring and NH signal at δ 9.3–10.2 ppm. The molecular ion peak in the mass spectra of **II** has low intensity. The presence of strong ion peaks with *m*/*z* 187 and $ArCO^+$ peaks indicates easy cleavage of the amide fragment. In most cases the $ArCO^+$ ion was the most abundant, except for compound **IIg**: the base peak in its mass spectrum was that with *m*/*z* 77 ($C_6H_5^+$). The fragmentation of the benzopyran system follows the retro-Diels–Alder pattern to produce an ion with *m*/*z* 120. Its further decomposition includes successive elimination of two CO molecules (*m*/*z* 92 and 64).

The IR spectra of 3-(5-aryl-1,3,4-oxadiazol-2-yl)-chromones **IIIa**–**IIIi** lack NH absorption at 3100–3200 cm^{-1}, and their ^1H NMR spectra contain no signal in the region δ 9.3–10.2 ppm. These data indicate rupture of the intramolecular hydrogen bond between 2-H and amide carbonyl oxygen atom in **II** because of cyclization. The signal from 2-H in compounds **III** appears as a narrow singlet in the region δ 5.8–6.1 ppm; the upfield shift of this signal relative to its position in the spectra of parent aroylhydrazones is explained by the effect of lone electron pair on the heteroatom in position 3. Compounds **III** possess an extended conjugation system, and the molecular ion peak is the most abundant in their mass spectra. The strong peak at *m*/*z* 173 results from cleavage of the oxadiazole ring.

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EXPERIMENTAL

The IR spectra were recorded on a Bruker FT-IR EQUINOX-55 spectrometer in KBr. The ^{1}H NMR spectra were obtained on a Bruker AX-200 instrument (200 MHz) using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference. The mass spectra were run on an HP-5988 mass spectrometer. TLC analysis was performed on GF-254 plates. The melting points were determined using an MP-S3 heating assembly (Japan). The elemental compositions were determined with the aid of an MT-3 automatic analyzer.

Aroylhydrazones IIa–IIi (general procedure). Equimolar amounts of compound **I** and appropriate aroylhydrazone (prepared by the known procedure [4]) were dissolved in 95% alcohol, several drops of glacial acetic acid were added, and the mixture was refluxed for 5–6 h. After cooling, the precipitate was filtered off and recrystallized from anhydrous alcohol.

3-(Benzoylhydrazonomethyl)chromone (IIa). Yield 78%, mp 176–178°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 3076 (S–H_{arom}), 1679 (C=O), 1636 (C=N), 1070 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 10.21 br.s (1H, NH), 8.87 s (1H, 2-H), 7.24–7.98 m (10H, CH=N, H_{arom}). Mass spectrum, *m*/*z*: 292 [M^+]. Found, %: C 70.31; H 4.19; N 9.68. $C_{17}H_{12}N_2O_3$. Calculated, %: C 69.86; H 4.14; N 9.58.

3-(*o*-Chlorobenzoylhydrazonomethyl)chromone (IIb). Yield 80%, mp 193–195°C. IR spectrum, ν, cm^{-1}: 3230 (NH), 3059 (C–H_{arom}), 1674 (C=O), 1633 (C=N), 1059 (C–O–C), 656 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 10.15 br.s (1H, NH), 8.77 s (1H, 2-H), 7.23–7.92 m (9H, CH=N, H_{arom}). Mass spectrum, *m*/*z*: 328, 326 [M^+]. Found, %: C 61.89; H 3.41; N 8.67. $C_{17}H_{11}ClN_2O_3$. Calculated, %: C 62.49; H 3.39; N 8.57.

3-(*o*-Nitrobenzoylhydrazonomethyl)chromone (IIc). Yield 95%, mp 206–207°C. IR spectrum, ν, cm^{-1}: 3267 (NH); 3079 (C–H_{arom}); 1666 (C=O); 1633 (C=N); 1520, 1341 (NO_2); 1071 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 9.74 br.s (1H, NH), 8.70 s (1H, 2-H), 8.42 d (1H, CH=N), 7.23–7.92 m (8H, H_{arom}). Mass spectrum, *m*/*z*: 337 [M^+]. Found, %: C 60.63; H 3.31; N 12.40. $C_{17}H_{11}N_3O_5$. Calculated, %: C 60.54; H 3.29; N 12.46.

3-(*p*-Nitrobenzoylhydrazonomethyl)chromone (IId). Yield 90%, mp 230–232°C. IR spectrum, ν, cm^{-1}: 3260 (NH); 3071 (C–H_{arom}); 1670 (C=O); 1636 (C=N); 1498, 1319 (NO_2); 1518, 1338 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 9.72 br.s (1H, NH), 8.76 s (1H, 2-H), 8.47 d (1H, CH=N), 7.25–7.89 m (8H, H_{arom}). Mass spectrum, *m*/*z*: 337 [M^+]. Found, %: C 60.32; H 3.21; N 12.58. $C_{17}H_{11}N_3O_5$. Calculated, %: C 60.54; H 3.29; N 12.45.

