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Tetrahydroquinazoline-substituted chromones from Diels–Alder reaction of (*E*)-2-styrylchromones and pyrimidine *ortho*-quinodimethane

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ABSTRACT

The Diels–Alder reaction of (*E*)-2-styrylchromones with a pyrimidine *ortho*-quinodimethane is reported for the first time. These cycloaddition reactions afford mixtures of two regioisomeric tetrahydroquinazoline-substituted chromones in moderate to excellent global yields. Irrespective of the substituents on the 2-styrylchromones, the 2-(7-aryl-4-methoxy-2-methyl-5,6,7,8-tetrahydroquinazolin-6-yl)chromone derivatives are always the major isomers.

2-Styrylchromones are a small group of naturally-occurring heterocyclic compounds. Since the isolation of the first natural 2-styrylchromone in 1986,[1] that showed to be a potent cytotoxic agent, a large number of publications have emerged involving the synthesis and transformation of this type of chromone derivatives.[2,3] A literature survey revealed that 2-styrylchromones have been typically prepared from *ortho*-hydroxyacetophenones where the aldol condensation/oxidative cyclization and the Baker–Venkataraman methods are the most promising approaches for the synthesis of a large variety of derivatives. As a result, a series of styrylchromone analogues were synthesized and several biological properties have been assigned to them, including anti-allergic, antioxidant, antifungal, anti-inflammatory, and antitumor activities.[3,4]

Besides the synthesis, studies on the reactivity of 2-styryl chromones and their use as synthons in the preparation of other important classes of compounds have been highlighted in the literature.[3] Most important is their reaction with hydrazines to afford several pyrazole derivatives[5,6] and also their interception in pericyclic reactions as dienes, dienophiles, and also as dipolarophiles. In the former case, the synthesis of several xanthone-type compounds was performed by cycloaddition reaction with maleic anhydride, *N*-arylmaleimides, and cyclic and acyclic enamines.[7–11] The reactions of these vinylchromones with diazomethane[12] and sodium azide[13,14] are the examples of their use as dipolarophiles to prepare 2-pyrazolines and 1,2,3-triazoles, respectively. To the best of our knowledge, the use of 2-styrylchromones as dienophiles in Diels–Alder reactions has only been reported by us in a couple of papers involving the symmetric *ortho*-benzoquinodimethane.[15,16] This extremely reactive diene was used in the synthesis of a large number of naphthylchromones and constitutes a versatile intermediate in other cycloaddition reactions.[17] Much less attention has been given to the chemistry of heteroaromatic analogues of *ortho*-quinodimethanes. The multi-step route, moderate yields, and a large number of secondary products are the limitations in the use of dienes in the preparation of these intermediates.[17–19] However, heterocyclic *ortho*-quinodimethanes are an attractive tool in the design of novel heteropolycyclic compounds.

Following our interest on the chemistry of *ortho*-quino dimethanes[20–23] and on the synthesis of heterocyclic compounds, we decided to study the Diels–Alder reaction of (*E*)-2-styrylchromones with a pyrimidine *ortho*-quinodimethane as a tool to establish a new synthetic route for novel tetrahydroquinazoline-substituted chromones and to study the regioselectivity of this reaction. Certain tetrahydroquinazolines, and their oxidized derivatives, are known to possess anti-inflammatory, antimicrobial, antioxidant, and antitumor activities;[24] some of them have been patented for their pharmacological[25] and biocidal properties.[26]

Recently we have reported the synthesis of novel flavone derivatives from the Diels–Alder reaction of (*E*)-2-styrylchromones with

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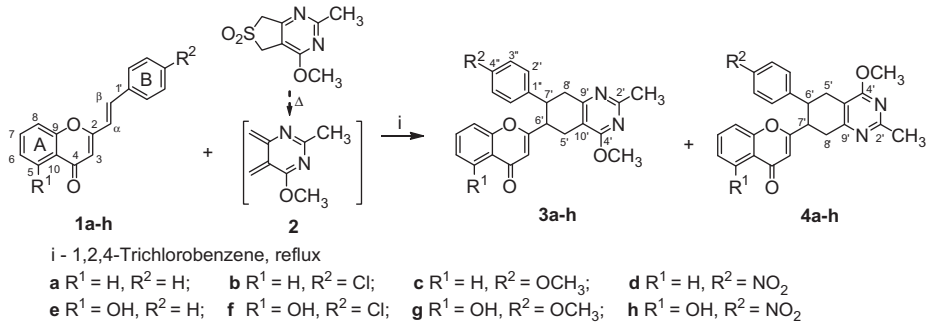


