Mechanistic Studies of the Ring Expansion Reaction of Isatylidenes to Quinolines

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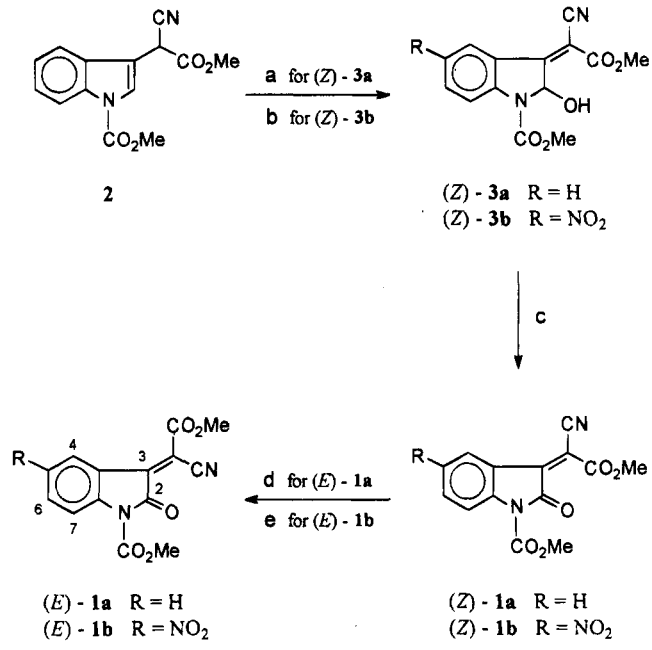
Introduction

The ring expansion reaction of isatylidene compounds is an effective method for the preparation of quinolines.[1] Suitable substrates are available either *via* a Knoevengel condensation of isatins with active methylene compounds[2] or by anionic reactions such as Michael- or Claisen-type condensations with oxindoles.[3] The formed adducts can undergo a further rearrangement to quinoline derivatives upon hydrolysis with either acid or base or by treatment with nucleophiles such as amines, alcohols or carbanions. The reaction is thought to proceed through a benzylidene intermediate,[4] which undergoes intramolecular nucleophilic cyclization to afford the 6-membered heterocycle. Herein we report a study of the reactivity of (*Z*)- and (*E*)-isatylidene derivatives **1a** and **1b** in methanol, with the goal of providing mechanistic information. Some of the studied molecules might be candidates for biological tests due to their high functionalization.

Results and Discussion

Compounds (*Z*)-**1a** and (*Z*)-**1b** were prepared by literature procedures.[5] Oxidation of the indole derivative **2** with nitric acid at 20 °C (molar ratio 1:15) afforded 2-hydroxyindolenine (*Z*)-**3a**, which was oxidized with chromium trioxide to give a 12:1 mixture of (*Z*)- and (*E*)-isatylidenes **1a** from which pure (*Z*)-**1a** was isolated by crystallization.[5] When the nitration reaction was run at 65 °C (molar ratio of **2** to HNO_3 1:49), the nitro analogue (*Z*)-**3b** was obtained and this was oxidized to give a 7:1 mixture of (*Z*)- and (*E*)-5-nitroisatylidenes **1b**, which was crystallized to give pure (*Z*)-**1b** (Scheme 1). Exposure of (*Z*)-isatylidene **1a** to dimethyl sulfoxide at room temperature afforded, upon dissolution, an equilibrated mixture of the corresponding geometrical isomers[6] [2:1 (*E*)/(*Z*) ratio], as determined by the observation of two signals for H-4 [(*Z*)-**1a**, 8.24; (*E*)-**1a**, 8.38; in $CDCl_3$] in the ^1H NMR spectra.[2c,7] Further recrystallization of this mixture from chloroform gave a final (*E*)/(*Z*) ratio of 6:1. The results discussed below were therefore obtained from (*E*)-**1a** admixed with (*Z*)-**1a**. In contrast, isomerically pure (*E*)-**1b** was obtained by thermal isomerization of (*Z*)-**1b**, followed by two recrystallizations from chloroform.

Scheme 1[a]



[a] Conditions: (a) HNO_3/AcOH, molar ratio of **2** to HNO_3 1:15, 20 °C, 8 h, ref 5; (b) HNO_3/AcOH, molar ratio of **2** to HNO_3 1:49, 65 °C, 15 min; (c) CrO_3/AcOH, 7 °C → rt, 3 h; (d) DMSO, 10 min, rt, (*E*)/(*Z*) ratio 6:1; (e) 170–171 °C, 3 min.

