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One-Pot Synthesis of Chromenylfurandicarboxylates and Cyclopenta[*b*]chromenedicarboxylates Involving Zwitterionic Intermediates. A DFT Investigation on the Regioselectivity of the Reaction

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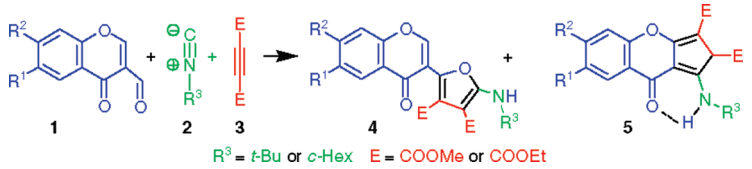

The reaction of 1:1 zwitterionic intermediates generated *in situ* from either *tert*-butylisocyanide or cyclohexylisocyanide and acetylenedicarboxylates with 3-formylchromones is described, whereupon either chromenylfurandicarboxylates or cyclopenta[*b*]chromenedicarboxylates are formed, depending on the nature of the chromone 6-position substituent and also on the acetylene ester group. In addition, from the reaction with a 1:2 zwitterionic intermediate, cyclohepta[*b*]chromenetetracarboxylates are isolated. The regioselectivity of the reaction was also investigated by DFT calculations. The geometries of the reactants, intermediate zwitterions, transition structures, and intermediate products, leading to the final products, were optimized using the B3LYP functional with the 6-31G(d) basis set. The structures of the products were elucidated by 1D and 2D NMR experiments. Full assignment of all ^{1}H and ^{13}C NMR chemical shifts has been achieved. Plausible mechanistic schemes are provided.

Introduction

In addition to forming the basic nucleus of an entire class of natural products, i.e., flavones,[1] the chromone moiety forms the important component of pharmacophores of a large number of molecules of medicinal significance.[2] Consequently, considerable attention is being devoted to isolation from natural resources, chemistry and synthesis of chromone derivatives, and evaluation of their biological activity with emphasis on their potential medicinal applications.[2−4] 3-Formylchromone has been extensively used in the formation of various heterocyclic systems. Since its convenient synthesis was reported in the 1970s, the synthesis and reactivity of this versatile compound has been the subject of numerous reviews.[5−8] 3-Formylchromone represents a very reactive system due to the presence of an unsaturated keto function, a conjugated second carbonyl group at C-3, and above all an electrophilic center at C-2, which is very reactive toward Michael addition often with opening of the γ-pyrone ring followed by a new cyclization.

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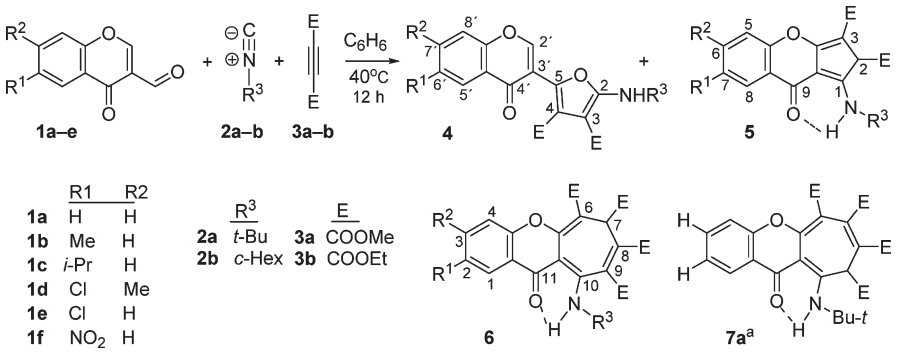
SCHEME 1. Reaction of 3-Formylchromones with Isocyanides and Acetylenedicarboxylates



[a]Compound **7a** was isolated by using only 5 mL of solvent.

TABLE 1. Reaction Products Obtained from Chromones 1, Isocyanides 2, and Acetylenedicarboxylates 3

entry	1	R^1	R^2	2	R^3	3	E	prod.	temp (°C)	4 (%)	5 (%)	6 (%)
1	**1a**	H	H	**2a**	*t*-Bu	**3a**	CO_2Me	**a**	40	42		12
2[a]	**1a**	H	H	**2a**	*t*-Bu	**3a**	CO_2Me	**a**	40	6		51
3	**1b**	Me	H	**2a**	*t*-Bu	**3a**	CO_2Me	**b**	40	28		
									55	35		
4	**1c**	*i*-Pr	H	**2a**	*t*-Bu	**3a**	CO_2Me	**c**	40	45		
5	**1d**	Cl	Me	**2a**	*t*-Bu	**3a**	CO_2Me	**d**	40	16	31	7
6	**1e**	Cl	H	**2a**	*t*-Bu	**3a**	CO_2Me	**e**	40		52	
7	**1f**	NO_2	H	**2a**	*t*-Bu	**3a**	CO_2Me	**f**	40	4	38	
									55	9	43	
8	**1a**	H	H	**2b**	*c*-Hex	**3a**	CO_2Me	**g**	40	27	44	
9	**1c**	*i*-Pr	H	**2a**	*c*-Hex	**3a**	CO_2Me	**h**	40	48		
10	**1e**	Cl	H	**2b**	*c*-Hex	**3a**	CO_2Me	**i**	40	3	48	
									55		46	
11	**1a**	H	H	**2a**	*t*-Bu	**3b**	CO_2Et	**j**	40		48	
12	**1c**	*i*-Pr	H	**2a**	*t*-Bu	**3b**	CO_2Et	**k**	40		38	
									55		32	
13	**1e**	Cl	H	**2a**	*t*-Bu	**3b**	CO_2Et	**l**	40		60	
14	**1a**	H	H	**2b**	*c*-Hex	**3b**	CO_2Et	**m**	55		48	
15	**1e**	Cl	H	**2b**	*c*-Hex	**3b**	CO_2Et	**n**	40		47	

[a]When the reaction was performed with 5 mL of solvent, **7a** was also obtained in 5% yield.

