Synthesis of Coumarins and Neoflavones through Zinc Chloride Catalyzed Hydroarylation of Acetylenic Esters with Phenols

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Abstract: Acetylenic esters react with oxygenated phenols under solvent-free conditions in the presence of only 5 mol% of zinc chloride as a catalyst to give coumarins and neoflavones in reasonable-to-good yields.

Key words: phenols, catalysis, arylations, heterocycles, alkynes, esters

Coumarins and 4-arylcoumarins (neoflavones) are a group of naturally occurring benzopyrone (2*H*-1-chromen-2-one) derivatives and, although they are widely distributed in the plant kingdom, their specific roles are not well understood.[1,2] Since coumarin was first isolated in 1820, many of its derivatives have been isolated and the interest in this family of compounds has focused on their biological activity.[1] Naturally occurring coumarins have been used in traditional medicine for thousands of years and their pharmacological and biochemical properties, as well as their therapeutic applications, depend on their patterns of substitution. For example, coumarin associated with troxerutin has been used in the treatment of varicose veins, hemorrhoids, and leg ulcers.[3] Natural furocoumarins such as psoralen and methoxsalen are used in the treatment of psoriasis, eczema, vitiligo, and cutaneous T-cell lymphoma.[4] Synthetic aminopsoralen has been used at European blood centers in the inactivation of infectious pathogens (bacteria, viruses, and protozoa) in platelets and plasma blood components prepared for transfusion support of patients.[5] Warfarin (Marevan®/Coumadin®), another synthetic coumarin, is an anticoagulant that is used clinically to prevent heart attacks, strokes, and blood clots.[6] Some natural and synthetic coumarins have also been reported to display antiviral[7] and antineoplastic activity in cell culture.[8]

The most common method for the synthesis of coumarins is the Peckmann condensation of phenols with β-keto esters promoted by acids, which was first described more than one hundred years ago,[9] and its variants. However, the need to use harsh conditions and a stoichiometric amount of the condensing agents limit the scope of this reaction. Several improved versions of the reaction have been reported, including the use of a set of new protic and Lewis acid catalysts,[10] immobilized[11] or recyclable catalysts,[12] microwave irradiation,[13] or ionic liquids.[14,15] The development of milder methods for the synthesis of coumarins has received considerable attention. A method involving Wittig reaction of *ortho*-hydroxy aromatic aldehydes followed by one-pot isomerization of the resulting cinnamate derivatives and cyclization has been used as a replacement for the classical method.[16] Efforts have also been made to synthesize coumarins from *ortho*-halophenols by using transition metal catalysts.[17] Trost et al.[18] developed the first palladium-catalyzed synthesis of coumarins from propiolic acid derivatives. This atom-economic synthesis does not use any halogenated phenols. Shi and He[19] synthesized coumarins directly by hydroarylation of aryl propiolates with phenols using gold(III) chloride and silver triflate as a catalyst system, whereas Oyamada and Kitamura[20] performed a similar reaction using potassium tetrachloroplatinate and silver triflate as the catalyst system. More recently, Yamamoto and Kirai reported a copper-catalyzed synthesis of 4-arylcoumarins, but in this case am arylboronic acid were used as the source of the in situ-generated arylpalladium intermediate.[21] In 1965, Kaufman and Kelly[22a] reported the hydroarylation of ethyl propiolate by benzene-1,3,5-triol (phloroglucinol) in the presence of a stoichiometric amount of zinc chloride under solvent-free conditions to give 5,7-dihydroxy-2*H*-chromen-2-one in a good yield. Surprisingly, this protocol has not been widely explored,[22b] and no attempts to use substoichiometric amounts of zinc chloride have been reported. This situation prompted us to study the Lewis acid promoted hydroarylation of ethyl propiolate with oxygenated phenols.

