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Uncatalyzed [4 + 2] Cycloadditions of 3-Nitrocoumarins with Vinyl Ethers in Solventless Conditions. A New Entry to Chromene Derivatives

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The [4 + 2] cycloadditions of 3-nitrocoumarins **5** with electron-rich dienophiles (ethyl vinyl ether (**8**), 2,3-dihydrofuran (**9**), and 3,4-dihydro-2*H*-pyran (**10**)) were investigated in water, in neat conditions, and in organic solvents. The cycloadditions do not require the use of catalysts and are highly endo diastereoselective, and in water the cyclic nitronates **13**, **18**, and **23** are converted into chromene derivatives via hydrolysis, decarboxylation, and acetalation reactions. A one-pot procedure based on consecutive reactions in neat/water conditions allows 3-nitrocoumarins **5** to be used as building blocks for the synthesis of chromanols and tetrahydrofuro- and tetrahydropyranochromenes. For the first time, the hydrolysis of cyclic nitronates having the C−O bond of 1,2-oxazine ring as a part of an acetal was investigated.

Introduction

The [4 + 2] cycloaddition of α,*β*-unsaturated nitroalkenes[1] has been investigated either with simple alkenes[2] or with a variety of electron-rich olefins such as silyl enol ethers,[3] enamines,[4] enolate anions,[3b,5] silyl ketene acetal,s[3a,b,6] and allylsilanes.[7] Important contributions have been made by researchers from the Denmark group.[8]

The reactions were usually carried out at low temperature, in organic solvent, and in the presence of Lewis acids. The resulting cycloadducts (1,2-oxazines *N*-oxide or nitronates) were converted into a variety of compounds such as nitroenamines,[4] pyrrolidines,[8a,d] cycloalkylamines,[8b,c,e,f,h] *γ*-diketones,[3,4] *γ*-nitroketones,[3,4] *γ*-keto alcohols,[9a] *N*-oxy-*β*-lactams,[10b] *β*,*γ*-unsaturated α-hydroxyimino esters,[11] and pyrrolizidine and indolizidine alkaloids[8g,j−m] by opening the 1,2-oxazine ring using hydrolytic, reductive, and oxidative processes or by [3 + 2] dipolar cycloaddition followed by reduction reactions.[8]

As a continuation of our investigations on organic reactions performed in water,[12] we recently reported[12h] the synthesis of optically active nitronates **3** and **4** by [4

* To whom correspondence should be addressed. Phone: +39 075 5855546. Fax: +39 075 5855560.

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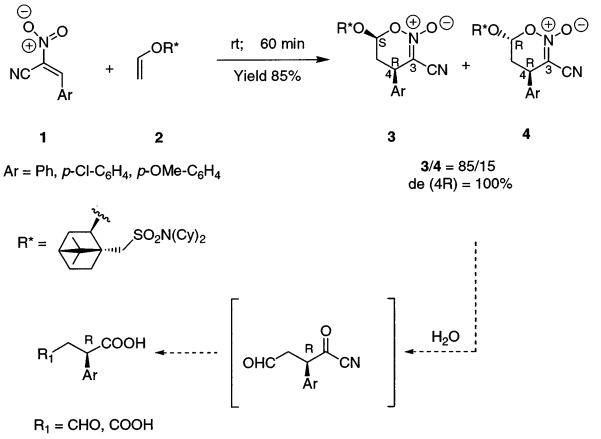
SCHEME 1



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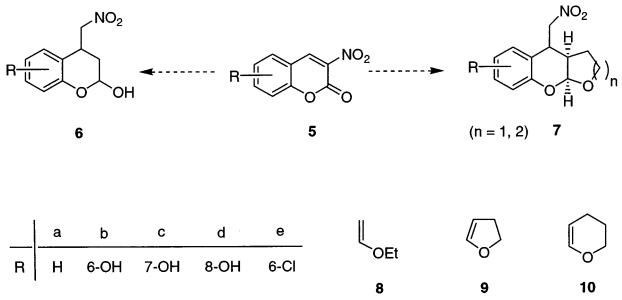

+ 2] cycloadditions of (*E*)-2-aryl-1-cyano-1-nitroethenes **1** with the enantiopure vinyl ether **2**. These reactions occur in the heterogeneous phase, under mild conditions, in good yield, and in a highly stereoselective way (Scheme 1).[13]

In an effort to carry out the synthesis of enantiopure aryl-substituted 3-formylpropionic acids and succinic acids from **1** (Scheme 1) by a one-pot procedure in aqueous medium, the oxazines **3** and **4** were submitted to hydrolysis and hydrolysis−oxidation reactions under various pH conditions, but none of the desired products were obtained.[14] This outcome was attributed to side reactions involving the intermediate hemiacetal (or the aldehyde functionality), arising from the fission of 1,2-oxazine-*N*-oxide ring. To circumvent this problem, we planned to trap the aldehydic group by nucleophilic intramolecular reaction in the aqueous medium. To develop this idea, we chose 3-nitrocoumarins **5** for the following reasons: besides having the required chemical functionalities, they (i) allow chromene derivatives of great interest to be prepared such as 3,4-dihydro-2*H*-1-benzopyrans **6** and cis-fused tetrahydrofuro- and tetrahydropyranochromenes **7** (Scheme 2), (ii) can be easily prepared from *o*-hydroxybenzaldehydes and nitroacetonitrile in aqueous medium by a one-pot procedure,[12a] and (iii) have been rarely used as building blocks in organic synthesis[15] and never previously used to generate nitronates. We wish to report the results of the [4 + 2] cycloadditions of 3-nitrocoumarin (**5a**) and some its derivatives **5b**−**e** with electron-rich alkenes **8**−**10** (Scheme 2) in water only, under neat conditions, and in organic solvents and the hydrolysis reaction of the corresponding nitronates.