Thereupon, compounds **1** can be readily converted into a broad range of heterocyclic systems, either by cycloaddition strategies[9,10] or through reaction with several nucleophiles[11,12] and particularly bis-nucleophiles.[13]

On the other hand, the rich and fascinating chemistry that stems from multicomponent reactions (MCRs) provides[14] a powerful tool toward the one-pot synthesis of diverse and complex "drug-like" heterocyclic compounds. A number of advantages make MCRs very popular in the community of combinatorial chemists: superior atom economy, simple procedures, the one-pot character, and the high and even increasing number of accessible backbones. MCRs that involve isocyanides are among the more versatile reactions[15] in terms of scaffolds and number of accessible compounds.

Against the literature background given above and in the context of our ongoing studies on heterocyclic construction involving chromone derivatives,[16] we were intrigued by the possibility of trapping the zwitterionic intermediates, derived from acetylenedicarboxylates and isocyanides, with chromones and formation of novel heterocyclic systems containing an intact chromone moiety.

Results and Discussion

Our initial experiments were focused on the reaction of *tert*-butylisocyanide and DMAD with 3-formylchromone.

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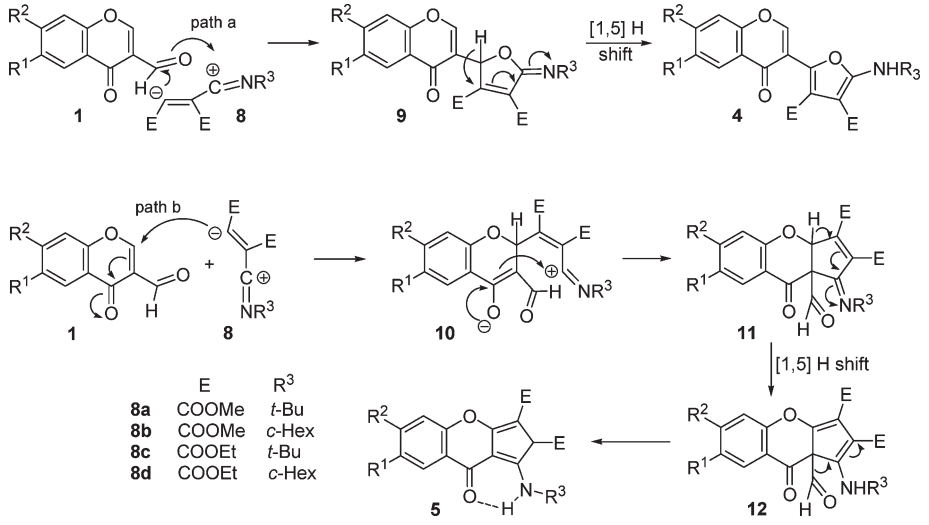
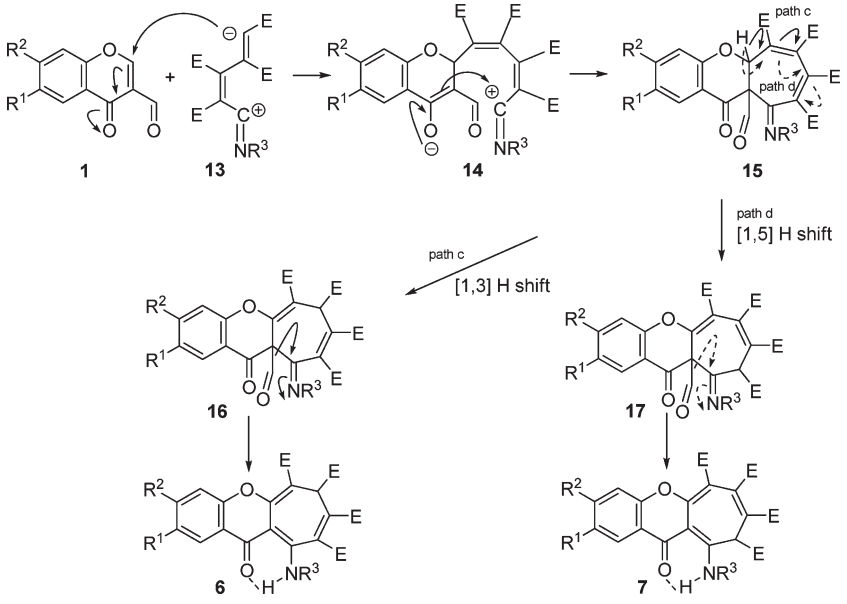
SCHEME 2. Mechanistic Rationalization for the Formation of Chromone Derivatives 4 and 5



