One-pot three component reaction involving cyclohexyl isocyanide for the synthesis of furo[3,4-*b*]chromenes

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On stirring an equimolar mixture of 4-oxo-4*H*-chromene-3-carbaldehyde, ninhydrin and cyclohexyl isocyanide in CH_2Cl_2-MeOH (7:1) at room temperature produces 3-cyclohexylimino-1-(2-hydroxy-1,3-dioxo-2,3-dihydro-1H-inden-2-yl)-1,3-dihydro-9H-furo[3,4-b]chromen-9-one which on hydrolysis produces 1-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-1*H*-furo[3,4-*b*]chromene-3,9-dione. The structure of the latter compound was confirmed by single crystal X-ray diffraction.

Keywords: 3-formylchromone, multicomponent reaction, isocyanide, furo[3,4-*b*]chromene, atom economy, chromene

Although furo[2,3-*b*]chromones are well studied with respect to synthesis and pharmaceutical activities,[1] furo[3,4-*b*]chromones are very scarce in the literature. This class of compounds were synthesised (i) by acid-catalysed cyclisation of α-keto-β-(*o*-hydroxybenzoyl)butyrolactone;[2] (ii) by oxidation of 3-benzoyl-2-benzylchromone with SeO_2;[3] (iii) by photolysis of 3-aroyl-2-furylchromone,[4,5] which are highly substituent–dependent; (iv) by heating ethyl 3-bromo-/acetoxy-methyl-4-oxo-chromene-2-carboxylate in a mixture of glacial acetic acid and concentrated HCl;[6] (v) by lithiation of the acetal generated from **1**, followed by trapping an aldehyde and subsequent cyclisation by unmasking the acetal;[7] (vi) by isocyanide-induced 3-component reaction using dibenzoylacetylene and resorcinol[8] and (vii) by condensation of ethyl pentafluorobenzoylpyruvate with aromatic aldehyde in the presence of piperidine or HCl.[9] So, it is of interest to search for easy route for the synthesis of furo[3,4-*b*]chromone moieties in various forms.

In connection to our earlier report on the isocyanide-induced reaction on 4-oxo-4*H*-chromene-3-carbaldehyde (**1**),[10] there was a misinterpretation in assigning a structure on the basis of ^{1}H NMR, ^{13}C NMR and mass spectral analysis. During the preparation of this manuscript, a report[11] on the same reaction predicted the actual structure without mentioning the previous report.[10] The product from the reaction of **1** and cyclohexyl isocyanide (**2**) was reported earlier to be pyrano[3,4-*b*]chromones **3**.[10] But from the single crystal X-ray diffraction (Table 1), it is confirmed to be furo[3,4-*b*]chromone **4** (Scheme 1). Structures **3** and **4** having the same molecular formula could not be distinguished on the basis of NMR or mass spectral analysis. From the ^{1}H NMR spectra, presence of two chromonyl moieties and one *N*-cyclohexyl moiety were discernible. A singlet at around δ7.1–7.2 may be assigned to H at C-1 in **3** or to exocyclic vinyl H in **4**. Compound **4a** was crystallised from CH_2Cl_2 and X-ray crystallography shows the presence of one solvent molecule in the crystal (Fig. 1).

The above reaction involves two molecules of **1** and one molecule of **2**. In order to increase the versatility of this reaction, one molecule of 3-formyl-4-chromone was replaced by such a carbonyl compound which possesses higher carbonyl group reactivity than that of **1**. On stirring an equimolar mixture of **1a**, ninhydrin (**5**) and **2** in methanol at room temperature for 12 h, a white precipitate appeared which was collected by filtration. The structure of the compound was established to be **6a** on the basis of IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis. ^{1}H NMR spectrum showed three singlets at δ 2.53, 5.85 and 7.32 of which the last signal was exchangeable with D_2O. It also contains signals for 11 protons from cyclohexyl unit and 7 aromatic protons. IR spectrum of **6a** showed signals at 3246 (O-H), 1716 (C=O), 1647 (C=O) cm^{-1}. ^{13}C NMR showed 27 signals having no isochronous carbon atom. The mass spectral data 458 $(M+H)^+$ and 480 $(M+Na)^+$ corroborate the structure. Compound **6b** and **6c** were also prepared in moderate yields (40–50%) from **1b** and **1c** respectively. Many attempts were made to improve the yield of **6** by changing the solvent. It was observed that a mixture of dichloromethane and methanol (7:1) gave a better yield (60–70%).

