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Generation of Pyrrolo[2,1-*a*]isoquinoline Derivatives from N-ylides: Synthetic Control and Structural Characterization

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ABSTRACT: *New pyrrolo[2,1-a]isoquinolines were obtained by two one-pot procedures via 1,3-dipolar cycloaddition between the isoquinolinium N-ylides and symmetrical acetylenic dipolarophiles, avoiding the formation of dihydro intermediates. For structural comparison, the dihydro derivatives obtained by a classical two-stage reaction were characterized by NMR and X-ray crystallography, allowing complete stereochemistry assignments.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:723–729, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20740

INTRODUCTION

Pyrrolo[2,1-*a*]isoquinoline is an aromatic N-heterocycle formally obtained by the condensation of isoquinoline with pyrrole, the nitrogen atom being at the junction. The synthesis, reactivity, and biological properties of pyrrolo[2,1-*a*]isoquinoline were reviewed in 1997 by Mikhailovskii and Shklyaev [1]. Subsequently, the interest in new syntheses [2] of the pyrrolo[2,1-*a*]isoquinolines increased steadily owing to their significant biological activity, especially for natural products such as lamellarins [3] and crispine [4] (Fig. 1).

One of the most versatile synthetic strategies starting from isoquinoline is the 1,3-dipolar cycloaddition of their corresponding ylides [1,2e,2f,5–9] with both acetylenic and olefinic dipolarophiles. Usually, the syntheses of pyrrolo[2,1-*a*]isoquinolines involve two distinct steps: In the first step, the isoquinolinium salts are prepared and in the second step these react with acetylenic or olefinic dipolarophiles in the presence of a base whose role is to generate the N-ylide in situ. By using acetylenic dipolarophiles, dihydro derivative intermediates are obtained along with the aromatic target products. The stereochemistry of such derivatives is of interest from the mechanistic point of view and thus received some attention [6–10].

Herein is reported the synthesis of new pyrrolo[2,1-*a*]isoquinoline derivatives by two one-pot procedures that avoid the isolation of the dihydro derivative intermediates. The one-pot reactions are well known for their simplicity and efficiency [11]. Also, the structure of a representative dihydro intermediate was studied by X-ray diffraction analysis in order to assign its stereochemistry.

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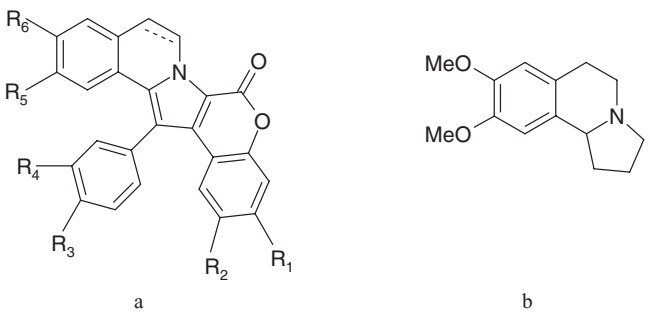


FIGURE 1 The structure of lamellarins (a) and crispine A (b).

RESULTS AND DISCUSSION

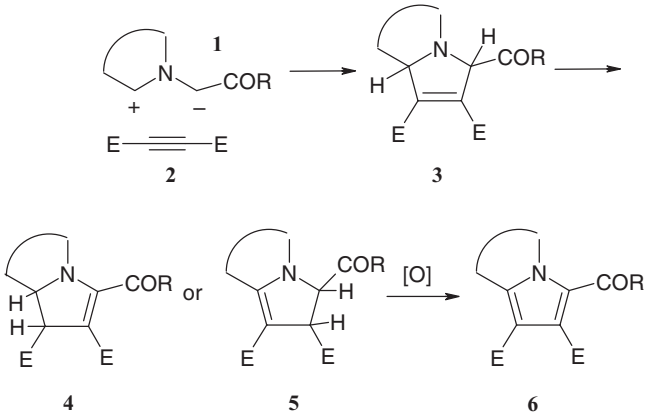
One of the promising methods in the synthesis of pyrroloazines is the 1,3-dipolar cycloaddition reaction of their corresponding N-ylides [5–10, 11a,b]. Usually, the reaction of the N-ylides **1** (Scheme 1) with the acetylenic dipolarophiles **2** leads to formation of the primary cycloadducts **3**, which rearrange to the dihydro intermediates **4** or **5** [6–9,10d,12,13]. Such intermediates are susceptible to further aromatization, under the reaction conditions or by using oxidant reagents, leading to fully aromatic pyrroloazines **6**. Intermediates of type **4** or **5** could be of interest for stereochemical reasons but their formation must be avoided in order to improve the yield of the desired aromatic compounds.