Treatment of isatylidene (*Z*)-**1a** with methanol under reflux furnished after 2 h exclusively the corresponding quinolinone **5a** (81%). The introduction of a nitro group at C-5 leads to a remarkable change in selectivity. Thus, under the same reaction conditions, the isatylidene (*Z*)-**1b** afforded after 30 min imine **6b** (72%), accompanied by trace amounts (<2%) of quinolinone **5b**, which was identified by ^1H NMR (see Experimental Section). The structures of **5a** and **6b** were verified by spectroscopy and elemental analysis. Conclusive evidence proving that the chemoselectivity of the ring expansion reaction is independent of the stereochemistry of the starting material was obtained from the selective conversion of the corresponding (*E*)-rich mixture of **1a** (6:1 ratio) to quinolinone **5a** and from (*E*)-**1b** to imine **6b** (Scheme 2). Consequently, the selective transformation of (*Z*)-**1a** to **5a** and of (*E*)-**1b** to **6b** involved an isomerization process, at some intermediate stage, which clearly is faster than the ring closure. Furthermore, TLC examination of the reaction mixture from (*Z*)-**1a** or (*Z*)-**1b** during the course of the reaction revealed that, in each case, the starting material disappeared to give a new component, which in turn slowly disappeared as the ring expansion products were formed.

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(6) (a) Morales-Ríos, M. S.; Mora-Pérez, Y.; Joseph-Nathan, P. *Magn. Reson. Chem.* **1992**, *30*, 1153. (b) Sandström, J. *Top. Stereochem.* **1983**, *14*, 156.

(7) (a) The anisotropic effect exerted by the carbonyl group at the unsaturated side chain promotes the deshielding of the H-4 signal in the (*E*)-isomers. (b) Autrey, R. L.; Tahk, F. C. *Tetrahedron* **1967**, *23*, 901. (c) Morales-Ríos, M. S. Bucio, M. A.; Joseph-Nathan, P. *Magn. Reson. Chem.* **1993**, *31*, 960.

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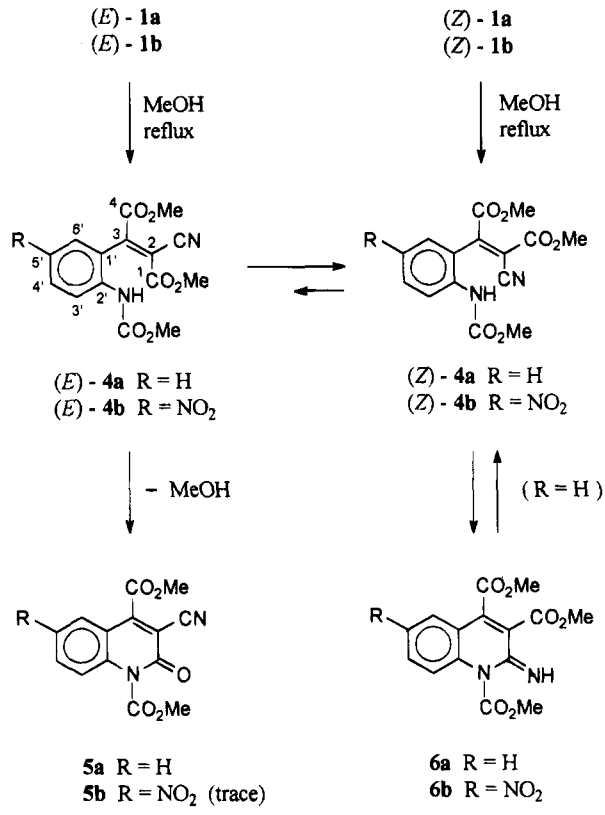
Scheme 2



To gain more detailed mechanistic information, we explored the possibility of isolating the postulated[4] benzylidene intermediates. Isatylidenes (*Z*)-**1a** and (*Z*)-**1b** were converted into the corresponding benzylidenes **4a** and **4b** when treated with methanol at room temperature. After crystallization a single isomer was isolated, as determined by ^{1}H NMR analysis, although it was not immediately clear whether the (*E*)- or (*Z*)-isomer was arising. At this stage, single crystals of **4b** suitable for X-ray diffraction, in the form of yellowish prisms, were obtained. A perspective view of the molecular structure is shown in Figure 1.[8] According to X-ray structure analysis, the aryl and nitrile groups are located *cis*, with the aryl group forming an angle of 54.7° with respect to the ethylenic plane. The ^{1}H NMR spectrum of a solution of (*Z*)-**4b** in $CDCl_3$ did not change during storage for 1 week at 4 ×bcC. This persistence allowed its rigorous characterization by NMR and elemental analysis. That compound **4a** indeed possesses the (*Z*) configuration was only tentative at this point. As expected, when the isolated benzylidenes **4a** and **4b** were submitted to the cyclization reaction under the conditions used for the corresponding isatylidenes, the cyclized quinolinone **5a** and imine **6b** were obtained in high yields, confirming that the benzylidene is the initial product of the rearrangement.

