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RECYCLIZATION OF 2-IMINO-2H-1-BENZOPYRANS UNDER THE INFLUENCE OF NUCLEOPHILIC REAGENTS. 1. NEW APPROACH TO THE SYNTHESIS OF 3-(1,3,4-OXADI-, THIADI-, AND TRIAZOLYL-2)COUMARINS

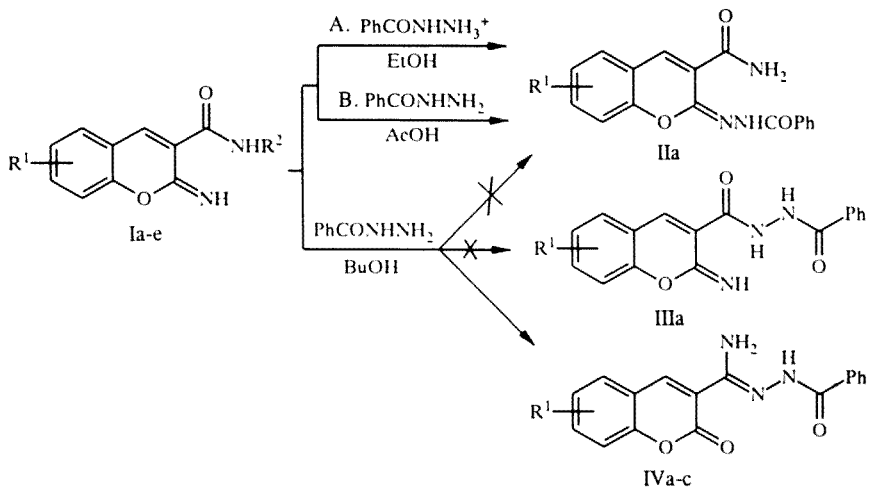
S. N. Kovalenko, V. A. Zubkov, V. P. Chernykh, A. V. Turov, and S. M. Ivkov

It has been found that under the action of hydrazides of carboxylic acids, 2-iminocoumarin-3-carboxamides are recyclized to $N^{(1)}$-acylamidrazones of coumarin-3-carboxylic acids. The use of $N^{(1)}$-acylamidrazones is proposed as a simple and effective means of synthesizing 3-(1,3,4-oxadi-, thiodi-, and triazolyl-2)coumarins. The possibilities of alternate schemes of synthesis are discussed, and a mechanism is suggested for the recyclization.

In an earlier study [1], we showed that the interaction of 2-imino-2H-1-benzopyrans (2-iminocoumarins) with primary amines results in the formation of 2-N-R-substituted iminocoumarins. Continuing these studies, we have investigated the chemical behavior of 2-iminocoumarin-3-carboxamides in reactions with hydrazides of acids.

We found that the interaction of 2-iminocoumarin-3-carboxamide (Ia) with benzhydrazide hydrochloride results in the formation of 2-(N-benzoylhydrazono)coumarin-3-carboxamide (IIa) (Scheme 1, Method A). Compound IIa was also obtained with a high yield by the interaction of compound Ia with benzhydrazide in glacial acetic acid (Method B). Here, the formation of the highly reactive salt of 2-iminocoumarin is not a result of acid–base exchange interaction of reagents as in the first case, but rather proceeds directly in the reaction medium. This reaction is analogous in character to the reactions of 2-iminocoumarins with primary amines [1].

Scheme 1



a) $R^1 = R^2 = H$; b) R^1 = 6-OMe, $R^2 = H$; c) R^1 = 7-NEt_2, $R^2 = H$; d) $R^1 = H$, R^2 = Me; e) $R^1 = H$, R^2 = Ph