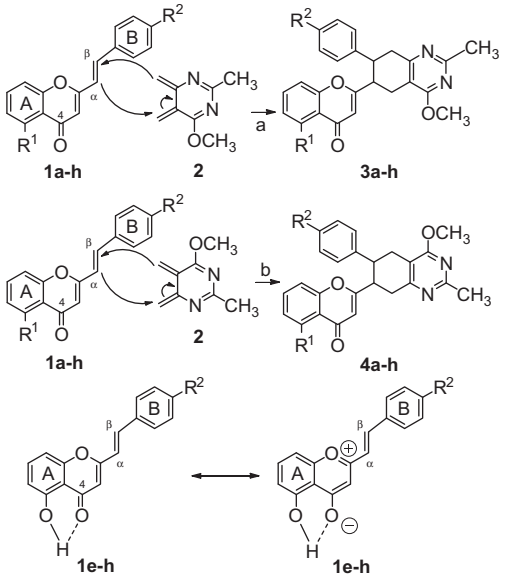
Scheme 1. Diels–Alder reaction of (*E*)-2-styrylchromones **1a**–**h** with pyrimidine *ortho*-quinodimethane **2**.

the symmetric *ortho*-benzoquinomethane.[15,16] The good results obtained led us to extend that work to the Diels–Alder reaction of (*E*)-2-styrylchromones **1a–h**[27] with the asymmetric pyrimidine *ortho*-quinodimethane **2** (Scheme 1). This reactive diene was generated *in situ* by thermal extrusion of sulfur dioxide from the corresponding sulfone 4-methoxy-2-methyl-5,7-dihydrothieno [3,4-*d*]pyrimidine 6,6-dioxide.[21] When chromone **1a** was reacted with an excess of sulfone (1.5 equiv) for 6 h in refluxing 1,2,4-trichlorobenzene, TLC showed not only the starting material **1a** but also two new compounds, with lower R_f values. The NMR data of the isolated products allowed to assign their structures to the expected regioisomers 2-(4-methoxy-2-methyl-7-phenyl-5,6,7,8-tetrahydroquinazolin-6-yl)chromone **3a**[28] (higher R_f value) and 2-(4-methoxy-2-methyl-6-phenyl-5,6,7,8-tetrahydroquinazolin-7-yl)chromone **4a**[29] (lower R_f value). The stereospecificity of the Diels–Alder reaction was confirmed by the typical *trans*-diaxial coupling constant $^3J_{H6'\text{-}H7'}$ = 10.0–10.8 Hz and by the NOESY spectra, where the absence of NOE cross peaks between the 6'-H and 7'-H signals indicates that the *trans* configuration of the dienophile **1a** was retained in the cycloadducts **3a** and **4a**. In order to obtain a total conversion of the starting chromone **1a**, another 0.5 equiv of sulfone was added to the reaction mixture and the reaction time was extended for more 4 h. However under these conditions **1a** was recovered in only 13% yield. After several unsuccessful attempts to improve the conversion rate, including longer reaction times that gave rise to higher degradation products, the best yields were obtained by the conditions described before (1.5 equiv of sulfone and under refluxing for 6 h). This methodology was also applied to the dienophiles **1b–h** (Table 1).[30]

Considering Table 1 one can conclude that the total yield in the cycloaddition reaction depends on the substituents of 2-styryl chromones **1a–h**. The presence of electron-donating groups in B-ring decreases the reactivity while the presence of electron-withdrawing substituents increases their reactivity as dienophiles. In terms of selectivity, the cycloadducts **3a–d** were obtained in better yields (37–43%) than the isomers **4a–d** (26–38%). According to the frontier orbital theory,[31,32] the regioselectivity of the Diels–Alder reaction depends on the interaction between the more favorable HOMO orbital of the diene and the LUMO orbital of the dienophile, which means that the higher electron density bond of the diene attacks the side of the double bond with lower electron density of the dienophile. Taking this into account and the yields of isomers **3a–d**, which do not vary significantly due to B-ring substitution, it seems that the formation of this isomer is controlled by the electron-withdrawing carbonyl group from the 2-styrylchromones **1a–d** and by the electron-donating methoxyl group from the pyrimidine *ortho*-quinodimethane **2** (path a, Scheme 2). These two favorable situations justify the referred regioselectivity. The yield of isomers **4a–d** is controlled by the B-ring substituent of 2-styrylchromones **1a–d**, being higher with an electron-withdrawing group (**4e**, 38%) and lower for an electron-donating group (**4c**, 26%) (path a, Scheme 2).

