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SYNTHESIS OF 3-(5-ARYL-1,3,4-OXADIAZOL-2-YL)CHROMONES

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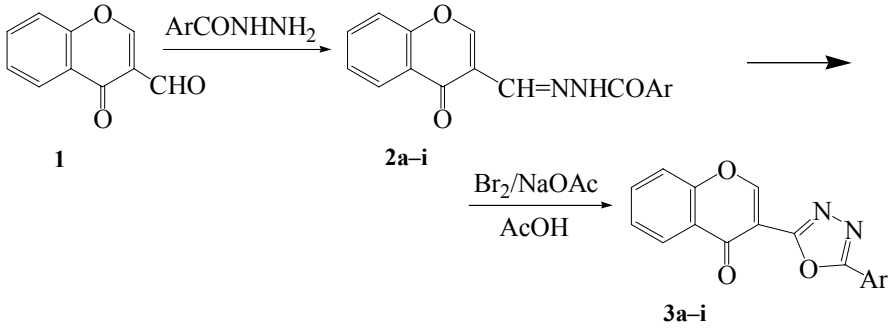
A general method was proposed for the synthesis of 3-(5-aryl-1,3,4-oxadiazol-2-yl)chromones starting from 3-formylchromone. This aldehyde yields acylhydrazones, from which the corresponding unstable nitrile imines are generated. These intermediates undergo intramolecular 1,3-dipolar cycloaddition.

Keywords: 3-hetarylchromones, 1,3,4-oxadiazoline, 3-formylchromone, synthesis.

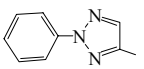
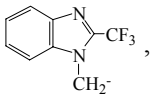
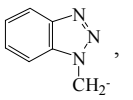
3-Hetarylchromones have a broad range of biological activity and display high anti-allergy, anti-cholesterol, hypolipidemic, antimicrobial, fungicidal, and antiblastic activity. Some of these compounds are also central nervous system stimulants [1]. Hence, considerable recent attention has been given to new compounds of this series.

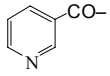
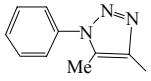
Frasinyuk and Khilya [1] have surveyed the methods for synthesizing 3-hetarylchromones and found two major approaches: 1) construction of the chromone system from substituted α-hetaryl-2-hydroxyacetophenones with participation of suitable reagents and 2) introduction of the heterocycle into a prepared chromone system. In the present work, we selected the second approach for the synthesis of previously unreported 3-(5-aryl-1,3,4-oxadiazol-2-yl)chromones starting from available 3-formylchromone (**1**) [2].



1 **2a–i** **3a–i**

2, **3** **a** Ar = Ph, **b** Ar = *o*-ClC_6H_4, **c** Ar = *o*-$(O_2N)C_6H_4$, **d** Ar = *p*-$(O_2N)C_6H_4$,

e Ar =  , **f** Ar =  , **g** Ar =  ,

h Ar =  , **i** Ar = 

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The reaction of **1** and aroylhydrazines gave the corresponding aroylhydrazones **2a-i**. Then, the action of bromine in the presence of sodium acetate on these hydrazones **2** gave intermediate nitrile imines [3], which undergo intramolecular cycloaddition to give 3-(5-aryl-1,3,4-oxadiazol-2-yl)chromones **3**.

The IR spectra of aroylhydrazones **2a-i** have characteristic bands at 3200-3300 (NH) and 1630-1650 cm^{-1} (C=O). The ^1H NMR spectra of aroylhydrazones **2a-i** show signals at 8.2-8.9 (pyrone 2-H) and 9.3-10.2 ppm (NH). The molecular ion peak in the mass spectra of these compounds has low intensity due to their instability. The appearance of peaks with mass number 187 and $ArCO^+$ peaks indicates that the C(O)–N bond is readily cleaved and the major peak usually corresponds to the $ArCO^+$ fragment except for **2g**, for which the $C_6H_5^+$ peak with mass number 77 predominates. The pyrone ring is split by a reverse Diels–Alder reaction, leading to a fragment with *m/z* 120. The stepwise loss of one CO group and formation of fragments with *m/z* 92 and 64 is then noted.

The IR spectra of 3-(5-aryl-1,3,4-oxadiazol-2-yl)chromones **3a-i** lack the band at 3200-3300 cm^{-1} found for hydrazones **2**. The ^1H NMR spectra of **3a-i** lack signals at 9.3-10.2 ppm. Proton 2-H of the pyrone ring is seen as a narrow signal at 5.8-6.1 ppm since it is affected by the unshared electron pair of the heteroatom of the heterocyclic substituent at C-3 of the chromone.