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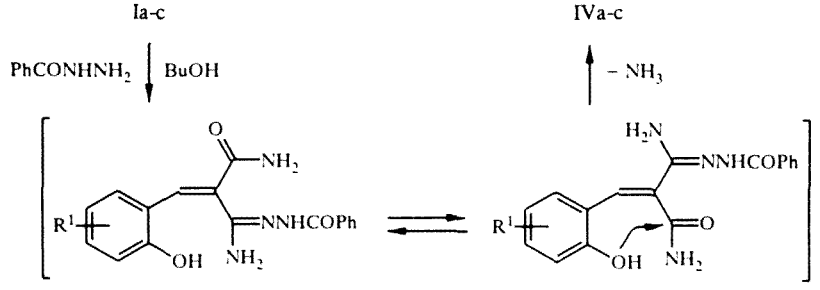
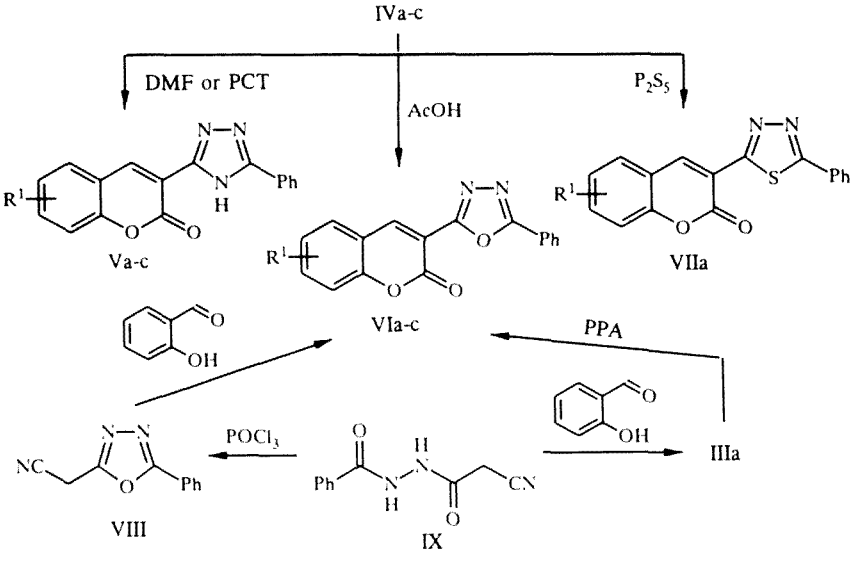
In the PMR spectrum of compound IIa, a signal is observed from magnetically nonequivalent amide protons (7.98 and 9.16 ppm), the location of which is characteristic for 2-(R-imino)coumarin-3-carboxamides [1]; also observed is a broadened signal from the proton of the NH group of the N-benzoylhydrazone fragment (11.25 ppm). The signal of the 4-H proton is manifested at 8.23 ppm; signals of aromatic protons are observed in the form of a complex multiplet at 7.22-7.90 ppm (Table 2).

However, when the reaction of Ia with benzhydrazide is performed in 1-butanol, the type of interaction that is characteristic for primary amines (leading to tar formation) is not observed; in contrast, a crystalline substance is recovered, differing from compound IIa in its characteristics. Moreover, this compound differs from compound IIIa, which was obtained by Knoevenagel condensation of salicylaldehyde with the N-benzoylhydrazide of cyanoacetic acid IX (Table 1, Scheme 2). In the PMR spectra of this new compound, a broadened signal is observed at 6.87 ppm from protons of the NH_2 group, and a signal at 10.09 ppm from the proton of the NH group.

Scheme 2



Scheme 3



In view of these facts, along with the complete data from instrumental analyses (Tables 1-3) and the results from studying the chemical conversions of the substance that was obtained and its derivatives (Scheme 3), we can state that in the interaction of the 2-iminocoumarin-3-carboxamides Ia-c with the hydrazide of benzoic acid in 1-butanol, a recyclization process takes place (Scheme 2), resulting in the formation of $N^{(1)}$-benzoylamidrazones of coumarin-3-carboxylic acids IVa-c.