SCHEME 3. Mechanistic Rationalization for the Formation of Compounds 6 and 7



Indeed, upon treatment of 3-formylchromone with DMAD in the presence of *tert*-butylisocyanide, in a 1:1.2:1.2 molar ratio, in 20 mL of benzene at 40 °C, the chromenylfurandicarboxylate **4a** was isolated as the main reaction product (42% yield) along with a minor product (12% yield) containing two molecules of DMAD, which was characterized as the cycloheptachromenetetracarboxylate **6a** (Scheme 1). By using only 5 mL of solvent but the same molar ratio, the yield of **6a** increased to 51% at the expense of **4a**, which was isolated only in 6% yield. In this case, compound **7a**, isomeric to **6a**, was also formed in 5% yield (Scheme 1 and Table 1). The use of a 2 molar ratio of DMAD did not promote the reaction, which became unclear and complicated, most probably as a result of extended polymerization of DMAD and formation of many minor products. The 6-methyl- and the 6-isopropyl-substituted chromones **1b** and **1c** reacted analogously, and the corresponding chromenylfurandicarboxylates **4b** and **4c** were isolated in 28% and 45% yield, respectively. Quite remarkably, in the case of electron-deficient chromones **1e** and **1f** the reaction followed a different pathway leading to the formation of the fused cyclopentachromenedicarboxylates **5e** (52% yield) and **5f** (38% yield). Finally, from the reaction of 6-chloro-7-methyl-chromone **1d**, containing both an electron-withdrawing and an electron-donating substituent, the chromenylfurandicarboxylate **4d** (16% yield) as well as the cyclopentachromenedicarboxylate **5d** (31%) along with cycloheptachromenetetracarboxylate **6d** (7%) were isolated. Analogous results were obtained by using cyclohexylisocyanide (Table 1, entries 8−10), whereupon it was confirmed that electron-donating substituents in the 6-position of the chromone moiety favor reaction with the aldehyde carbonyl, leading to chromenylfurandicarboxylates **4** (entry 9). Unexpectedly, by changing the ester from DMAD to diethyl acetylenedicarboxylate (**2b**), in all cases the cyclopentachromenedicarboxylates **5** were preferentially formed (Table 1, entries 11−15). Finally, a change in the reaction

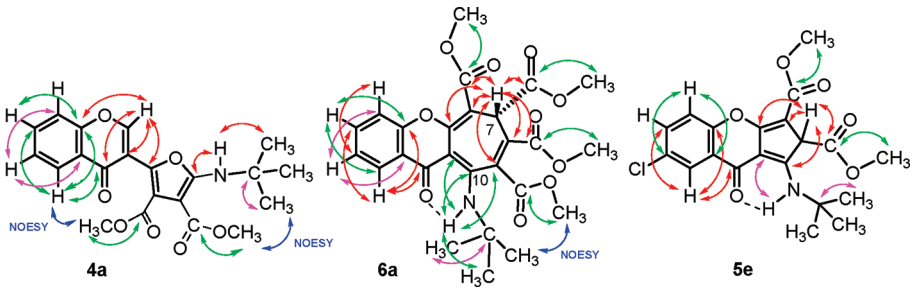


FIGURE 1. COLOC correlations between protons and carbons (via $^{2}J_{C-H}$ and $^{3}J_{C-H}$) in compounds **4a**, **6a**, and **5e**. Some NOESY correlations are also indicated.

TABLE 2. Selected Geometrical Parameters and Thermochemical Data of Reactant Complexes, Transition States, and Intermediates for the Reaction of 1a + 8a

	1a + 8a[a]	TS4a	9a		TS5a	11a
$\Delta\Delta E^{b}$	0	3.26[c]	−59.94[d]		3.41[c]	−41.59[d]
C1−C2[e]	1.361	1.353	1.351	C1−C2	1.396	1.561
C3−O4	1.220	1.249	1.453	C3−O4	1.228	1.210
C5−C6	1.360	1.359	1.343	C5−C6	1.357	1.342
C6−C7	1.419	1.424	1.477	C6−C7	1.422	1.484
C3−C5		2.238	1.513	C1−C5	2.293	1.512
O4−C7		2.677	1.380	C2−C7	3.299	1.598
C7−N	1.161	1.158	1.223	C7−N	1.158	1.262
C6−C7−N[f]	176.5	174.6	124.0	C6−C7−N	177.7	117.9
O4−C3−C5−C7[g]		2.2	0.4	C2−C1−C5−C7	2.5	−11.8
C5−C6−C7−N		−158.4	179.6	C5−C6−C7−N	−143.0	171.6
ν^{h}		−101.5		ν	−140.3	

[a] **1a** + **8a** E_{total} = −1933.702358 au. [b] Relative energy (kcal/mol). [c] Activation energy $\Delta G^{\ddagger}$. [d] Energy of the reaction $\Delta G°$. [e] Bond length or interatomic distance (Å). [f] Bond angle (deg). [g] Bond torsional angle (deg). [h] Imaginary frequency (cm^{-1}). For atom numbering see Figure 2.

temperature from 40 to 55 °C did not seem to have a substantial effect on the reaction outcome.

Mechanistically, for the formation of the chromenylfurandicarboxylates **4** (Scheme 2, path a), it is conceivable that the zwitterionic intermediate **8**, initially formed by the 1:1 interaction between the isocyanide and acetylenedicarboxylate, adds to the aldehyde carbonyl leading to a dipolar species. Cyclization of the latter leads to the 2-imino-furan-derivative **9**, from which subsequently, after [1,5] hydride shift, the chromenylfurandicarboxylates **4** are formed as the end products.