3-(2-Phenyl-1,2,3-triazol-4-ylcarbonylhydrazonomethyl)chromone (IIe). Yield 54%, mp 250–251.5°C. IR spectrum, ν, cm^{-1}: 3251 (NH), 3043 (C–H_{arom}), 1636 (C=O), 1617 (C=N), 1097 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 9.83 br.s (1H, NH), 8.35 s (1H, 2-H), 8.20 s (1H, 5-H, triazole), 7.25–8.03 m (10H, H_{arom}). Mass spectrum, *m*/*z*: 359 [M^+]. Found, %: C 64.19; H 3.69; N 19.79. $C_{19}H_{13}N_5O_3$. Calculated, %: C 63.51; H 3.65; N 19.49.

3-(2-Trifluoromethyl-1-benzimidazolylacetylhydrazonomethyl)chromone (IIf). Yield 85%, mp 225–227°C. IR spectrum, ν, cm^{-1}: 3220 (NH), 2994 (C–H_{arom}), 1698 (C=O), 1639 (C=N), 1119 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 9.32 br.s (1H, NH), 8.58 s (1H, 2-H), 8.31 d (1H, CH=N), 7.24–7.92 m (8H, H_{arom}), 5.94 s (2H, CH_2). Mass spectrum, *m*/*z*: 414 [M^+]. Found, %: C 57.95; H 3.20; N 13.63. $C_{20}H_{13}F_3N_4O_3$. Calculated, %: C 57.98; H 3.16; N 13.52.

3-(1-Benzotriazolylacetylhydrazonomethyl)chromone (IIg). Yield 61%, mp 240–241°C. IR spectrum, ν, cm^{-1}: 3219 (NH), 2990 (C–H_{arom}), 1698 (C=O), 1640 (C=N), 1109 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 9.63 br.s (1H, NH), 8.52 s (1H, 2-H), 8.30 d (1H, CH=N), 7.23–7.86 m (8H, H_{arom}), 5.52 s (2H, CH_2). Mass spectrum, *m*/*z*: 347 [M^+]. Found, %: C 62.20; H 3.80; N 20.21. $C_{18}H_{13}N_5O_3$. Calculated, %: C 62.25; H 3.77; N 20.16.

3-(Nicotinoylhydrazonomethyl)chromone (IIh). Yield 90%, mp 214–216°C. IR spectrum, ν, cm^{-1}: 3262 (NH), 3093 (C–H_{arom}), 1682 (C=O), 1648 (C=N), 1046 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 9.96 br.s (1H, NH), 8.92 and 8.81 (2H, 2-H and 5-H, pyridine), 8.2 s (1H, 2-H), 7.33–7.74 m (7H, CH=N, H_{arom}, 4-H, pyridine). Mass spectrum, *m*/*z*: 293 [M^+]. Found, %: C 66.04; H 3.83; N 14.53. $C_{16}H_{11}N_3O_3$. Calculated, %: C 65.53; H 3.78; N 14.33.

3-(5-Methyl-1-phenyl-1,2,3-triazol-4-ylcarbonylhydrazonomethyl)chromone (IIi). Yield 92%, mp 223.5–225°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 3069 (C–H_{arom}), 1677 (C=O), 1641 (C=N), 1059 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 8.82 br.s (1H, NH), 8.5 s (1H, 2-H), 8.25 d (1H, CH=N), 7.56–7.26 m (9H, H_{arom}), 2.69 s (3H, CH_3). Mass spectrum, *m*/*z*: 373 [M^+]. Found, %: C 64.56; H 3.98; N 18.82. $C_{20}H_{15}N_5O_3$. Calculated, %: C 64.34; H 4.05; N 18.76.

3-(2-Aryl-1,3,4-oxadiazol-5-yl)chromones IIIa–IIIi (general procedure). A solution of 2.2 mmol of

bromine in 5 ml of glacial acetic acid was added dropwise on cooling to a solution of 2 mmol of aroylhydrazone **IIa**–**IIi** and 10 mmol of anhydrous sodium acetate in 10 ml of glacial acetic acid. The mixture was stirred for 2–3 h at room temperature and was poured onto crushed ice. The precipitate was filtered off and recrystallized from anhydrous alcohol.

3-(5-Phenyl-1,3,4-oxadiazol-2-yl)chromone (IIIa). Yield 62%, mp 224–226°C. IR spectrum, ν, cm^{-1}: 3044 (C–H_{arom}), 1683 (C=O), 1629 (C=N), 1029 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.24–7.99 m (9H, H_{arom}), 5.93 s (1H, 2-H). Mass spectrum, *m*/*z*: 290 [M^+]. Found, %: C 70.66; H 3.51; N 9.73. $C_{17}H_{10}N_2O_3$. Calculated, %: C 70.34; H 3.47; N 9.65.

