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RECYCLIZATION OF 2-IMINO-2H-1-BENZOPYRANS BY THE ACTION OF NUCLEOPHILIC REAGENTS 4.* USE OF 2-(N-AROYLHYDRAZONO)COUMARIN-3-CARBOXAMIDES FOR THE SYNTHESIS OF 3-(1,3,4-OXADIAZOL-2-YL)COUMARINS

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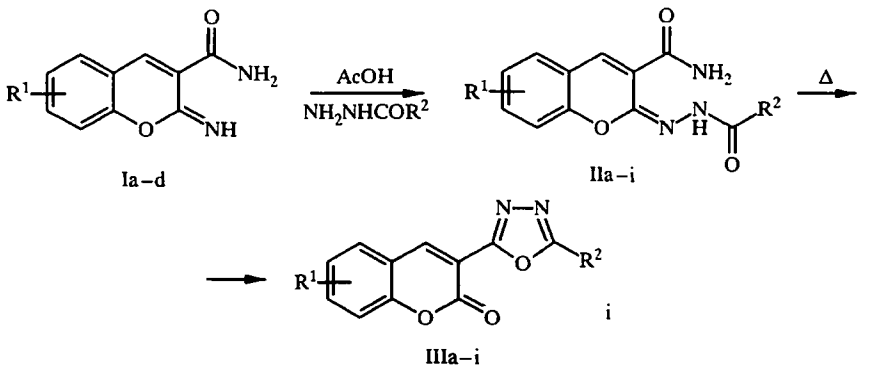
A new method for the synthesis of 3-(1,3,4-oxadiazol-2-yl)coumarins is proposed. It is based on the recyclization of 2-(N-aroylhydrazono)coumarin-3-carboxamides, which are readily obtained by the reaction of 2-iminocoumarin-3-carboxamides with arenecarboxylic hydrazides in an acidic medium. Advantages of the given method over alternative synthetic schemes were shown. Proposals on the mechanism of reaction were made.

We showed previously [2] that 2-iminocoumarin-3-carboxamides are readily recyclized by hydrazides of carboxylic acids on the heating in butan-1-ol to give $N_{(1)}$-acylamidrazones of coumarin-3-carboxylic acids. If this reaction is conducted in glacial acetic acid, the opening of the iminolactone ring of the 2-iminocoumarin-3-carboxamides (Ia-d) does not occur, as also in the case of primary amines [3], and products of substitution at the position 2 of the coumarin — 2-(N-aroylhydrazono)coumarin-3-carboxamides (IIa-i) — are formed.



Ia–d IIa–i IIIa–i

I a R^1 = H; b R^1 = 6-*n*-C_6H_{13}, 7-OH; c R^1 = 7-$N(C_2H_5)_2$; d R^1 = 5,6-benzo; II, III a R^1 = H, R^2 = Ph; b R^1 = H, R^2 = 4-FC_6H_4; c R^1 = 6-*n*-C_6H_{13}, 7-OH; R^2 = Ph; d R^1 = 7-$N(C_2H_5)_2$, R^2 = Ph; e R^1 = 7-$N(C_2H_5)_2$, R^2 = 4-$CH_3C_6H_4$; f R^1 = 7-$N(C_2H_5)_2$, R^2 = 2-ClC_6H_4; g R^1 = 7-$N(C_2H_5)_2$, R^2 = γ-Py; h R^1 = 5,6-benzo, R^2 = Ph; i R^1 = 5,6-benzo, R^2 = 4-$CH_3OC_6H_4$

* For Communication 3, see [1].