However, electron-withdrawing substituents in the 6-postion of the chromone moiety probably render the C-2 carbon more electron-deficient than the aldehyde carbon and the 1:1 zwitterionic intermediate **8** attacks, instead of the aldehyde carbonyl carbon, preferentially the C-2 chromone carbon (Scheme 2, path b) leading to intermediate **10**, which upon ring closure gives **11**. By [1,5] hydride shift **11** is transformed to **12**, which most probably during the workup procedure is deformylated to give the isolated product **5**. DFT calculations for the conversion of **11** to **12** and subsequently to **5** showed that this conversion is predicted to be energy favored for **11e** to **12e** by 6.37 kcal/mol and for the formyl abstraction to the final product **5e** by 34.65 kcal/mol (see Table 7 in Computational Analysis).

When the concentration of the reacting species is increased, the isocyanide adds to two molecules of DMAD in tandem, to furnish the zwitterionic intermediate **13** (Scheme 3). This intermediate attacks the C-2 chromone carbon, to afford **14**. Ring closure leading to **15**, followed by [1,3] hydride shift to **16** (path c), and finally loss of the formyl group gives the end products **6**. In an analogous manner the second cycloheptachromenetetracarboxylate **7a** can be formed by the less favored [1,5] hydride shift (Scheme 3, dashed arrows, path d).

The structural characterization of the products **4**−**7** was based on rigorous spectroscopic analysis including IR, NMR (^{1}H, ^{13}C, COSY, NOESY, HETCOR, and COLOC), mass spectra, and elemental analysis data.

In Figure 1 the COLOC correlations between protons and carbons via $^{2}J_{C-H}$ and $^{3}J_{C-H}$ in compounds **4a**, **6a**, and **5e** are depicted. Some NOESY correlations are also indicated. The NOESY correlations in **4a** between the *tert*-butyl protons and the methoxy protons at δ 3.77 and of the methoxy protons at δ 3.92 with the 5′-H reveal their proximity. For detailed structure assignment see Supporting Information.

Computational Analysis

Because some of the experimental results presented in Table 1 were unpredictable, a theoretical investigation for the formation of products **4** or **5** was undertaken. The reactions of the unsubstituted chromone **1a** and of the 6-chloro derivative **1e** with the four zwitterions **8a**−**8d** resulting from all possible combinations between acetylenedicarboxylates with the two isocyanides (Scheme 2) were investigated.

Reactants, transition states, and products were built by ChemDraw (ChemDraw7) and subsequently optimized by density functional theory (DFT) using the B3LYP level with the 6-31G(d) basis set as implemented in the Gaussian 03 W

TABLE 3. Selected B3LYP/6-31G* Thermochemical Data and Geometrical Parameters of Transition States TS4 and TS5

1 + 8	TS4	E_{total}[a]	C3−C5[b]	O4−C7[b]	ν[c]	TS5	E_{total}[a]	C1−C5	C2−C7	ν[c]
1a + 8a	**a**	−1393.697163	2.238	2.677	−150.14	**a**	−1393.696925	2.293	3.299	−140.34
1e + 8a	**e**	−1853.301485	2.241	2.698	−149.49	**e**	−1853.301996	2.332	3.347	−122.50
1a + 8b	**g**	−1471.075641	2.238	2.771	−166.00	**g**	−1471.081029	2.283	3.267	−138.80
1e + 8b	**i**	−1930.682380	2.205	2.659	−156.72	**i**	−1930.684326	2.281	3.395	−135.18
1a + 8c	**j**	−1472.278817	2.238	2.701	−143.03	**j**	−1472.278881	2.311	3.308	−132.20
1e + 8c	**l**	−1931.882987	2.245	2.719	−135.30	**l**	−1931.883628	2.344	3.359	−117.00
1a + 8d	**m**	−1549.659210	2.241	2.631	−157.30	**m**	−1549.662606	2.297	3.277	−132.92
1e + 8d	**n**	−2009.263694	2.255	2.665	−141.45	**n**	−2009.267624	2.333	3.290	−117.33

[a]Sum of electronic and zero-point energies (au). [b]Interatomic distance (Å). For atom numbering see Figure 2. [c]Imaginary frequency (cm^{-1}).

TABLE 4. Selected B3LYP/6-31G* Thermochemical Data of Transition States TS4 and TS5 and of Intermediates 9 and 11

reactants	TS4	TS5	$\Delta\Delta G^{*a}$	$\Delta\Delta G^{*b}$	9[c]	11[c]	$\Delta\Delta G^{\circ d}$
1a + 8a	**4a**	**5a**	−0.15	−0.57	−1393.797884	−1393.768640	−18.35
1e + 8a	**4e**	**5e**	0.32	0.35	−1853.399200	−1853.370030	−18.30
1a + 8b	**4g**	**5g**	3.38	2.39	−1471.181977	−1471.164930	−10.70
1e + 8b	**4i**	**5i**	1.22	0.44	−1930.785178	−1930.766898	−11.47
1a + 8c	**4j**	**5j**	0.04	0.56	−1472.377096	−1472.349751	−17.16
1e + 8c	**4l**	**5l**	0.40	0.47	−1931.981458	−1931.951303	−18.92
1a + 8d	**4m**	**5m**	2.16	0.91	−1549.763304	−1549.745499	−11.17
1e + 8d	**4n**	**5n**	2.47	1.02	−2009.367274	−2009.348208	−11.96