SCHEME 3

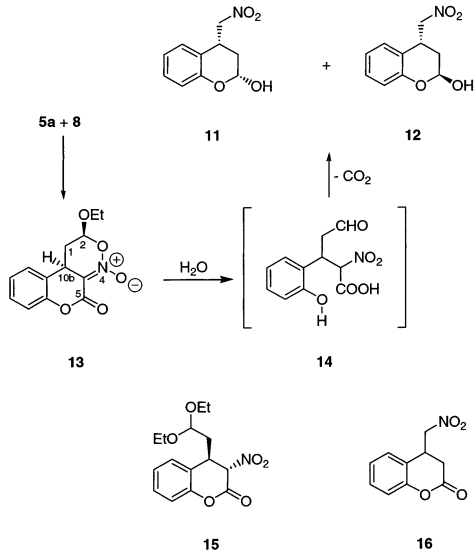

TABLE 1. [4 + 2] Cycloadditions of 3-Nitrocoumarin (5a) with Ethyl Vinyl Ether (EVE) (8) at 20 °C

entry	medium	EVE (**8**) (mol/equiv)	time (h)	products (%)	yield[a] (%)
1	H_2O (pH 8.3)	2	9	**11** (56), **12** (44)	56
2	H_2O (pH 4.5)	4	24	**11** (56), **12** (44)	40
3	neat	8	3	**13**	90
4	neat + H_2O (pH 8.3)	8	3−8[b]	**11** (56), **12** (44)	60
5	CH_2Cl_2	4	1	**13**	80
6	MeCOMe	4	2	**13**	80
7	PhH	4	6	**13**	80
8	*n*-C_6H_{14}	4	6		
9	EtOH	4	1	**15**[c]	97

[a] Yield of isolated products. [b] The first value refers to the reaction carried out under neat conditions and the second to the hydrolysis of **13**. [c] 95:5 mixture of cis/trans streoisomers.

Results and Discussion

Nitrocoumarin **5a** reacted with ethyl vinyl ether (**8**) (2 mol/equiv) in aqueous $NaHCO_3$ (pH 8.3)[16] under heterogeneous conditions at 20 °C giving after 9 h a mixture of chromanols **11** and **12** in 56/44 ratio with 56% overall yield (Scheme 3, Table 1, entry 1). At pH 4.5, the reaction time was longer, the yield was lower, and 4 mol/equiv of **8** was necessary (Table 1, entry 2). Working under neat conditions (Table 1, entry 3), the expected nitronate **13** was isolated in 90% yield as the sole reaction product,

(13) The cycloaddition reactions were totally enantioselective and endo stereoselective. The trans adducts **4** which, in principle, are derived from an exo-type addition, are the result of the epimerization at C-6 of kinetically favoured cis adduct **3**.[8c, 12h]

(14) The hydrolysis of cyclic nitronates gives good results when the C−O bond of the 1,2-oxazine *N*-oxide ring is a part of a ketal and the nucleophilic attack of water produces a secondary alcohol[9] or a ketone.[4b,d] Hydrolysis of cyclic nitronates that have the C−O bond of the 1,2-oxazine ring as a part of an acetal was investigated in dichloromethane.[9b] Methanolysis, in dry methanol, allows isolation of the γ-nitro aldehyde protected as acetal.[11]

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(16) The choice of pH is important for the success of the reaction considering the stability of vinyl ethers **8**−**10** (basic pH) and of 3-nitrocoumarins **5** (acid pH).

and analogous results were obtained by carrying out the cycloaddition reaction under homogeneous conditions in organic solvents with the exception of *n*-hexane where no reaction occurred (Table 1, entry 5−8). The cycloadduct **13** in water (pH 8.3, 20 °C, 8 h) gave a mixture of **11** and **12** in 60% yield and again in a 56/44 ratio. The same result was obtained by in situ hydrolysis of **13** derived from the cycloaddition performed under neat conditions (Table 1, entry 4). In ethanol, the reaction between **5a** and **8** was fast and gave the acetal **15** as the main diastereoisomer (trans/cis = 95/5), which in water (pH 4.5, 80 °C, 2 h) produced the mixture of chromanols **11** and **12**, again in 56/44 ratio. Oxidation of the mixture of **11** and **12** with pyridinium chlorochromate at room temperature gave **16** in 94% yield.

All these facts indicate that under neat conditions and in organic solvent the cycloaddition reaction between **5a** and **8** is totally regioselective and endo-selective. It can also be assumed that this occurs in water too, and therefore, the mixture of chromanols **11** and **12** should result from the hydrolysis of nitronate **13**, which first produces the intermediate **14**, which then undergoes decarboxylation and subsequent unstereoselective intramolecular acetalation. The total endo diastereoselectivity of the cycloaddition reaction between **5a** and **8** can be explained on the basis of strong secondary orbital interactions between the oxygen of **8** and the nitrogen atom of **5a** present in the endo transition state; these interactions are absent in the exo transition state.