To determine whether the isomerization process occurs at the stage of starting material or at the stage of benzylidene intermediate, the reactivity of isatylidenes

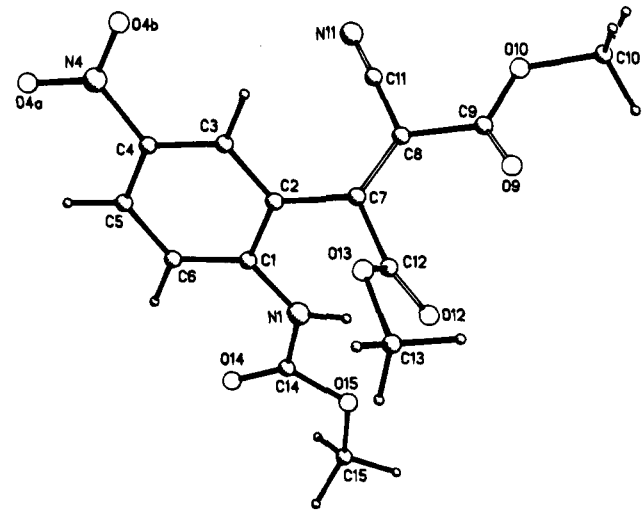


Figure 1. X-ray crystallographic computer-generated perspective drawing of (*Z*)-**4b**.[8a]

Table 1. (*E*)/(*Z*) Equilibration of Benzylidenes 4a and 4b in CD_3OD at 25 °C[a,b]

time, h	0.1	0.5	1.0	1.3	3.0
4a (*E*)/(*Z*) ratio	1:1	1:2.5	1:5	1:8	1:8
time, h	0.1	0.5	1.3	2.1	3.5
4b (*E*)/(*Z*) ratio	4:1	2:1	1:1	1:2	1:2

[a] The ratios of (*E*)- and (*Z*)-isomers were determined from the peak area integrations of the CO_2Me resonances at 3.66 and 3.71 ppm for (*E*)-**4a**, at 3.72 and 3.90 ppm for (*Z*)-**4a**, at 3.69 and 3.80 ppm for (*E*)-**4b**, and at 3.83 and 3.93 ppm for (*Z*)-**4b**. Data were collected over time using a program in which each spectrum was comprised of 16 scans. [b] Estimated reproducibility ±3%.

1a and **1b** was examined under controlled conditions. To shed light on the process at early conversion, the reaction of (*E*)-**1b** with methanol-d_4 was monitored by ^{1}H NMR spectroscopy at 25 °C. The initial observable product was the benzylidene intermediate **4b** as a mixture of isomers, with the (*E*)-isomer predominating (Table 1). After 2.1 h equilibration was reached, as monitored by a gradual increase of the set of signals assigned to the (*Z*)-isomer and the corresponding decrease of the set of signals for the (*E*)-isomer. At the end of this reaction period no significant amount of the corresponding imine **6b** was formed. Thus, opening of (*E*)-**1b** with methanol seems to be very fast to give predominately (*E*)-**4b**, which then equilibrates. At the equilibrium the (*E*)/(*Z*) ratio was 1:2 with the (*Z*)-isomer favored. The same **4b**-(*E*)/(*Z*) ratios were obtained irrespective of the initial **1b**-(*E*)/(*Z*) ratio. Further transformation of this mixture was achieved by heating under refluxing methanol-d_4 for 30 min. This reaction period is characterized by a gradual loss of the two sets of signals for the (*E*)- and (*Z*)-**4b** isomers (with the (*E*)/(*Z*) ratio remaining constant, 1:2) and the corresponding growth of the signal set for imine **6b**. The described facts suggest the sequence of reactions leading to the formation of imine **6b**, as is shown in Scheme 2.