[a]Relative activation energy $\Delta\Delta G^*$ (kcal/mol); $\Delta\Delta G^* = \Delta G^*_{\mathbf{TS4}} - \Delta G^*_{\mathbf{TS5}}$. Positive value means **TS5** is favored over **TS4**. As in Table 3, zero-point energy corrections are included. [b]Relative activation energy $\Delta\Delta G^*$ calculated using the PCM model. The calculated total energies without zero-point energy corrections are −1394.095211 au and −1394.094295 au for **4a** and **5a**, respectively. [c]Sum of electronic and zero-point energies (au). [d]Relative free energy of the reaction $\Delta\Delta G^\circ = \Delta G^\circ_{\mathbf{9}} - \Delta G^\circ_{\mathbf{11}}$ (kcal/mol). Negative value means **9** is more stable than **11**.

package.[17] The corresponding transition states of the reactions were located in three steps. In the first step the structures of the reactants formylchromones **1**, the zwitterionic intermediates **8** and the intermediates **9** and **11** were optimized at the above level of theory. In the second step the **TS**s were found using the Synchronous Transit-Guided Quasi-Newton (STQN) method (QST3 approach),[18] whereas the resulted structures were used as input to recalculate the force constants and locate the final transition structures. Subsequent frequency calculations were carried out to verify that the **TS**s have only one imaginary frequency. Since nonpolar solvent (benzene) was used, gas-phase transition structures were located and optimized for both reaction paths a and b (Scheme 2), and the results are summarized in Tables 2, 3, and 4. The atom numbering shown in Figure 2 is arbitrary for simplicity reasons and is used throughout this section.

In Table 2 some selected geometrical parameters as well as thermochemical data for the transition structures **TS4a** and **TS5a** depicted in Figure 2 are presented, whereas in Table 3 the total energies, as sum of electronic and zero-point energies, as well as the new forming bond lengths and the imaginary frequencies of all **TS**s studied, are given. The activation energy of the reaction is computed to be relatively low, 3.26 and 3.41 kcal/mol for **TS4a** and **TS5a**, respectively (Figure 2 and Table 4), in agreement with the mild temperature (~40 C°) used. Even this small calculated energy difference ($\Delta\Delta G^* = 0.15$ kcal/mol) seems to be enough to differentiate the products favoring intermediate **9a**, leading finally to **4a**. In the rest of the transition states presented in Table 4, **TS5**s are predicted to be favored over **TS4**s by a small energy difference varying from 0.04 to 3.38 kcal/mol, leading thus to final products **5** in agreement with the experimental results. Even when the solvent effect of benzene was evaluated using the Polarizable Continuum Model (PCM),[19] these energy differences remained small, varying from 0.44 to 2.39 kcal/mol. As a result, experimentally, in the case of reaction of **1a** with **8b** both products **4g** and **5g** are isolated in substantial yields, 27% and 44%, respectively.

Considering the relative Free Energy of the reaction $\Delta\Delta G^\circ$, which actually shows the relative stability of intermediates **9** and **11**, the calculations predict **9** to be favored over **11**. The large energy barrier depicted in Figure 2 for both hypothetically reversible reactions probably does not permit thermal equilibration of the products on the basis of their stabilization ranking.

To understand the role of the substituents in position 6 of the chromone ring, and because the experimental results in Table 1 show the trend that electron-withdrawing groups favor products **5**, the electronic charges of the reacting atoms C1, C2, C3, and O4 of formylchromones **1a**, **1b**, **1e**, and **1f** were examined. The Natural Orbital calculations were carried out on the optimized structures, and the Mulliken atomic charges are presented in Table 5, where hydrogen charges were summed up into C1 and C3 atomic charges. It is noticeable that going from a methyl to a nitro substituent a

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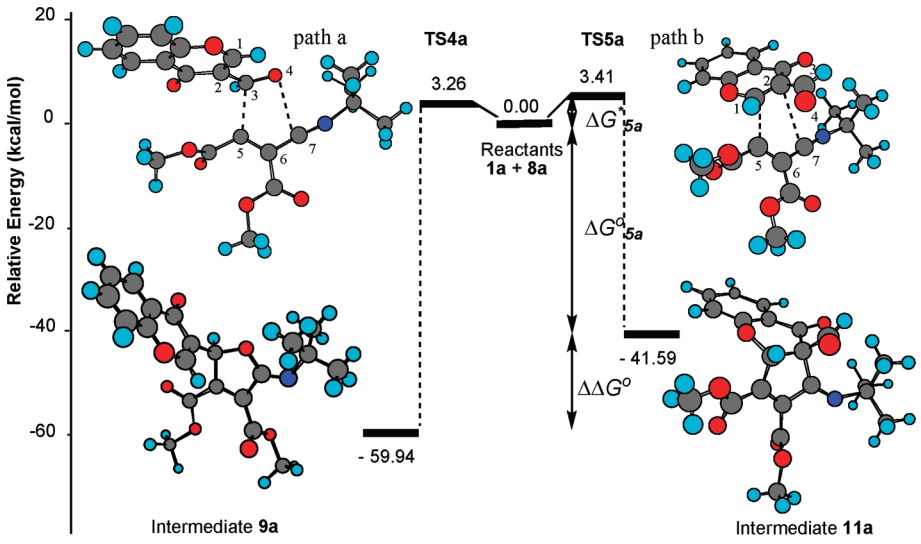

FIGURE 2. Energy profiles for the formation of intermediates **9a** and **11a** through the **TS4a** and **TS5a** leading finally to the products **4a** and **5a**, respectively. The atom numbering is arbitrary for simplicity reasons.