First, we examined the reaction of benzene-1,3,5-triol (**1a**) or resorcinol (**1c**) with 1.5 equivalents of ethyl propiolate (**2a**) under solvent-free conditions in the presence of stoichiometric amounts of zinc chloride or boron trifluoride etherate at 100 °C (Scheme 1) for comparison with the previously reported results.[22a] Both reactions were complete after 10 minutes, but whereas the expected coumarins **3a** and **3g**, respectively, were formed in good yields in the presence of zinc chloride, the cinnamates **4a** and **4c** were obtained as mixtures of isomers in the presence of boron trifluoride etherate, suggesting that the electrophilic substitution at the aromatic ring is the first step in the formation of the coumarin. The ability of zinc chloride to coordinate to both ethyl propiolate (lowering its LUMO energy) and to the phenol appears to be responsi-

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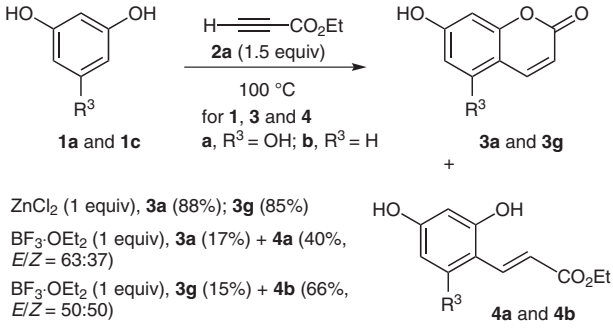
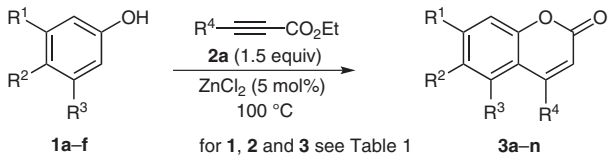


Scheme 1 Hydroarylation of ethyl propiolate (**2a**) with benzene-1,3,5-triol (**1a**) or resorcinol (**1c**) in the presence of zinc chloride or boron trifluoride etherate

ble for the regio- and stereoselectivity of the electrophilic aromatic substitution step, in which a *cis*-cinnamic ester intermediate must be formed, and for the good yields of coumarins that are obtained. We then selected zinc chloride for further studies.

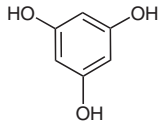
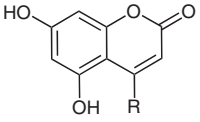
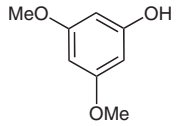
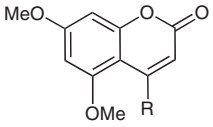
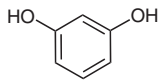
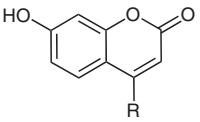
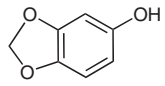
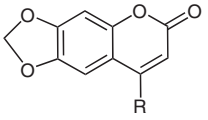
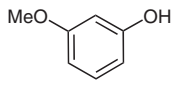
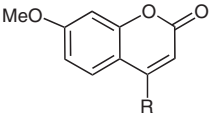
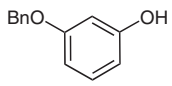
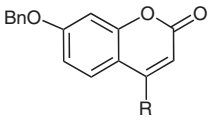
The hydroarylation of acetylenic esters **2a–c** with phenols **1a–f** (Scheme 2) gave the known products shown in



Scheme 2 Hydroarylation of propiolates **2a–c** with phenols **1a–f** in the presence of 5 mol% of zinc chloride

Table 1. Initially, we gradually reduced the amount of catalyst in the reaction of benzene-1,3,5-triol (**1a**) with ethyl propiolate (**2a**), and in the presence of 5 mol% of zinc chloride, the coumarin **3a** was obtained in 88% yield (Table 1, entry 1) after only five minutes. It is noteworthy that Kaufman and Kelly reported an 85% yield after 12 hours of reaction when a stoichiometric amount of zinc chloride was used.[22a] With the catalytic amount of zinc chloride under solvent-free conditions, the propiolates **2b** and **2c** also reacted with **1a** within five minutes to give the coumarin **3b** (entry 2) and the isoflavone **3c** (entry 3), respectively, in excellent yields.