An analogous NMR-monitored reaction of the (*E*)-rich mixture of **1a**, treated under the same conditions, afforded after 1.3 h an equilibrated mixture of (*Z*)- and (*E*)-benzylidenes **4a** in which the (*Z*)-benzylidene exceeded the (*E*)-isomer by 8:1, as reported in Table 1. We verified that at the equilibrium pure (*Z*)-**1a** afforded the same (*E*)/(*Z*) ratio as the (*E*)-rich mixture. At 25 °C the equilibria constants[9] $K_1 = 8.0 \pm 0.24$ and $K_2 = 2.0 \pm 0.04$ were estimated by integration of the corresponding CO_2-

(8) (a) The atom numbering scheme for the X-ray structure shown for compound (*Z*)-**4b** is different from the numbering scheme used to assign the chemical name for this compound, as is used through out the text. (b) The authors have deposited atomic coordinates for structure (*Z*)-**4b** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EK, U.K.

Table 2. Selected ^{1}H NMR Spectral Data Used To Assign the Stereochemistries of Benzylidenes 4a and 4b in $CDCl_3$

	δ (ppm)			δ (ppm)	
compd	H-3′	H-6′	compd	H-3′	H-6′
(*Z*)-**4a**	8.05	7.32	(*Z*)-**4b**	8.50	8.19
(*E*)-**4a**	7.81	7.10	(*E*)-**4b**	8.31	7.99

Me resonances in the ^{1}H NMR spectra recorded in methanol-d_4. At 298 K these data translate into $\Delta\Delta G_1 = -0.41$ kcal/mol and $\Delta\Delta G_2 = -1.23$ kcal/mol for the equilibria. At 25 °C the benzylidene **4a** equilibrates with $t_{1/2}$ of 27 min, while under the same conditions **4b** equilibrates with $t_{1/2}$ of 120 min. From these data, it is clear that **4b** equilibrates about four times slower than **4a**. On the basis of the data given above, it became apparent that the cyclized products **5a** and **6b** arise *via* the thermodynamic equilibration of the initially formed benzylidene intermediate rather than from a preequilibration of the starting material.[6] Moreover, it is clear that the rate-limiting step is the cyclization of the benzylidene intermediate and not its formation. It is assumed that the electron-attracting ester group at N-1 of the isatylidene system induces an acceleration of the ring opening step to yield the intermediate, whereby in the second step the same substituent decreases the rate of quinoline formation, thus allowing for the isolation of intermediates.

The stereochemistry of the isomeric benzylidenes was assigned on the basis of the X-ray study of (*Z*)-**4b** (*vide supra*) and the observed differences in the ^{1}H NMR spectroscopic chemical shifts between the isomeric pairs (*Z*)-**4a**/(*E*)-**4a** and (*Z*)-**4b**/(*E*)-**4b** in $CDCl_3$ (Table 2). The consistent chemical shift differences for the signals due to H-3′ and H-6′ appear to be of diagnostic value. In all cases H-3′ and H-6′ for the (*Z*)-isomer occur at lower field than those of the (*E*)-isomer. The ^{1}H NMR signals of the isomeric mixture of (*E*)- and (*Z*)-**4b** could be fully assigned in methanol-d_4, as could the signals of (*Z*)-**4a** in a mixture with (*E*)-**4a**. However the aromatic protons of the latter compound appear complex and overlapped (see Experimental Section).

The lower stability of the (*E*)-benzylidenes as compared to their (*Z*) counterparts may be caused by unfavorable steric interactions imposed by the bulky ester group at C-2 with the aryl group, and this may be an important contributing factor governing chemoselectivity. Accordingly, the ring expansion of (*Z*)- or (*E*)-**1b** proceeds *via* (*Z*)-**4b** to give imine **6b**. In sharp contrast, the reaction of (*Z*)- or (*E*)-**1a** proceeds *via* (*E*)-**4a**, less favored in the equilibrium with (*Z*)-**4a**, to give quinolinone **5a**. The obvious first explanation for the lack of imine product derived from the (*Z*)-benzylidene **4a** is that the imine formation involves a reversible step. This reversible step leads back to the formation of compound (*E*)-**4a**, which furnishes quinolinone **5a** through the only irreversible step (*E*)-**4a** → **5a**, irrespective of the ratio at the equilibrium in which the two benzylidene intermediates are formed. With this in mind, the isatylidene (*Z*)-**1a** was refluxed in methanol and the reaction was stopped before completion. The ^{1}H NMR spectroscopic analysis in $CDCl_3$ after 10 min clearly revealed a mixture of four compounds: the quinolinone **5a**, the (*Z*)- and (*E*)-benzylidenes **4a**, and the expected imine **6a** in a *ca.* 8:8:1:8 ratio.[10] Contact of this mixture with silica gel resulted in a substantially changed ratio, due to equilibration[11] between the (*Z*)- and (*E*)-benzylidenes **4a** and the imine **6a**, with quinolinone **5a** being the main component of the mixture. Attempts to isolate imine **6a** in pure form were unsuccessful. We carried out a comparative experiment using the (*Z*)-benzylidene **4a** as starting material, under the same conditions as described above. As expected, the composition and ratio of the crude product mixture was close to that obtained from **5a**. Regarding these results, it is evident that under refluxing methanol the (*Z*)-benzylidene **4a** effectively cyclizes to imine **6a**, which in turn undergoes a ring opening reaction *via* a reversible ring–chain tautomerism that ultimately allows the formation of the observed thermodynamically stable quinolinone **5a**. Consequently, the reversible formation of imine **6a** is the prime reason why isatylidene (*Z*)-**1a** undergoes the ring expansion reaction slower, as compared to (*Z*)-**1b**. The described facts suggest a sequence of reactions leading to the formation of quinolinone **5a**, which is shown in Scheme 2.