The initial step apparently is a nucleophilic attack, by the NH_2 group of the benzhydrazide, at the carbon atom of the imino group of the carboxamides Ia-c, with opening of the "iminolactone" ring. Next, as a consequence of cis-trans isomerization of the intermediate, an intramolecular interaction takes place between the phenolic hydroxyl and the carbamide group, accompanied by evolution of ammonia; this results in closure of the coumarin ring and the formation of $N^{(1)}$-benzoylamidrazones of coumarin-3-carboxylic acids IVa-c.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	mp, °C	IR spectra (KBr), ν, cm^{-1} (and assignment)	Electronic absorption spectra (ethanol), λ_{max}, nm	Yield, % (and method)
IIa	$C_{17}H_{13}N_3O_3$	226...227	3305, 3238, 3110 (NH), 1698, 1678 (C=O), 1650 (C=N)	219, 267, 325, 361	70 (A), 92 (B)
IIIa	$C_{17}H_{13}N_3O_3$	214...216	3419, 3338, 3170 (NH), 1703, 1682 (C=O), 1659 (C=N)	219, 292, 303, 344	62
IVa	$C_{17}H_{13}N_3O_3$	187...189	3418, 3181 (NH), 1704, 1682 (C=O), 1658 (C=N)	215, 283, 377	87
IVb	$C_{18}H_{15}N_3O_4$	210...212	3403, 3195 (NH), 1702 (C=O)	225, 291, 380	91
IVc	$C_{21}H_{22}N_4O_3$	235...238	3358, 3232 (NH), 1705, 1690 (C=O), 1643 (C=N)	256, 444	84
Va	$C_{17}H_{11}N_3O_2$	232...234	3254 (NH), 1735 (C=O)	233, 339	91 (A), 70 (B), 38 (C)
Vb	$C_{18}H_{13}N_3O_3$	243...245	3254 (NH), 1720, 1704 (C=O)	233, 344	86
Vc	$C_{21}H_{20}N_4O_2$	198...199	3301 (NH), 1702 (C=O)	258, 429	78
VIa	$C_{17}H_{10}N_2O_3$	216...218	1744 (C=O)	256, 323, 342	78
VIb	$C_{18}H_{12}N_2O_4$	207...209	1738 (C=O)	234, 346	73
VIc	$C_{21}H_{19}N_3O_3$	186...189	1712 (C=O)	249, 420	69
VIIa	$C_{17}H_{10}N_2O_2S$	231...232	1720 (C=O)	234, 279, 358	75

N-Substituted amides of 2-iminocoumarin-3-carboxylic acid (N-methyl derivative Id and N-phenyl derivative Ie) interact with benzhydrazide in 1-butanol in the same manner. In the case of the N-methylamide Id, the reaction proceeds at the same rate as in the case of the 2-iminocoumarin-3 carboxamide Ia. When the 3-N-phenylamide Ie is used as the initial reagent, the yield of the $N^{(1)}$-benzoylamidrazone IVa is only 30% after refluxing the reaction mixture for 3 h. These facts indicate that the recyclization of the amides of 2-iminocoumarin-3-carboxylic acid under the action of benzhydrazide depends considerably on the character of the "leaving group" and on steric factors in the stage of coumarin ring closure.

Traditional methods of obtaining $N^{(1)}$-acylamidrazones [2] for compounds of the coumarin series do not give acceptable results. Therefore, the formation of $N^{(1)}$-acylamidrazones of coumarin-3-carboxylic acids as a result of recyclization of 2-iminocoumarin-3-carboxamides under the action of hydrazides of acids can be proposed as a new approach to the synthesis of 3-(1,3,4-oxadi-, thiadi-, and triazolyl-2)coumarins (Scheme 3).

Thus far, only a few studies have been published on syntheses of 3-(1,3,4-oxadi-, thiadi-, and triazolyl-2)coumarins [3-7]; these have been accomplished through standard schemes of obtaining diazoles, and the syntheses encountered difficulties inseparating and purifying the intermediate or final products. The scheme we are proposing for the synthesis of 3-(1,3,4-oxadi-, thiadi-, and triazolyl-2)coumarins offers a means for circumventing these synthetic difficulties quite easily, and also for obtaining structures that are practically impossible to synthesize by the generally accepted methods.

3-(5-Phenyl-1,3,4-triazolyl-2)coumarins Va-c were obtained by refluxing the $N^{(1)}$-benzoylamidrazones IVa-c in high-boiling solvents — in p-chlorotoluene (PCT) for 5-6 h, or in DMF for 30-40 min. Even though the intramolecular cyclodehydration in PCT requires a considerably longer time than in DMF, the PCT has the advantage of near-quantitative yields and the formation of a purer substance.

3-(5-Phenyl-1,3,4-oxadiazolyl-2)coumarins VIa-c were synthesized by brief refluxing of the $N^{(1)}$-benzoylamidrazones IVa-c in glacial acetic acid, either with or without catalytic additions of concentrated sulfuric acid. Under these conditions, protonation of the imino group of the amidrazone and intramolecular cyclodehydration proceed with detachment of not a water molecule, as in the first case, but rather an ammonium ion, with the formation of a 1,3,4-oxadiazole ring.