Table 1 Yields of the Reactions Shown in Scheme 2

Entry	Phenol	$RC{\equiv}CCO_2Et$	Coumarin		Time	Yield (%)	N/S[e]	Mp (°C)
1		**2a**: R = H		**3a**: R = H	5 min	88[a]	N[15,23,24]	261–262
2		**2b**: R = Me		**3b**: R = Me	5 min	84[b]	N[18,24,25]	280–282
3		**2c**: R = Ph		**3c**: R = Ph	5 min	95[b]	N[26]	239–239.5
	1a							
4		**2a**: R = H		**3d**: R = H	30 min	73[c]	N[15,24]	138–140
5		**2b**: R = Me		**3e**: R = Me	30 min	77[b]	N[18,24]	168–169
6		**2c**: R = Ph		**3f**: R = Ph	12 h	71[b]	N[20,27]	150–152
	1b							
7		**2a**: R = H		**3g**: R = H	30 min	85[a]	N[2,23,24]	230–231
8		**2b**: R = Me		**3h**: R = Me	3 h	88[b]	N[18,24]	155–156
9		**2c**: R = Ph		**3i**: R = Ph	12 h	54[b]	N[26,28]	210–211
	1c							
10		**2a**: R = H		**3j**: R = H	1 h	70[c]	N[15,29]	223–226
11		**2b**: R = Me		**3k**: R = Me	1 h	31[c]	N[27,29]	149–150
12		**2c**: R = Ph		**3l**: R = Ph	12 h	nr[d]	S[20]	–
	1d							
13		**2a**: R = H		**3m**: R = H[f]	12 h	15[c]	N[15,25]	116–119
	1e							
14		**2a**: R = H		**3n**: R = H[g]	12 h	7[c]	S[17,23]	154–157
	1f							

[a] Yields of purified compounds after crystallization (H_2O).
[b] Yields of purified compounds after crystallization (hexane).
[c] Yields of purified compounds after chromatography (neutral alumina).
[d] No reaction.
[e] N = natural; S = synthetic.
[f] Mixture of isomers (60:40).
[g] Mixture of isomers (52:48).

3,5-Dimethoxyphenol (**1b**) was much less reactive than the triol **1a**, and its reaction with **2a** and **2b** took 30 minutes to complete, giving the coumarins **3d** and **3e**, respectively, in slight lower yields (entries 4 and 5, respectively). For the less reactive propiolate **2c**, the reaction was incomplete after five hours, but when left overnight it gave **3f** in a reasonable yield (entry 6).

Resorcinol (**1c**) showed a similar reactivity to the 3,5-dimethoxyphenol (**1b**), and its reactions with **2a–c** gave the coumarins **3g** and **3h** and the isoflavone **3i**, respectively, in the same reaction times and with slightly better yields (entries 7–9).

Surprisingly, 1,3-benzodioxol-5-ol (**1d**; sesamol) was less reactive than **1b**. Whereas its reaction with the more-reactive ethyl propiolate (**2a**) took one hour leading regioselectively to coumarin **3j** in good yield (entry 10), its reaction with **2b** gave coumarin **3k** in only a moderate yield (entry 11), and it did not react with **2c**, even after 12 hours (entry 12).

When the less-activated phenols **1e** and **1f** were allowed to react with **2a**, the corresponding coumarins **3m** and **3n** were obtained in poor yields in mixture with the corresponding regioisomeric coumarins in ratios of 60:40 and 58:42, respectively (entries 13 and 14). However, these products can be obtained in high yield by methylation or benzylation, respectively, of coumarin **3g**.[23]

In conclusion, the scope of the hydroarylation of propiolates with phenols in the presence of 5 mol% of zinc chloride was studied for the first time. Activated phenols gave coumarins or neoflavones in reasonable-to-good yields. The method provides an atom-economic synthesis of coumarins and neoflavones using an inexpensive Lewis acid catalyst, and permits the synthesis of twelve naturally occurring coumarins and neoflavones.