We also decided to perform the cycloaddition reaction of **5a** with cyclic vinyl ethers such as dihydrofuran **9** and dihydropyran **10**. In these cases, the formation of a cyclic hemiacetal intermediate was expected and the molecular models indicated that a high diastereoselective transhemiacetalation should occur. Furthermore, the process is of synthetic interest because it allows cis-fused tetrahydrofuro- and tetrahydropyranobenzopyrans **7** to be synthesized. These skeletons are present in natural products of biological interest such as serrulatenol,[17a,b] piscerythrol,[17c] and alboatrin,[17d] but their syntheses have been scarcely investigated.[17d,18]

Nitrocoumarin **5a** reacted with **9** in aqueous $NaHCO_3$ at 30 °C for 1 h and gave quantitatively a mixture of nitrohemiacetals **17** (Scheme 4, Table 2, entry 1). The mixture, isolated and heated for 2 h at 80 °C in water at pH 4.5, afforded cis-fused tetrahydrofuro[2,3-*b*]chromenes **19a** and **20a** in an 88/12 ratio with 67% overall yield (Table 2, entry 2). In organic solvents (Table 2, entries 3−7), the reaction was slower and gave the endo nitronate **18** (endo/exo = 98/2). After 1 h, only 24−47% of **18** was produced in dichloromethane, acetone, and benzene solution; in *n*-hexane, no product was observed and a quantitative conversion of **5a** in benzene required 8 h. Under neat conditions, the reaction quantitatively afforded **18** in only 15 min (Table 2, entry 8). The nitronate **18** (endo/exo = 98/2) in water (pH 4.5, 80 °C, 2 h) gave **19a** and **20a** (98/2, respectively) with 70% yield (Table 2, entry 9). The formation of **19a** in aqueous medium from **5a** and **9** can, once more, be explained by the following sequential reactions: (i) [4 + 2] cycloaddition of these reagents to give the nitronate **18**, (ii) hydrolysis of the 1,2-oxazine ring of **18** to afford the nitrohemiacetal **17**, and (iii) hydrolysis of the lactone, decarboxylation, and intramolecular acetalation to furnish the tetrahydrofurochromene **19a**.

SCHEME 4

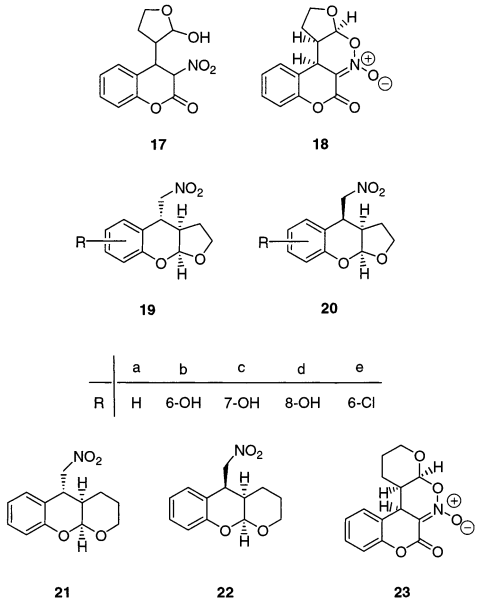

TABLE 2. [4 + 2] Cycloadditions of 3-Nitrocoumarin (5a) with 2,3-Dihydrofuran (9)[a] and 3,4-Dihydro-2*H*-pyran (10)[b]

entry	vinyl ether	medium	*T* (°C)	time (h)	products (%)	yield (%)
1	**9**	H_2O (pH 8.3)	30	1	**17**	100
2	**9**	H_2O (pH 8.3; 4.5)[c]	30−80[c]	1−2[c]	**19a** (88), **20a**(12)	67
3	**9**	CH_2Cl_2	30	1	**18**[d]	46
4	**9**	MeCOMe	30	1	**18**[d]	47
5	**9**	PhH	30	1	**18**[d]	24
6	**9**	PhH	30	8	**18**[d]	100
7	**9**	*n*-C_6H_{14}	30	1		
8	**9**	neat	30	0.25	**18**[d]	94
9	**9**	neat + H_2O (pH 4.5)	30−80[c]	0.25−2[c]	**19a** (98), **20a**(2)	70
10	**10**	H_2O (pH 8.3)	30	6		
11	**10**	H_2O (pH 4.5)	80	6	**21** (80), **22** (20)	74
12	**10**	CH_2Cl_2	40	6	**23**[e]	14
13	**10**	MeCOMe	56	6	**23**[e]	26
14	**10**	PhH	80	6	**23**[e]	11
15	**10**	*n*-C_6H_{14}	70	6		
16	**10**	neat	80	6	**23**[e]	96
17	**10**	neat + H_2O (pH 4.5)	80	6−6[c]	**21** (97), **22** (3)	60

[a] 2 mol/equiv. [b] 4 mol/equiv. [c] See text. [d] Endo/exo = 98/2. [e] Endo/exo = 97/3.

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TABLE 3. Synthesis of Tetrahydrofurochromenes by a One-Pot Consecutive Process Performed under Neat Conditions Followed by Treatment with Water

entry	coumarin	DHF[a] (mol/equiv)	time[b] (h)	products (%)	yield[c] (%)
1	**5a**	2	0.25	**19a** (98), **20a** (2)	70
2	**5b**	10	3	**19b** (97), **20b** (3)	57
3	**5c**	10	24	**19c** (95), **20c** (5)	37
4	**5d**	10	10	**19d** (96), **20a** (4)	44
5	**5e**	4	0.5	**19e** (99), **20e** (1)	32

[a] Dihydrofuran **9**. [b] Reaction time of cycloaddition carried out under neat conditions at 30 °C. The transformation of the nitronate was performed by adding water at pH 4.5 to the crude reaction mixture and heating at 80 °C for 2 h. [c] Overall isolated yield of main reaction product.

The optimum protocol to prepare **19a** by a one-pot procedure involves carrying out the cycloaddition under neat conditions and then adding water in situ prior to workup. This one-pot multistep consecutive process, performed in neat conditions and in water, was used to synthesize substituted tetrahydrofurochromenes **19b**−**e**. The results are reported in Table 3. The processes are highly endo diastereoselective and occur with satisfactory overall yields considering that five main sequential reactions are involved. The same one-pot processes carried out exclusively in water at pH 8.3 required less excess of **9** (2−4 mol/equiv) and a comparable cycloaddition reaction time, but were less diastereoselective (**19**/**20** = ca. 90/10) and gave lower yields (by ca. 10%) than those reported in Table 3.