Table 1
Yields obtained in the Diels–Alder reaction of (*E*)-2-styryl chromones **1a**–**h** with pyrimidine *ortho*-quinodimethane **2**

	Yield **3** (%)	Yield **4** (%)	Total yield (%)	Recovered **1** (%)
a	43	32	75	13
b	42	32	74	20
c	37	26	63	36
d	43	38	81	7
e	34	27	61	19
f	29	23	52	37
g	28	20	48	45
h	52	35	87	5



Scheme 2. Reaction mechanism for the formation of both tetrahydroquinazoline-substituted chromone isomers.

The introduction of a 5-hydroxyl group in the A-ring of 2-styrylchromones **1e–g** promotes a decrease in the total yield of the cycloaddition reaction with pyrimidine *ortho*-quinodimethane **2** when compared with unsubstituted A-ring 2-styrylchromones **1a–c** (Table 1). It was predicted that the hydrogen bond between the 5-OH group and the 4-C=O should increase the reactivity of the dienophile (Cα=Cβ). However, the results pointed to another direction. We can postulate that the strong hydrogen bond and the possibility of resonance of the chromone core led to a weaker

carbonyl group effect on the electron density of the Cα=Cβ double bond than expected (Scheme 2). The exception occurred for the reaction with the 4'-nitro-derivative **1h** where the best total yield was accomplished (87%). Here, the electron-withdrawing effect of the 4'-nitro group enhances the deshielding effect of the chromone unit. Analyzing the regioselectivity on the formation of both 5-hydroxy-cycloadduct isomers, **3e–h** were obtained in better yields (28–52%) than cycloadducts **4e**–**h** (20–35%). These results are in agreement with the frontier orbital theory referred for adducts **3a–d**/**4a–d**.

The main feature in the aliphatic region of the ^{1}H NMR spectra of adducts **3a–h** and **4a–h** is the singlets corresponding to the resonance of 2'-CH_3 and 4'-OCH_3 at 2.58–2.60 and 3.97–4.00 ppm, respectively. The unequivocal assignment of the six aliphatic proton resonances (H-5', H-6', H-7' and H-8') allowed us to distinguish between isomers **3a–h** and **4a–h**. The connectivities found in the HMBC spectra, namely that of H-5' with C-2 and C-4' in the case of **3a–h** and of those protons with C-4' and C-1'' in the case of **4a–h**, allowed us to unequivocally identify the structures of these compounds. The signals corresponding to the resonance of H-6' and H-7' are reversed in both isomers. The deshielding effect of the phenyl group led the H-7' protons to appear at a higher frequency value (3.40–3.62 ppm) than the H-6' protons (2.96–3.23 ppm) for adducts **3a–h** while for adducts **4a–h** the resonance of the H-7' protons appears at a lower frequency values (3.11–3.37 ppm) than for the H-6' protons (3.11–3.53 ppm). The $^3J_{H6'\text{-}H7'}$ = 10.0–10.8 Hz (typical coupling constant of *trans*-diaxial protons) and the absence of NOE cross peaks observed in the NOESY spectra between the signals of H-6' and H-7' indicate that the *trans* configuration of the starting materials[27] was retained in adducts **3a–h** and **4a–h**.

Other important and characteristic signals of adducts **3a–h** and **4a–h** are the singlets at 5.95–6.07 ppm corresponding to the resonance of H-3. The H-5 resonance of compounds **3a–d** and **4a–d** always appears as a double doublet at high frequency values (8.06–8.09 ppm) due to the mesomeric and anisotropic deshielding effect of the carbonyl group at *peri* position. For 5-hydroxy-derivatives **3e**–**h** and **4e–h** it was also possible to identify the singlet corresponding to the 5-OH resonance at 12.23–12.38 ppm. The high frequency values of these resonances are due to intramolecular hydrogen bond of the hydroxyl proton with the carbonyl group.