These results also seem to support the important role that substituents on the benzene ring can play in the ring–chain tautomerism, and consequently in the stability of the imine. Particularly, the strong negative resonance and inductive effects of the nitro group are responsible at least in part for the irreversibility of the reaction imine **6b** → (*Z*)-benzylidene. This fact can be explained reasonable by the weaker nucleophilicity of the nitrogen atom of the carbamate group.

This report presents the experimental details of the chemoselective conversion of (*Z*)- and (*E*)-isatylidenes to quinoline derivatives. The various steps of this process have been elucidated by ^{1}H NMR observation of intermediates produced in the reaction, as well as by the first isolation and characterization of (*Z*)- and (*E*)-benzylidenes already postulated as intermediates in these rearrangements.[12] Equilibration of (*E*)- and (*Z*)-benzylidenes in methanol-d_4 at 25 °C has been observed and accounts in part for the preparation of the same product independent of the double bond configuration in the substrate. The observed chemoselectivity of the ring expansion reaction is largely dependent on both the thermodynamic stability of the open-chain intermediates and of the cyclized products. These concepts and transformations may additionally apply to related ring expansion reactions.

Experimental Section

Melting point determinations are uncorrected. Chromatography was performed with silica gel 60 (Aldrich) 230–400 mesh, with the indicated solvents; R_f values were determined on silica gel coated aluminum sheets using AcOEt/hexane (1:1) as eluent. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. IR spectra were recorded in $CHCl_3$ solutions. The absolute methanol (Mallinckrodt) and the deuterated methanol (d_4 99.5% D, Aldrich) were used as received. Methyl (*Z*)-3-(1-cyano-2-methoxy-2-oxoethylidene)-2,3-dihydro-2-oxo-1*H*-indole-1-carboxylate (**1a**) was prepared as described elsewhere.[5] Elemental analyses were performed by the Microanalytical Laboratory, Elbach, Germany.

(9) (9) K_1 = [(*Z*)-**4a**/(*E*)-**4a**]; K_2 = [(*Z*)-**4b**/(*E*)-**4b**].

(10) The ^{1}H NMR assignment of imine **6a** (in $CDCl_3$), admixed with (*Z*)- and (*E*)-**4a** and **5a**, is as follows: 3.84 (s, 3H, Me), 3.97 (s, 3H, Me), 4.05 (s, 3H, Me), 7.51 (td, 1H, H-7), 7.72 (brd, 1H, H-5), 7.79 (td, 1H, H-6), 8.02 (brd, 1H, H-8), 9.69 (brs, 1H, imine). The R_f of **6a** is 0.63. Compounds (*Z*)-**4a** and **5a** were identified by comparison with the ^{1}H NMR spectra of pure samples.

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(12) Yoshida, K.; Otomasu, H. *Yakugaku Zasshi* **1976**, *96*, 33.