Formation of **6** may be rationalised as follows: isocyanide prefers 1,4-addition over 1,2-addition on α, β-unsaturated carbonyl compounds.[12–14] Isocyanide **2** attacks C-2 position of chromone moiety in **1** to form **7**, which intramolecularly cyclises to **8**. It then tautomerises to chromone-fused 2-aminofuran **9** (Scheme 2). In absence of any other carbonyl

Table 1 Crystal data of compound **4a** and **12a**

	Compound **4a**	Compound **12a**
Chemical formula	$C_{30}H_{27}Cl_2NO_5$	$C_{21}H_{12}O_7$
Formula weight	552.43	376.31
Crystal system	Triclinic	Triclinic
Space group	P-1	P-1
Unit cell dimensions		
	a = 8.9449 (4) Å	*a* = 11.3453 (6) Å
	b = 11.8775 (6) Å	*b* = 12.7065 (9) Å
	c = 13.9083 (8) Å	*c* = 13.4497(8) Å
	α = 112.523 (5)°	α = 114.756 (6)°
	β = 101.640 (4)°	β = 106.315 (5)°
	γ = 98.105 (4)°	γ = 93.883 (5)°
Unit cell volume	1297.39 (12) Å^3	1651.16 (18) Å^3
Formula number, Z	2	4
Density (calculated)	1.414 g cm^{-3}	1.514 g cm^{-3}
Crystal size max (mm)	0.30	0.24
Crystal size mid (mm)	0.05	0.03
Crystal size min (mm)	0.05	0.03
Absorption coefficient/μ	0.293	0.115
F(000)	576	776
Data collection in a θ range	2.68–30.00°	2.83–30.00°
Diffraction refelection range	−12<*h*>=12	−15<*h*>=11
	−14<*k*>=16	−17<*k*>=17
	−19<*l*>=11	−18<*l*>=18
Diffraction reflection unique:		
Reflections collected/ unique	7336/4796 [R_{int} = 0.0164]	9214/5350 [R_{int} = 0.0216]
Goodness of fit on F^2	0.925	0.853
Reflection threshold	I>2σ(I)	I>2σ(I)
	R^1 = 0.0436,	R^1 = 0.0466,
	wR^2 = 0.1022	wR^2 = 0.0919
(R indices defined as R^1)		

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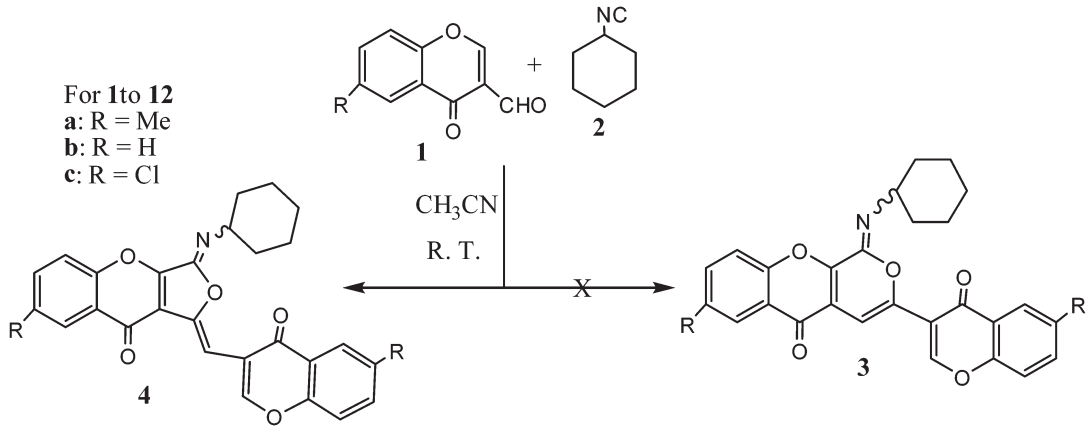


