1,6-Conjugated Addition of Nitromethane to (*E*)-2-Styrylchromones: A New Synthesis of Novel 2-Substituted 4-Arylpyrrole Derivatives

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Abstract: The 1,6-conjugate addition of nitromethane to (*E*)-2-styrylchromones were achieved, in moderate to good yields, by using DBU as organocatalyst. Reduction studies on the 2-(2-aryl-3-nitropropyl)chromone adducts formed surprisingly led to novel 2-substituted 4-arylpyrrole derivatives. These new derivatives are formed from nitro-group reduction, followed by a 1,4-Michael-type addition of the primary amine intermediate to the α,β-unsaturated carbonyl system of the chromone moiety and concomitant heterocyclic ring opening.

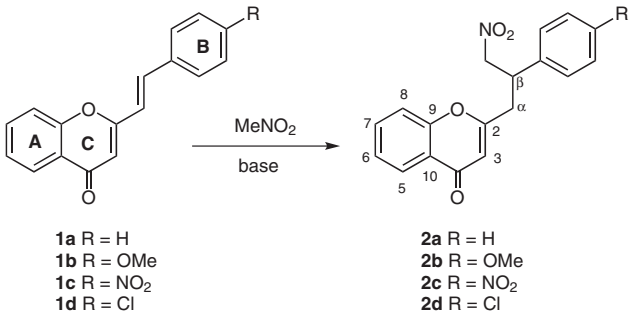
Key words: (*E*)-2-styrylchromones, nitromethane, 1,6-conjugated addition, 1,4-Michael addition, 2-substituted 4-arylpyrroles, DBU

2-Styrylchromones constitute a group of oxygen heterocyclic compounds which, although scarce in nature,[1] have been widely synthesized and studied for their biological activities.[2] (*E*)-2-Styrylchromones are easily prepared in good overall yields according to a three-step sequence, by using 2′-hydroxyacetophenones and the appropriate cinnamoyl chlorides as starting materials.[3] Biological evaluations of a number of synthesized 2-styrylchromone derivatives revealed the significant anti-allergic,[4] antitumor,[1a,b,5] antiviral,[6] antioxidant,[7] and anti-inflammatory[8] activities of these compounds and also their use as antagonists of the A3 adenosine receptor.[9] In view of the important biological activities described in the literature for this group of compounds, 2-styrylchromones represent a rather important substrate for numerous transformations.

The conjugate addition of carbon nucleophiles to electron-deficient alkenes is one of the most important methods available for carbon–carbon bond-forming reactions.[10] Furthermore, the asymmetric catalysis of this reaction has become an efficient synthetic tool for the formation of tertiary and quaternary carbon stereocenters, important for the development of new potentially important bioactive compounds.[11] In addition, the use of chiral metal-free organocatalysts has been the object of intense studies due to their potential application to chemical transformation in pharmaceutical industry.

A large number of publications describing asymmetric 1,4-conjugate additions of carbon nucleophiles is available but the analogous asymmetric 1,6-addition methods are underdeveloped.[12,13] The presence of several electrophilic sites in extended conjugated systems and the difficulties in controlling the regioselectivity explain the limited results in this area. Considering asymmetric 1,4-conjugate additions, previous work within the group[14] had led to the development of a general and efficient asymmetric organocatalytic addition of malononitrile and nitromethane to 1,5-diarylpenta-2,4-dien-1-ones catalyzed by cinchona organocatalysts. The reactions afforded excellent enantioselectivities (up to 99%), high yields (up to 97%), and exclusive 1,4-addition regioselectivity.[14]

To the best of our knowledge no example of 1,6-conjugate additions to (*E*)-2-styrylchromones has been described in the literature. Therefore, the potential of this new reaction led us to pursue the addition of nitromethane to (*E*)-2-styrylchromones (Scheme 1).



Scheme 1 1,6-Conjugate additions of nitromethane to (*E*)-2-styrylchromones **1a–d**

To investigate the reactivity of compound **1a** towards the conjugate addition of nitromethane we first examined the action of some typical poorly nucleophilic amine bases (Scheme 1). *trans*-2,5-Dimethylpiperazine (DMP), pyridine, *N*,*N*-diisopropylethylamine (Hünig's base), imidazole, 4-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN), and 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD) were considered for the 1,6-conjugate addition at room temperature without the use of any solvent (Table 1).