Chromones **3a-a** have a stable conjugation system. Thus, the molecular ion is the major peak in their mass spectra. As a consequence, the oxadiazole ring is readily cleaved and a strong peak with *m/z* 173 $([M - ArCN_2])^+$) is noted.

EXPERIMENTAL

GF-254 Plates were used for thin-layer chromatography. The melting points were determined using an MP-S3 table manufactured in Japan. An MT-3 automatic analyzer was used for elemental analysis. The IR spectra were taken on a Bruker EQUINOX-55 FT-IR spectrometer for KBr pellets. The ^1H NMR spectra were taken on a Bruker AX-200 spectrometer at 200 MHz in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard. The mass spectra were taken on a HP 5988 automatic mass spectrometer.

General Method for the Preparation of Aroylhydrazones 2a-i. 3-Formylchromone **1** and aroylhydrazones obtained taking account of the work of Chen [4] were mixed in equivalent amounts and then dissolved in 95% aq. ethanol. A few drops of glacial acetic acid were added and the mixture was heated at reflux for 5-6 h. After cooling, the crystalline precipitate was filtered off and recrystallized from abs. ethanol to give aroylhydrazones **2a-i**.

Hydrazone 2a was obtained in 78% yield; mp 176-178°C. IR spectrum, ν, cm^{-1}: 3280 (–NH–), 3076 (Ar–H), 1679 (C=O), 1636 (C=N), 1070 (C–O–C). ^1H NMR spectrum, δ, ppm: 10.21 (1H, br. s, NH); 8.87 (1H, s, 2-H); 7.24-7.98 (10H, m, CH=N, Ar-H). 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.

Hydrazone 2b was obtained in 80% yield; mp 193-195°C. IR spectrum, ν, cm^{-1}: 3230 (–NH–), 3059 (Ar–H), 1674 (C=O), 1633 (C=N), 1059 (C–O–C), 656 (C–Cl). ^1H NMR spectrum, δ, ppm: 10.15 (1H, br. s, NH); 8.77 (1H, s, 2-H); 7.23-7.92 (9H, m, CH=N, Ar–H). 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.

Hydrazone 2c was obtained in 95% yield; mp 206-207°C. IR spectrum, ν, cm^{-1}: 3267 (–NH–), 3079 (Ar–H), 1666 (C=O), 1633 (C=N), 1520, 1341 ($–NO_2$), 1071 (C–O–C). ^1H NMR spectrum, δ, ppm: 9.74 (1H, br. s, NH); 8.70 (1H, s, 2-H); 8.42 (1H, d, CH=N); 7.23-7.92 (8H, m, Ar–H). 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.

Hydrazone 2d was obtained in 90% yield; mp 230-232°C. IR spectrum, ν, cm^{-1}: 3260 (–NH–), 3071 (Ar–H), 1670 (C=O), 1636 (C=N), 1498, 1319 ($–NO_2$), 1518, 1338 (C–O–C). ^1H NMR spectrum, δ, ppm: 9.72 (1H, br. s, NH); 8.76 (1H, s, 2-H); 8.47 (1H, d, CH=N); 7.25-7.98 (8H, m, Ar–H). 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.

Hydrazone 2e was obtained in 54% yield; mp 250-251.5°C. IR spectrum, ν, cm^{-1}: 3251 (–NH–), 3043 (Ar–H), 1636 (C=O), 1617 (C=N), 1097 (C–O–C). ^1H NMR spectrum, δ, ppm: 9.83 (1H, br. s, NH); 8.35 (1H, s, 2-H); 8.20 (1H, s, triazole H); 7.25-8.03 (10H, m, Ar–H). 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.

Hydrazone 2f was obtained in 85% yield; mp 225-227°C. IR spectrum, ν, cm^{-1}: 3220 (–NH–), 2994 (Ar–H), 1698 (C=O), 1639 (C=N), 1119 (C–O–C). ^1H NMR spectrum, δ, ppm: 9.32 (1H, br. s, NH); 8.58 (1H, s, 2-H); 8.31 (1H, d, CH=N); 7.24-7.92 (8H, m, Ar–H); 5.94 (2H, s, 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.

Hydrazone 2g was obtained in 61% yield; mp 240-241°C. IR spectrum, ν, cm^{-1}: 3219 (–NH–), 2990 (Ar–H), 1698 (C=O), 1640 (C=N), 1109 (C–O–C). ^1H NMR spectrum, δ, ppm: 9.63 (1H, br. s, NH); 8.52 (1H, s, 2-H); 8.30 (1H, d, CH=N); 7.23-7.86 (8H, m, Ar–H); 5.52 (2H, s, 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.