Analogous results were obtained by using 2,3-dihydropyran **10**. The reaction of **5a** with **10** works in aqueous medium at pH 4.5 (Table 2, compare entries 10 and 11). Under these conditions and at 80 °C, tetrahydropyranochromenes **21** and **22** (80/20 ratio) were isolated in 74% overall yield. In organic solvents at reflux (Table 2, entries 12−15) discouraging results were obtained: long reaction times were required and a low yield of cycloadduct **23** were observed. This is probably ascribable to **10** being less stable in organic medium than in water. Working under neat conditions, the nitronate **23** (endo/exo = 97/3) was isolated in excellent yield (Table 2, entry 16) and converted in situ with water at pH 4.5 into **21** (97%) and **22** (3%) in 60% overall yield (Table 2, entry 17).[19]

Structure of Compounds. Compounds **13**, **16**, **18**, **19**, **21**, and **23** were isolated as pure compounds, while attempts to separate the diastereoisomers **11** and **12** were unsuccessful and the structures of these two compounds were assigned by using enriched mixtures. The configurations of all the compounds were assigned on the basis of ^{1}H NMR coupling constant values and NOE experiments. Characterization data for all of the compounds are reported in the Experimental Section and in the Supporting Information. The data recorded for **11**, **12**, and **13** are briefly discussed as an example.

The saturation of H_4 proton frequency of **11** does not give an NOE effect on proton H_2 (and vice versa) excluding a cis diaxial relationship between these two hydrogens. The vicinal coupling constant values of protons H_4 and H_3 [$J(H_4-H_{3\beta}) = 4.8$ Hz; $J(H_4-H_{3\alpha}) = 4.8$ Hz] and H_2 and H_3 [$J(H_2-H_{3\beta}) = 2.7$ Hz; $J(H_2-H_{3\alpha}) = 2.7$ Hz] are typical of an equatorial−axial and equatorial−equatorial relationship. Protons H_4 and H_2 are therefore cis and in equatorial position. The axial position of CH_2NO_2 and OH substituents is probably favored by a hydrogen bond between the proton of the hydroxy group and one of the oxygen of the nitro group. No NOE effect was also observed on the proton H_2 of **12** from the saturation of H_4 which excludes, also for this compound, a cis diaxial relationship between H_4 and H_2. The coupling constant values of H_4 with H_3 protons [$J(H_4-H_{3\alpha}) = 8.9$ Hz; $J(H_4-H_{3\beta}) = 5.5$ Hz] and H_2 with H_3 [$J(H_2-H_{3\alpha} = 4.8$ Hz; $J(H_2-H_{3\beta}) = 2.7$ Hz] are typical of axial−axial, axial−equatorial, and equatorial−equatorial relationships, respectively. The protons H_4 and H_2 are trans to each other in axial and equatorial positions, respectively.

The saturation of H_2 proton frequency of **13** gives NOE effects on protons H_{10b} and $H_{1\alpha}$, and the saturation of H_{10b} frequency gives a NOE effect on proton $H_{1\alpha}$. Protons H_{10b} and H_2 are therefore in axial positions. This is also supported by vicinal coupling constant values of H_{10b}, H_1 and H_2; $J(H_{10b}-H_{1\alpha}) = 12.1$ Hz and $J(H_{10b}-H_{1\beta}) = 6.4$ Hz are typical of an axial−axial and axial−equatorial relationship of H_{10b}, $H_{1\beta}$, and $H_{1\alpha}$ protons. The values of $J(H_2-H_{1\beta} = 7.3$ Hz and $J(H_2-H_{1\alpha}) = 4.1$ Hz lead to the same conclusion for the H_2, $H_{1\beta}$, and $H_{1\alpha}$ protons.

Conclusions

Nitrocoumarins **5** are valuable building blocks for synthesizing chromene derivatives such as chromanols and tetrahydrofuro- and tetrahydropyranochromenes by a one-pot innovative procedure carried out exclusively in water or by a consecutive process performed in neat/water conditions. The nitronates arising from [4 + 2] cycloadditions of 3-nitrocoumarins with electron-rich olefins were obtained in a highly endo-selective way without using catalysts. They were then converted into chromene derivatives via hydrolysis, decarboxylation, and transacetalation reactions. The hydrolysis of cyclic nitronates having the C−O bond of the 1,2-oxazine ring as a part of an acetal was investigated for the first time in water only.

The reactions performed in water occurred in the heterogeneous phase and allowed better results to be obtained than when they are carried out in homogeneous organic solution. The high acid/base reactivity of water, which is sometimes considered to be an unfavorable chemical property because it interferes with the desired reaction, is fundamental for the success of chromene derivative synthesis from 3-nitrocoumarins by a one-pot process. The utility of water in developing environmentally benign chemical processes and its unexpected potential as a reaction medium on reaction rates and product selectivity encourage us to continue these studies.

