SYNTHESIS OF 3-(3′-ACETYL-5′-AROYL-1′,3′,4′--OXADIAZOLYL-2′)-CHROMONES

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A general method has been proposed for synthesizing 3-(3′-acetyl-5′-aroyl-1′,3′,4′-oxadiazolyl-2′)-chromones that has been based on conversion of 3-formylchromones to acylhydrazones and of the acylhydrazones into the heterocyclic chromones.

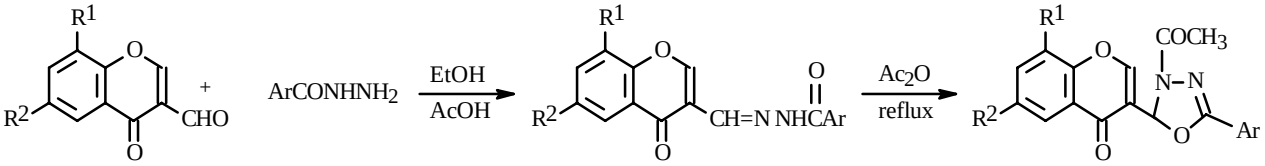
Key words: substituted 3-formylchromones, aroylhydrazones, 3-(3′-acetyl-5′-aroyl-1′,3′,4′-oxadiazolyl-2′)-chromones.

3-Heterylchromones are known to possess a wide spectrum of biological activity including antiallergic, anticholesteric, hypolipidemic, antimicrobial, fungicidal, and antiblastic activities and act as CNS stimulants [1]. Therefore, much attention has recently been paid to the synthesis of new compounds.

Methods for synthesizing 3-heterylchromones have been reviewed [1]. Two principal approaches are known: construction of the chromone system from substituted α-hetaryl-2-hydroxyacetophenones with the appropriate reagents and introduction of a heterocycle into an existing chromone system.

We selected the second approach for synthesizing previously unknown (but promising for resolving scientific issues) 3-(3′-acetyl-5′-aroyl-1′,3′,4′-oxadiazolyl-2′)-chromones (**3**) that is based on the use of available 3-formylchromone (**1**) [2].

Reaction of 3-formylchromone and aroylhydrazines produced the corresponding aroylhydrazones **2a-l**. Then, reaction with acetic anhydride gave 3-(3′-acetyl-5′-aroyl-1′,3′,4′-oxadiazolyl-2′)-chromones (**3a-l**).



1 a-l **2 a - l** **3 a -l**

2-3	R^1	R^2	Ar
a	H	CH_3	C_6H_5
b	H	CH_3	*o*-ClC_6H_4
c	H	CH_3	*p*-$CH_3OC_6H_4$
d	H	CH_3	*p*-$NO_2C_6H_4$
e	H	Br	C_6H_5
f	H	Br	*o*-ClC_6H_5
g	H	Br	*p*-$CH_3OC_6H_4$
h	H	Br	*p*-$NO_2C_6H_4$
i	Cl	Cl	C_6H_5
j	Cl	Cl	*o*-ClC_6H_5
k	Cl	Cl	*p*-$CH_3OC_6H_4$
l	Cl	Cl	*p*-$NO_2C_6H_4$

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TABLE 1. Properties of Compounds **2-3**

Compound	Empirical formula	Yield, %	mp, °C
2a	$C_{18}H_{14}N_2O_3$	85	209-210
2b	$C_{18}H_{13}ClN_2O_3$	75	234-235
2c	$C_{19}H_{16}N_2O_4$	60	214-216
2d	$C_{18}H_{13}N_3O_5$	57	235-236
2e	$C_{17}H_{10}BrN_2O_3$	88	217-218
2f	$C_{17}H_{10}ClBrN_2O_4$	72	197-198
2g	$C_{18}H_{13}BrN_2O_4$	62	207-208
2h	$C_{17}H_{10}BrN_3O_5$	70	195-196
2i	$C_{17}H_{10}Cl_2N_2O_3$	82	211-213
2j	$C_{17}H_9Cl_3N_2O_3$	60	176-177
2k	$C_{18}H_{12}Cl_2N_2O_4$	55	188-190
2l	$C_{17}H_9Cl_2N_3O_5$	51	283-284
3a	$C_{20}H_{16}N_2O_4$	80	173-174
3b	$C_{20}H_{15}ClN_2O_4$	52	187-188
3c	$C_{21}H_{18}N_2O_5$	47	248-249
3d	$C_{20}H_{15}N_3O_6$	43	222-224
3e	$C_{19}H_{13}BrN_2O_4$	79	215-216
3f	$C_{19}H_{12}ClBrN_2O_4$	51	206-207
3g	$C_{20}H_{15}BrN_2O_5$	47	233-234
3h	$C_{19}H_{14}BrN_3O_6$	42	228-229
3i	$C_{19}H_{12}Cl_2N_2O_4$	83	136-137
3j	$C_{19}H_{11}Cl_3N_2O_4$	52	204-205
3k	$C_{20}H_{14}Cl_2N_2O_5$	44	239-241
3l	$C_{19}H_{11}Cl_2N_3O_6$	54	212-214

The structures of **2** and **3** (Table 1) were confirmed using analytical data (analytical results for the synthesized compounds agreed with those calculated) and PMR, IR, and mass spectra. The PMR and mass spectral results for **2a-l** and **3a-l** are listed in Table 2.

The IR spectra of **2a-l** exhibit characteristic absorption bands (cm^{-1}) at 3100-3200 (NH), 1660-1670 (C=O), 1620-1640 (C=N), and 1590-1610 (cyclochromones).