Hydrazone 2h was obtained in 90% yield; mp 214-216°C. IR spectrum, ν, cm^{-1}: 3262 (–NH–), 3093 (Ar–H), 1682 (C=O), 1648 (C=N), 1046 (C–O–C). ^1H NMR spectrum, δ, ppm: 9.96 (1H, br. s, NH); 8.92, 8.81 (2H, Py–H); 8.2 (1H, s, 2-H); 7.33-7.74 (7H, m, Ar–H, Py–H). 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.

Hydrazone 2i was obtained in 92% yield; mp 223.5-225°C. IR spectrum, ν, cm^{-1}: 3240 (–NH–), 3069 (Ar–H), 1677 (C=O), 1641 (C=N), 1059 (C–O–C). ^1H NMR spectrum, δ, ppm: 9.56 (1H, br. s, NH); 8.5 (1H, s, 2-H); 8.25 (1H, d, CH=N); 7.56-7.26 (9H, m, Ar–H); 2.69 (3H, s, 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.

General Method for the Preparation of 3-(5-Aryl-1,3,4-oxadiazol-2-yl)chromones 3a-i. A sample of bromine (2.2 mmol) in glacial acetic (5 ml) was added dropwise to a solution of aroylhydrazone **2a-i** (2 mmol) and fused sodium acetate (10 mmol) in glacial acetic acid (10 ml) and stirred vigorously for 2-3 h at room temperature. The reaction mixture was poured into chopped ice. The precipitate formed was recrystallized from absolute ethanol to give chromones **3a-i**.

3-(5-Phenyl-1,3,4-oxadiazol-2-yl)chromone (3a) was obtained in 62% yield; mp 224-226°C. IR spectrum, ν, cm^{-1}: 3044 (Ar–H), 1683 (Ar–H), 1683 (C=O), 1629 (C=N), 1029 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.24-7.99 (9H, m, Ar–H); 5.93 (1H, s, 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 (3b) was obtained in 71% yield; mp 202-205°C. IR spectrum, ν, cm^{-1}: 3025 (Ar–H), 1690 (C=O), 1635 (C=N), 1044 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.25-7.83 (8H, m, Ar–H); 6.01 (1H, s, 2-H). Mass spectrum, *m/z* 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 (3c) was obtained in 68% yield; mp 222-224°C. IR spectrum, ν, cm^{-1}: 3058 (Ar–H), 1672 (C=O), 1627 (C=N), 1520, 1341 (–NO_2), 1088 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.34-8.12 (8H, m, Ar–H); 5.82 (1H, s, 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 (3d) was obtained in 61% yield; mp 258-260°C. IR spectrum, ν, cm^{-1}: 3079 (Ar–H), 1681 (C=O), 1632 (C=N), 1498, 1319 (–NO_2), 1060 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.5-7.8 (8H, m, Ar–H); 5.84 (1H, s, 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 (3e) was obtained in 50% yield; mp >280°C. IR spectrum, ν, cm^{-1}: 2980 (Ar–H), 1697 (C=O), 1653 (C=N), 1013 (C–O–C). ^1H NMR spectrum, δ, ppm: 7.40-8.14 (10H, m, triazole H, Ar–H); 5.95 (1H, s, 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-Trifluoromethylbenzimidazol-1-ylmethyl)-1,3,4-oxadiazol-2-yl]chromone (3f) was obtained in 80% yield; mp 236-238°C. IR spectrum, ν, cm^{-1}: 3020 (Ar–H), 2994 (–CH_2), 1688 (C=O), 1638 (C=N), 1114 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 7.22-7.94 (8H, m, Ar–H); 5.80 (1H, s, 2-H); 5.52 (2H, s, 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-(Benzotriazol-1-ylmethyl)-1,3,4-oxadiazol-2-yl]chromone (3g) was obtained in 52% yield; mp 254-256°C. IR spectrum, ν, cm^{-1}: 3089 (Ar–H), 2958 (–CH_2), 1694 (C=O), 1646 (C=N), 1100 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 7.24-7.76 (8H, m, Ar–H); 5.84 (1H, s, 2-H); 5.33 (2H, s, 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-(Pyridin-3-yl)-1,3,4-oxadiazol-2-yl]chromone (3h) was obtained in 55% yield; mp 199-201°C. IR spectrum, ν, cm^{-1}: 3046 (Ar–H), 1677 (C=O), 1620 (C=N), 1081 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 9.33, 8.90, 8.71, 8.12 (4H, Py-H); 7.59-7.94 (4H, m, Ar–H); 5.90 (1H, s, 2-H). Mass spectrum, *m/z* $[M]^+$. 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 (3i) was obtained in 75% yield; mp 218-220°C. IR spectrum, ν, cm^{-1}: 3067 (Ar–H), 1669 (C=O), 1633 (C=N), 1056 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 7.24-7.55 (9H, m, Ar–H); 6.05 (1H, s, 2-H); 2.65 (3H, s, 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 13.53; N 18.86.

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