Scheme 1

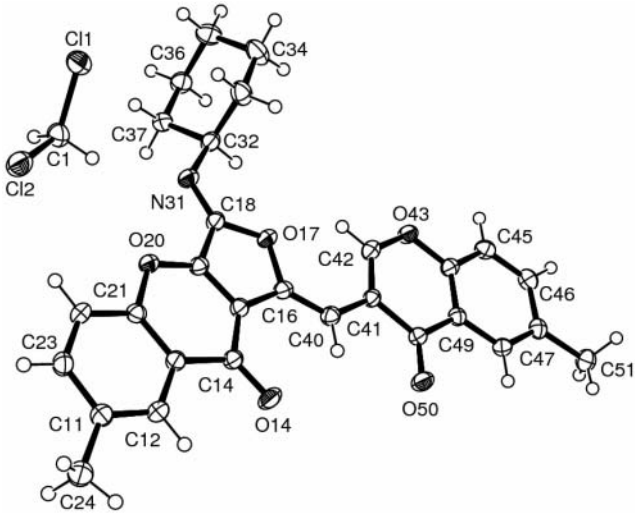


Fig. 1 ORTEP diagram of **4a** with thermal ellipsoids drawn at 50% probability level.

compound, intermediate **9** attacks a second molecule of aldehyde **1** to form **10** and finally dehydrates to **4**. But in the presence of **5**, which contributes a more reactive carbonyl function than that of **1**, **9** reacts with **5** to form **6**.

Unlike the previous report[10] for the formation of **4** from **1** and **2**, in this case no dehydration takes place on **6** although a 3°-alcohol function is present. On heating **6** with conc. H_2SO_4 or with $KHSO_4$, the reaction mixture failed to produce the dehydrated product. Mode of reactions of **4** and **6** also differ when treated with HCl in methanol. Compound **4** underwent a rearrangement[10] to produce a lactam **11**, whereas **6** under similar condition produced the hydrolysed product lactone **12** (Scheme 3). The structure of **12** was established on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. Finally the structure was confirmed by single crystal X-ray diffraction (Table 1 and Fig. 2).

In conclusion, we have developed an isocyanide-induced three component reaction with 100% atom economy involving 3-formyl-4-chromone and ninhydrin to produce hitherto unreported chromones fused with iminolactones.

Experimental

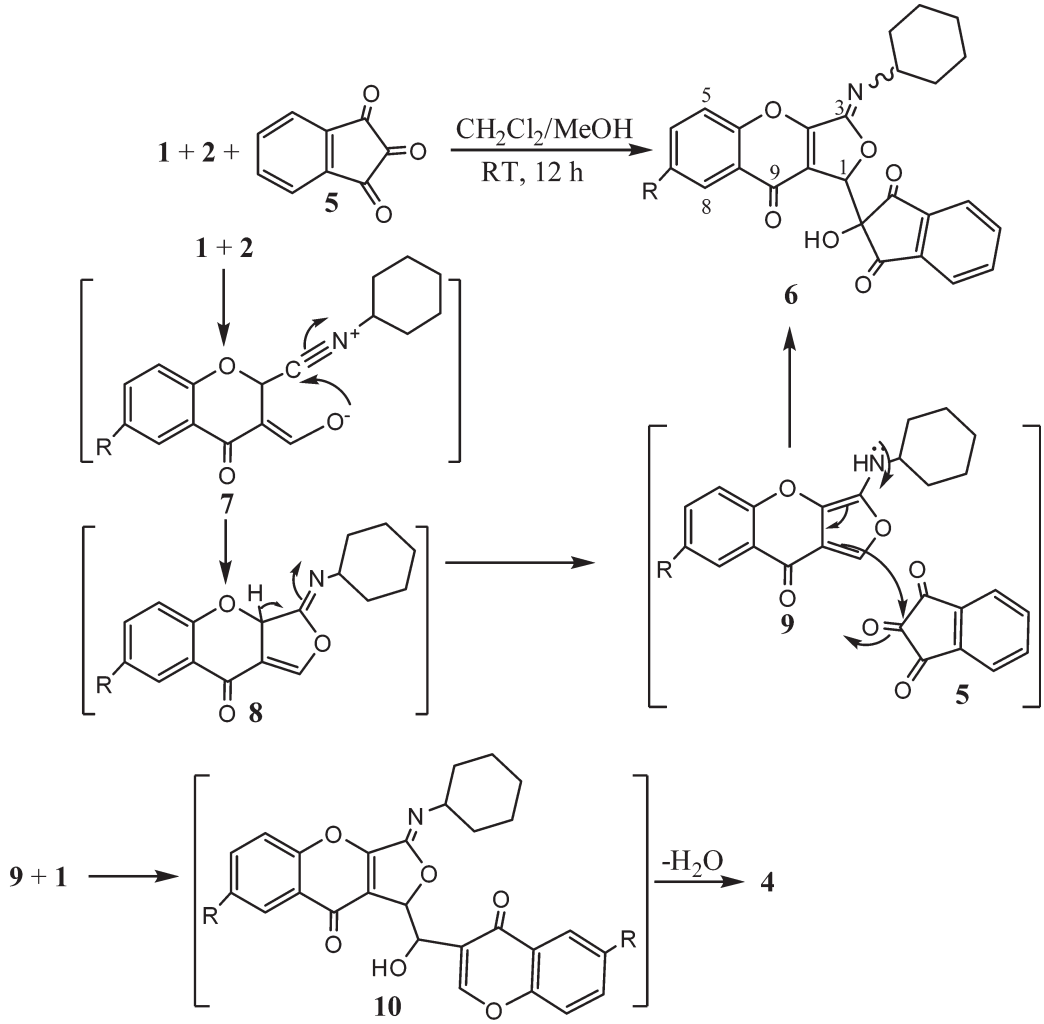
IR spectra were recorded in KBr on a Beckman IR 20A instrument, ^{1}H NMR spectra in $CDCl_3$ on a Bruker 300 MHz spectrometer, mass spectra on a Qtof Micro YA 263 instrument and elemental analysis on a Perkin Elmer 240C elemental analyser. Light petroleum refers to the fraction with distillation range 60–80 °C.