DMP, Hünig's base, pyridine, imidazole, and DMAP were totally inefficient, and the starting material was recovered (67–100%). Similarly, the use of an inorganic base, such as K_2CO_3, was inefficient in promoting the reaction. However, the use of a stronger base such as DBU under the same conditions afforded the desired 2-(3-nitro-2-phenylpropyl)chromone (**2a**)[15,16] in 84% yield after 6.5 hours of reaction time (Table 1, entry 1). The main fea-

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tures in the ^{1}H NMR spectrum of **2a** were the signals of the diastereotopic α protons at δ = 3.09 (^3J = 6.5 Hz; ^2J =14.5 Hz) and 3.00 ppm (^3J = 8.8 Hz; ^2J = 14.5 Hz; see Scheme 1 for numbering). Additionally, the presence of a multiplet at δ = 4.11–4.01 ppm and a doublet at δ = 4.72 ppm (^3J = 7.6 Hz), corresponding to the β- and the α-CH_2 protons, respectively, revealed the regioselective 1,6-addition of nitromethane to the α,β,γ,δ-unsaturated carbonyl system.

These results led us to consider bases with similar or higher basicity, namely DBN and TBD, but their use led to a decrease in the yield (Table 1, entries 2–4).

Table 1 Base Screening for the Addition of Nitromethane to (*E*)-Styrylchromone **1a**[a]

Entry	Base	Time (h)	**1a** (recovered, %)	Yield (%) of **2a**[b]
1	DBU	6.5	–	84
2	DBN	24	–	59
3	TBD	48	7	70
4	PSTBD	30	3	64

[a] Reactions were carried out using **1a** (30 mg, 0.121 mmol), 20 mol% of base, and nitromethane (0.33 mL) at r.t. under a nitrogen atmosphere.
[b] Yield of isolated product **2a** after chromatography.

The next step was the extension of the 1,6-conjugate addition of nitromethane to other (*E*)-2-styrylchromones using the DBU as the chosen organocatalyst.[15] The corresponding 2-(2-aryl-3-nitropropyl)chromone derivatives **2b–d** were obtained in moderate to good yields (Scheme 1, Table 2).

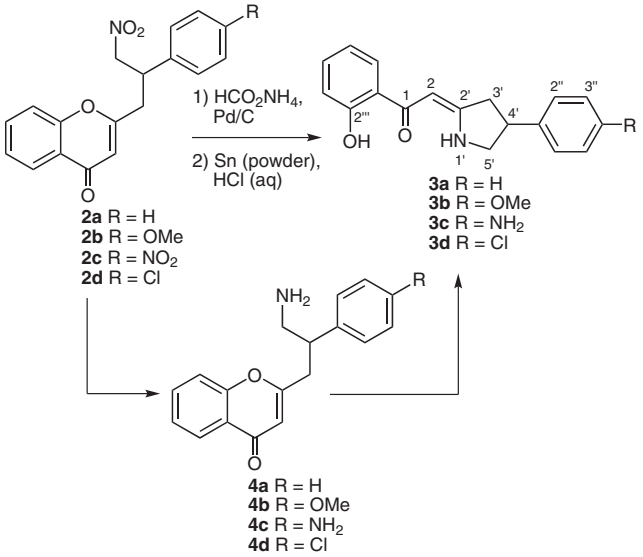
The formation of **2a–d** is dependent on the B-ring substituent of the starting materials **1a–d**. The unsubstituted compound **1a** is the most reactive leading to the formation of the 2-(3-nitro-2-phenylpropyl)chromone (**2a**) in good yield (Table 2, entry 1). The introduction of a substituent at the *para* position of the ring B clearly diminishes the reactivity towards the 1,6-conjugate addition of nitromethane. To achieve similar yields (Table 2, entry 3) for the reaction of compound **1b**, bearing an electron-donating substituent (R = OMe), it was required to use 0.4 mol equivalents of base and increase the reaction time. With compound **1d** (R = Cl), the 1,6-conjugate addition only took place at 65 °C when compound **2d** was obtained in 72% (Table 2, entry 11). The difficulty came when compound **1c**, bearing an electron-withdrawing substituent (R = NO_2), was used as starting material. The reaction, carried out using **1c** and nitromethane in the presence of DBU at room temperature under a nitrogen atmosphere, yielded the desired product **2c** in only 6% yield with recovery of 75% of the starting material **1c** (Table 2, entry 4). Heating the reaction mixture did not increase the yield significantly (11%, Table 2, entry 5). It was then decided to exploit the use of a polar solvent since it was clear during the reaction that the solubility of **1c** was a problem. The use of refluxing THF or MeCN led to no improvement on the product yield (Table 2, entries 6 and 7). However, when DMSO was used in sufficient amount to dissolve the starting material completely (Table 2, entry 8) the yield was improved. After two hours, the desired product **2c** was obtained in 50% yield, and no starting material was recovered.