The most important features of the ^{13}C NMR spectra of the adducts **3a–h** and **4a–h** are: (i) the carbon resonances of the pyrimidine 2'-CH_3 and 4'-OCH_3 at 25.6-25.7 and 53.7-53.9 ppm, respectively; (ii) the resonance of the carbonyl carbon at 177.7–178.1 ppm for **3a–d** and **4a–d** and at 182.9–183.2 ppm for 5-hydroxy-derivatives **3e–h** and **4e–h**. Obviously, the introduction of the 5-hydroxyl groups also promotes changes in the resonance of carbon C-5, which appeared at higher frequency values (160.6–160.7 ppm) for adducts **3e–h** and **4e–h** than for adducts **3a–d** and **4a–d** which appeared at 125.6–125.8 ppm.

Contrary to the ^{1}H NMR spectra, in the ^{13}C NMR spectra of **3a–h** the C-6' resonances (45.1–45.9 ppm) appear at higher frequency values than C-7' (42.0–42.9 ppm), while for **4a–h** is the reverse, with C-6' resonances (42.2–43.1 ppm) appearing at lower frequency values than C-7' (45.0–45.7 ppm). A detailed analysis of the 2D NMR experiments allowed the assignment of the remaining protonated and non-protonated carbon resonances and the correlations found in the HMBC (Fig. 1) and NOESY spectra provided unequivocal support for the structures of the new synthesized adducts **3a–h** and **4a–h**.

In conclusion, we report for the first time the cycloaddition reaction of (*E*)-2-styrylchromones with an asymmetrical heterocyclic *ortho*-quinodimethane, generated in situ by thermolysis of a pyrimidine fused 3-sulfolene. In all cases, the Diels–Alder reaction provided two regioisomers: 2-(7-aryl-4-methoxy-2-methyl-5,6,7,8-tetrahydroquinazolin-6-yl)chromones and 2-(6-aryl-4-methoxy-2-methyl-5,6,7,8-tetrahydroquinazolin-7-yl)chromones, being the former the major ones.

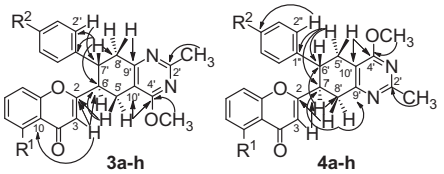


Figure 1. Main connectivities found in the HMBC spectra of adducts **3a**–**h** and **4a**–**h**.

Acknowledgments

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28. *2-(7-Phenyl-4-methoxy-2-methyl-5,6,7,8-tetrahydroquinazolin-6-yl)-4H-chromen-4-one* (***3a***): 43% yield; mp 191–193 °C (white powder, recrystallization from cyclohexane/CH_2Cl_2). ^{1}H NMR: δ = 2.60 (s, 3H, 2′-CH_3), 2.98-3.13 (m, 2H, 2 × H-5′), 3.13-3.17 (m, 2H, 2 × H-8′), 3.18 (dt, 1H, *J* = 10.4 and 5.4 Hz, H-6′), 3.48 (dt, 1H, *J* = 10.4 and 7.2 Hz, H-7′), 3.99 (s, 3H, 4′-OCH_3), 6.03 (s, 1H, H-3), 7.09-7.22 (m, 5H, H-2″,3″,4″,5″,6″), 7.34 (ddd, 1H, *J* = 7.9, 7.8 and 0.9 Hz, H-6), 7.38 (br d, 1H, *J* = 8.2 Hz, H-8), 7.62 (ddd, 1H, *J* 8.2, 7.8 and 1.6 Hz, H-7), 8.07 (dd, 1H, *J* = 7.9 and 1.6 Hz, H-5) ppm. ^{13}C NMR: δ = 25.7 (2′-CH_3), 26.6 (C-5′), 39.0 (C-8′), 42.9 (C-7′), 45.6 (C-6′), 53.8 (4′-OCH_3), 110.9 (C-10′), 111.0 (C-3), 117.6 (C-8), 123.6 (C-10), 125.0 (C-6), 125.6 (C-5), 127.1 (C-2″,6″), 127.2 (C-4″), 128.8 (C-3″,5″), 133.5 (C-7), 141.5 (C-1″), 156.2 (C-9), 163.0 (C-9′), 165.2 (C-2′), 167.1 (C-4′), 169.2 (C-2), 178.0 (C-4) ppm. EI-MS: *m/z* (%) = 398 ($M^{+\cdot}$, 100), 383 (5), 321

(6), 307 (12), 277 (8), 253 (9), 239 (67), 225 (17), 163 (9), 150 (17), 128 (5), 121 (8), 92 (5), 91 (10), 77 (4), 56 (31). $C_{25}H_{22}N_2O_3 \cdot {}^1/_4H_2O$ (402.95): calcd C 74.68, N 6.97, H 5.62; found C 74.79, N 6.97, H 5.23.