TABLE 5. Electronic Charges[a] and Relative Change[b] in Electronic Charges Δq on Atoms Involved in Transition States TS4 and TS5 in some 6-Substituted Formylchromones

	substituent			
atom	Me	H	Cl	NO_2
		Atomic Charge		
C1	0.2996[b]	0.3011	0.3053	0.3092
C2	−0.0394	−0.0381	−0.0389	−0.0366
C3	0.3557[b]	0.3570	0.3615	0.3686
O4	−0.4206	−0.4191	−0.4157	−0.4102
		Relative Atomic Charge		
C1	0.0	0.0015[c]	0.0057	0.0096
C2	0.0	0.0013	0.0005	0.0028
C3	0.0	0.0013	0.0058	0.0129
O4	0.0	0.0015	0.0049	0.0104

[a]Calculated by B3LYP/6-31G(d). [b]Hydrogen charge summed up with carbon's charge. [c]$\Delta q_{(X)} = q_{(X)} - q_{(Me)}$

TABLE 6. Atomic Charges[a] and Relative Change[b] in Atomic Charges Δq on Atoms Involved in Transition States TS4 and TS5 in the Zwitterions 8a-8d

	substituent			
atom	**8a**	**8b**	**8c**	**8d**
		Atomic Charge		
C5	−0.1252	−0.1228	−0.1296	−0.1265
C7	0.4810	0.4684	0.4809	0.4674
		Relative Atomic Charge		
C5	−0.0024[b]	−0.00	0.0068	−0.0037
C7	0.0136[c]	0.0010	0.0135	0.00

[a]Calculated by B3LYP/6-31G(d) (in electrons). [b]$\Delta q_{(X)} = q_{(X)} - q_{(\mathbf{8b})}$. [c]$\Delta q_{(X)} = q_{(X)} - q_{(\mathbf{8d})}$.

TABLE 7. B3LYP/6-31G(d) Thermochemical Data for Intermediates Leading to Products 5

R^1	**11**[a]	**12**[a]	**5**[a]	$\Delta E^b_{12,11}$	$\Delta E_{5,12}$
H	−1393.768640	−1393.777297	−1280.507641	5.43	33.89
Cl	−1853.370030	−1853.380186	−1740.111746	6.37	34.65

[a]Sum of electronic and zero-point energies (au). [b]Energy differences $\Delta E_{12,11} = E_{12} - E_{11}$ and $\Delta E_{5,12} = (E_5 + E_{HCOOH}) - (E_{12} + E_{H_2O})$ are given in kcal/mol. For water and formic acid the following energy values were calculated and used: $E_{H_2O} = -76.399551$ au, $E_{HCOOH} = -189.723208$ au.

relative increase in positive electron charge Δq on all atoms is observed. Looking particularly on the variation of charge on atoms C1 and O4, a significant increase is observed, which in combination with the relative activation energies in the transition states ($\Delta\Delta G^*$ in Table 4) governs the reaction pathway. An analogous calculation of C5 and C7 atomic charges for zwitterions **8a**−**8d** was carried out, and the results are given in Table 6. The net charge on C5 in ethyl derivatives **8c** and **8d** is significantly higher than the corresponding charge in **8b** and relatively higher than that in **8a**. These charge differences either on formylchromones **1** or on zwitterions **8** seem to play a critical role for the stabilization of the transition states, governing thus the formation of the final products **4** or **5** in agreement with the experimental results.

Finally, for steric reasons the addition at the formyl carbonyl is expected to be more favored. However, the approach seems to be more complicated, as shown by the experimental results. Generally, in all transition structures the approaching atoms are almost coplanar and the isocyanide moiety in the zwitterion **8** is almost linear, as indicated by the value of ∼177° for the C6−C7−N bond angle. The bigger distance for C2−C7 in **TS5a** (Figure 2) compared to the corresponding distance O4−C7 in **TS4a** can be attributed to stereochemical interactions of *tert*-butyl group with the formyl group, which interactions are smaller in **TS5a**. For reaction path a an asynchronous approach is predicted, since in **TS4a** the newly formed bonds C3−C5 and O4−C7 differ significantly in their interatomic distances, the approaching beginning first between atoms C3−C5 affording then intermediate **9a**. An analogous approach is predicted in path b for the formation of bonds C1−C5 and C2−C7 leading to intermediate **11**.

In Table 7 the DFT computational results for the conversion of **11** to **12** and then by deformylation to products **5** are presented. The energy difference $\Delta E_{12,11} = E_{12} - E_{11}$ is estimated to be equal to 5.43 kcal/mol for the unsubstituted chromone **1a** and to 6.37 kcal/mol for the 6-chloro-chromone

1e, and this amount of energy seems to be enough for the spontaneous hydrogen shift. The action of water on intermediates **12** during the workup procedure leads to formation of products **5**, most probably by formic acid abstraction, which are estimated to have an energy profit for the unsubstituted chromone of 33.89 kcal/mol and for the chloro-substituted chromone of 34.65 kcal/mol. This amount of energy justifies the spontaneous conversion of **12** to the isolated products **5**, in accordance to experimental results.

Optimized geometries (in Cartesian coordinates) for all zwitterions **8a**−**8d**, transition structures **4a**−**4n** and **5a**−**5n**, intermediates **9a**−**9n**, **11a**−**11n**, **12a**, and **12e**, and products **5a**, **5e** are provided in Supporting Information.

