A Novel and Efficient Synthesis of 3-[(4,5-Dihydro-1*H*-pyrrol-3-yl)carbonyl]-2*H*-chromen-2-ones (= 3-[(4,5-Dihydro-1*H*-pyrrol-3-yl)carbonyl]-2*H*-1-benzopyran-2-ones)

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An efficient one-pot synthesis of 3-[(4,5-dihydro-1*H*-pyrrol-3-yl)carbonyl]-2*H*-chromen-2-one (= 3-[(4,5-dihydro-1*H*-pyrrol-3yl)carbonyl]-2*H*-1-benzopyran-2-one) derivatives **4** by a four-component reaction of a salicylaldehyde **1**, 4-hydroxy-6-methyl-2*H*-pyran-2-one, a benzylamine **2**, and a diaroylacetylene (= 1,4-diarylbut-2-yne-1,4-dione) **3** in EtOH is reported. This new protocol has the advantages of high yields (*Table*), and convenient operation. The structures of these coumarin (= 2*H*-1-benzopyran-2-one) derivatives, which are important compounds in organic chemistry, were confirmed spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this reaction is proposed (*Scheme 2*).

Introduction. – Coumarins (= 2*H*-1-benzopyran-2-ones) and their derivatives form an elite class of compounds, occupying an important place in the realm of natural products and synthetic organic chemistry. They are widely present in higher plants such as Rutaceae, Apiaceae, Asteraceae, Leguminosae, and Thymelaeaceae, as well as occur as animal and microbial metabolites [1]. Coumarins have various bioactivities, for example, inhibition of platelet aggregation [2], antibacterial [3] and anticancer activity [4], inhibition of steroid 5α-reductase [5], and inhibition of HIV-1 protease [6]. Coumarins have also been used in the preparation of insecticides [7], optical brighteners [8], and dispersed fluorescent and tunable laser dyes [1]. Accordingly, many reports have described various structures and biological evaluations of numerous coumarin analogs newly synthesized or isolated from plants [9].

N-Atom-containing heterocyclic compound are also important natural and synthetic materials. The remarkable ability of these heterocyclic cores to serve both as biomimetics and active pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs and designed medicinal agents in medicinal chemistry [10]. In particular, N-containing heterocycles are prevalent in many drugs [11], thus synthetic chemists are increasingly motivated to discover new methods for the rapid construction of pharmacologically important drug-like compounds [12]. The development of new approaches for the efficient construction of these heterocycles continues to be essential for accessing natural products and their structural analogues. Accordingly, and because of their scarce occurrence in exotic organisms, novel strategies for the synthesis of N-heterocycles have received considerable attention in the past decades [13].

Their properties have turned coumarin and pyrrolidine derivatives into interesting targets for organic chemists. In the course of our research program into the design of new routes for the synthesis of new heterocyclic compounds, we were interested in the synthesis of heterocyclic compounds containing both the coumarin and the pyrrolidine skeleton by a one-pot and four-component reaction sequence.

Results and Discussion. – According to the importance of coumarin and pyrrole derivatives, we became attracted to investigate reactions of coumarin-substituted enamines and diaroylacetylenes (=1,4-diarylbut-2-yne-1,4-diones). Our new synthetic route is shown in *Scheme 1*. The sequential four-component reaction of salicylaldehydes (=2-hydroxybenzaldehydes) **1**, 4-hydroxy-6-methyl-2*H*-pyran-2-one, diaroylacetylenes **3**, and benzylamines **2** was performed within 4 h in EtOH in the presence of one drop of piperidine to produce 3-[(4,5-dihydro-1*H*-pyrrol-3-yl)carbonyl]-2*H*-chromen-2-ones **4** in excellent yields (*Table*).

Scheme 1. *Synthesis of 3-[(4,5-Dihydro-1*H*-pyrrol-3-yl)carbonyl]-2*H*-chromen-2-ones.* For R, Ar, and Ar′, see the *Table*.

