An Efficient Isocyanide-Based Three-Component Diastereoselective Synthesis of Chromane-3,4-dicarboxamides

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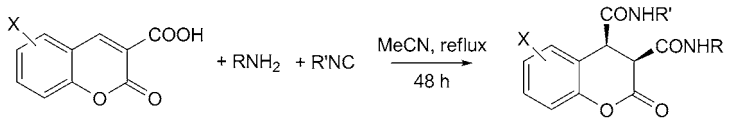
An efficient method for the diastereoselective synthesis of chromane-3,4-dicarboxamide*s via* the three-component reaction of 2-oxo-2*H*-chromene-3-carboxylic acids, amines, and isocyanides in MeCN is reported.

Introduction. – Due to the wide range of pharmacological activities of chromanes [1–6], research on these compounds is still very attractive, and the main interest is directed toward the synthesis of compounds with enhanced pharmacological activities. Despite continuous search for the development of new isocyanide-based multi-component reactions for the synthesis of various potentially important compounds, to the best of our knowledge, the synthesis of chromane-3,4-dicarboxamides by a multi-component procedure has not been reported so far. As part of our program, aimed at developing new isocyanide-based multicomponent reactions [7–10], herein, we describe an efficient synthetic approach to 2-oxochroman-3,4-dicarboxamides by an isocyanide-based three-component reaction.

Results and Discussion. – Heating of 2-oxo-2*H*-chromene-3-carboxylic acids **1**, anilines **2**, and isocyanides **3** at reflux led in the absence of any catalyst in MeCN to the formation of 2-oxochroman-3,4-dicarboxamide derivatives **4** in good yields (*Table*). ^{1}H-NMR Spectra of the crude products clearly indicated the formation of **4**. All the products were characterized by IR and ^{1}H-NMR spectroscopy, mass spectrometry, and elemental analysis.

The mass spectrum of **4a** displayed the molecular-ion peak at *m*/*z* 392. The IR spectrum of **4a** exhibited absorption bands, due to CO groups, at 1777, 1697 and 1658 cm^{-1}. A broad absorption band for the NH groups was observed at 3327 cm^{-1}. The ^{1}H-NMR spectrum of **4a** consisted of *multiplet*s attributed to the cyclohexyl rings (δ(H) 1.22–2.24) and the NHC*H* resonance (δ(H) 4.12), and two *doublet*s for the two CH H-atoms (δ(H) 3.80 and 4.62, $J = 5.1$). Two broad signals (δ(H) 7.69 and 9.24) were observed for the NH groups. The aromatic H-atoms gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H-decoupled ^{13}C-NMR spectra of **4a** exhibited 18 distinct resonances confirming the proposed structure. The characteristic C-atom signals of **4a** at δ(C) 47.7, 55.2, 51.8, 166.2, 174.1, and 177.7, were attributed to two CH, CH–NH, two CONH, and O–C=O groups, respectively.

Table. *Synthesis of 2-Oxochromane-3,4-dicarboxamides* **4**



1 **2** **3** **4**

Product	X	R	R′	Yield [%]
4a	H	Ph	cHex[a])	90
4b	6-Br	3,4-Me_2–C_6H_3	cHex	80
4c	6-Br	4-MeO–C_6H_4	cHex	67
4d	8-OH	4-Br–C_6H_4	cHex	87
4e	6-Cl	4-Cl–C_6H_4	2,6-$Me_2C_6H_3$	75
4f	6-Me	2-MeO–C_6H_4	*tert*-Bu	70
4g	H	4-Me–C_6H_4	cHex	80

[a]) cHex = Cyclohexyl.

It should be noted that two pairs of diastereoisomers were formed in the reaction. ^{1}H-NMR spectra of the crude mixture without any purification revealed a mixture of two diastereoisomers. The *cis*-diastereoisomer was the major isomer. The *trans*-diastereoisomer was present in small quantities. It is removed in the course of the purification process. Therefore, the reaction is diastereoselective. The expected *cis*-configuration of the major diastereoisomer was established by NOE difference spectroscopy and by analysis of vicinal coupling constants of H–C(3) and H–C(4) (*Fig.*). The major isomer **4a** showed, upon irradiation of H–C(4) (δ(H) 4.62, J = 5.1), an enhancement effect on H–C(3) (3%).