In addition, the 1,3,4-oxadiazole VIa was obtained by alternative syntheses — by a Knoevenagel condensation of salicylaldehyde with 2-phenyl-5-(cyanomethyl)-1,3,4-oxadiazole VIII, and by cyclodehydration of the N-benzoylhydrazide of 2-iminocoumarin-3-carboxamide IIIa in polyphosphoric acid (PPA) (Scheme 3). However, the yields in these cases were substantially lower.

The $N^{(1)}$-acylamidrazone group also offers additional possibilities for heterocyclization. Thus, upon refluxing the $N^{(1)}$-benzoylamidrazone IVa with phosphorus pentasulfide, 3-(5-phenyl-1,3,4-thiadiazolyl-2)coumarin (VIIa) is obtained.

TABLE 2. PMR Spectra of Synthesized Compounds (DMSO-d_6)

Compound	Chemical shift δ, ppm, and SSCC (J), Hz			
	NH	1H, s, 4-H	H_{arom}	other protons
IIa	11,25 (1H, s, CONH), 9,16 (1H, s, $CONH_2$), 7,98 (1H, s, $CONH_2$)	8,23	7,22...7,90 (9H, m)	—
IIIa*	12,30 (1H, s, C=NH), 10,95 (1H, s, CONH), 9,18 (1H, s, CONH)	8,60	6,90...8,10 (9H, m)	—
IVa	10,09 (1H, s, CONH), 6,87 (2H, s, NH_2)	8,57	7,40...7,90 (9H, m)	—
IVb	10,03 (1H, s, CONH), 6,84 (2H, s, NH_2)	8,58	7,20...7,95 (8H, m)	3,84 (3H, s, CH_3)
Va	14,20 (1H, s, NH)	8,95	7,41...8,12 (9H, m)	—
Vb	14,20 (1H, s, NH)	8,92	7,20...8,15 (8H, m)	3,83 (3H, s, CH_3)
Vc	13,81 (1H, s, NH)	8,70	6,63 (1H, d, [1,9], 8-H), 6,78 (1H, d.d, [8,8;1,9], 6-H), 7,40...7,50 (3H, m, (3',4',5')-H), 7,70 (1H, d, [8,8], 5-H), 8,00...8,20 (2H, m,(2',6')-H)	1,14 (6H, t, $N(CH_2\underline{CH_3})_2$), 3,46 (4H, q, $N(\underline{CH_2}CH_3)_2$)
VIa	—	9,02	7,45...8,13 (9H, m)	—
VIIa	—	9,22	7,45...8,08 (9H, m)	—

*Interacts with DMSO-d_6 upon heating.

As can be seen from the physicochemical data in Tables 1-3, the IR spectra of the $N^{(1)}$-benzoylamidrazones IVa-c exhibit two bands of νNH (3418-3358 and 3232-3181 cm^{-1}), with the bands approaching each other as the electron-donor strength of the substituent R^1 in the coumarin ring increases. The high-frequency vibration of the nonassociated N–H bond in the 3418-3358 cm^{-1} region is characteristic for the $N^{(1)}$-benzoylamidrazones, and it is a means of distinguishing them from the original 2-iminocoumarin-3-carboxamides Ia-c, which have two bands and an inflection on the high-frequency band in the 3290-3280 and 3141-3127 cm^{-1} regions, and also a means of distinguishing them from the isomeric N-substituted 2-iminocoumarin IIa (three bands at 3305, 3238, and 3110 cm^{-1}). For the other isomer, IIIa, we observe two bands of νNH at practically the same frequencies as for the $N^{(1)}$-benzoylamidrazone IVa (3418 and 3168 cm^{-1}); however, at 3338 cm^{-1}, we observe still another band of νNH of the imino group. The bands of stretching vibrations of the C=O of the lactone, amide, and hydrazide groups of compounds IIa, IIIa, and IVa-c are relatively uninformative for structural analysis, since they are located in a rather narrow interval of frequencies (1705-1678 cm^{-1}), and they overlap in most cases. Upon formation of the heterocycle in position 3 of the coumarin, these bands disappear, and the νC=O band of the lactone group of the coumarin is strongly shifted toward higher frequencies (1744-1702 cm^{-1}). For the 1,3,4-triazoles Va-c, in addition, a νNH band is noted in the 3301-3254 cm^{-1} region.