Table 2 1,6-Conjugate Additions of Nitromethane to (*E*)-2-Styrylchromones **1a–d** Using DBU as Base[a]

Entry	R	**1a–d** (recovered, %)	Yield (%)[b]	Time (h)	Solvent
1	H	–	84	6.5	–
2	OMe	36	47	6.5	–
3[c]	OMe	14	71	24	–
4	NO_2	75	6	6.5	–
5[d]	NO_2	52	11	6.5	–
6[e]	NO_2	75	4	72	THF
7[e]	NO_2	39	7	72	MeCN
8[f]	NO_2	–	50	2	DMSO
9	Cl	30	28	6.5	–
10[c]	Cl	38	26	48	–
11[d]	Cl	–	72	6.5	–

[a] Reactions were carried out using **1a–d** (30 mg), 20 mol% of base, and nitromethane (0.33 mL) at r.t. under a nitrogen atmosphere.
[b] Yield of isolated products after chromatography.
[c] Conditions: 0.4 equiv of DBU were used.
[d] This reaction was carried out at 65 °C.
[e] Reactions were carried out under reflux using 0.5 mL of solvent.
[f] This reaction was carried out at 100 °C and using 3 mL of solvent.

We subsequently considered a further transformation of the new derivatives **2a–d** to prepare the corresponding amino derivatives **4a–d**. We initiated reduction studies using compound **2a** and ammonium formate (5 equiv) in the presence of Pd/C (10%) using methanol as solvent (Method A, Scheme 2), which had been successfully used for the preparation of 3-aminoflavones.[17] In this study, the authors found that, if the reaction did not occur in the first five minutes, it was necessary to add more catalyst for reaction evolution. For compound **2a**, even after the addition of more catalyst, the reaction did not take place. When using acetone, described as an appropriate solvent for the reduction of 3-aminoflavones,[17] a new compound was formed in small quantities (15% yield) after leaving the reaction overnight with recovery of 42% of compound **2a**. This new compound was found to be the pyrrole derivative **3a**[18] (Scheme 2), formed through a 1,4-Michael-type addition of the primary amino group to the α,β-unsaturated system in the intermediate **4a** with concurrent opening of the chromone nucleus.



Scheme 2 Transformation of 2-(2-aryl-3-nitropropyl)chromones **2a–d** into (*Z*)-2-hydroxyphenyl (4-phenylpyrrolidin-2-ylidene)methyl ketones **3a–d**

Attempting to obtain the 2-(3-amino-2-phenylpropyl)chromone (**4a**), it was decided to repeat the reaction but using double the quantities of catalyst [Pd/C (10%)] and ammonium formate (10 equiv). After four hours, no starting material was observed by TLC, and the reaction was quenched by filtrating through Celite.[19] This reaction led once more, after purification through column chromatography, to the isolation of pure compound **3a** in 20% yield. Method A was subsequently extended to the remaining nitropropyl derivatives **2b–d**. Formation of derivative **3c** (R = NO_2) could be observed during TLC analysis of the reaction, but it was not isolated in significant quantities. Compound **3d** (R = Cl) was obtained in a similar yield to the unsubstituted **3a** (23%) while, for compound **2b**, the desired product **3b** (R = OMe) was obtained in low yield (13%, Table 3).