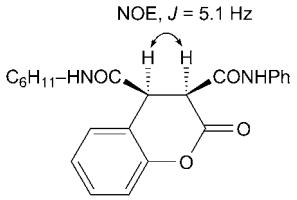
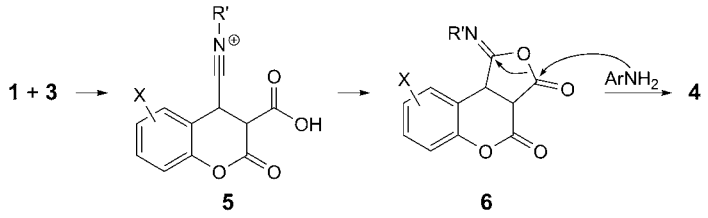


Figure. *Coupling constants and NOEs of compound* **4a**

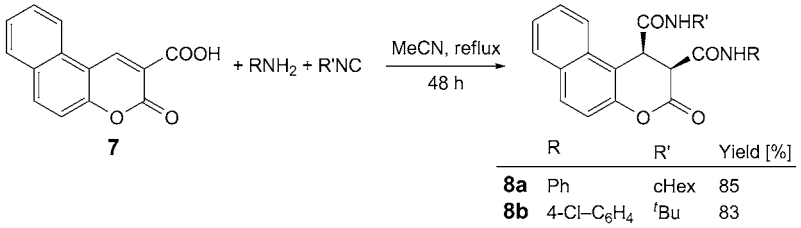
The formation of products **4** can be rationalized by the initial formation of intermediate **5** *via* condensation reaction of **1** and **3**. The following intramolecular reaction of the carboxy group with the nitrilium entity leads to formation of 'iminolactone' **6** [11]. Finally, nucleophilic attack of amine **2** at the C=O group of **6** affords product **4** (*Scheme 1*).

To further explore the potential of this three-component protocol for the synthesis of fused 2-oxochromane-dicarboxamides, we replaced 2-oxo-2*H*-chromene-3-carboxylic acids **1** by 3-oxo-3*H*-benzo[*f*]chromene-2-carboxylic acid **7** and obtained 2,3-dihydro-3-oxo-1*H*-benzo[*f*]chromane-1,2-dicarboxamides **8** in good yields (*Scheme 2*).

Scheme 1. *Proposed Mechanism of the Reaction Leading to* **4**



Scheme 2. *Synthesis of Benzo[f]chromane-dicarboxamides*



	R	R'	Yield [%]
8a	Ph	cHex	85
8b	4-Cl–C_6H_4	^{t}Bu	83

When the reaction was carried out with aliphatic amine such as ethanamine or propanamine, TLC and ^{1}H-NMR spectra of the mixture indicated a mixture of starting materials and numerous products. The yield of the expected products was very low.

In conclusion, we have described an efficient and one-pot isocyanide-based three-component synthesis of 2-oxochromane-3,4-dicarboxamides starting from simple and readily available precursors under neutral conditions without any activation or modifications. The products are of potential synthetic and pharmacological interest.

Experimental Part

General. The chemicals were obtained from *Fluka* and *Merck* and used without purification. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra (KBr): *Bomem MB-series*, FT-IR apparatus; in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-300 AVANCE* spectrometer, recorded at 300.13 and 75.47 MHz, resp., in (D_6)DMSO; δ in ppm rel. to Me_4Si (=0 ppm), J in Hz. EI-MS (70 eV): *Finningan-MAT 8430* mass spectrometer; in *m*/*z*. Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

General Procedure for Preparation of **4** (*Table*). A mixture of 2-oxo-2*H*-chromene-3-carboxylic acid **1** (1 mmol), aniline **2** (1 mmol), and isocyanide **3** (1 mmol) in MeCN (4 ml) was stirred for 48 h at reflux temp. After completion of the reaction (TLC; AcOEt/hexane 1:1), the mixture was cooled to r.t. The solvent was evaporated, and the residue was recrystallized from $CHCl_3$/hexane 1:3 to afford the pure product **4**.