Methyl (*Z* and *E*)-3-(1-Cyano-2-methoxy-2-oxoethylidene)-2,3-dihydro-5-nitro-2-oxo-1*H*-indole-1-carboxylate (1b). Following a modified procedure,[5] to a stirred solution of **2** (1 g, 3.7 mmol) in 15 mL of glacial acetic acid, at 65 °C, was rapidly added 11.5 mL of HNO_3 (*d* 1.4). The mixture was stirred for additional 15 min at the same temperature. The resulting dark red solution was cooled to room temperature and then poured onto cracked ice. The precipitate which had formed was collected by suction filtration and washed four times with water. The wet mixture was dissolved in about 70 mL of AcOEt, washed three times with brine, and dried over Na_2SO_4. Excess solvent was evaporated *in vacuo*, the 1.1 g of the crude 1:12 mixture of **3a** (R_f = 0.52) and **3b** (R_f = 0.31), obtained as a yellow solid, was dissolved in 88 mL of glacial acetic acid at 10 °C, and then 1.1 g (11.0 mmol) of CrO_3 in 4.4 mL of water was added with stirring. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 3 h. The resulting dark brown solution was poured onto cracked ice, and the yellow precipitate formed was filtered off, washed three times with water, and dissolved in 50 mL of AcOEt. The solution was washed three times with brine and dried over Na_2SO_4. After evaporation of the solvent, 660 mg of reaction products was obtained. The ^1H NMR analysis of the crude mixture, in chloroform-*d*, indicated the presence of (*Z*)- and (*E*)-**1b** in a ratio of 7:1. Also some of the isatylidene (*Z*)-**1a** was observed (<8%, its spectral data were identical with previously published values[5]). Pure (*Z*)-**1b** was isolated by fractional crystallization from chloroform–hexane, giving 438 mg (36%, R_f = 0.70) of (*Z*)-**1b** as yellow powder: mp 171–173 °C; IR ν ($CHCl_3$, cm^{-1}) 2260, 1768, 1748, 1534, 1348; ^1H NMR ($CDCl_3$) δ 4.03 (s, 3H, Me), 4.09 (s, 3H, Me), 8.26 (d, 1H, J = 8.8 Hz, H-7), 8.48 (dd, 1H, J = 9.1, 2.3 Hz, H-6), 9.10 (d, 1H, J = 2.3 Hz, H-4); ^{13}C NMR could not be obtained due to low solubility in $CDCl_3$. Anal. Calcd for $C_{14}H_9N_3O_7$: C, 50.77; H, 2.74; N, 12.69; O, 33.81. Found: C, 50.58; H, 2.84; N, 12.63; O, 33.60.

Conversion of (*Z*)-1b to (*E*)-1b. A sample of solid (*Z*)-**1b** (400 mg, 1.21 mmol) was heated at 170–171 °C in a Pyrex Petri dish over a hot plate for 3 min. During this time, the solid melted and resolidified. The crude product consisted of a 5:1 mixture of (*E*)- and (*Z*)-**1b**, as determined by ^1H NMR. Isomerically pure (*E*)-**1b** was obtained after two recrystallizations from chloroform, giving 305 mg (76%, R_f = 0.62) of (*E*)-**1b** as an orange powder: mp 204–205 °C (from chloroform); IR ($CHCl_3$, cm^{-1}) ν 2260, 1770, 1748, 1532, 1346; ^1H NMR ($CDCl_3$) δ 4.10 (s, 6H, 2Me), 8.28 (d, 1H, J = 9.1 Hz, H-7), 8.49 (dd, 1H, J = 9.1, 2.4 Hz, H-6), 9.42 (d, 1H, J = 2.4 Hz, H-4); ^{13}C NMR (DMSO-d_6) δ 54.5, 54.6, 107.7, 113.9, 115.6, 119.7, 124.1, 130.6, 142.5, 143.8, 146.5, 149.9, 161.3, 161.6.

General Procedure for the Reaction of Isatylidenes (*Z*)-1a and (*Z*)-1b with Methanol. A solution of isatylidene (1.5 mmol) in anhydrous MeOH (80 mL) was stirred at the indicated temperature until TLC analysis indicated the absence of starting material. The solvent was removed under reduced pressure, and the resulting powder was purified by recrystallization. Pure (*Z*)-**4a**, (*Z*)-**4b**, **5a**, and **6b** were obtained as yellow solids.