All the reagents and solvents were purchased from the Aldrich Chemical Co. and used without purification. Melting points were determined with a Thomas–Hoover apparatus. Column chromatography was performed on neutral alumina (Neutra-90) 70–290 mesh (Vetec). IR spectra were recorded on an IR Prestige-21 spectrometer (Shimadzu). UV spectra were recorded on a Shimadzu UV-Visible Spectrophotometer UV-1601. NMR spectra were recorded on a Varian 400 (400 MHz) spectrometer.

Hydroarylation of Propiolates by Phenols in the Presence of Zinc Chloride; General Procedure

$ZnCl_2$ (0.049 g; 5 mol%) was added to a soln of the appropriate phenol **1a–k** (7.24 mmol) in an adequate amount of the propiolate **2a–c** (10.66 mmol) heated to 100 °C. The resulting mixture was stirred at 100 °C for the time shown in Table 1 and then cooled to r.t. 5% aq HCl (10 mL) was then added. In the reactions of **1a** and **1c**, the resulting solid was filtered off and crystallized (H_2O) to give **3a–c** and **3e–i** as crystalline solids. In the reactions of **1b** and **1d–k**, the mixture was extracted with EtOAc (3 × 10 mL), and the extracts were dried (Na_2SO_4) and concentrated to give a residue that was purified by column chromatography (basic alumina, 30% EtOAc–hexane) to give the coumarins as pale yellow solids (Table 1).

5,7-Dihydroxy-2*H*-chromen-2-one (3a)
Mp 261–262 °C.

IR (KBr): 3192, 1700, 1640, 1610, 1570, 1475, 1361, 1303, 1244, 1153, 1130, 1070, 817 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 6.03 (d, *J* = 9.6 Hz, 1 H, H-3), 6.18 (d, *J* = 1.7 Hz, 1 H, H-8), 6.26 (d, *J* = 1.7 Hz, 1 H, H-6), 7.96 (d, *J* = 9.6 Hz, 1 H, H-4), 10.36 and 10.64 (br s, 2 H).

UV (MeOH): λ_{max} = 334, 260 nm.

5,7-Dihydroxy-4-methyl-2*H*-chromen-2-one (3b)
Mp 280–282 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.49 (d, $J_{4,3}$ = 1.0 Hz, 3 H, CH_3), 5.85 (d, $J_{3,4}$ = 1.0 Hz, 1 H, H-3), 6.17 (d, $J_{6,8}$ = 2.3 Hz, 1 H, H-6), 6.26 (d, $J_{8,6}$ = 2.3 Hz, 1 H, H-8), 10.28 and 10.50 (br s, 2 H, OH).

5,7-Dihydroxy-4-phenyl-2*H*-chromen-2-one (3c)
Mp 239–239.5 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.74 (s, 1 H, H-3), 6.16 (d, $J_{6,8}$ = 2.1 Hz, 1 H, H-6), 6.26 (d, $J_{8,6}$ = 2.1 Hz, 1 H, H-8), 7.31–7.38 (m, 5 H, H-Ar).

5,7-Dimethoxy-2*H*-chromen-2-one (3d)
Mp 138–140 °C.

IR (KBr): 2945, 1712, 1616, 1222, 1205, 1153, 1116, 817 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 6.15 (d, *J* = 9.6 Hz, 1 H, H-3), 6.28 (d, $J_{6,8}$ = 2.1 Hz, 1 H, H-6), 6.42 (d, $J_{8,6}$ = 2.1 Hz, 1 H, H-8), 7.96 (d, *J* = 9.6 Hz, 1 H, H-4).

UV (CH_2Cl_2): λ_{max} = 324, 255, 246, 228 nm.

5,7-Dimethoxy-4-methyl-2*H*-chromen-2-one (3e)
Mp 168–169 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 5.94 (s, 1 H, H-3), 6.20 (d, $J_{6,8}$ = 2.3 Hz, 1 H, H-6), 6.42 (d, $J_{8,6}$ = 2.3 Hz, 1 H, H-8).