Conclusions

The present work demonstrates the versatility of chromones in bringing about one-pot synthetic procedures, the outcome of the reaction depending on both the nature of the chromone substituents and the ester group in acetylenedicarboxylates. Thus, DMAD and electron-donating substituents in the chromone moiety favor reaction with the aldehyde carbonyl, leading to chromenylfurandicarboxylates **4**, whereas electron-withdrawing substituents favor reaction from the C2=C3 double bond, leading to cyclopentachromenedicarboxylates **5**. By changing the dimethyl acetylenedicarboxylate to diethyl acetylenedicarboxylate, the cyclopentachromenedicarboxylates **5** were preferentially formed in all cases. Theoretical DFT calculations that have been carried out for the first time on chromone moieties support the experimental results.

In all studied reactions our initial goal, namely, the isolation of products with an intact chromone moiety, was achieved. In addition, to our knowledge, the isolation of chromenylfurandicarboxylates **4** constitutes one of very few examples of a preferential attack to the formyl carbonyl over the C-2 carbon of a nonactivated chromone leading to formation of chromenyl heterocycles.[20] To the contrary, TMSCl-activated chromones have been found to be more susceptible to nucleophilic attack to this carbon[21] leading to formation either of quinoline or of pyridobenzimidazole derivatives. Highly functionalized 2-aminofuran derivatives are isolated from the reaction of various carbonyl compounds with isocyanides and acetylenedicarboxylates.[22] Moreover, the few chromenylfurans reported in the literature show substantial biological activity.[23] Concerning the formation of cyclopentachromenedicarboxylates **5**, the isolation of some natural cyclopentanobenzopyran-4-ones (coniochaetones, wrightiadione, coniothyrione), which have been ascribed antifungal and other medicinal properties[24] and syntheses of which involve multistep processes,[25] have been reported. In addition, although the synthesis of some cyclopentenobenzopyranones is known,[26] no reference has been made of a cyclopentadiene ring fused to a chromone moiety. Finally, the formation of **6** and eventually **7** represent the first examples of a seven-membered ring formed by an attack of a 1:2 zwitterionic intermediate to a C=C double bond.

Experimental Section

General Procedure. Reaction of 3-Formylchromones (1) with Isocyanides (2) and Acetylenedicarboxylates (3) in 20 mL of Solvent. To a stirred thermostated at 40 °C solution of 3-formylchromone (1.0 mmol) and acetylenedicarboxylate (1.2 mmol) in benzene (20 mL) was added isocyanide (1.2 mmol) via a syringe, and the reaction mixture was stirred at 40 °C until chromone was consumed completely (followed by TLC, approximately 12 h). On completion of the reaction, the solvent was removed under reduced pressure, and the residue was subjected to chromatography (silica gel 60, Fluka) using petroleum ether−AcOEt 7:1 as eluent, slowly increasing the polarity up to 4:1 to give in elution order compounds **4**, and/or **6** and/or **5** (see Table 1).

Data for Dimethyl 2-(*tert*-Butylamino)-5-(4-oxo-4*H*-chromen-3-yl)furan-3,4-dicarboxylate (4a). Pale yellow crystals; mp 146−147 °C (CH_2Cl_2−petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 3.77 (s, 3H, 3-OCH_3), 3.92 (s, 3H, 4-OCH_3), 6.92 (br s, 1H, NH), 7.37 (ddd, J = 8.0, J = 7.1, J = 1.0 Hz, 6′-H), 7.45 (ddd, J = 8.5, J = 1.0, J = 0.3 Hz, 1H, 8′-H), 7.67 (ddd, J = 8.5, J = 7.1, J = 1.75 Hz, 1H, 7′-H), 8.23 (s, 1H, 2′-H), 8.27 (ddd, J = 8.0, J = 1.75, J = 0.3 Hz, 1H, 5′-H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 29.9 ($C(CH_3)_3$), 51.2 (3-OCH_3), 52.4 (4-OCH_3), 52.8 ($C(CH_3)_3$), 88.3 (C-3), 115.8 (C-3′), 117.6 (C-4), 118.1 (C-8′), 123.8 (C-4a′), 125.5 (C-6′), 126.5 (C-5′), 133.6 (C-5), 133.8 (C-7′), 152.9 (C-2′), 155.8 (C-8a′), 161.7 (C-2), 165.11 (3-C=O), 165.14 (4-C=O), 173.7 (C-4′). IR (KBr) ν 3444, 1727, 1670 cm^{-1}. LC-MS (ESI) m/z (%) 422 (M^+ + Na, 100), 400 (M^+ + H, 50), 368 (15). Anal. Calcd for $C_{21}H_{21}NO_7$ (399.39): C, 63.15; H, 5.30; N, 3.51. Found: C, 63.46; H, 5.40; N 3.42.

Data for Tetramethyl 10-(*tert*-Butylamino)-11-oxo-7,11-dihydrocyclohepta[*b*]chromene-6,7,8,9-tetracarboxylate (6a). Yellow crystals; mp 185−188 °C (CH_2Cl_2−petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H, $C(CH_3)_3$), 3.56 (s, 3H, 7-OCH_3), 3.71 (s, 3H, 9-OCH_3), 3.84 (s, 3H, 6-OCH_3 or 8-OCH_3), 3.86 (s, 3H, 6-OCH_3 or 8-OCH_3), 5.10 (s, 1H, 7-H), 7.21 (ddd, J = 7.9, J = 7.1, J = 1.0 Hz, 2-H), 7.25 (ddd, J = 8.4, J = 1.0, J = 0.4 Hz, 1H, 4-H), 7.56 (ddd, J = 8.4, J = 7.1, J = 1.7 Hz, 1H, 3-H), 8.04 (ddd, J = 7.9, J = 1.7, J = 0.4 Hz, 1H, 1-H), 13.20 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.5 ($C(CH_3)_3$), 44.6 (C-7), 52.0 (6-OCH_3 or 8-OCH_3), 52.7 (9-OCH_3), 52.8 (7-OCH_3), 53.0 (6-OCH_3 or 8-OCH_3), 57.8 ($C(CH_3)_3$), 100.7 (C-10a), 101.2 (C-6), 116.9 (C-4), 120.5 (C-11a), 121.1 (C-9), 123.2 (C-2), 125.8 (C-1), 134.5