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TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Yield, %	mp, °C	Found, % / Calculated, % N	IR spectra (KBr), cm^{-1} (assignment)	ESA (ethanol), λ_{max}, nm (ε)
IIIa	$C_{17}H_{10}N_2O_3$	78	216...218	9,65 / 9,73	1744 ($\nu_{C=O}$)	342 (20000)
IIIb	$C_{17}H_9N_2O_3F$	55	241...243	9,09 / 9,01	1494, 1610 ($\nu_{C=C}$) 1745 ($\nu_{C=O}$)	257 (11000) 339 (17500)
IIIc	$C_{23}H_{22}N_2O_4$	68	241...242	7,17 / 7,22	1570, 1618 ($\nu_{C=C}$) 1744 ($\nu_{C=O}$) 2922, 2851 (ν_{C-H}) 3088 (ν_{O-H})	265 (14800) 382 (32000)
IIId	$C_{21}H_{19}N_3O_3$	69	199...201	11,63 / 11,55	1526, 1582 ($\nu_{C=C}$) 1726 ($\nu_{C=O}$) 2972, 2931 (ν_{C-H})	241 (16500) 283 (11400) 441 (51000)
IIIe	$C_{22}H_{21}N_3O_3$	72	231...232	11,19 / 11,12	1529, 1621 ($\nu_{C=C}$) 1730 ($\nu_{C=O}$) 2963, 2923 2870 (ν_{C-H})	247 (20400) 287 (13800) 441 (55000)
IIIf	$C_{21}H_{18}N_3O_3Cl$	56	195...197	10,62 / 10,71	1582, 1618 ($\nu_{C=C}$) 1735 ($\nu_{C=O}$) 2968, 2928 (ν_{C-H})	250 (16000) 440 (54200)
IIIg	$C_{20}H_{18}N_4O_3$	74	220...222	15,46 / 15,57	1524, 1580 ($\nu_{C=C}$) 1724 ($\nu_{C=O}$) 2978, 2934 (ν_{C-H})	251 (13700) 446 (48600)
IIIh	$C_{21}H_{12}N_2O_3$	76	223...225	8,23 / 8,36	1564, 1603 ($\nu_{C=C}$) 1751 ($\nu_{C=O}$)	231 (49300) 261 (37400) 393 (21100)
IIIi	$C_{23}H_{16}N_2O_4$	82	234...236	7,56 / 7,49	1566, 1611 ($\nu_{C=C}$) 1739 ($\nu_{C=O}$)	265 (27000) 394 (27300)

We found that when the compounds (IIa-i) are heated in high-boiling solvents (*o*-dichlorobenzene, nitrobenzene, quinoline) or when the reaction is performed in a melt for 10-30 min, they are readily converted with good yields to the 3-(1,3,4-oxadiazol-2-yl)coumarins (IIIa-i) (Tables 1, 2).

On account of amide—imidol tautomerism, the 2-(N-aroylhydrazono)coumarin-3-carboxamides (IIa-i) probably have the capacity for intramolecular attack of the hydroxyl group of the imidol form at the electron-deficient carbon atom at the position 2 of the coumarin. Opening of the iminolactone ring and closing of the 1,3,4-oxadiazole ring thereby occur. Further, the intermediate undergoes *cis-trans* isomerization, and repeated nucleophilic attack occurs at the carbamide group, leading to the formation of the lactone ring.

The characteristics of the 3-(1,3,4-oxadiazol-2-yl)coumarins obtained by the proposed method and by the cyclization of $N_{(1)}$-acylamidrazones of coumarin-3-carboxylic acids are identical. However, the products formed in the recyclization of the 2-(N-aroylhydrazono)coumarin-3-carboxamides (IIa-i) are obtained purer and, as a rule, with higher yields since the cyclization of $N_{(1)}$-acylamidrazones to 1,3,4-oxadiazoles may be accompanied by the formation of 1,3,4-triazole derivatives.

It was established that the introduction of substituents of an electron-donor nature into the molecule of (IIa-i), both into the the nucleus of the coumarin fragment and into the aryl group, appreciably facilitates the recyclization process. In contrast, electron-acceptor groups appreciably decrease the rate of the reaction. That is

probably associated with the stabilization of the imidol form of the compound (IIa-i) due to the conjugation of the aryl and coumarin part. In the case of electron-acceptor substituents, the reaction should be conducted under more drastic conditions, for example by increasing the time of heating, or by utilizing quinoline as the reaction medium.