Good quality single crystals of **4a** and **12a** were obtained from slow evaporation of solvent (CH_2Cl_2) at room temperature and they were used for structural analysis. X-ray data were measured with Mo-Kα radiation at 150 K using the Oxford Diffraction X-Calibur CCD System. Data analysis was carried out with the Crysalis program[15] and the structures were solved with the SHELXS-97 program.[16] For both the structures the non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon and oxygen were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atoms to which they were attached. Absorption corrections were carried out with the ABSPACK program.[17] The structures were refined on F^2 using the SHELXL-97 program.[16] Crystallographic data are collected in Table 1. CCDC 809699 (for compound **12a**) and CCDC 809700 (for compound **4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk).

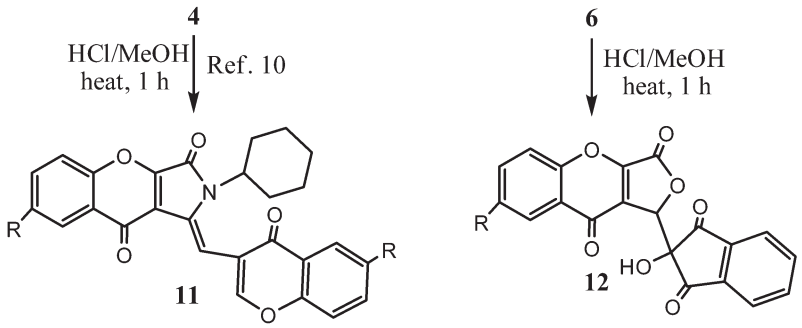
*Synthesis of 3-cyclohexylimino-1-(2-hydroxy-1,3-dioxo-2,3-dihydro-1H-inden-2-yl)-1,3-dihydro-9H-furo[3,4-b]chromen-9-ones (***6a–c***)*
Aldehyde **1** (1 mmol) and **5** (1 mmol) were dissolved in a mixture of dichloromethane (7 mL) and methanol (1 mL). To the resultant mixture, **2** (1 mmol) was added and stirred at room temperature for 12 h. The reaction mixture on concentration produced **6**, which was crystallised from chloroform-light petroleum (70:30) to afford white crystalline solids **6a–c**.