Experimental Section

Reagents were purchased and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 400 or 200 MHz for proton and at 100.6 or 50.3 MHz for carbon nuclei in $CDCl_3$, CD_3COCD_3, or in CD_3SOCD_3. GC−MS analyses were carried out at 70 eV. GC analyses were performed with an SPB-5 fused silica capillary column (30 m, 0.25 mm diameter)

(19) The two series of experiments 2, 8, 9 and 11, 16, 17 of Table 2 seem to indicate that the cycloadditions of **5a** with **9** and **10** are more diastereoselective when carried out under neat conditions than when they are performed in water.

using an "on column" injector system and a FID detector with hydrogen as the carrier gas. IR spectra were recorded with a FT-IR instrument, using $CHCl_3$ as solvent. Column chromatographies were carried out on silica gel 230−400 mesh. The pH values of the reactions were controlled using a pH-meter apparatus with a combined refillable pH electrode. Melting points are uncorrected. 3-Nitrocoumarins **5a**−**e**[20] and chromanone **16**[21] are known compounds, but short analytical data were reported for **5b**−**e** and **16**. 3-Nitrocoumarins **5a**−**e** were prepared by a one-pot procedure in water as previously described.[12a]

6-Hydroxy-3-nitrocoumarin (**5b**)**:** 84% yield; brown solid; mp = 219−221 °C (ethanol) (lit.[20a] mp = 215−218 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29−7.39 (m, 3H), 8.93 (s, 1H), 9.02−9.15 (bs, OH); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 154.5, 152.0, 148.5, 135.8, 117.2, CH 142.0, 124.0, 117.5, 114.4; IR ($CHCl_3$) cm^{-1} 3686 (s), 3448 (b), 3018 (m), 1755 (m), 1600 (s). Anal. Calcd for $C_9H_5NO_5$: C, 52.19; H, 2.43; N, 6.76. Found: C, 52.23; H, 2.38; N, 6.75.

7-Hydroxy-3-nitrocoumarin (**5c**)**:** 92% yield; yellow solid; mp = 270−273 °C (ethanol/ethyl acetate/petroleum ether 3/3.5/3.5); ^{1}H NMR (200 MHz, CD_3COCD_3) δ 6.85 (bd, J = 2.3 Hz, 1H), 7.02 (dd, J = 2.3, 8.7 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 9.01 (s, 1H), 10.22−10.42 (bs, OH); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 166.0, 165.9, 158.4, 152.8, 110.3, CH, 144.1, 133.9, 115.6, 103.0; IR ($CHCl_3$) cm^{-1} 3124 (b), 1755 (m), 1605 (s), 1317 (m). Anal. Calcd for $C_9H_5NO_5$: C, 52.19; H, 2.43; N, 6.76. Found: C, 52.31; H, 2.39; N, 6.69.

8-Hydroxy-3-nitrocoumarin (**5d**): 86% yield; brown solid; mp = 234−236 °C (ethyl acetate/petroleum ether 6/4); ^{1}H NMR (200 MHz, CD_3COCD_3) δ 7.28−7.40 (m, 2H), 7.46 (dd, J = 2.8, 6.8 Hz, 1H), 8.99 (s, 1H), 9.28−9.52 (bs, OH); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 152.0, 144.9, 143.5, 135.8, 117.9, CH 143.1, 126.1, 122.3, 121.9; IR ($CHCl_3$) cm^{-1} 3619 (m), 3440 (b), 2976 (s), 1753 (w), 1608 (w), 1241 (m), 1046 (s). Anal. Calcd for $C_9H_5NO_5$: C, 52.19; H, 2.43; N, 6.76. Found: C, 52.01; H, 2.51; N, 6.65.

6-Chloro-3-nitrocoumarin (**5e**)**:** 93% yield; yellow solid; mp = 179−180 °C (ethyl acetate/petroleum ether 5/5) (lit.[20b] mp = 176−177 °C); ^{1}H NMR (200 MHz, CD_3COCD_3) δ 7.53 (bd, J = 8.9 Hz, 1H), 7.87 (dd, J = 2.6, 8.9 Hz, 1H), 8.09 (bd, J = 2.6 Hz, 1H), 9.02 (s, 1H); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 153.9, 152.1, 137.0, 130.6, 118.7, CH, 141.6, 135.8, 130.5, 119.1; IR ($CHCl_3$) cm^{-1} 3457 (b), 2976 (s), 1768 (s), 1605 (m), 1563 (m), 1046 (s); MS *m*/*z* (relative intensity) 225 (M^+, 55), 125 (38), 123 (100). Anal. Calcd for $C_9H_4ClNO_4$: C, 47.92; H, 1.79; N, 6.21. Found C, 47.99; H, 1.74; N, 6.28.

One-Pot Synthesis of Chromanols 11 and 12 in Water. 3-Nitrocoumarin (**5a**) (0.382 g, 2 mmol) and $NaHCO_3$ (0.420 g, 5 mmol) were added with stirring to 10 mL of distilled water at 20 °C. The heterogeneous reaction mixture was stirred for 5 min, and ethyl vinyl ether (**8**) (0.288 g, 4 mmol) was added dropwise in 5 min. After 45 min, the reaction mixture became homogeneous. The reaction was monitored by TLC (ethyl acetate/petroleum ether 3/7), and after 9 h it was cooled in an ice bath. The pH value of the reaction medium was 8.3, which was then adjusted to pH 4.0 by adding a cold 50% H_2SO_4 aqueous solution, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), evaporated under reduced pressure, and purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 15/85) to give 0.234 g (56% yield) of a diastereoisomeric mixture of chromanols **11/12** as a slightly yellow oil in 56/44 ratio (Table 1, entry 1).

***cis*-4-(Nitromethyl)chroman-2-ol** (**11**)**:** characterized in an enriched mixture; ^{1}H NMR (200 MHz, $CDCl_3$ + D_2O) δ 1.90−2.25 (m, 2H), 3.73 (dddd, J = 4.8, 4.8, 5.9, 9.3 Hz, 1H), 4.73 (dd, J = 9.3, 12.7 Hz, 1H), 5.02 (dd, J = 5.9, 12.8 Hz, 1H), 5.74 (t, J = 2.7 Hz, 1H), 6.80−7.30 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ C 151.3, 119.8, CH 129.1, 128.8, 121.6, 117.7, 91.5, 30.9, CH_2 80.5, 28.9.

