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

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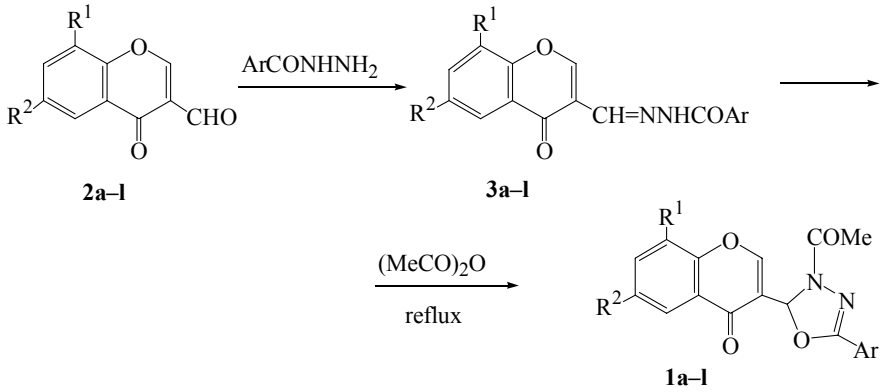
A method is proposed for the synthesis of 3-(3-acetyl-5-aryl-2,3-dihydro-1,3,4-oxadiazol-2-yl)chromones which consists of the conversion of 3-formylchromones to aroylhydrazones and their subsequent heterocyclization using acetic anhydride.

Keywords: 3-hetarylchromones, 1,3,4-oxadiazolines.

3-Hetarylchromones show a broad range of biological actions. They show high antiallergic, anticholesteremic, hypolipidemic, antimicrobial, fungicidal, and antiblastic activity, as well they are stimulators of the central nervous system [1]. For this reason much attention has been paid to the synthesis of novel compounds in recent times.

Methods for the synthesis of 3-hetarylchromones has been collected in the review [1]. Two proposed basic routes have been identified. The first is the construction of the chromone system from substituted α-hetaryl-2-hydroxyacetophenones and the second is the introduction of the heterocycle into a prepared chromone system.

In the present work we have selected the second approach to the synthesis of the previously unknown 3-(3-acetyl-5-aryl-2,3-dihydro-1,3,4-oxadiazol-2-yl)chromones **1a-l** using the available 3-formylchromones **2a-l** [2, 3].



2a–l **3a–l** **1a–l**

1–3 a R^1 = H, R^2 = Me, Ar = Ph; **b** Ar = *o*-ClC_6H_4, **c** Ar = *p*-$MeOC_6H_4$, **d** Ar = *p*-$O_2NC_6H_4$, **e** R^1 = H, R^2 = Br, Ar = Ph; **f** Ar = *o*-ClC_6H_4, **g** Ar = *p*-$MeOC_6H_4$, **h** Ar = *p*-$O_2NC_6H_4$, **i** R^1 = R^2 = Cl, Ar = Ph; **j** Ar = *o*-ClC_6H_4, **k** Ar = *p*-$MeOC_6H_4$, **l** Ar = *p*-$O_2NC_6H_4$

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Treatment of the 3-formylchromones with aroylhydrazines gave the corresponding aroylhydrazones **3a-l**. In the presence of acetic anhydride these undergo heterocyclization to give the 3-(3-acetyl-5-aryl-2,3-dihydro-1,3,4-oxadiazol-2-yl)chromones **1a-l**.

The structures of compounds **1a-l** and **3a-l** were confirmed by elemental analytical data and from IR, ^{1}H NMR, and mass spectra. The characteristics of compounds **1a-l** and **3a-l** are given in Table 1 and the ^{1}H NMR and mass spectra in Tables 2 and 3.