5,7-Dimethoxy-4-phenyl-2*H*-chromen-2-one (3f)
Mp 150–152 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.42 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 6.00 (s, 1 H, H-3), 6.23 (d, $J_{6,8}$ = 2.3 Hz, 1 H, H-6), 6.53 (d, $J_{8,6}$ = 2.3 Hz, 1 H, H-8), 7.25–7.27 (m, 3 H, H-Ar), 7.36–7.38 (m, 2 H, H-Ar).

7-Hydroxy-2*H*-chromen-2-one (Umbelliferone) (3g)
Mp 230–231 °C.

IR (KBr): 3134, 1650, 1620, 1560, 1455, 1406, 1321, 1234, 1128, 835 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 6.18 (d, $J_{3,4}$ = 9.4 Hz, 1 H, H-3), 6.71 (d, $J_{8,6}$ = 2.2 Hz, 1 H, H-8), 6.79 (dd, $J_{6,5}$ = 8.5 Hz and $J_{6,8}$ = 2.3 Hz, 1 H, H-6), 7.45 (d, *J* = 8.5 Hz, 1 H, H-5), 7.74 (d, $J_{4,3}$ = 9.6 Hz, 1 H, H-4).

UV (MeOH): λ_{max} = 324, 204 nm.

7-Hydroxy-4-methyl-2*H*-chromen-2-one (3h)
Mp 155–156 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.37 (s, 3 H, CH_3), 6.13 (s, 1 H, H-3), 6.70 (d, $J_{8,6}$ = 2.3 Hz, 1 H, H-8), 6.81 (dd, $J_{6,5}$ = 8.7 Hz and $J_{6,8}$ = 2.3 Hz, 1 H, H-6), 7.59 (d, $J_{5,6}$ = 8.7 Hz, 1 H, H-5), 10.5 (br s, 1 H, OH).

7-Hydroxy-4-phenyl-2*H*-chromen-2-one (3i)
Mp 110–111 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.15 (s, 1 H, H-3), 6.79 (dd, $J_{6,5}$ = 8.7 and $J_{6,8}$ = 2.3 Hz, 1 H, H-6), 6.81 (d, $J_{8,6}$ = 2.2 Hz, 1 H, H-8), 7.28 (d, $J_{5,6}$ = 8.7 Hz, 1 H, H-5), 7.49–7.57 (m, 5 H, H-Ar), 10.64 (br s, 1 H, OH).

6*H*-[1,3]Dioxolo[4,5-*g*]chromen-6-one (Ayapin) (3j)
Mp 223–226 °C.

IR (KBr): 2916, 1720, 1629, 1579, 1489, 1452, 1269, 1257, 1122, 1041, 941, 883 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (s, 2 H, OCH_2O), 6.27 (d, *J* = 9.5 Hz, 1 H, H-3), 6.81 (s, 1 H, H-5), 6.82 (s, 1 H, H-8), 7.57 (d, *J* = 9.5 Hz, 1 H, H-4).

UV (CH_2Cl_2): λ_{max} = 346, 294, 233 nm.

8-Methyl-6*H*-[1,3]dioxolo[4,5-*g*]chromen-6-one (3k)
Mp 149–150 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (d, $^4J_{4,3}$ = 1.2 Hz, 3 H, CH_3) 6.07 (s, 2 H, OCH_2O), 6.16 (d, $^4J_{3,4}$ = 1.2 Hz, 1 H, H-3), 6.82 (s, 1 H, H-8), 6.96 (s, 1 H, H-6).

7-Methoxy-2*H*-chromen-2-one (3m)
Mp 116–119 °C.

IR (KBr): 2926, 1707, 1612, 1506, 1466, 1400, 1352, 1282, 1232, 1205, 1124, 1026, 980, 829 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, OCH_3), 6.33 (d, $J_{3,4}$ = 9.7 Hz, 1 H, H-3), 6.82 (d, *J* = 2.3 Hz, 1 H, H-8), 6.84 (dd, *J* = 8.5 and 2.4 Hz, 1 H, H-6), 7.37 (d, *J* = 8.5 Hz, 1 H, H-5), 8.08 (d, $J_{4,3}$ = 9.7 Hz, 1 H, H-4).

UV (CH_2Cl_2): λ_{max} = 436, 346 nm.