In the electronic absorption spectra of the $N^{(1)}$-benzoylamidrazones IVa-c, a bathochromic shift of the long-wave band is observed, in contrast to the spectra of the 2-iminocoumarin-3-carboxamides Ia-e. The isomeric N-benzoylhydrazide IIIa has a spectrum similar to that of the 2-iminocoumarin-3-carboxamide Ia (λ_{max} 345, 296 nm), with the difference that the fine structure of the spectrum is washed out. For the N-substituted 2-iminocoumarin IIa, a bathochromic shift of the long-wave band is also characteristic, but it is less pronounced than for the $N^{(1)}$-benzoylamidrazone IVa. The long-wave shift of the first band in the electronic absorption spectra of the $N^{(1)}$-benzoylamidrazones is due to the formation of a strong intramolecular hydrogen bond in these structures. Upon conversion of the $N^{(1)}$-benzoylamidrazones to 3-heterylcoumarins, the long-wave band undergoes a hypsochromic shift and a hyperchromic effect.

In the PMR spectra of the $N^{(1)}$-benzoylamidrazones IVa-c, there is a broadened signal of protons of the NH_2 group (6.84-6.87 ppm), indicating that the $N^{(1)}$-benzoylamidrazones exist in the tautomeric amine form, with the protons of the NH_2 group magnetically equivalent, in contrast to the NH_2 group protons of the carboxamides Ia-c and IIa. The signal of the NH group proton of the $N^{(1)}$-benzoylamidrazones is observed in the 10.03-10.09 ppm region. Upon the formation of the 1,3,4-oxadi- and thiadiazoles VIa and VIIa, these signals disappear; but in the case of the 1,3,4-triazoles Va-c, an NH proton signal

TABLE 3. Mass Spectra of Certain Synthesized Compounds

Compound	*m/z* (and I_{rel}, %)
Ia	188(84), 172(13), 171(100), 146(7), 145(70), 144(13), 143(47), 118(46), 116(10), 115(14)
IIIa	307(37), 290(6), 230(7), 190(8), 174(26), 172(35), 145(32), 146(7), 118(25), 116(7), 106(7), 105(100)
Va	289(100), 261(12), 232(5), 205(7), 130(45), 118(81)
VIa	290(26), 262(5), 206(14), 189(12), 173(32), 105(100)
VIII	185(85), 145(71), 129(8), 118(7), 105(100), 103(19), 89(25), 77(93)

appears in the 13.81-14.20 ppm region. For all of the compounds, the signals of the aromatic protons have the form of complex multiplets in the 6.63-8.20 ppm region, but there is a singlet from the proton in position 4 of the coumarin, in the 8.23-9.22 ppm region.

Thus, the action of hydrazides of carboxylic acids on 2-iminocoumarin-3-carboxamides results in their recyclization to $N^{(1)}$-acylamidrazones of coumarin-3-carboxylic acids, which can be converted quite easily to 3-(1,3,4-oxadi-, thiadi-, and triazolyl-2)coumarins.

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded on a Specord M-80 spectrometer in KBr tablets. The electronic absorption spectra were measured on a Specord M-40 spectrophotometer in ethanol. The PMR spectra were recorded on a Bruker WP-100 SY instrument in DMSO-d_6, internal standard TMS. The mass spectra were obtained in a Finnigan MAT-4615B instrument with ballistic heating of the sample, ionization energy 70 eV.

Elemental analyses for C, H, and N matched the calculated results.

General Procedure for Obtaining 2-Iminocoumarin-3-carboxamides Ia-e. Equimolar quantities (0.01 mole) of the corresponding salicylaldehyde and cyanoacetamide were dissolved in a minimum quantity of ethanol, and a few drops of piperidine were added. The solution was stirred vigorously. The resulting precipitate was filtered off, dried, and crystallized from a suitable solvent.

2-(N-Benzoylhydrazono)coumarin-3-carboxamide (IIa, $C_{17}H_{13}N_3O_3$). Method A. A solution of 1.88 g (0.01 mole) of 2-iminocoumarin-3-carboxamide Ia and 1.73 g (0.01 mole) of benzhydrazine hydrochloride in 30 ml of absolute ethanol was refluxed for 20-30 min. Precipitation of NH_4Cl was observed. The reaction mixture was diluted with 100-150 ml of water. The precipitate was filtered off and dried. Yield 2.15 g (70%).