TABLE 1. Characteristics of Compounds **1a-l** and **3a-l**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1a	$C_{20}H_{16}N_2O_4$	68.91 / 68.96	4.65 / 4.63	8.07 / 8.04	173-174	80
1b	$C_{20}H_{15}ClN_2O_4$	62.70 / 62.75	3.96 / 3.95	7.35 / 7.32	187-188	52
1c	$C_{21}H_{18}N_2O_5$	66.60 / 66.66	4.81 / 4.79	7.36 / 7.40	248-249	47
1d	$C_{20}H_{15}N_3O_6$	61.06 / 61.07	3.86 / 3.84	10.71 / 10.68	222-224	43
1e	$C_{19}H_{13}BrN_2O_4$	55.20 / 55.23	3.19 / 3.17	6.81 / 6.78	215-216	79
1f	$C_{19}H_{12}ClBrN_2O_4$	51.01 / 50.98	2.72 / 2.70	6.29 / 6.26	206-207	51
1g	$C_{20}H_{15}BrN_2O_5$	54.23 / 54.19	3.43 / 3.41	6.35 / 6.32	233-234	47
1h	$C_{19}H_{12}BrN_3O_6$	49.85 / 49.80	2.65 / 2.64	9.19 / 9.17	228-229	42
1i	$C_{19}H_{12}Cl_2N_2O_4$	56.66 / 56.60	3.02 / 3.00	6.92 / 6.95	136-137	83
1j	$C_{19}H_{11}Cl_3N_2O_4$	52.16 / 52.14	2.56 / 2.53	6.44 / 6.40	204-205	52
1k	$C_{20}H_{14}Cl_2N_2O_5$	55.47 / 55.45	3.24 / 3.26	6.49 / 6.47	239-241	44
1l	$C_{19}H_{11}Cl_2N_3O_6$	50.89 / 50.91	2.48 / 2.47	9.39 / 9.37	212-214	54
3a	$C_{18}H_{14}N_2O_3$	70.54 / 70.58	4.64 / 4.61	9.13 / 9.15	209-210	85
3b	$C_{18}H_{13}ClN_2O_3$	63.40 / 63.44	3.87 / 3.85	8.24 / 8.22	234-235	75
3c	$C_{19}H_{16}N_2O_4$	67.90 / 67.85	4.77 / 4.79	8.40 / 8.33	214-216	60
3d	$C_{18}H_{13}N_3O_5$	61.60 / 61.54	3.71 / 3.73	12.04 / 11.96	235-236	57
3e	$C_{17}H_{11}BrN_2O_3$	55.11 / 55.01	2.97 / 2.99	7.58 / 7.55	217-218	88
3f	$C_{17}H_{10}ClBrN_2O_3$	50.40 / 50.34	2.49 / 2.48	6.94 / 6.91	197-198	72
3g	$C_{18}H_{13}BrN_2O_4$	53.92 / 53.89	3.28 / 3.27	7.01 / 6.98	207-208	62
3h	$C_{17}H_{10}BrN_3O_5$	49.09 / 49.06	2.44 / 2.42	10.08 / 10.10	195-196	70
3i	$C_{17}H_{10}Cl_2N_2O_3$	56.58 / 56.53	2.80 / 2.79	7.70 / 7.76	211-213	82
3j	$C_{17}H_9Cl_3N_2O_3$	51.58 / 51.61	2.30 / 2.29	7.11 / 7.08	176-177	60
3k	$C_{18}H_{12}Cl_2N_2O_4$	55.30 / 55.26	3.07 / 3.09	7.18 / 7.16	188-190	55
3l	$C_{17}H_9Cl_2N_3O_5$	50.24 / 50.27	2.24 / 2.23	10.39 / 10.35	283-284	51