7-(Benzyloxy)-2*H*-chromen-2-one (3n)
Mp 154–157 °C.

IR (KBr): 3107, 3030, 2922, 2880, 2851, 2361, 2343, 2332, 1724, 1711, 1614, 1508, 1398, 1385, 1352, 1281, 1220, 1124, 1003, 841 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 5.13 (s, 2 H, OCH_2), 6.26 (d, *J* = 9.5 Hz, 1 H, H-3), 6.89 (d, *J* = 2.2 Hz, 1 H, H-Ar), 6.92 (dd, *J* = 8.5 and *J* = 2.4 Hz, 1 H, H-Ar), 7.35–7.44 (m, 6 H, H-Ar), 7.64 (d, *J* = 9.5 Hz, 1 H, H-4).

UV (CH_2Cl_2): λ_{max} = 319, 233 nm.

Ethyl (2*E*/2*Z*)-3-(2,4,6-Trihydroxyphenyl)acrylate [Mixture of (*E*)-4a and (*Z*)-4a]
^{1}H NMR (400 MHz, CD_3OD): δ = 1.39 (t, *J* = 7.0 Hz, 3 H, CH_3 of *Z*-isomer), 1.46 (t, *J* = 7.0 Hz, 3 H, CH_3 of *E*-isomer), 4.06 (q, *J* = 7.0 Hz, 2 H, CH_2 of *Z*-isomer), 4.12 (q, *J* = 7.0 Hz, 2 H, CH_2 of *E*-isomer), 6.07 (d, $J_{2,3}$ = 9.6 Hz, 1 H, H-2 of *E*-isomer), 6.09 (d, $J_{2,3}$ = 9.6 Hz, 1 H, H-2 of *Z*-isomer), 6.28–6.30 (m, 2 H, H-Ar), 6.35 (d, *J* = 2.0 Hz, 1 H, H-Ar of *E*-isomer), 6.37 (d, *J* = 2.0 Hz, 1 H, H-Ar of *Z*-isomer), 8.06 (dd, *J* = 9.6 and *J* = 0.8 Hz, 1 H, H-3 of *E*-isomer), 8.08 (dd, *J* = 9.6 and *J* = 0.8 Hz, 1 H, H-3 of *Z*-isomer).

Ethyl (2*E*)-3-(2,4-Dihydroxyphenyl)acrylate [(*E*)-4b]
^{1}H NMR (400 MHz, CD_3OD): δ = 1.42 (t, *J* = 7.0 Hz, 3 H, CH_3), 4.12 (q, *J* = 7.0 Hz, 2 H, CH_2), 6.23 (d, $J_{2,3}$ = 9.5 Hz, 1 H, H-2), 6.87 (d, $J_{3,5}$ = 2.3 Hz, 1 H, H-3), 6.90 (dd, $J_{5,6}$ = 8.6 and $J_{5,3}$ = 2.4 Hz, 1 H, H-5), 7.51 (d, $J_{6,5}$ = 8.6, 1 H, H-6), 7.87 (d, $J_{3,2}$ = 9.6 Hz, 1 H, H-3).

UV (CH_2Cl_2): λ_{max} = 322, 316, 205 cm^{-1}.

Ethyl (2*Z*)-3-(2,4-Dihydroxyphenyl)acrylate [(*Z*)-4b]
^{1}H NMR (400 MHz, CD_3OD): δ = 1.48 (t, *J* = 7.0 Hz, 3 H, CH_3), 4.21 (q, *J* = 7.0 Hz, 2 H, CH_2), 6.34 (d, $J_{2,3}$ = 9.7 Hz, 1 H, H-2), 6.87–6.91 (m, 2 H, H-5 and H-3), 7.50 (d, $J_{6,5}$ = 8.4 Hz, 1 H, H-6 of *E*-isomer), 7.51 (d, $J_{6,5}$ = 8.4, 1 H, H-6 of *Z*-isomer), 8.21 (d, $J_{3,2}$ = 9.7 Hz, 1 H, H-3).

UV (CH_2Cl_2): λ_{max} = 299, 239, 206 cm^{-1}.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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