(*Z*)-Dimethyl 2-Cyano-3-(2-(*N*-carbomethoxyamino)phenyl)-2-butenedioate (4a). Compound (*Z*)-**1a** was stirred at ambient temperature for 30 min, yielding 191 mg (40%, R_f = 0.59) of (*Z*)-**4a**: mp 124–125 °C (from chloroform–hexane); IR ($CHCl_3$, cm^{-1}) ν 3420, 3352, 2232, 1732; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H, Me), 3.90 (s, 3H, Me), 3.93 (s, 3H, Me), 7.22 (td, 1H, J = 7.8, 1.6 Hz, H-5′), 7.32 (dd, 1H, J = 7.8, 1.6 Hz, H-6′), 7.50 (td, 1H, J = 7.8, 1.6 Hz, H-4′), 7.51 (br, 1H, exchanges upon addition of D_2O, NH), 8.05 (brd, 1H, J = 7.8 Hz, H-3′); ^1H NMR (CD_3OD) δ 3.72 (s, 3H, Me), 3.79 (s, 3H, Me), 3.90 (s, 3H, Me) 7.33 (td, 1H, H5′), 7.49 (very br, 1H, H3′), 7.54 (td, 1H, H4′), 7.56 (d, 1H, H6′); ^{13}C NMR ($CDCl_3$) δ 52.2, 54.0, 110.7, 112.7, 122.0, 122.1, 124.3, 128.9, 132.3, 135.8, 153.9, 158.0, 160.3, 165.9.

(*E*)-Dimethyl 2-Cyano-3-(2-(*N*-carbomethoxyamino)-phenyl)-2-butenedioate (4a). The formation of (*E*)-**4a** could be established by ^1H NMR. The (*E*)-rich mixture of **1a** [6:1 (*E*)/(*Z*) ratio, 3 mg] was dissolved in 0.5 mL of dry MeOH. The solvent was quickly removed under vacuum, and the residue was redissolved in 0.6 mL of $CDCl_3$. The ^1H NMR data for the benzylidene (*E*)-**4a** admixed with its (*Z*)-isomer [(*E*)/(*Z*) ratio 1:1] are as follows: δ 3.69 (s, 3H, Me), 3.76 (s, 3H, Me), 3.90 (s, 3H, Me), 7.10 (dd, 1H J = 7.8, 1.6 Hz, H-6′), 7.16 (td, 1H, J = 7.8, 1.6 Hz, H-5′), 7.44 (td, 1H, J = 7.8, 1.6 Hz, H-4′), 7.51 (br, 1H, exchanges upon addition of D_2O, NH), 7.81 (brd, 1H, J = 7.8 Hz, H-3′); ^1H NMR (CD_3OD) δ 3.66 (s, 3H, Me), 3.71 (s, 3H, Me), 3.79 (s, 3H, Me) 7.20–7.60 (m, partially overlapped with the (*Z*)-isomer, ArH).

(*Z*)-Dimethyl 2-Cyano-3-(2-(*N*-carbomethoxyamino)-5-nitrophenyl)-2-butenedioate (4b). Compound (*Z*)-**1b** was stirred at ambient temperature for 30 min, yielding 332 mg (61%, R_f = 0.56) of (*Z*)-**4b**: mp 195–196 °C dec (from chloroform–hexane); IR ($CHCl_3$, cm^{-1}) ν 3412, 3340, 2260, 1748, 1516, 1346; ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H, Me), 3.95 (s, 3H, Me), 3.98 (s, 3H, Me), 8.07 (br, 1H, exchanges upon addition of D_2O, NH), 8.19 (d, 1H, J = 2.7 Hz, H-6′), 8.35 (dd, 1H, J = 9.3, 2.7 Hz, H-4′), 8.50 (d, 1H, J = 9.3 Hz, H-3′); ^1H NMR (CD_3OD) δ 3.78 (s, 3H, Me), 3.83 (s, 3H, Me), 3.93 (s, 3H, Me), 8.03 (d, 1H, H3′), 8.44 (dd, 1H, H4′), 8.45 (d, 1H, H6′); ^{13}C NMR ($CDCl_3$) δ 53.2, 54.3, 54.0, 111.8, 112.9, 120.4, 120.7, 124.8, 127.4, 141.9, 142.8, 153.1, 155.2, 159.6, 165.6. Anal. Calcd for $C_{15}H_{13}N_3O_8$: C, 49.59; H, 3.61; N, 11.57; O, 35.23. Found: C, 49.50; H, 3.60; N, 11.51; O, 35.07. The structure and configuration of (*Z*)-**4b** has been confirmed by single crystal X-ray diffraction.[8]