3-(5-*o*-Chlorophenyl-1,3,4-oxadiazol-2-yl)chromone (IIIb). Yield 71%, mp 202–205°C. IR spectrum, ν, cm^{-1}: 3025 (C–H_{arom}), 1690 (C=O), 1635 (C=N), 1044 (C–O–C), 654 (C–Cl). ^1H NMR spectrum, δ, ppm: 7.25–7.83 m (8H, H_{arom}), 6.01 s (1H, 2-H). Mass spectrum, *m*/*z*: 326/324 [M^+]. Found, %: C 62.62; H 2.83; N 8.77. $C_{17}H_9ClN_2O_3$. Calculated, %: C 62.88; H 2.79; N 8.63.

3-(5-*o*-Nitrophenyl-1,3,4-oxadiazol-2-yl)chromone (IIIc). Yield 68%, mp 222–224°C. IR spectrum, ν, cm^{-1}: 3058 (C–H_{arom}); 1672 (C=O); 1627 (C=N); 1520, 1341 (NO_2); 1088 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.34–8.12 m (8H, H_{arom}), 5.82 s (1H, 2-H). Mass spectrum, *m*/*z*: 335 [M^+]. Found, %: C 60.20; H 2.79; N 12.70. $C_{17}H_9N_3O_5$. Calculated, %: C 60.90; H 2.71; N 12.53.

3-(5-*p*-Nitrophenyl-1,3,4-oxadiazol-2-yl)chromone (IIId). Yield 61%, mp 258–260°C. IR spectrum, ν, cm^{-1}: 3079 (C–H_{arom}); 1681 (C=O); 1632 (C=N); 1498, 1319 (NO_2); 1060 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.5–7.8 m (8H, H_{arom}), 5.84 s (1H, 2-H). Mass spectrum, *m*/*z*: 335 [M^+]. Found, %: C 61.08; H 2.74; N 12.57. $C_{17}H_9N_3O_5$. Calculated, %: C 60.90; H 2.71; N 12.53.

3-[5-(2-Phenyl-1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl]chromone (IIIe). Yield 50%, mp >280°C. IR spectrum, ν, cm^{-1}: 2980 (C–$H_{arom.}$), 1697 (C=O), 1653 (C=N), 1013 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.40–8.14 m (10H, 5-H in triazole, H_{arom}), 5.95 s (1H, 2-H). Mass spectrum, *m*/*z*: 357 [M^+]. Found, %: C 63.71; H 3.16; N 19.76. $C_{19}H_{11}N_5O_3$. Calculated, %: C 63.87; H 3.10; N 19.60.

3-[5-(2-Trifluoromethyl-1-benzimidazolylmethyl)-1,3,4-oxadiazol-2-yl]chromone (IIIf). Yield 80%, mp 236–238°C. IR spectrum, ν, cm^{-1}: 3020 (C–H_{arom}), 2994 (C–H_{aliph}), 1688 (C=O), 1638 (C=N), 1114 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.22–7.94 m (8H, H_{arom}), 5.80 s (1H, 2-H), 5.52 s (2H, CH_2). Mass spectrum, *m*/*z*: 412 [M^+]. Found, %: C 58.23; H 2.71; N 13.63. $C_{20}H_{11}F_3N_4O_3$. Calculated, %: C 58.26; H 2.69; N 13.59.

3-[5-(1-Benzotriazolylmethyl)-1,3,4-oxadiazol-2-yl]chromone (IIIg). Yield 52%, mp 254–256°C. IR spectrum, ν, cm^{-1}: 3089 (C–H_{arom}), 2958 (C–H_{aliph}), 1694 (C=O), 1646 (C=N), 1100 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.24–7.76 m (8H, H_{arom}), 5.84 s (1H, 2-H), 5.33 s (2H, CH_2). Mass spectrum, *m*/*z*: 345 [M^+]. Found, %: C 62.78; H 3.26; N 20.38. $C_{18}H_{11}N_5O_3$. Calculated, %: C 62.61; H 3.21; N 20.28.

3-[5-(3-Pyridyl)-1,3,4-oxadiazol-2-yl]chromone (IIIh). Yield 55%, mp 199–201°C. IR spectrum, ν, cm^{-1}: 3046 (C–H_{arom}), 1677 (C=O), 1620 (C=N), 1081 (C–O–C). ^1H NMR spectrum, δ, ppm: 9.33, 8.90, 8.71, 8.12 (4H, pyridine); 7.59–7.94 m (4H, chromone); 5.90 s (1H, 2-H). Mass spectrum, *m*/*z*: 291 [M^+]. Found, %: C 65.90; H 3.01; N 14.48. $C_{16}H_9N_3O_3$. Calculated, %: C 65.98; H 3.11; N 14.43.

3-[5-(5-Methyl-1-phenyl-1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl]chromone (IIIi). Yield 75%, mp 218–220°C. IR spectrum, ν, cm^{-1}: 3067 (C–H_{arom}), 1669 (C=O), 1633 (C=N), 1056 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.24–7.55 m (9H, H_{arom}), 6.05 s (1H, 2-H), 7.2–7.55 m (9H, H_{arom}), 2.65 s (3H, CH_3). Mass spectrum, *m*/*z*: 371 [M^+]. Found, %: C 64.71; H 3.57; N 18.91. $C_{20}H_{13}N_5O_3$. Calculated, %: C 64.69; H 3.53; N 18.86.

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