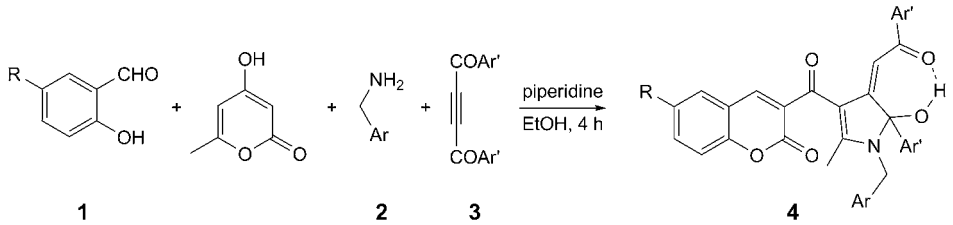


Table. *Prepared 3-[(4,5-Dihydro-1*H*-pyrrol-3-yl)carbonyl]-2*H*-chromen-2-ones* **4**

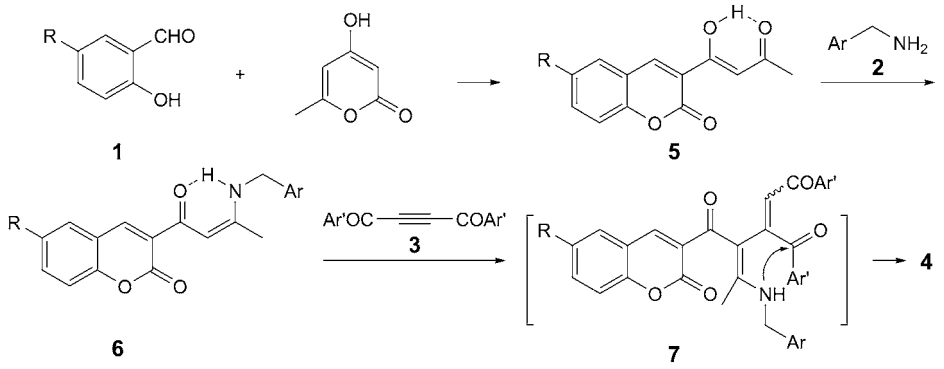
Product	R	Ar	Ar′	Yield [%]
4a	H	Ph	Ph	71
4b	MeO	Ph	Ph	75
4c	H	Ph	4-Me–C_6H_4	70
4d	H	4-Me–C_6H_4	4-Me–C_6H_4	78

The structures of compounds **4a**–**4d** were deduced from their elemental analysis, IR, and high-field ^{1}H- and ^{13}C-NMR spectra. The mass spectrum of **4b** displayed the molecular-ion peak at *m*/*z* 583, in agreement with the proposed structure. Its IR spectrum showed absorption bands due to the OH-stretching frequency at 3443 cm^{-1}, and absorption bands at 1717, 1610, 1525, 1408, and 1247 cm^{-1} were assigned to the CO, C=C and C–O groups, respectively. The ^{1}H-NMR spectrum of **4b** showed two *s* for the Me and MeO groups (δ(H) 2.18 and 3.86), an *AB* signal for the CH_2N group because these H-atoms are diastereotopic (δ(H) 4.43 and 4.62, ^2J = 16.8 Hz), one *s*, three *d*, and two *m* for aromatic H-atoms (δ(H) 7.00, 7.15 (^3J = 7.0 Hz), 7.70 (^3J = 7.3 Hz), 7.80 (^3J = 7.3 Hz), 7.19–7.25, and 7.29–7.33), and three *s* for an olefinic H-atom, the CH of the coumarin moiety, and an OH group, (δ(H) 7.62, 8.01, and 9.05, resp.). The ^{1}H-

decoupled ^{13}C-NMR spectrum of **4b** showed 30 distinct resonances in agreement with the suggested structure.

A possible mechanism for the reaction is proposed on the basis of known reactions [14–17] (*Scheme 2*). At first condensation of salicylaldehyde **1** and 4-hydroxy-6-methyl-2*H*-pyran-2-one gives intermediate **5** [14–16]. The latter reacts with a benzylamine **2** possibly *via* an imine formation, and imine ⇌ enamine tautomerization leads to enamine **6**. Finally, nucleophilic addition of enamine **6** to diaroylacetylene **3** [17] and cyclization give the product **4** in good yields. To support the proposed mechanism, the structures of intermediates **5b** and **6a** in the synthesis of **4b** and **4a**, respectively, were established by ^{1}H- and ^{13}C-NMR spectroscopy.