*(3*R**,4*R**)-*N*^{4}*-Cyclohexyl-3,4-dihydro-2-oxo-*N*^{3}*-phenyl-2*H*-chromene-3,4-dicarboxamide* (**4a**). Yield: 90%. White powder. M.p. 230–232°. IR 3327 (NH), 1777, 1697, 1658 (C=O). ^{1}H-NMR: 1.04–2.08 (*m*, 5 CH_2); 3.88 (*d*, J=5.6, CH); 3.96–4.01 (*m*, CH of cHex); 4.18 (*d*, J=5.6, CH); 6.73–6.83 (*m*, 2 arom. H); 7.05–7.18 (*m*, 3 arom. H); 7.23–7.59 (*m*, 4 arom. H); 10.01 (br. *s*, NH); 10.45 (*s*, NH). ^{13}C-NMR: 25.3; 25.7; 28.7; 47.7; 51.8; 55.2; 115.7; 119.6; 124.2; 124.4; 129.3; 129.6; 131.9; 138.9; 155.6; 166.2; 174.1; 177.7. EI-MS: 392 (M^+). Anal. calc. for $C_{23}H_{24}N_2O_4$ (392.45): C 70.39, H 6.16, N 7.14; found: C 70.48, H 6.09, N 7.05.

*(3*R**,4*R**)-6-Bromo-*N*^{4}-cyclohexyl-*N*^{3}-(3,4-dimethylphenyl)-3,4-dihydro-2-oxo-2*H*-chromene-3,4-dicarboxamide* (**4b**). Yield: 80%. White powder. M.p. 211–213°. IR 3332 (NH), 1777, 1696, 1660 (C=O).

^{1}H-NMR: 1.08–2.04 (*m*, 5 CH_2); 2.16 (*s*, Me); 2.17 (*s*, Me); 3.87–3.90 (*m*, CH of cHex); 3.94 (*d*, *J* = 5.2, CH); 4.24 (*d*, *J* = 5.1, CH); 7.05–7.07 (*m*, 1 arom. H); 7.09–7.12 (*m*, 1 arom. H); 7.26–7.43 (*m*, 4 arom. H); 10.26 (br. *s*, NH); 10.35 (*s*, NH). ^{13}C-NMR: 19.3; 20.0; 25.2; 25.7; 28.7; 36.3; 47.1; 51.9; 54.7; 110.4; 117.2; 117.7; 120.8; 126.7; 130.1; 132.1; 132.3; 134.3; 136.6; 137.0; 155.1; 165.7; 174.1; 177.3. EI-MS: 500 (M^+), 498 (M^+). Anal. calc. for $C_{25}H_{27}BrN_2O_4$ (499.40): C 60.13, H 5.45, N 5.61; found: C 60.02, H 5.40, N 5.50.

*(3*R**,4*R**)-6-Bromo-*N^4*-cyclohexyl-3,4-dihydro-*N^3*-(4-methoxyphenyl)-2-oxo-2*H*-chromene-3,4-dicarboxamide* (**4c**). Yield: 67%. White powder. M.p. >250°. IR 3332 (NH), 1777, 1695, 1657 (C=O). ^{1}H-NMR: 1.08–2.05 (*m*, 5 CH_2); 3.71 (*s*, MeO); 3.90 (br. *s*, CH of cHex, CH); 4.22 (br. *s*, CH); 6.76 (*d*, *J* = 8.9, 1 arom. H); 6.89–7.03 (*m*, 2 arom. H); 7.31 (*d*, *J* = 7.8, 1 arom. H); 7.43–7.51 (*m*, 3 arom. H); 10.29 (br. *s*, NH); 10.35 (*s*, NH). ^{13}C-NMR: 25.3; 25.7; 28.6; 31.1; 36.3; 47.1; 51.9; 54.6; 55.6; 110.4; 114.4; 117.7; 121.2; 126.7; 131.9; 134.3; 155.1; 156.1; 162.9; 165.5; 174.1; 177.3. EI-MS: 502 (M^+), 500 (M^+). Anal. calc. for $C_{24}H_{25}BrN_2O_5$ (501.37): C 57.49, H 5.03, N 5.59; found: C 57.42, H 5.10, N 5.53.