TABLE 2. ^{1}H NMR Spectra of Compounds **1a-l** and **3a-l**

Com-pound	^{1}H NMR spectrum, δ, ppm
1a	8.83 (1H, s, 2-H); 8.39-7.28 (8H, m, 5, 7, 8-H, Ar–H); 7.01(1H, s, 2'-H); 2.33 (3H, s, CH_3); 2.37 (3H, s, $COCH_3$)
1b	8.89 (1H, s, 2-H); 8.29-7.25 (7H, m, 5, 7, 8-H, Ar–H); 7.07 (1H, s, 2'-H); 2.30 (3H, s, CH_3); 2.35 (3H, s, $COCH_3$)
1c	8.92 (1H, s, 2-H); 8.23-7.16 (7H, m, 5, 7, 8-H, Ar–H); 7.09 (1H, s, 2'-H); 2.28 (3H, s, CH_3); 2.37 (3H, s, $COCH_3$); 3.59 (3H, s, OCH_3)
1d	8.81 (1H, s, 2-H); 8.39-7.28 (7H, m, 5, 7, 8-H, Ar–H); 7.12 (1H, s, 2'-H); 2.28 (3H, s, $COCH_3$)
1e	8.87 (1H, s, 2-H); 8.31-7.22 (7H, m, 5, 7, 8-H, Ar–H); 7.07 (1H, s, 2'-H); 2.37 (3H, s, $COCH_3$)
1f	8.79 (1H, s, 2-H); 8.35-7.18 (7H, m, 5, 7, 8-H, Ar–H); 7.12 (1H, s, 2'-H); 2.28 (3H, s, $COCH_3$)
1g	8.95 (1H, s, 2-H); 8.28-7.12 (7H, m, 5, 7, 8-H, Ar–H); 7.09 (1H, s, 2'-H); 2.28 (3H, s, $COCH_3$); 3.62 (3H, s, OCH_3)
1h	8.91 (1H, s, 2-H); 8.25-7.10 (7H, m, 5, 7, 8-H, Ar–H); 7.03 (1H, s, 2'-H); 2.39 (3H, s, $COCH_3$)
1i	8.88 (1H, s, 2-H); 8.13-7.22 (7H, m, 5, 7-H, Ar–H); 7.15 (1H, s, 2'-H); 2.37 (3H, s, $COCH_3$)
1j	8.91 (1H, s, 2-H); 8.28-7.23 (6H, m, 5, 7-H, Ar–H); 7.09 (1H, s, 2'-H); 2.28 (3H, s, $COCH_3$)
1k	8.91 (1H, s, 2-H); 8.19-7.18 (6H, m, 5, 7-H, Ar–H); 7.03 (1H, s, 2'-H); 2.38 (3H, s, $COCH_3$); 3.65 (3H, s, OCH_3)
1l	8.94 (1H, s, 2-H); 8.25-7.13 (6H, m, 5, 7-H, Ar–H); 7.00 (1H, s, 2'-H); 2.31 (3H, s, $COCH_3$)
3a	12.21 (1H, br. s, NH); 8.87 (1H, s, 2-H); 7.24-7.98 (9H, m, CH=N, 5, 7, 8-H, Ar–H); 2.31(3H, s, CH_3)
3b	12.15 (1H, br. s, NH); 8.77 (1H, s, 2-H); 7.23-7.92 (8H, m, CH=N, 5, 7, 8-H, Ar–H); 2.31(3H, s, CH_3)
3c	12.08 (1H, br. s, NH); 8.70 (1H, s, 2-H); 7.28-8.10 (8H, m, CH=N, 5, 7, 8-H, Ar–H); 2.31(3H, s, CH_3); 3.56(3H, s, OCH_3)
3d	11.89 (1H, br. s, NH); 8.76 (1H, s, 2-H); 7.12-8.21 (8H, m, CH=N, 5, 7, 8-H, Ar–H)
3e	11.98 (1H, br. s, NH); 8.79 (1H, s, 2-H); 7.22-8.19 (9H, m, CH=N, 5, 7, 8-H, Ar–H)
3f	11.89 (1H, br. s, NH); 8.76 (1H, s, 2-H); 7.12-8.21 (8H, m, CH=N, 5, 7, 8-H, Ar–H)
3g	12.00 (1H, br. s, NH); 8.52 (1H, s, 2-H); 7.23-8.25 (8H, m, CH=N, 5, 7, 8-H, Ar–H); 3.66 (3H, s, OCH_3)
3h	11,95 (1H, br. s, NH); 8.92 (1H, s, 2-H); 7.23-8.25 (8H, m, CH=N, 5, 7, 8-H, Ar–H)
3i	12.02 (1H, br. s, NH); 8.58 (1H, s, 2-H); 7.23-8.33 (8H, m, CH=N, 5, 7-H, Ar–H)
3j	11.83 (1H, br. s, N–H); 8.97 (1H, s, 2-H); 7.21-8.17 (7H, m, CH=N, 5, 7-H, Ar–H)
3k	11.98 (1H, br. s, N–H); 8.97 (1H, s, 2-H); 7.13-8.32 (7H, m, CH=N, 5, 7-H, Ar–H); 3.66 (3H, s, OCH_3)
3l	12.10 (1H, br. s, N–H); 8.95 (1H, s, 2-H); 7.22-8.38 (7H, m, CH=N, 5, 7-H, Ar–H)