***trans*-4-(Nitromethyl)chroman-2-ol** (**12**)**:** characterized in an enriched mixture; ^{1}H NMR (200 MHz, $CDCl_3$ + D_2O) δ1.90−2.25 (m, 2H), 3.89 (dddd, J = 5.1 Hz, J = 5.5, 8.9, 9.3 Hz, 1H), 4.51 (dd, J = 9.3 Hz, J = 12.4, 1H), 4.84 (dd, J = 5.1 Hz, J = 12.4 Hz, 1H), 5.65 (dd, J = 2.7 Hz, J = 4.8 Hz, 1H), 6.80−7.30 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ C 151.8, 119.9, CH 129.0, 126.7, 119.8, 117.8, 90.7, 30.0, CH_2 79.9, 31.1.

***trans*-4-(2,2-Diethoxyethyl)-3-nitrochroman-2-one (15).** Ethyl vinyl ether (**8**) (0.576 g, 8 mmol) was added dropwise to a solution of 3-nitrocoumarin (**5a**) (0.382 g, 2 mmol) in ethanol (10 mL) at 20 °C and the reaction mixture left under stirring at this temperature for 1 h. The orange alcoholic solution was evaporated under reduced pressure, and the residual oil was chromatographed on silica gel (acetic acid/ethyl acetate/petroleum ether = 15/15/70) to give 0.590 g (97% yield) of **15** (95/5 trans/cis diastereoisomeric mixture) as a yellow oil (Table 1, entry 9): ^{1}H NMR (200 MHz, CD_3COCD_3) δ 1.10 (t, J = 7.0 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H), 1.89−2.17 (m, 2H), 3.29−3.77 (m, 4H), 4.16 (td, J = 3.7, 7.0 Hz, 1H), 4.60 (t, J = 5.1 Hz, 1H), 6.04 (d, J = 3.7 Hz, 1H), 7.12−7.30 (m, 2H), 7.35−7.45 (m, 2H); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 158.2, 149.9, 121.6, CH 129.6, 128.7, 125.6, 117.0, 100.7, 85.5, 32.6, CH_2 61.8, 61.6, 35.7, CH_3 14.8, 14.7; IR ($CHCl_3$) cm^{-1} 2981 (m), 1784 (s), 1563 (s), 1488 (m), 1460 (m), 1371 (m), 1249 (m), 1177 (s), 1123 (m), 1062 (s). Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.37; H, 6.10; N, 4.59.

4-(Nitromethyl)chroman-2-one (16). To a suspension of pyridine chlorochromate (0.648 g, 3 mmol) in dichloromethane (6 mL), left under stirring at room temperature for 5 min, was added a dichloromethane solution (3 mL) of chromanols **11** and **12** (0.314 g, 1.5 mmol) rapidly at room temperature, and the reaction was stirred for 30 h. The black reaction mixture was filtered, and the solid was washed twice with ethyl acetate. The organic layers were collected, dried (Na_2SO_4), evaporated under reduced pressure, and the residue purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 10/90) to give 0.292 g (94%) of chromanone **16** as slightly yellow oil: ^{1}H NMR (200 MHz, CD_3COCD_3) δ 2.93 (dd, J = 4.2, 16.7 Hz, 1H), 3.18 (dd, J = 6.5, 16.7 Hz, 1H), 3.97−4.10 (m, 1H), 4.85 (abx system, 2H), 7.04−7.27 (m, 2H), 7.33−7.43 (m, 2H); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 166.0, 151.8, 121.5, CH 129.7, 128.1, 124.7, 117.1, 33.5, CH_2 77.8, 31.2; IR ($CHCl_3$) cm^{-1} 3029 (w), 1776 (s), 1550 (s), 1490 (m), 1458 (m), 1162 (m). Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.83; H, 4.48; N, 6.69.

Synthesis of Nitronates 13, 18, and 23 under Neat Conditions. Typical Procedure. 3-Nitrocoumarin (**5a**) (0.382 g, 2 mmol) and the suitable vinyl ether (for mol/equiv see Tables 1 and 2) were mixed in a 5 mL flask thermostated at the temperature indicated in Tables 1 and 2. The heterogeneous reaction mixture was stirred for the appropriate time (Tables 1 and 2), and the resulting white solid was recrystallized to give the cycloadduct.

***cis*-2-Ethoxy-1,10b-dihydro-2*H*,5*H*-chromeno[3,4-*c*][1,2]-oxazin-5-one 4-oxide (13)**: yield 90% (Table 1, entry 3); white solid; mp = 104−106 °C (diethyl ether); ^{1}H NMR (200 MHz, CD_3COCD_3) δ 1.23 (t, J = 7.2 Hz, 3H), 2.13 (ddd, J = 4.1, 12.1, 13.5 Hz, 1H), 3.16 (ddd, J = 6.4, 7.3, 13.6 Hz, 1H), 3.68 (dq, J = 7.1, 9.5 Hz, 1H), 4.07 (dq, J = 7.1, 9.5 Hz, 1H), 4.22 (dd, J = 6.4, 12.1 Hz, 1H), 5.65 (dd, J = 4.1, 7.4 Hz, 1H), 7.03−7.48 (m, 4H); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 153.1, 148.8, 119.0, 115.3, CH 129.3, 127.0, 125.0, 117.3, 104.5, 33.4, CH_2 65.6, 38.8, CH_3 14.5. Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.43; H, 4.98; N, 5.39.

3a,11c-*cis*-11b,11c-*cis*-1,2,11b,11c-Tetrahydro-3a*H*,6*H*-chromeno[3,4-*c*]furo[3,2-*e*][1,2]oxazin-6-one 5-oxide (18): yield 94% (Table 2, entry 8); white solid; mp = 153−154 °C (dry acetone); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.76 (m, 1H), 1.99

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(m, 1H), 3.65 (dddd, J = 4.8, 5.3, 7.1, 10.2 Hz, 1H), 3.85−4.16 (m, 2H), 4.46 (d, J = 4.8 Hz, 1H), 6.16 (d, J = 7.1 Hz, 1H), 7.05−7.40 (m, 4H); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 153.1, 151.1, 119.6, 115.1, CH 130.1, 128.8, 125.8, 117.7, 110.6, 47.2, 38.3, CH_2 69.7, 26.8. Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.87; H, 4.29; N, 5.39.