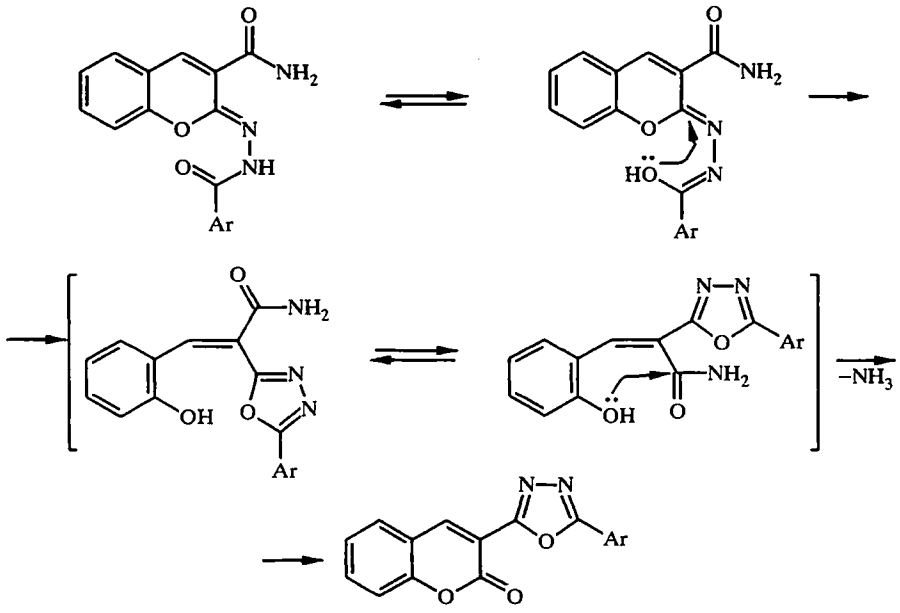

TABLE 2. PMR Spectral Characteristics of the Compounds Synthesized (DMSO-d_6)

Compound	Chemical shift, δ, ppm		
	1H, s, 4-H	H_{arom}	other protons
IIIa	9,02	7,45...8,13 (9H, m)	—
IIIb	9,01	7,48 (4H, m, (8,6,3',5')-H); 7,75 (1H, t, 7-H) 7,96 (1H, d, 5-H); 8,17 (2H, m, (2',6')-H)	—
IIIc	8,85	6,82 (1H, s, 8-H); 7,64 (4H, m, (3',4',5',5)-H) 8,09 (2H, m, (2',6')-H)	0,86 (3H, t, $C\underline{H}_3(CH_2)_4CH_2$) 1,30 (8H, m, $CH_3(C\underline{H}_2)_4CH_2$) 1,56 (2H, m, $CH_3(CH_2)_4C\underline{H}_2$) 11,09 (1H, s, OH)
IIId	8,62	6,55 (1H, d, 8-H); 6,70 (1H, dd, 6-H) 7,52...7,60 (4H, m, (3',4',5',5)-H) 8,05...8,12 (2H, m, (2',6')-H)	1,21 (6H, t, $N(CH_2C\underline{H}_3)_2$) 3,50 (4H, q, $N(C\underline{H}_2CH_3)_2$)
IIIe	8,66	6,61 (1H, d, 8-H); 6,82 (1H, dd, 6-H) 7,45 (2H, d, (3',5')-H); 7,65 (1H, d, 5-H) 7,96 (2H, d, (2',6')-H)	1,17 (6H, t, $N(CH_2C\underline{H}_3)_2$) 2,42 (3H, s, CH_3) 3,50 (4H, q, $N(C\underline{H}_2CH_3)_2$)
IIIf	8,63	6,56 (1H, d, 8-H); 6,75 (1H, dd, 6-H) 7,52...7,68 (4H, m, (3',4',5',5)-H) 8,04 (1H, dd, (2')-H)	1,20 (6H, t, $N(CH_2C\underline{H}_3)_2$) 3,49 (4H, q, $N(C\underline{H}_2CH_3)_2$)
IIIg	8,75	6,61 (1H, d, 8-H); 6,80 (1H, dd, 6-H) 7,63 (1H, d, 5-H); 7,97 (2H, d, β-H) 8,84 (2H, d, α-H)	1,15 (6H, t, $N(CH_2C\underline{H}_3)_2$) 3,48 (4H, q, $N(C\underline{H}_2CH_3)_2$)
IIIh	9,61	7,56...7,67 (5H, m, (3',5',4,7,10)-H) 7,79 (1H, t, 6-H); 8,05 (1H, d, 5-H) 8,20 (2H, m, (2',6')-H); 8,29 (1H, dd, 8-H) 8,71 (1H, d, 9-H)	—
IIIi	9,59	7,13 (2H, dd, (2',6')'-H); 7,60 (1H, d, 10-H) 7,66 (1H, d, 7-H); 7,80 (1H, t, 6-H) 8,03...8,16 (3H, m, (5,2',6')-H) 8,28 (1H, d, 8-H); 8,73 (1H, d, 9-H)	2,76 (3H, s, OCH_3)