Scheme 2. *A Plausible Mechanism for the Formation of Products* **4a**–**4d**. For R, Ar, and Ar′, see the *Table*.



In summary, we described a novel approach to the synthesis of 3-[(4,5-dihydro-1*H*-pyrrol-3-yl)carbonyl]-2*H*-chromen-2-ones by a one-pot and sequential four-component reaction between salicylaldehydes, 4-hydroxy-6-methyl-2*H*-pyran-2-one, benzylamines, and diaroylacetylenes. Characteristics of this method are good yields of the products, a simple procedure, inexpensive starting materials, and the synthesis of new coumarin derivatives.

Experimental Part

General. All starting materials were obtained from *Merck* (Germany) and *Fluka* (Switzerland) and were used without further purification. Diaroylacetylenes **3** were prepared according to published procedures [18][19]. M.p.: *Electrothermal-9100* apparatus. IR Spectra: *Shimadzu-IR-460* spectrometer; in KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-DRX-500-Avance* FT-NMR instrument; at 500 and 125 MHz, resp.; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. EI-MS: *Finnigan-MAT-8430* mass spectrometer, ionization potential 70 eV; in m/z (rel.%). Elemental analyses for C, H, and N: *Heraeus CHN-O-Rapid* analyzer.

General Procedure (exemplified for **4a**). A soln. of salicylaldeyde (**1a**; 0.122 g, 1 mmol) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (0.126 g, 1 mmol) in EtOH (5 ml) and one drop of piperidine were magnetically stirred for 1 h under reflux. Then benzenemethanamine (**2a**; 0.107 g, 1 mmol) was added and the soln. was stirred for 1 h under reflux. After this time, 1,4-diphenylbut-2-yne-1,4-dione (**3a**;

0.234 g, 1 mmol) was slowly added to the mixture at r.t. and stirred for 2 h. After completion of the reaction, the mixture was filtered and the precipitate washed with cold EtOH: pure **4a**.

*3-{[(4Z)-4,5-Dihydro-5-hydroxy-2-methyl-4-(2-oxo-2-phenylethylidene)-5-phenyl-1-(phenylmethyl)-1*H*-pyrrol-3-yl]carbonyl}-2*H*-1-benzopyran-2-one* (**4a**): Yield 392 mg (71%). Yellow powder. M.p. 201–203°. IR: 3427 (OH), 1719 (br., 3 C=O), 1608 (C=C), 1524 and 1460 (Ar), 1240 (C–O). ^{1}H-NMR: 2.14 (*s*, 3 H); 4.52 (*d*, ^2J = 15.5, 1 H); 4.65 (*d*, ^2J = 15.5, 1 H); 7.10 (*s*, 2 H); 7.23–7.31 (*m*, 8 H); 7.42–7.49 (*m*, 3 H); 7.59–7.66 (*m*, 6 H); 7.86 (*s*, 1 H); 8.37 (*s*, 1 H); 8.91 (*s*, 1 H). ^{13}C-NMR: 15.42; 45.41; 95.90; 106.45; 110.22; 116.34; 118.56; 125.07; 125.68; 126.69; 127.16; 127.69; 128.00; 128.37; 128.60; 128.74; 129.66; 129.87; 132.72; 133.27; 136.21; 138.33; 138.92; 143.63; 153.76; 158.36; 166.43; 172.08; 182.83; 190.27. EI-MS: 553 (47, M^+), 535 (10), 448 (37), 380 (80), 291 (100), 263 (56), 236 (16), 173 (27), 106 (41), 91 (43). Anal. calc. for $C_{36}H_{27}NO_5$ (553.61): C 78.10, H 4.92, N 2.53; found: C 77.24, H 4.82, N 2.55.