4a,12c-*cis*-12b,12c-*cis*-2,3,12b,12c-Tetrahydro-1*H*, 4a*H*,7*H*-chromeno[3,4-*c*]pyrano[3,2-*e*][1,2]oxazin-7-one 6-oxide (23): yield 96% (Table 2, entry 16); white solid; mp = 119−120 °C (dry acetone); ^{1}H NMR (200 MHz, CD_3SOCD_3) δ 1.06−1.28 (m, 1H), 1.36−1.52 (m, 1H), 1.54−1.79 (m, 2H), 2.94−3.09 (m, 1H), 3.66 (td, J = 3.4, 11.3 Hz, 1H), 3.68−3.84 (m, 1H), 4.68 (d, J = 4.0 Hz, 1H), 6.09 (d, J = 3.8 Hz, 1H), 7.07 (dd, J = 1.3, 8.0 Hz, 1H), 7.17−7.27 (m, 1H), 7.28−7.40 (m, 1H), 7.47 (bd, J = 7.5 Hz, 1H); ^{13}C NMR (50.3 MHz, CD_3SOCD_3) δ C 153.6, 149.7, 117.7, 109.4, CH 129.0, 127.2, 124.8, 116.6, 102.9, 36.7, 31.1, CH_2 61.5, 22.8, 18.5. Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.14; H, 4.68; N, 5.15.

One-Pot Synthesis of Tetrahydro-4*H*-furo[2,3-*b*]chromenes (19a−e). Typical Procedure. A mixture of nitrocoumarin (**5a**−**e**) (2 mmol) and dihydrofuran **9** (for mol/equiv see Table 3) was stirred at 30 °C for the appropriate time (Table 3). Distilled water (20 mL) was then added, and the resulting pH value was 4.5. The mixture was then warmed at 80 °C, stirred at this temperature for 2 h, cooled to room temperature, saturated with NaCl, and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), evaporated under reduced pressure, and purified by column chromatography on silica gel to give diastereoisomeric mixtures of **19a**−**e/20a**−**e** (yields in Table 3).

3a,4-*trans*-3a,9a-*cis*-4-(Nitromethyl)-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromene (19a): eluted with ethyl acetate/petroleum ether = 1/9; white solid; mp = 88−90 °C (diethyl ether/petroleum ether = 8/2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.63 (m, 1H), 2.14 (m, 1H), 2.74 (ddd, J = 1.8, 5.5, 9.6 Hz, 1H), 3.69 (ddd, J = 1.8, 7.1, 8.7 Hz, 1H), 3.89 (m, 2H), 4.48−4.67 (abx system, 2H), 5.80 (d, J = 5.4 Hz, 1H), 6.90−7.30 (m, 4 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ C 152.9, 119.5, CH 129.7, 129.3, 122.0, 117.7, 99.7, 40.3, 37.3, CH_2 78.8, 67.4, 28.2; IR ($CHCl_3$) cm^{-1} 3025 (w), 1588 (m), 1552 (s), 1488 (m), 1377 (m), 1219 (m), 1044 (m), 978 (m); MS *m*/*z* (relative intensity) 235 (M^+, 12), 187 (37), 160 (100), 131 (55), 115 (35), 107 (77), 91 (83). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.20; H, 5.49; N, 5.99.

3a,4-*trans*-3a,9a-*cis*-4-(Nitromethyl)-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromen-6-ol (19b): eluted with ethyl acetate/petroleum ether = 3/7; pale yellow and thick oil; ^{1}H NMR (200 MHz, CD_3COCD_3) δ 1.40−1.65 (m, 1H), 2.08−2.23 (m, 1H), 2.73−2.88 (m, 1H), 3.61 (td, J = 1.8, 7.8 Hz, 1H), 3.68−3.78 (m, 2H), 4.68 (dd, J = 8.0, 12.7 Hz, 1H), 4.83 (dd, J = 7.5, 12.7 Hz, 1H), 5.73 (d, J = 5.8 Hz, 1H), 6.62−6.73 (m, 3H), 8.09 (bs, OH); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 151.4, 145.4, 121.9, CH 117.8, 115.6, 115.4, 100.0, 40.1, 37.3, CH_2 78.0, 66.6, 27.9; IR ($CHCl_3$) cm^{-1} 3321 (b), 3024 (m), 1554 (s), 1499 (s), 1376 (m), 1213 (s), 1042 (m), 982 (m); MS *m*/*z* (relative intensity) 251 (M^+, 60), 203 (50), 176 (100), 147 (40), 123 (47), 107 (53). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.44; H, 5.30; N, 5.52.