(*E*)-Dimethyl 2-Cyano-3-(2-(*N*-carbomethoxyamino)-5-nitrophenyl)-2-butenedioate (4b). The benzylidene (*E*)-**4b** (R_f = 0.39), admixed with its (*Z*)-isomer, was formed using the same procedure as for (*E*)-**4a**. The ^1H NMR data for the benzylidene (*E*)-**4b** admixed with its (*Z*)-isomer [(*E*)/(*Z*) ratio 4:1] are as follows in $CDCl_3$: δ 3.77 (s, 3H, Me), 3.83 (s, 3H, Me), 3.96 (s, 3H, Me), 7.99 (d, 1H, J = 2.7 Hz, H-6′), 8.07 (br, 1H, exchanges upon addition of D_2O, NH), 8.28 (dd, 1H, J = 9.3, 2.7 Hz, H-4′), 8.31 (d, 1H, J = 9.3 Hz, H-3′); ^1H NMR (CD_3OD) δ 3.69 (s, 3H, Me), 3.75 (s, 3H, Me), 3.80 (s, 3H, Me), 7.92 (d, 1H, H3′), 8.18 (d, 1H, H6′), 8.42 (dd, 1H, H4′).

1,4-Dicarbomethoxy-3-cyano-1,2-dihydro-2-quinolinone (5a). Compound (*Z*)-**1a**[5] was refluxed for 3 h, yielding 347 mg (81%, R_f = 0.44) of **5a**: mp 134–136 °C (from methanol). The same compound was isolated (79% yield) when a solution containing 100 mg of the (*E*)-rich mixture of **1a** [6:1 (*E*)/(*Z*) ratio] in 10 mL of dry MeOH was refluxed for 3 h: IR ($CHCl_3$, cm^{-1}) ν 2238, 1780, 1746, 1680; ^1H NMR ($CDCl_3$) δ 4.13 (s, 3H, Me), 4.19 (s, 3H, Me), 7.17 (distorted dd, 1H, J = 8.1, 1.0 Hz, H-8), 7.40 (distorted td, 1H, J = 7.3, 1.0 Hz, H-6), 7.73 and 7.74 (overlapping m, each 1H, H-5 and H-7); ^{13}C NMR ($CDCl_3$) δ 54.2, 57.1, 105.4, 112.3, 114.9, 115.0, 124.9, 128.1, 135.1, 137.5, 150.9, 151.4, 155.7, 163.2. Anal. Calcd for $C_{14}H_{10}N_2O_5$: C, 58.75; H, 3.52; N, 9.79; O, 27.95. Found: C, 58.59; H, 3.69; N, 9.75; O, 27.77.

1,3,4-Tricarbomethoxy-6-nitro-1,2-dihydro-2-iminoquinoline (6b). Compound (*Z*)-**1b** was refluxed for 30 min, yielding 392 mg (72%, R_f = 0.44) of **6b**: mp 170–172 °C (from methanol). Further reflux of **6b** under standard reaction conditions for 8 h left it unchanged. The same compound **6b** was isolated (71% yield) when a solution containing 100 mg of (*E*)-**1b** in 16 mL of dry MeOH was refluxed for 30 min: IR ($CHCl_3$, cm^{-1}) ν 3322, 1744, 1716, 1514, 1344; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H, Me), 4.01 (s, 3H, Me), 4.12 (s, 3H, Me), 8.08 (d, 1H, J = 9.3 Hz, H-8), 8.51 (dd, 1H, J = 9.3, 2.5 Hz, H-7), 8.63 (d, 1H, J = 2.5 Hz, H-5), 9.87 (brs, 1H, exchanges upon addition of D_2O, NH imine); ^{13}C NMR ($CDCl_3$) δ 53.0, 53.6, 53.8, 112.7, 119.4, 122.8, 126.1, 130.2, 145.3, 145.8, 150.6, 152.0, 165.3, 165.6. Anal. Calcd for $C_{15}H_{13}N_3O_8$: C, 49.59; H, 3.61; N, 11.57; O, 35.23. Found: C, 49.71; H, 3.70; N, 11.57; O, 35.08.

1,4-Dicarbomethoxy-3-cyano-1,2-dihydro-6-nitro-2-quinolinone (5b). The mother liquors of **6b** were subjected to column chromatography eluting with AcOEt 10% in hexane, thus affording quinolinone **5b** (<2%, R_f = 0.55) as yellow oil: IR ($CHCl_3$, cm^{-1}) ν 2260, 1790, 1744, 1534, 1342; ^1H NMR ($CDCl_3$) δ 4.20 (s, 3H, Me), 4.23 (s, 3H, Me), 7.33 (d, 1H, J = 9.3 Hz, H-8), 8.53 (dd, 1H, J = 9.3, 2.4 Hz, H-7), 8.75 (d, 1H, J = 2.4 Hz, H-5).

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