Unequivocal proton assignments for all the pyrrole derivatives were achieved with COSY, HSQC, HMBC, and NOESY experiments. The ^{1}H NMR spectrum of compound **3a** exhibited two sharp singlets at δ = 13.80 and 9.95 ppm, assigned to the hydroxy and pyrrolic amino proton resonances, respectively. These two sharp signals indicate the presence of two highly deshielded protons due to two intramolecular hydrogen bonds with the carbonyl group. The NOESY spectrum of **3a** presented NOE cross peaks between the signals of H-2 with those of H-3′ of the pyrrole ring and also H-6‴ of the phenyl ring A, supporting the close proximity between them and thus pointing out for a *Z*-configuration of the double bond (see Scheme 2 for numbering).

In order to improve the yield of compounds **3a–d** a different approach was attempted. Treatment of the 2-(3-nitro-2-phenylpropyl)chromone (**2a**) with an excess of hydrated stannous chloride,[20] in a 1:3 mixture of hydrochloric acid and acetic acid at 65 °C, similarly led to the formation of compound **3a** in a trace amount. The reduction of the 2-(3-nitro-2-phenylpropyl)chromone (**2a**) was also performed using method B [Sn (powder) and HCl (aq), Scheme 2],[20,21] which afforded, once more, compound **3a** but in a slightly higher yield (30%). The reduction reaction using method B was also extended to the other 2-(2-aryl-3-nitropropyl)chromones **2b–d** (Table 3), leading to compounds **3b–d** being obtained in better yields. Interestingly, with this method it was possible to isolate compound **3c** (R = NH_2) in a good yield (56%). In this case, not only the 1,4-Michael addition of the primary amino group had occurred with concurrent opening of the chromone nucleus but also the reduction of the aromatic nitro group had taken place leading to **3c**.

The formation of compound **3c** was confirmed by analysis of the ^{1}H NMR data. The low frequency values observed in the ^{1}H NMR spectrum for the two doublets corresponding to the proton resonances of H-2″,6″ and H-3″,5″ at δ = 7.04 and 6.67 ppm, respectively (see Scheme 2 for numbering), confirm the presence of the aromatic amino group. This set of signals in the presence of an aromatic nitro group normally show resonances at higher frequencies values, typically at around δ = 8.00 and 7.50 ppm for the protons at the *ortho* and *meta* positions, respectively, to the nitro group. The ^{1}H NMR spectrum of compound **3c** also exhibits, among other characteristic signals for this group of compounds, two sharp singlets at δ = 13.83 and 9.93 ppm, assigned to the proton resonances of the hydroxy and pyrrolic amino groups, respectively.

Table 3 Reduction Reaction of 2-(2-Aryl-3-nitropropyl)chromones **2a–d**

Entry	R	Yield of method A (%)[a,b]	Yield of method B (%)[a,b]
1	H	20	30
2	OMe	13	32
3	NO_2	–	56
4	Cl	23	21

[a] Yield of isolated products after chromatography.
[b] No starting material was recovered.

In conclusion, we have described herein the successful 1,6-conjugate addition of nitromethane to (*E*)-2-styrylchromones in the presence of DBU as an organocatalyst. The reduction of the 2-(2-aryl-3-nitropropyl)chromone derivatives so obtained by two different methods that lead to novel 2-substituted 4-arylpyrrole derivatives is also described. The formation of these compounds involves nitro-group reduction, followed by a 1,4-Michael-type addition of the primary amine intermediate at carbon C-2 of the chromone moiety with concurrent opening of the chromone nucleus to form (*Z*)-(4-arylpyrrolidin-2-ylidene)methyl 2-hydroxyphenyl ketones.

Acknowledgment

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(15) **Typical Procedure for the Preparation of 2-(2-Aryl-3-nitromethyl)chromones 2a–d**
A flask containing the appropriate (*E*)-2-styrylchromone **1a–d** (0.104 mmol), nitromethane (0.33 mL), and DBU (3 μL, 0.021 mmol) was flushed with nitrogen and stirred vigorously at r.t. After the appropriate time (Table 2), the solvent was evaporated under reduced pressure. The residue was taken in EtOAc and purified by preparative TLC on silica. Elution with hexane–EtOAc (7:3 or 1:1) gave the desired products **2a–d** (for yields see Table 2).