The IR spectra of the aroylhydrazones **3a-l** show characteristic absorption bands at 3100-3200 (NH), 1660-1670 (C=O), 1620-1640 (C=N), and 1590-1610 cm^{-1}. The ^{1}H NMR spectra of aroylhydrazones **3a-l** show signals in the range 8.5-9.0 ppm for the 2-H of the pyrone ring and at 11.8-12.2 ppm for the NH group proton. Due to the instability of the aroylhydrazones the molecular ion peak in their mass spectra was of low intensity. The appearance of peaks for $[M\text{-}ArCO]^+$ shows that the amide C–N bond undergoes fission readily. The chromone ring is broken *via* a retro Diels–Alder reaction and is then stabilized by a stepwise fission at the single CO group.

The IR spectra of the 3-(3-acetyl-5-aryl-2,3-dihydro-1,3,4-oxadiazol-2-yl)chromones **1a-l** show the absence of the absorption bands at 3100-3200 cm^{-1}. Instead there are found bands characteristic of chromones (1592-1620 and 1475-1510 cm^{-1}) and an acetyl group (1750-1760 cm^{-1}). The signal for the NH in the region 11.8-12.2 ppm is absent in the ^{1}H NMR spectra.

TABLE 3. Mass Spectra of Compounds **1a-l** and **3a-l**

Com-pound	Mass spectrum, *m/z* (%)
1a	348 (M^+, 3), 305(100), 187, 160, 135, 91, 77, 51, 43(48)
1b	384 ($[M+2]^+$, 1), 382 (M^+, 3), 341(33), 339(100), 187, 160, 135, 91, 77, 51, 43(52)
1c	378 (M^+, 4), 335(100), 187, 160, 135, 91, 77, 51, 43(60)
1d	393 ((M^+, 6), 350(100), 187, 173, 160, 135, 91, 77, 65, 43(50)
1e	414 ($[M+2]^+$, 2), 412 (M^+, 2), 371, 369(100), 266, 264, 252, 250, 240, 238, 224, 215, 213, 121,119, 43(62)
1f	450 ($[M+4]^+$, 1), 448 ($[M+2]^+$, 4), 446 (M^+, 3), 407, 405, 403(100), 253, 251, 226, 224, 201, 199, 121, 119, 43(38)
1g	444 ($[M+2]^+$, 2), 442 (M^+, 2), 401(98), 399(100), 253, 251, 226, 224, 201, 199, 43(49)
1h	459 ($[M+2]^+$, 3), 457 (M^+, 4), 416(97), 414(100), 253, 251, 226, 224, 201, 199, 43(60)
1i	402 (M^+, 1), 363(12), 361(67), 359(100), 245, 243, 241, 218, 216, 214, 189, 43(49)
1j	436 (M^+, 2), 397(10), 395(66), 393(100), 245, 243, 241, 218, 216, 214, 189, 43(51)
1k	432 (M^+, 1), 393(11), 391(67), 389(100), 245, 243, 241, 218, 216, 214, 189, 43(46)
1l	451 ($[M+4]^+$, 1), 449 ($[M+2]^+$, 5), 447 (M^+, 8), 408, 406, 404(100), 245, 243, 241, 218, 216, 214, 189, 43(53)
3a	306 (M^+,10), 278, 262, 260, 201, 173, 172, 160, 135, 105(100), 91, 77, 65
3b	342 ($[M+2]^+$, 6), 340 (M^+,19), 298, 296, 173, 172, 160, 141(30), 139(100), 135, 91, 77, 65
3c	336 (M^+,5), 292, 173, 172, 160, 135(100), 91, 77, 65
3d	351 (M^+,7), 323, 307, 305, 173, 172, 150(100), 135, 91, 77, 65