6a: Yield (285 mg, 62%); m.p. 208–210 °C; IR: ν_{max} 3246, 2930, 1716, 1647 cm^{-1}; ^{1}H NMR: δ($CDCl_3$) 0.45–0.48 (1H, m, cyclohexyl-H), 0.73–0.94 (2H, m, cyclohexyl-H), 1.00–1.17 (3H, m, cyclohexyl-H), 1.23–1.31 (2H, m, cyclohexyl-H), 1.47–1.50 (1H, m, cyclohexyl-H), 1.55–1.73 (1H, m, cyclohexyl-H), 2.53 (3H, s, CH_3), 3.05 (1H, quintet, J = 6.7 Hz, N–C*H*), 5.85 (1H, s, 1-H), 7.32 (1H, s, exchangeable, OH), 7.60-7.66 (2H, m, ArH), 7.84-7.87 (2H, m, ArH), 7.89-7.96 (1H, m, ArH), 8.12 (1H, br.d, J = 7.5 Hz, ArH), 8.16 (1H, br.s, 8-H); ^{13}C NMR: δ 20.9, 24.4, 24.7, 25.2, 31.9, 33.3, 56.6, 76.3, 81.1, 118.8, 123.2, 123.3, 123.7, 125.1, 125.7, 136.3, 136.6, 136.9, 137.0, 140.9, 141.7, 148.6, 153.8, 155.2, 176.1, 196.5, 198.0; MS (Positive ion electrospray): *m/z* 458 [M + H]$^+$, 480 [M + Na]$^+$. Anal Calcd for $C_{27}H_{23}NO_6$: C, 70.89; H, 5.07; N, 3.06. Found: C, 71.10; H, 4.98; N, 3.00%.

6b: Yield (310 mg, 70%); m.p. 198–200 °C; IR: ν_{max} 3300, 2940, 1720, 1650 cm^{-1}; ^{1}H NMR: δ($CDCl_3$) 0.46–0.50 (1H, m, cyclohexyl-H), 0.73–0.90 (2H, m, cyclohexyl-H), 1.00–1.17 (2H, m, cyclohexyl-H), 1.23–1.36 (3H, m, cyclohexyl-H), 1.47–1.51 (1H, m, cyclohexyl-H), 1.55–1.74 (1H, m, cyclohexyl-H), 3.06 (1H, quintet, J = 6.9 Hz, N–C*H*), 5.86 (1H, s, 1-H), 7.23 (1H, s, exchangeable, OH), 7.58 (1H, br.t, J = 7.5 Hz, ArH), 7.73 (1H, br.d, J = 8.4 Hz, 5-H), 7.80–7.86 (3H, m, ArH), 7.89–7.96 (1H, m, ArH), 8.13 (1H, br.d, J = 7.5 Hz, ArH), 8.38 (1H, br.d, J = 7.8 Hz, 8-H). Anal Calcd for $C_{26}H_{21}NO_6$: C, 70.42; H, 4.77; N, 3.16. Found: C, 70.11; H, 4.58; N, 3.01%.



Scheme 2



Scheme 3

6c: Yield (285 mg, 60%); m.p. 212–214 °C; IR: ν_{max} 3250, 2980, 1710, 1640 cm^{-1}; ^1H NMR: δ($CDCl_3$) 0.46–0.49 (1H, m, cyclohexyl-H), 0.69–0.90 (2H, m, cyclohexyl-H), 1.00–1.17 (2H, m, cyclohexyl-H), 1.22–1.36 (3H, m, cyclohexyl-H), 1.47–1.51 (1H, m, cyclohexyl-H), 1.55–1.72 (1H, m, cyclohexyl-H), 3.06 (1H, quintet, *J* = 6.6 Hz, N–C*H*), 5.86 (1H, s, 1-H), 6.97 (1H, s, exchangeable, OH), 7.69 (1H, d, *J* = 9.0 Hz, 5-H), 7.77 (1H, dd, *J* = 9.0, 2.1 Hz, 6-H), 7.83–7.91 (2H, m, ArH), 7.93–7.98 (1H, m, ArH), 8.13 (1H, br.d, *J* = 7.5 Hz, ArH), 8.34 (1H, br.d, *J* = 2.1 Hz, 8-H). Anal Calcd for $C_{26}H_{20}NClO_6$: C, 65.35; H, 4.22; N, 2.93. Found: C, 65.11; H, 4.06; N, 3.02%.