*3-{[(4Z)-4,5-Dihydro-6-hydroxy-2-methyl-4-(2-oxo-2-phenylethylidene)-5-phenyl-1-(phenylmethyl)-1*H*-pyrrol-3-yl]carbonyl}-6-methoxy-2*H*-1-benzopyran-2-one* (**4b**): Yield 437 mg (75%). Orange powder. M.p. 183–185°. IR: 3443 (OH), 1717 (br., 3 C=O), 1610 (C=C), 1525 and 1408 (Ar), 1247 (C–O). ^{1}H-NMR: 2.18 (*s*, 3 H); 3.86 (*s*, 3 H); 4.43 (*d*, ^2J = 16.8, 1 H); 4.62 (*d*, ^2J = 16.8, 1 H); 7.00 (*s*, 1 H); 7.15 (*d*, ^3J = 7.0, 2 H); 7.19–7.25 (*m*, 7 H); 7.29–7.33 (*m*, 3 H); 7.39 (*t*, ^3J = 7.0, 1 H); 7.62 (*s*, 1 H); 7.70 (*d*, ^3J = 7.3, 2 H); 7.80 (*d*, ^3J = 7.3, 2 H); 8.01 (*s*, 1 H); 9.05 (*s*, 1 H). ^{13}C-NMR: 15.67; 46.47; 55.90; 96.50; 108.38; 110.56; 111.15; 117.75; 119.06; 121.20; 126.01; 126.84; 127.51; 128.16; 128.33; 128.71; 128.80; 131.23; 132.24; 135.92; 138.95; 138.98; 143.43; 148.93; 156.42; 158.91; 165.89; 171.35; 183.09; 191.84. EI-MS: 583 (40, M^+), 478 (23), 400 (41), 380 (54), 321 (100), 263 (27), 236 (28), 203 (22), 91 (33). Anal. calc. for $C_{37}H_{29}NO_6$ (583.64): C 76.14, H 5.01, N 2.40; found: C 75.84, H 4.99, N 2.43.

*3-{[(4Z)-4,5-Dihydro-5-hydroxy-2-methyl-5-(4-methylphenyl)-4-[2-(4-methylphenyl)-2-oxoethylidene]-1-(phenylmethyl)-1*H*-pyrrol-3-yl}carbonyl}-2*H*-1-benzopyran-2-one* (**4c**): Yield 406 mg (70%). Yellow powder. M.p. 215–217°. IR: 3433 (OH), 1723 (br., 3 C=O), 1610 (C=C), 1521 and 1408 (Ar), 1244 (C–O). ^{1}H-NMR: 2.13 (*s*, 3 H); 2.26 (*s*, 3 H); 2.31 (*s*, 3 H); 4.38 (*d*, ^2J = 16.7, 1 H); 4.62 (*d*, ^2J = 16.7, 1 H); 7.04 (*d*, ^3J = 7.9, 2 H); 7.10 (*d*, ^3J = 7.9, 2 H); 7.17 (*d*, ^3J = 6.9, 2 H); 7.22 (*d*, ^3J = 6.9, 2 H); 7.25 (*s*, 1 H); 7.34 (*t*, ^3J = 7.5, 1 H); 7.40 (*d*, ^3J = 8.3, 1 H); 7.56–7.66 (*m*, 7 H); 8.05 (*s*, 1 H); 9.10 (br. *s*, 1 H). ^{13}C-NMR: 15.67; 21.11; 21.51; 46.47; 96.50; 108.53; 111.20; 116.70; 118.75; 124.92; 125.33; 125.91; 126.89; 127.47; 128.55; 128.70; 128.81; 128.84; 128.86; 129.03; 129.28; 132.97; 136.08; 138.50; 143.03; 143.39; 154.41; 158.72; 165.46; 170.99; 182.85; 191.45. EI-MS: 581 (16, M^+), 551 (24), 523 (20), 408 (27), 368 (83), 313 (38), 264 (42), 236 (100), 152 (41), 98 (65). Anal. calc. for $C_{38}H_{31}NO_5$ (581.66): C 78.47, H 5.37, N 2.41; found: C 78.0, H 5.31, N 2.47.