(16) **Physical Data of 2-(3-Nitro-2-phenylpropyl)-4*H*-chromen-4-one (2a)**
Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (1 H, dd, *J* = 1.6, 8.1 Hz, H-5), 7.65 (1 H, ddd, *J* = 1.6, 7.0, 8.5 Hz, H-7), 7.41–7.18 (7 H, m, H-Ph, H-6, and H-8), 6.03 (1 H, s, H-3), 4.72 (2 H, d, *J* = 7.6 Hz, β-CH_2NO_2), 4.11–4.01 (1 H, m, H-β), 3.09 (1 H, dd, *J* = 6.5, 14.5 Hz, H-α), 3.00 (1 H, dd, *J* = 8.8, 14.5 Hz, H-α). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.7 (C-4), 164.8 (C-2), 156.2 (C-9), 137.2 (C-1′), 133.7 (C-7), 129.2 (C-3′,5′), 128.3 (C-4′), 127.2 (C-2′,6′), 125.7 (C-5), 125.2 (C-6), 123.5 (C-10), 117.7 (C-8), 111.8 (C-3), 79.4 (β-*C*H_2NO_2), 41.9 (C-β), 38.1 (C-α). HRMS (ESI$^+$): *m/z* calcd for $C_{18}H_{16}NO_4$ [M + H]$^+$: 310.1074; found: 310.1074.

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(18) **(*Z*)-(2-Hydroxyphenyl) (4-Phenylpyrrolidin-2-ylidene)methyl Ketone (3a)**
Yellow solid; mp 113–115 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 13.80 (1 H, s, OH), 9.95 (1 H, s, NH), 7.65 (1 H, dd, *J* = 1.4, 8.0 Hz, H-6‴), 7.37–7.24 (6 H, m, H-Ph and H-4‴), 6.93 (1 H, dd, *J* = 1.0, 8.3 Hz, H-3‴), 6.82–6.79 (1 H, m, H-5‴), 5.87 (1 H, s, H-2), 4.08 (1 H, ddd, *J* = 1.0, 7.7, 10.6 Hz, H-5′), 3.71 (1 H, dd, *J* = 7.7, 10.6 Hz, H-5′), 3.64 (1 H, quin, *J* = 7.7 Hz, H-4′), 3.19 (1 H, dd, *J* = 7.7, 16.9 Hz, H-3′), 2.93 (1 H, dd, *J* = 7.6, 16.9 Hz, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.3 (C-1), 168.6 (C-2′), 162.3 (C-2‴), 141.8 (C-1″), 133.5 (C-4‴), 128.9 (C-3″,5″), 127.7 (C-6‴), 127.2 (C-4″), 126.8 (C-2″,6″), 120.3 (C-1‴), 118.2 (C-3‴), 118.1 (C-5‴), 85.4 (C-2), 55.2 (C-5′), 41.2 (C-3′), 40.7 (C-4′). HRMS (ESI$^+$): *m/z* calcd for $C_{18}H_{18}NO_2$ [M + H]$^+$: 280.1332; found: 280.1332.

(19) **Typical Procedure for the Preparation of the 2-Substituted 4-Arylpyrrole Derivatives 3a–d Using Method A**
Ammonium formate (0.864 mmol) and Pd/C (10%; 7.0 mg) were added to a solution of the appropriate 2-(2-aryl-3-nitropropyl)-4*H*-chromen-4-one **2a–d** (0.082 mmol) in acetone (1 mL), and the reaction mixture was refluxed for 1 h. After cooling to r.t., the reaction mixture was filtered through Celite, and the organic layer was evaporated to dryness. The residue was purified by preparative TLC on silica and eluted with a mixture of hexane–EtOAc (7:3) to give **3a–d** (for yields see Table 3).

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(21) **Typical Procedure for the Preparation of the 2-Substituted 4-Arylpyrrole Derivatives 3a–d Using Method B**
To a solution of the appropriate 2-(2-aryl-3-nitropropyl)-4*H*-

chromen-4-one **2a–d** (0.082 mmol) in $CHCl_3$ (10 mL), tin (powder, 0.81 g) and concd HCl (2.7 mL) were added, and the reaction mixture was stirred for 2 h at r.t. After this period, the reaction mixture was neutralized with $NaHCO_3$, filtered through Celite, and the solid residue washed with H_2O and $CHCl_3$. The filtrate was extracted with $CHCl_3$ (3×15 mL), the organic layer dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC on silica eluting with a mixture of hexane–EtOAc (7:3) to afford **3a–d** (for yields see Table 3).