Hydrolysis of iminolactone **6**

Iminolactone **6** (1 mmol) was dissolved in methanol (10 mL) and concentrated HCl (two drops) was added. The resultant mixture was heated under reflux for 1 h. Solvent was removed from the reaction mixture under reduced pressure. Ice water (10 g) was added to the concentrate to afford a white solid, which was filtered, washed with water, dried in air and crystallised from chloroform-light petroleum to afford 1-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-1*H*-furo[3,4-*b*]chromene-3,9-dione **12**.

12a: Yield (225 mg, 60%); m.p. 262–264 °C; IR: ν_{max} 3250, 2950, 1730, 1710, 1650 cm^{-1}; ^1H NMR: δ($CDCl_3$) 2.56 (3H, s, CH_3), 5.93 (1H, s, 1-H), 7.22 (1H, s, exchangeable, OH), 7.63 (1H, d, *J* = 8.4 Hz, 5-H), 7.73 (1H, br.d, *J* = 8.4 Hz, 6-H), 7.88–7.98 (3H, m, ArH), 8.13 (1H, br.d, *J* = 7.5 Hz, ArH), 8.20 (1H, br.s, 8-H); ^{13}C NMR: δ 21.1, 74.2, 78.1, 118.9, 123.3, 123.9, 124.4, 126.0, 131.2, 136.9, 137.2, 137.8, 137.9, 140.6, 141.4, 148.9, 155.1, 161.7, 176.1, 195.0, 197.3; MS (Positive ion electrospray): *m/z* 377 $[M + H]^+$, 399 $[M + Na]^+$. Anal Calcd for $C_{21}H_{12}O_7$: C, 67.03; H, 3.21. Found: C, 66.92; H, 3.11%.

12b: Yield (200 mg, 55%); m.p. 234–236 °C; IR: ν_{max} 3290, 2960, 1735, 1710, 1660 cm^{-1}; ^1H NMR: δ($CDCl_3$) 5.95 (1H, s, 1-H), 7.15

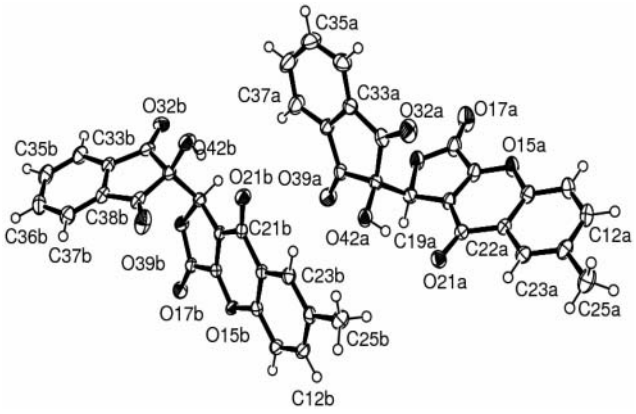


Fig. 2 ORTEP diagram of **12a** with thermal ellipsoids drawn at 50% probability level.

(1H, s, exchangeable, OH), 7.68 (1H, br.dd, *J* = 7.8, 7.5 Hz, 7-H), 7.74 (1H, br.d, *J* = 8.4 Hz, 5-H), 7.86-7.99 (4H, m, ArH), 8.13 (1H, br.d, *J* = 7.2 Hz, ArH), 8.42 (1H, br.d, *J* = 7.8 Hz, 8-H). Anal Calcd for $C_{20}H_{10}O_7$: C, 66.31; H, 2.78. Found: C, 66.40; H, 2.69%.

12c: Yield (235 mg, 58%); m.p. 240–242 °C; IR: ν_{max} 3250, 2970, 1730, 1705, 1655 cm^{-1}; ^1H NMR: δ($CDCl_3$) 5.94 (1H, s, 1-H), 6.87 (1H, s, exchangeable, OH), 7.70 (1H, d, *J* = 9.0 Hz, 5-H), 7.84–7.91 (2H, m, ArH), 7.94–8.00 (2H, m, ArH), 8.13 (1H, br.d, *J* = 7.2 Hz, ArH), 8.37 (1H, d, *J* = 2.4 Hz, 8-H). Anal Calcd for $C_{20}H_9ClO_7$: C, 60.55; H, 2.29. Found: C, 60.37; H, 2.21%.

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