*3-{[(4Z)-4,5-Dihydro-5-hydroxy-2-methyl-5-(4-methylphenyl)-1-[(4-methylphenyl)methyl]-4-[2-(4-methylphenyl)-2-oxoethylidene]-1*H*-pyrrol-3-yl}carbonyl}-2*H*-1-benzoyran-2-one* (**4d**): Yield 464 mg (78%). Orange powder. M.p. 198–201°. IR: 3438 (OH), 1721 (br., 3 C=O), 1608 (C=C), 1518 and 1406 (Ar), 1241 (C–O). ^{1}H-NMR: 2.16 (*s*, 3 H); 2.29 (*s*, 3 H); 2.31 (*s*, 3 H); 2.35 (*s*, 3 H); 4.35 (*d*, ^2J = 16.7, 1 H); 4.57 (*d*, ^2J = 16.7, 1 H); 7.03–7.07 (*m*, 6 H); 7.11 (*d*, ^3J = 7.9, 2 H); 7.34 (*t*, ^3J = 7.5, 1 H); 7.40 (*d*, ^3J = 8.3, 1 H); 7.59–7.67 (*m*, 7 H); 8.04 (*s*, 1 H); 9.08 (*s*, 1 H). ^{13}C-NMR: 15.23; 20.53; 20.64; 21.03; 45.82; 96.06; 107.96; 110.41; 116.22; 118.28; 124.43; 125.44; 126.40; 128.07; 128.36; 128.37; 128.54; 128.89; 130.66; 132.46; 132.50; 135.68; 135.96; 136.71; 137.99; 142.52; 142.83; 153.92; 158.24; 165.06; 170.60; 182.31; 190.95. EI-MS: 595 (24, M^+), 476 (19), 422 (35), 384 (72), 333 (27), 305 (77), 160 (64), 119 (67), 105 (100). Anal. calc. for $C_{39}H_{33}NO_5$ (595.69): C 78.64, H 5.58, N 2.35; found: C 78.23, H 5.53, N 2.41.

*3-[(1Z)-1-Hydroxy-3-oxobut-1-en-1-yl]-6-methoxy-2*H*-1-benzopyran-2-one* (**5b**). A soln. of 2-hydroxy-5-methoxybenzaldehyde (**1b**, 0.152 g, 1 mmol) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (0.126 g, 1 mmol) in EtOH (5 ml) and one drop of piperidine was magnetically stirred for 1 h under reflux. After cooling of the mixture to r.t., the mixture was filtered and the precipitate washed with cold EtOH: pure intermediate **5b** (239 mg, 80%). Yellow powder. M.p. 170° (dec.). ^{1}H-NMR: 2.27 (*s*, 3 H); 3.86 (*s*, 3 H); 7.03 (*d*, ^4J = 3.0, 1 H); 7.03 (*s*, 1 H); 7.21 (*dd*, ^3J = 9.1, ^4J = 3.0, 1 H); 7.29 (*d*, ^3J = 9.1, 1 H); 8.60 (*s*, 1 H); 15.87 (*s*, 1 H). ^{13}C-NMR: 27.55; 55.88; 101.65; 110.53; 117.65; 118.82; 120.78; 122.43; 145.20; 149.02; 156.37; 158.18; 171.95; 199.73.

*3-{(2Z)-1-Oxo-3[(phenylmethyl)amino]but-2-en-1-yl}-2*H*-1-benzopyran-2-one* (**6a**). A soln. of salicylaldehyde (**1a**, 0.122 g, 1 mmol) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (0.126 g, 1 mmol) in EtOH (5 ml) and one drop of piperidine was magnetically stirred for 1 h under reflux. Then,

benzenemethanamine (**2a**, 0.107 g, 1 mmol) was added, and the soln. was stirred for another 1 h under reflux. After cooling of the mixture to r.t., the mixture was filtered and the precipitate washed with cold EtOH: pure intermediate **6a** (271 mg, 85%). Yellow crystals. M.p. 185–188° (dec.). ^{1}H-NMR: 2.13 (*s*, 3 H); 4.58 (*d*, ^3J = 6.0, 2 H); 6.40 (*s*, 1 H); 7.26–7.39 (*m*, 7 H); 7.57 (*t*, ^3J = 7.8, 1 H); 7.60 (*d*, ^3J = 7.8, 1 H); 8.57 (*s*, 1 H); 12.01 (*s*, 1 H). ^{13}C-NMR: 19.11; 46.86; 95.76; 115.86; 118.72; 123.98; 125.98; 126.48; 127.26; 128.50; 128.75; 132.25; 136.69; 144.41; 154.02; 159.04; 166.53; 180.11.

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