Method B. A solution of 1.88 g (0.01 mole) of 2-iminocoumarin-3-carboxamide Ia and 1.36 g (0.01 mole) of benzhydrazide was dissolved in 20 ml of glacial acetic acid and heated for 5-10 min. The precipitate was filtered off, washed with water, and dried. Yield 2.82 g (92%) (from 2-propanol).

N-Benzoylhydrazide of 2-Iminocoumarin-3-carboxylic Acid (IIIa, $C_{17}H_{13}N_3O_3$). To a solution containing 1.3 ml (0.011 mole) of salicylaldehyde and 2.03 g (0.01 mole) of the N-benzoylhydrazide of cyanoacetic acid (IX) in 30 ml of ethanol, a few drops of piperidine were added. The mixture was stirred vigorously for 20-30 min. The precipitate was filtered off, washed with ethanol, and dried. Yield 1.90 g (62%) (from 1-butanol).

General Procedure for Obtaining $N^{(1)}$-Benzoylamidrazones of Coumarin-3-carboxylic Acids IVa-c. Equimolar quantities (0.01 mole) of 2-iminocoumarin-3-carboxamide Ia-e and benzhydrazide, in 30-50 ml of 1-butanol, were refluxed for 15-30 min. Evolution of ammonia was observed. The precipitate was filtered off, washed with hot ethanol, and dried.

General Procedure for Obtaining 3-(5-Phenyl-1,3,4-triazolyl-2)coumarins Va-c. A solution of 0.01 mole of the corresponding $N^{(1)}$-benzoylamidrazone IVa-c in 20-30 ml of DMF was refluxed for 30 min, or a solution in p-chlorotoluene was refluxed for 5-6 h). The resulting precipitate was filtered off, dried, and crystallized from a suitable solvent.

General Procedures for Obtaining 3-(5-Phenyl-1,3,4-oxadiazolyl-2)coumarins VIa-c. Method A. To a solution of 0.01 mole of the corresponding $N^{(1)}$-benzoylamidrazone IVa-c in 20 ml of glacial acetic acid, concentrated H_2SO_4 was added, and the mixture was heated for 15-20 min. The reaction mass was diluted with water. The precipitate was treated with ammonia solution, filtered off, dried, and crystallized from a suitable solvent.

Method B. To a solution of 0.46 g (0.0025 mole) of 2-phenyl-5-(cyanomethyl)-1,3,4-oxadiazole (VIII) in 5 ml of 70% ethanol, 0.26 ml (0.0025 mole) of salicylaldehyde and 1-2 drops of piperidine were added. The precipitate was filtered off, washed with ethanol, and dried. Yield 0.51 g (70%) (from 2-propanol).

Method C. A mixture of 1.54 g (0.005 mole) of the N-benzoylhydrazide of 2-iminocoumarin-3-carboxylic acid (IIIa) and 2 g of polyphosphoric acid was heated for 30 min at 100°C. The mixture was diluted with water. The precipitate was filtered off, washed with ethanol, and dried. Yield 0.28 g (38%) (from 2-propanol).

3-(5-Phenyl-1,3,4-thiadiazolyl-2)coumarin (VIIa, $C_{17}H_{10}N_2O_2S$). A mixture of 1.54 g (0.005 mole) of the $N^{(1)}$-benzoylamidrazone IVa and 1 g of P_2S_5 was refluxed in 40 ml of ethyl acetate for 2.5 h. The precipitate was filtered off, washed with ethanol, and dried. Yield 1.15 g (75%) (from 1-butanol).

2-Phenyl-5-(cyanomethyl)-1,3,4-oxadiazole (VIII, $C_{10}H_7N_3O$). A solution of 2.0 g (0.01 mole) of the N-benzoylhydrazide of cyanoacetic acid (IX) was refluxed in 10 ml of $POCl_3$ for 10-15 min. The reaction mixture was cooled and poured onto ice. The resulting precipitate was filtered off, washed with a saturated sodium acetate solution, and dried. Yield 1.30 g (70%), mp 119-120°C (from 1-butanol).

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