As follows from the physicochemical data (Tables 1 and 2), the IR spectra of the compounds synthesized show the strong band of the stretching vibrations of the C=O lactone group of the coumarin ring at 1724-1751 cm^{-1}. The C=C bands of the aromatic vibrations appear at 1580-1630 cm^{-1}. The vibrations of the C=N bonds of the 1,3,4-oxadiazole ring are virtually unseen.

The PMR spectra of the compounds obtained contain signals of the aromatic protons at 6.55-8.84 ppm and the singlet of the proton at the position 4 of the coumarin at 8.62-9.61 ppm (Table 2).

Therefore, it follows from the facts presented that it is expedient to utilize the cyclization of $N_{(1)}$-acylamidrazones of coumarin-3-carboxylic acids for the synthesis of 3-(1,3,4-triazol-2-yl)coumarins [2], whereas the method based on the recyclization of 2-(N-aroylhydrazono)coumarin-3-carboxamides has significant advantages for the synthesis of 3-(1,3,4-oxadiazol-2-yl)coumarins.

EXPERIMENTAL

The IR spectra of the compounds synthesized were registered on the Specord M-80 spectrometer using tablets of KBr. The ESA was measured on the Specord M-40 spectrophotometer in ethanol. The PMR spectra were recorded on the Bruker WM-360 instrument in DMSO-d_6, and the internal standard was TMS.

General Method for the Synthesis of 2-(N-Aroylhydrazono)coumarin-3-carboxamides (IIa-i). The corresponding 2-iminocoumarin-3-carboxamide (0.01 mol) is dissolved in 20-25 ml of glacial acetic acid. To the resulting solution are added equimolecular amounts of the aromatic acid hydrazide. The mixture is acidified with 1-2 drops of concentrated H_2SO_4, carefully stirred, heated to 40-50°C, and left for 2-3 h. The precipitated residue is filtered off, washed with ethanol, and dried.

General Method for the Synthesis of 3-(5-Aryl-1,3,4-oxadiazol-2-yl)coumarins (IIIa-i). The corresponding 2-(N-aroylhydrazono)coumarin-3-carboxamide (0.005 mol) is heated in the minimal amount of nitrobenzene or another high-boiling solvent for 10-40 min. The mixture is cooled. The precipitated residue is filtered off, washed carefully with ether, and recrystallized from a suitable solvent.

REFERENCES

1. S. N. Kovalenko, M. V. Vasil'ev, I. V. Sorokina, V. P. Chernykh, A. V. Turov, and S. A. Rudnev, Khim. Geterotsikl. Soedin., No. 12, 1664 (1998).
2. S. N. Kovalenko, V. A. Zubkov, V. P. Chernykh, A. V. Turov, and S. M. Ivkov, Khim. Geterotsikl. Soedin., No. 2, 186 (1996).
3. V. A. Zubkov, S. N. Kovalenko, V. P. Chernykh, and S. M. Ivkov, Khim. Geterotsikl. Soedin., No. 6, 760 (1994).