*(3*R**,4*R**)-N^3-(4-Bromophenyl)-N^4-cyclohexyl-3,4-dihydro-8-hydroxy-2-oxo-2*H*-chromene-3,4-dicarboxamide* (**4d**). Yield: 87%. White powder. M.p. 232–233°. IR 3429 (OH), 3346 (NH), 1764, 1681 (C=O). ^{1}H-NMR: 1.12–2.04 (*m*, 5 CH_2); 3.88–3.96 (*m*, CH of cHex, CH); 4.12 (br. *s*, CH); 6.58 (br. *s*, 2 arom. H); 6.75 (br. *s*, 1 arom. H); 7.50–7.54 (*m*, 4 arom. H); 8.92 (br. *s*, OH); 9.51 (br. *s*, NH); 10.59 (*s*, NH). ^{13}C-NMR: 24.7; 26.9; 28.1; 32.1; 43.3; 47.6; 51.1; 111.7; 115.2; 117.3; 120.5; 127.9; 134.0; 139.5; 141.4; 158.5; 162.2; 169.7; 173.4; 177.8. EI-MS: 488 (M^+), 486 (M^+). Anal. calc. for $C_{23}H_{23}BrN_2O_5$ (487.34): C 56.68, H 4.76, N 5.75; found: C 56.57, H 4.67, N 5.84.

*(3*R**,4*R**)-6-Chloro-*N^3*-(4-chlorophenyl)-*N^4*-(2,6-dimethylphenyl)-3,4-dihydro-2-oxo-2*H*-chromene-3,4-dicarboxamide* (**4e**). Yield: 75%. White powder. M.p. 214–216°. IR 3340 (NH), 1783, 1710 (C=O). ^{1}H-NMR: 2.08 (*s*, Me); 2.18 (*s*, Me); 4.37 (*d*, *J* = 4.7, CH); 4.62 (*d*, *J* = 4.7, CH); 6.90 (*d*, *J* = 8.6, 1 arom. H); 7.19–7.31 (*m*, 4 arom. H); 7.37–7.43 (*m*, 3 arom. H); 7.62–7.65 (*m*, 2 arom. H); 10.65 (*s*, NH); 10.71 (*s*, NH). ^{13}C-NMR: 13.4; 13.6; 43.7; 50.8; 112.9; 117.1; 118.7; 120.8; 123.9; 124.5; 124.7; 125.1; 125.4; 126.7; 127.7; 131.9; 132.6; 133.4; 150.3; 158.6; 161.9; 168.6; 171.8. EI-MS: 482 (M^+). Anal. calc. for $C_{25}H_{20}Cl_2N_2O_4$ (483.34): C 62.12, H 4.17, N 5.80; found: C 62.01, H 4.10, N 5.74.

*(3*R**,4*R**)-N^4-(*tert*-Butyl)-3,4-dihydro-N^3-(2-methoxyphenyl)-6-methyl-2-oxo-2*H*-chromene-3,4-dicarboxamide* (**4f**). Yield: 70%. Cream powder. M.p. 232–234°. IR 3404 (NH), 1745, 1701 (C=O). ^{1}H-NMR: 1.25 (*s*, *t*-Bu); 2.17 (*s*, Me); 3.74 (*s*, MeO); 3.99 (*d*, *J* = 4.5, CH); 4.27 (*d*, *J* = 4.5, CH); 6.75–7.98 (*m*, 7 arom. H); 9.59 (*s*, NH); 9.79 (*s*, NH). EI-MS: 410 (M^+). Anal. calc. for $C_{23}H_{26}N_2O_5$ (410.46): C 67.30, H 6.38, N 6.82; found: C 67.18, H 6.30, N 6.92.