29. *2-(6-Phenyl-4-methoxy-2-methyl-5,6,7,8-tetrahydroquinazolin-7-yl)-4H-chromen-4-one* (***4a***): 32% yield; mp 180–182 °C (white powder, recrystallization from cyclohexane/CH_2Cl_2). ^{1}H NMR: δ = 2.60 (s, 3H, 2′-CH_3), 2.80 (dd, 1H, *J* = 17.6 and 10.7 Hz, H-5′), 3.09 (dd, 1H, *J* = 17.6 and 5.3 Hz, H-5′), 3.14-3.33 (m, 3H, H-7′ and 2 × H-8′), 3.36 (dt, 1H, *J* = 10.7 and 5.3 Hz, H-6′), 3.97 (s, 3H, 4′-OCH_3), 6.04 (s, 1H, H-3), 7.09-7.19 (m, 5H, H-2″,3″,4″,5″,6″), 7.33 (ddd, 1H, *J* = 7.9, 7.8 and 0.9 Hz, H-6), 7.37 (br d, 1H, *J* = 8.3 Hz, H-8), 7.61 (ddd, 1H, *J* = 8.3, 7.8 and 1.7 Hz, H-7), 8.06 (dd, 1H, *J* = 7.9 and 1.7 Hz, H-5) ppm. ^{13}C NMR: δ = 25.6 (2′-CH_3), 29.7 (C-5′), 35.8 (C-8′), 43.0 (C-6′), 45.3 (C-7′), 53.7 (4′-OCH_3), 110.9 (C-3), 112.1 (C-10′), 117.5 (C-8), 123.5 (C-10), 125.0 (C-6), 125.6 (C-5), 127.1 (C-2″,6″,4″), 128.7 (C-3″,5″), 133.5 (C-7), 141.8 (C-1″), 156.2 (C-9), 161.8 (C-9′), 165.0 (C-2′), 167.0 (C-4′), 168.8 (C-2), 178.0 (C-4) ppm. EI-MS: *m*/*z* (%) = 398 ($M^{+\cdot}$, 100), 383 (7), 369 (6), 321 (10), 307 (44), 293 (6), 277 (12), 249 (12), 239 (25), 225 (4), 163 (19), 150 (23), 128 (6), 121 (11), 92 (6), 91 (10), 79 (6), 56 (27). HRMS (EI) $C_{25}H_{22}N_2O_3$ [$M^{+\cdot}$]: calcd 398.1630, found 398.1631.

30. *Diels–Alder reaction of (E)-styrylchromones* ***1a–h*** *with pyrimidine ortho-quinodimethane* ***2***: A solution of appropriate (*E*)-2-styryl chromones **1a–h** (0.4 mmol) and 4-methoxy-2-methyl-5,7-dihydrothieno[3,4-*d*]pyrimidine 6,6-dioxide (0.13 g; 0.6 mmol) in 1,2,4-trichlorobenzene (10 mL), under nitrogen atmosphere, was heated at reflux for 6 hours. Then more 4-methoxy-2-methyl-5,7-dihydrothieno[3,4-*d*]pyrimidine 6,6-dioxide (0.09 g; 0.2 mmol) was added and the reflux maintained for 4 hours. After cooling to room temperature, the reaction mixture was purified by silica gel column chromatography. Elution with light petroleum removed 1,2,4-trichlorobenzene while elution with acetone afforded the crude residue. Acetone was evaporated and the residue was separated by preparative silica gel thin layer chromatography (eluent: a 9:1 mixture of chloroform:acetone), leading to the isolation of the unreacted starting materials **1a–h** (highest R_f value) and the adducts **3a–h** and **4a–h** (lowest R_f values).
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