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(C-3), 141.8 (C-8), 154.7 (C-4a), 157.9 (C-10), 158.6 (C-5a), 164.4 (9-C=O), 165.6, 166.2 (6-C=O and 8-C=O), 170.2 (7-C=O), 179.7 (C-11). IR (KBr) ν 3447, 1732, 1667, 1628 cm^{-1}. LC-MS (ESI) m/z (%) 514 (M^+ + H, 100), 482 (14). Anal. Calcd for $C_{26}H_{27}NO_{10}$ (513.49): C, 60.81; H, 5.30; N, 2.73. Found: C, 60.66; H, 5.40; N 2.83.

Under the same reaction conditions of 6-chloro-3-formylchromone (**1e**) with DMAD and *tert*-butylisocyanide the cyclopentachromene derivative **5e** was isolated in 52% yield.

Data for Dimethyl 1-(*tert*-Butylamino)-7-chloro-9-oxo-2,9-dihydrocyclopenta[*b*]chromene-2,3-dicarboxylate (5e). Yellow crystals, mp 208−210 °C (CH_2Cl_2−petroleum ether). ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H, C(CH_3)$_3$), 3.74 (s, 3H, 2-OCH_3), 3.78 (s, 3H, 3-OCH_3), 4.67 (d, J = 1.6 Hz, 1H, 2-H) (coupled with the 1-NH proton), 7.31 (d, J = 8.8 Hz, 1H, 5-H), 7.49 (dd, J = 8.8, J = 2.7 Hz, 1H, 6-H), 7.94 (d, J = 2.7 Hz, 1H, 8-H), 10.27 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4 (C(CH_3)$_3$), 50.9 (3-OCH_3), 51.4 (C-2), 53.1 (2-OCH_3), 56.2 (C(CH_3)$_3$), 89.3 (C-3), 104.6 (C-9a), 119.4 (C-5), 123.1 (C-8a), 124.9 (C-8), 130.1 (C-7), 134.0 (C-6), 154.9 (C-4a), 163.0 (3-C=O), 164.2 (C-1), 167.2 (C-3a), 168.5 (2-C=O), 173.7 (C-9). IR (KBr) ν 3446, 1726, 1672, 1638 cm^{-1}. LC-MS (ESI) m/z (%) 438/440 (M^+ + Na, 100). Anal. Calcd for $C_{20}H_{20}ClNO_6$ (405.82): C, 59.19; H, 4.97; N, 3.45. Found: C, 59.26; H, 5.05; N 3.34.

Reaction of Formylchromone 1a with DMAD and *tert*-Butylisocyanide in 5 mL of Solvent. The same procedure described above as General Procedure was followed by using only 5 mL benzene. The chromatography of the residue on silica gel gave **4a** (6%), **6a** (51%) and **7a** (5%).

Data for Tetramethyl 10-(*tert*-Butylamino)-11-oxo-9,11-dihydrocyclohepta[*b*]chromene-6,7,8,9-tetracarboxylate (7a). Yield 5%; yellow crystals; mp 174−176 °C (CH_2Cl_2−petroleum ether). ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H, C(CH_3)$_3$), 3.65 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.02 (s, 1H, 9-H), 7.45 (ddd, J = 8.2, J = 7.3, J = 1.0 Hz, 2-H), 7.46 (dd, J = 8.3, J = 1.0 Hz, 1H, 4-H), 7.70 (ddd, J = 8.3, J = 7.3, J = 1.7 Hz, 1H, 3-H), 8.23 (dd, J = 8.2, J = 1.7 Hz, 1H, 1-H), 10.49 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8 (C(CH_3)$_3$), 50.6 (C-9), 51.3 (OCH_3), 52.2 (9-OCH_3), 52.6 (OCH_3), 52.8 (OCH_3), 57.8 (C(CH_3)$_3$), 96.1 (C-6), 114.4 (C-10a), 117.9 (C-4), 122.8 (C-11a), 123.5 (C-7), 126.0 (C-2), 126.7 (C-1), 134.1 (C-3), 140.1 (C-8), 154.0 (C-4a), 155.0 (C-10), 161.9 (C-5a), 166.2 (C=O), 167.8 (C=O), 168.2 (C=O), 169.5 (C=O), 174.9 (C-11). IR (KBr) ν 3447, 1752, 1736, 1722, 1654 cm^{-1}. LC-MS (ESI) m/z (%) 514 (M^+ +H, 100), 482 (5), 458 (28). Anal. Calcd for $C_{26}H_{27}NO_{10}$ (513.49): C, 60.81; H, 5.30; N, 2.73. Found: C, 60.92; H, 5.26; N 2.82.

Supporting Information Available: Experimental procedures. Analytical and spectral characterization data. Cartesian coordinates of zwitterions **8a**−**8d**; intermediates **9a**−**9n**, **11a**−**11n**, **12a**, and **12e**; transition structures **4a**−**4n** and **5a**−**5n**; and products **5a** and **5e**. ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.