*(3*R**,4*R**)-N^4-Cyclohexyl-3,4-dihydro-N^3-(4-methylphenyl)-2-oxo-2*H*-chromene-3,4-dicarboxamide* (**4g**). Yield: 80%. Cream powder. M.p. 140–142°. IR 3346 (NH), 1751, 1698 (C=O). ^{1}H-NMR: 1.09–2.07 (*m*, 5 CH_2); 2.24 (*s*, Me); 3.87–3.90 (*m*, CH of cHex); 3.93 (*d*, *J* = 5.3, CH); 4.16 (*d*, *J* = 5.3, CH); 6.73–6.82 (*m*, 2 arom. H); 7.10–7.17 (*m*, 5 arom. H); 7.47 (*d*, *J* = 8.9, 2 arom. H); 9.98 (br. *s*, NH); 10.35 (*s*, NH). ^{13}C-NMR: 20.9; 25.3; 25.7; 28.7; 47.7; 51.8; 55.2; 115.7; 119.6; 124.2; 129.6; 129.7; 131.9; 133.4; 136.5; 155.5; 165.9; 174.2; 177.7. EI-MS: 406 (M^+). Anal. calc. for $C_{24}H_{26}N_2O_4$ (406.47): C 70.92, H 6.45, N 6.89; found: C 70.85, H 6.51, N 6.95.

*(1*R**,2*R**)-N^1-Cyclohexyl-2,3-dihydro-3-oxo-*N^2*-phenyl-1*H*-benzo[f]chromene-1,2-dicarboxamide* (**8a**). Yield: 85%. White powder. M.p. 274–276°. IR 3324 (NH), 1694, 1659 (C=O). ^{1}H-NMR: 1.11–2.13 (*m*, 5 CH_2); 3.97 (br. *s*, CH of cHex); 4.05 (*d*, *J* = 4.8, CH); 5.04 (*d*, *J* = 4.8, CH); 7.06–7.82 (*m*, 11 arom. H); 7.83 (br. *s*, NH); 10.40 (*s*, NH). ^{13}C-NMR: 25.3; 25.7; 28.7; 28.8; 41.4; 51.2; 55.2; 115.6; 118.1; 119.7; 121.7; 123.2; 124.6; 127.7; 128.4; 129.1; 129.4; 129.9; 133.7; 138.6; 153.5; 166.1; 173.9; 178.1. EI-MS: 442 (M^+). Anal. calc. for $C_{27}H_{26}N_2O_4$ (442.51): C 73.28, H 5.92, N 6.33; found: C 73.19, H 5.85, N 6.24.

*(1*R**,2*R**)-N^1-(*tert*-Butyl)-N^2-(4-chlorophenyl)-2,3-dihydro-3-oxo-1*H*-benzo[f]chromene-1,2-dicarboxamide* (**8b**). Yield: 83%. White powder. M.p. 232–233°. IR 3392 (NH), 1769, 1743, 1657 (C=O). ^{1}H-NMR: 1.16 (*s*, Me_3C); 4.17 (br. *s*, CH); 4.75 (br. *s*, CH); 7.30–8.25 (*m*, 10 arom. H); 8.28 (br. *s*, NH); 10.63 (*s*, NH). ^{13}C-NMR: 28.3; 41.5; 55.4; 58.6; 115.8; 118.1; 121.4; 121.6; 123.3; 127.7; 128.3; 128.4; 129.1; 129.3; 129.9; 133.7; 137.4; 153.3; 166.6; 174.8; 179.0. EI-MS: 450 (M^+). Anal. calc. for $C_{25}H_{23}ClN_2O_4$ (450.91): C 66.59, H 5.14, N 6.21; found: C 66.52, H 5.19, N 6.16.

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