The PMR spectra of **2a-l** contain signals (ppm) at 8.5-9.0 (2-H proton of the pyrone ring) and 11.8-12.2 (NH proton). The peak for the molecular ion is weak owing to the instability of the aroylhydrazones. The appearance of $[M - ArCO]^+$ peaks indicates that the acidic amide bond is readily cleaved. The chromone ring undergoes a reverse Diels—Alder reaction to produce a fragment. Then, CO groups are lost stepwise.

Absorption bands (cm^{-1}) at 3100-3200 disappear in the IR spectra of **3a-l**. Bands characteristic of the chromone moiety (1592-1620), heterocycles (1475-1510), and acetyl groups (1750-1760) appear. The PMR spectra lack signals at 11.8-12.2 ppm. This indicates that heterocyclic compounds containing the oxadiazolyl fragment are already prepared. The 2-H proton of the pyrone ring appears in the spectra of **3** as a narrow signal at 8.8-8.9 ppm [3].

The study of the mass spectra of **3a-l** showed that the peak for the molecular ion is also weak (usually <10%). The base peak is $[M - COCH_3]^+$. The chromone ring cleaves via a reverse Diels—Alder reaction, etc.

TABLE 2. PMR and Mass Spectra of Compounds **2-3**

Compound	PMR, δ, ppm	Mass, *m/z*
2a	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)	306
2b	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)	341
2c	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)	336
2d	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)	351
2e	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)	370
2f	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)	422
2g	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)	401
2h	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)	416
2i	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)	361
2j	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)	396
2k	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)	391
2l	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)	406
2a	8.83 (1H, s, 2-H), 8.39~7.28 (8H, m, 5, 7, 8-H, ph-H), 7.01 (1H, s, 2′-H), 2.33 (3H, s, CH_3), 2.37 (3H, s, $COCH_3$)	348
3b	8.89 (1H, s, 2-H), 8.29~7.25 (7H, m, 5, 7, 8-H, ph-H), 7.07 (1H, s, 2′-H), 2.30 (3H, s, CH_3), 2.35 (3H, s, $COCH_3$)	383
3c	8.92 (1H, s, 2-H), 8.23~7.16 (7H, m, 5, 7, 8-H, ph-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)	378
3d	8.81 (1H, s, 2-H), 8.39~7.28 (7H, m, 5, 7, 8-H, ph-H), 7.12 (1H, s, 2′-H), 2.28 (3H, s, $COCH_3$)	393(4), 350 (100)
3e	8.87 (1H, s, 2-H), 8.31~7.22 (7H, m, 5, 7, 8-H, ph-H), 7.07 (1H, s, 2′-H), 2.37 (3H, s, $COCH_3$)	413
3f	8.79 (1H, s, 2-H), 8.35~7.18 (7H, m, 5, 7, 8-H, ph-H), 7.12 (1H, s, 2′-H), 2.28 (3H, s, $COCH_3$)	448
3g	8.95 (1H, s, 2-H), 8.28~7.12 (7H, m, 5, 7, 8-H, ph-H), 7.09 (1H, s, 2′-H), 2.28 (3H, s, $COCH_3$), 3.62 (3H, s, OCH_3)	443
3h	8.91 (1H, s, 2-H), 8.25~7.10 (7H, m, 5, 7, 8-H, ph-H), 7.03 (1H, s, 2′-H), 2.39 (3H, s, $COCH_3$)	460
3i	8.88 (1H, s, 2-H), 8.13~7.22 (7H, m, 5, 7-H, ph-H), 7.15 (1H, s, 2′-H), 2.37 (3H, s, $COCH_3$)	403
3j	8.91 (1H, s, 2-H), 8.28~7.23 (6H, m, 5, 7-H, ph-H), 7.09 (1H, s, 2′-H), 2.28 (3H, s, $COCH_3$)	438
3k	8.91 (1H, s, 2-H), 8.19~7.18 (6H, m, 5, 7-H, ph-H), 7.03 (1H, s, 2′-H), 2.38 (3H, s, $COCH_3$), 3.65 (3H, s, OCH_3)	433
3l	8.94 (1H, s, 2-H), 8.25~7.13 (6H, m, 5, 7-H, ph-H), 7.00 (1H, s, 2′-H), 2.31 (3H, s, $COCH_3$)	448

EXPERIMENTAL

GF-254 plates were used for TLC. Melting points were measured on an MP-S3 (Japan) heating stage. An automated MT-3 analyzer was used for elemental analysis. IR spectra were recorded on a Bruker FT-IR Equinox-55 (KBr) instrument; PMR spectra, on a Bruker AX 80 (^{1}H, 80 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 with TMS internal standard; mass spectra, on an HP 5988 AMS instrument.

General Method for Preparing Aroylhydrazones 2a-l. A mixture of equivalent amounts of **1** and aroylhydrazones prepared according to the literature method [2, 4] was dissolved in ethanol (95%), treated with several drops of glacial acetic acid, and refluxed for 5-6 h. The crystals that precipitated after cooling were filtered off and recrystallized from absolute ethanol to give **2a-l**.

General Method for Preparing Aroylhydrazones 3a-l. Aroylhydrazones **2a-l** (2 mmole) were treated with acetic anhydride and stirred and boiled for 2 h. The reaction mixture was cooled and poured into ice water. The precipitate was filtered off, washed with water, dried, and recrystallized from DMF/EtOH/H_2O to give **3a-l**.

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