3a,4-*trans*-3a,9a-*cis*-4-(Nitromethyl)-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromen-7-ol (19c): eluted with ethyl acetate/petroleum ether = 5/5; white solid; mp = 212−213 °C (ethyl acetate/petroleum ether 5/5); ^{1}H NMR (200 MHz, CD_3COCD_3) δ 1.32−1.63 (m, 1H), 2.00−2.20 (m, 1H), 2.63−2.78 (m, 1H), 3.68 (td, J = 1.4, 7.6 Hz, 1H), 3.78 (dd, J = 5.8, 8.6 Hz, 2H), 4.61 (dd, J = 7.6, 12.6 Hz, 1H), 4.75 (dd, J = 7.8, 12.6 Hz, 1H), 5.71 (d, J = 5.2 Hz, 1H), 6.28 (d, J = 2.3 Hz, 1H), 6.38 (dd, J = 2.4, 8.2 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 8.36 (bs, OH); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 158.8, 154.5, 111.3, CH 130.7, 109.5, 104.4, 100.1, 40.8, 36.9, CH_2 79.7, 67.4, 28.4; IR ($CHCl_3$) cm^{-1} 3249 (b), 2930 (m), 1623 (m), 1553 (s), 1510 (m), 1465 (m), 1377 (m), 1159 (m), 993 (m); MS *m*/*z* (relative intensity) 251 (M^+, 43), 203 (43), 191 (53), 176 (100), 123 (90). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.33; H, 5.20; N, 5.61.

3a,4-*trans*-3a,9a-*cis*-4-(Nitromethyl)-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromen-8-ol (19d): eluted with ethyl acetate/petroleum ether = 5/5; colorless and thick oil; ^{1}H NMR (200 MHz, CD_3COCD_3) δ 1.42−1.63 (m, 1H), 2.08−2.22 (m, 1H), 2.75−2.89 (m, 1H), 3.70 (td, J = 1.8, 7.7 Hz, 1H), 3.75−3.84 (m, 2H), 4.70 (dd, J = 7.6, 12.8 Hz, 1H), 4.84 (dd, J = 7.9, 12.8 Hz, 1H), 5.83 (d, J = 5.4 Hz, 1H), 6.63−6.71 (m, 1H), 6.73−6.82 (m, 2H), 7.69 (bs, OH); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 146.1, 140.6, 121.4, CH 121.9, 120.1, 115.6, 100.5, 40.8, 37.2, CH_2 78.9, 67.4, 28.3; IR ($CHCl_3$) cm^{-1} 3540 (b), 3025 (w), 2982 (w), 1553 (s), 1482 (s), 1377 (m), 1222 (m), 1053 (m), 972 (m); MS *m*/*z* (relative intensity) 251 (M^+, 66), 203 (48), 176 (100), 175 (45), 147 (38), 123 (49), 107 (45), 77 (42). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.31; H, 5.30; N, 5.55.

3a,4-*trans*-3a,9a-*cis*-6-Chloro-4-(nitromethyl)-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromene (19e): eluted with ethyl acetate/petroleum ether = 5/5; white solid; mp = 137−139 °C (ethyl acetate/petroleum ether 4/6); ^{1}H NMR (200 MHz, CD_3COCD_3) δ 1.45−1.67 (m, 1H), 2.11−2.28 (m, 1H), 2.80−2.93 (m, 1H), 3.79 (td, J = 1.8, 7.7 Hz, 1H), 3.80−3.88 (m, 2H), 4.77 (dd, J = 7.4, 13.1 Hz, 1H), 4.90 (dd, J = 7.8, 13.1 Hz, 1H), 5.82 (d, J = 5.2 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 7.19−7.31 (m, 2H); ^{13}C NMR (50.3 MHz, CD_3COCD_3) δ C 152.8, 126.2, 123.0, CH 130.1, 129.9, 119.6, 100.8, 40.9, 37.3, CH_2 79.2, 67.9, 28.7; IR ($CHCl_3$) cm^{-1} 2975 (m), 1553 (s), 1479 (m), 1372 (m), 1219 (m), 1038 (m), 880 (m); MS *m*/*z* (relative intensity) 271 (M^+ + 2, 12), 269 (M^+, 34), 221 (44), 196 (35), 194 (100), 193 (34), 141 (44). Anal. Calcd for $C_{12}H_{12}ClNO_4$: C, 53.44; H, 4.49; N, 5.19. Found: C, 53.31; H, 4.45; N, 5.15.

One-Pot Synthesis of 4a,5-*trans*-4a,10a-*cis*-5-(Nitromethyl)-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromene (21). Nitrocoumarin **5a** (0.382 g, 2 mmol) and dihydropyran **10** (0.672 g, 8 mmol) were mixed in a 25 mL flask thermostated at 80 °C and equipped with a magnetic stirrer and a condenser. The heterogeneous reaction mixture was stirred for 6 h; 20 mL of distilled water was then added, and the resulting pH value was 4.5. The reaction mixture was stirred at this temperature for an additional 6 h. The cooled reaction mixture was saturated with NaCl and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), evaporated under reduced pressure, and purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 20/80) to give 0.299 g (60% yield) of a 97/3 diastereoisomeric mixture of **21** and **22**. **21**: white solid; mp = 117−118 °C (diethyl ether/petroleum ether 2/8); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45−1.95 (m, 4H), 2.09 (m, 1H), 3.44 (ddd, J = 1.6, 7.3, 8.6 Hz, 1H), 3.76 (m, 1H), 3.97 (dt, J = 2.6, 11.6 Hz, 1H), 4.44−4.65 (abx system, 2H), 5.44 (d, J = 2.5 Hz, 1H), 6.87−7.30 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ C 153.1, 117.0, CH 129.3, 129.3, 121.4, 117.3, 93.0, 40.3, 34.1, CH_2 79.8, 60.8, 24.5, 23.3; IR ($CHCl_3$) cm^{-1} 3145 (m), 1578 (m), 1550 (s), 1477 (m), 1365 (m), 1218 (m), 1042 (m), 974 (m); MS *m*/*z* (relative intensity) 249 (M^+, 23), 201 (339), 172 (100), 145 (72), 131 (69), 107 (79), 91 (68). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.55; H, 6.09; N, 5.59.

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Supporting Information Available: Analytical data with ^{1}H and ^{13}C NMR peak assignments and NOE interactions of compounds **11**−**13**, **15**, **16**, **18**, **19a**−**e**, **21**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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