3e	372 ($[M+2]^+$, 9), 370 (M^+, 10), 344, 342, 326, 324, 239, 237, 173, 172, 135(100), 77, 65
3f	408 ($[M+6]^+$, 1), 406 ($[M+4]^+$, 4), 404 ($[M+2]^+$, 3), 360, 239, 237, 141(32), 139(100)
3g	402 ($[M+2]^+$, 5), 400 (M^+, 6), 374, 372, 358, 356, 239, 237, 202, 135(100)
3h	417 ($[M+2]^+$, 4), 415 (M^+, 5), 389, 387, 373, 371, 239, 237, 201, 199, 150(100)
3i	364 ($[M+4]^+$, 0.7), 362 ($[M+2]^+$, 4), 360 (M^+, 6), 336, 334, 332, 227, 172, 135, 105(100)
3j	400 ($[M+6]^+$, 0.1), 398 ($[M+4]^+$, 1), 396 ($[M+2]^+$, 3), 394(M^+, 3), 350, 229, 141(32), 139(100
3k	394 ($[M+4]^+$, 0.5), 392 ($[M+2]^+$, 3), 390 (M^+, 4), 348, 231, 229, 227, 202, 135(100)
3l	409 ($[M+4]^+$, 0.4), 407 ($[M+2]^+$, 3), 405 (M^+, 4), 381, 379, 377, 229, 227, 150(100)

The 2-H proton of the pyrone ring is seen as a sharp signal in the region 8.8-8.9 ppm [4] in the spectra of the products **1a-l**. The mass spectra of the products **1a-l** show a low intensity peak for the molecular ion (generally less than 10%), the main peak being for $[M\text{-}COCH_3]^+$. Subsequent fragmentation is similar to that described above for the aroylhydrazones **3a-l**.

EXPERIMENTAL

Thin-layer chromatographic analysis was carried out on GF-254 plates. Melting points were measured on an MP-S3 heating table (Japan). Elemental analysis was carried out using an MT-3 automatic analyzer. IR spectra were taken on a Bruker EQUINOX-55 FT-IR machine using KBr and ^1H NMR spectra on a Bruker AX 80 (80 MHz) machine using $CDCl_3$ or DMSO-d_6 solvent and TMS internal standard. Mass spectra were recorded on an HP 5988 AMS instrument.

General Method for Preparing the Aroylhydrazones (3a-l). Equal amounts of compounds **2a-l** and the aroylhydrazines (obtained as in [2, 5]) were mixed and dissolved in 95% alcohol. Several drops of glacial acetic acid were added and the mixture was refluxed for 5-6 h with use of a reflux condenser. After cooling, the crystals formed were filtered off and recrystallized from absolute alcohol to give the aroylhydrazones **3a-l**.

General Method for Preparing 3-(3-Acetyl-5-aryl-2,3-dihydro-1,3,4-oxadiazol-2-yl)chromones (1a-l). Acetic anhydride was added to the aroylhydrazone **3a-l** (2 mmol) and refluxed for 2 h. After cooling, the reaction mixture was poured into iced water. The precipitate was filtered off, washed with water, dried, and recrystallized from DMF–EtOH–H_2O to give the products **1a-l**.

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