Our interest in obtaining pyrroloazines [10d,e–11c,d] by 1,3-dipolar cycloaddition reaction led us to investigate the synthesis of pyrrolo[2,1-*a*]isoquinolines by two simple one-pot procedures. Thus, the first procedure involves the use of tetrakispyridinecobalt(II) dichromate (TPCD) as oxidizing agent in order to direct the reaction toward the fully aromatic target compounds (Scheme 2, path A). The salts **7**, obtained in a previous step by the reaction of isoquinoline and substituted 2-bromoacetophenones, are mixed with the corresponding acetylenic dipolarophile in the presence of triethylamine and TPCD, leading directly to the aromatic pyrrolo[2,1-*a*]isoquinolines **8**. The oxidant reagent TPCD was used in the cycloaddition reaction between the N-heteroaromatic ylides and olefinic dipolarophiles [14].

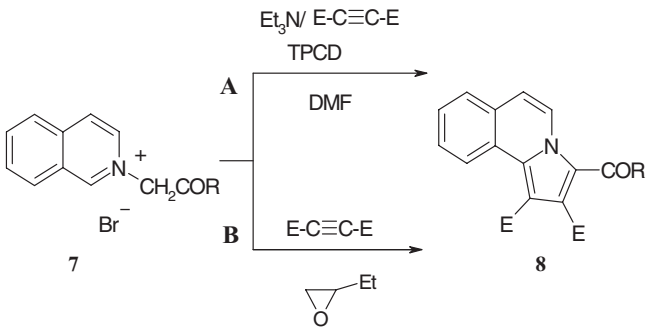
The second synthetic procedure toward pyrrolo[2,1-*a*]isoquinoline derivatives involves the use of epoxides such as 1,2-epoxybutane, which plays both the role of the reaction medium and proton scavenger. Thus, the bromide ion from the salt attacks the oxirane ring with formation of an alkoxide, which extracts one of the methylene protons in the isoquinolinium bromide generating the corresponding N-ylide. The one-pot procedure consists only in mixing the reactants under reflux for 40 h. The fully aromatic compounds **8** are obtained in good yields (Scheme 2, path B).

Using these two one-pot procedures, a series of 12 variously substituted pyrrolo[2,1-a]isoquinoline derivatives were obtained in good yields (Table 1). It can be noticed that the yields obtained using path A are generally slightly higher than the ones corresponding to path B.

The structures of the new compounds **8a–l** were assigned by NMR spectroscopy. The spectra are in good accordance with the proposed structures. The main characteristic of the ^{1}H NMR spectra are the signals of the hydrogen atoms H-5 and H-6, which appear as two doublets with the coupling constant $J = 7.4$ Hz. The hydrogens H-5 and H-10 are the most deshielded protons in the range 8.60–8.84 ppm. The hydrogen H-6 appears shielded in the range 7.06–7.26 ppm. An interesting observation could be made for the compounds **8a, 8c**, and **8l**, which present the signal of H-5 strongly deshielded at ~9.50 ppm, most probably due to the influence of the ortho substitution on the 2,4-dichlorobenzoyl substituent. H-10 appears deshielded due to spatial vicinity of the



SCHEME 1



SCHEME 2

TABLE 1 New Pyrrolo[2,1-*a*]isoquinolines

Compound	*E*	*R*	*Yield (%) Method A/B)*
8a	CO_2Me	2,4-$Cl_2C_6H_3$	71/64
8b	CO_2Me	3-$MeOC_6H_4$	61/49
8c	CO_2Et	2,4-$Cl_2C_6H_3$	68/61
8d	CO_2Et	4-BrC_6H_4	58/60
8e	CO_2iPr	C_6H_5	75/72
8f	CO_2iPr	4-MeC_6H_4	85/67
8g	CO_2iPr	4-$C_6H_5C_6H_4$	81/78
8h	CO_2iPr	3-$NO_2C_6H_4$	80/73
8i	CO_2iPr	4-FC_6H_4	77/70
8j	CO_2iPr	4-ClC_6H_4	72/66
8k	CO_2iPr	4-BrC_6H_4	87/75
8l	CO_2iPr	2,4-$Cl_2C_6H_3$	75/68

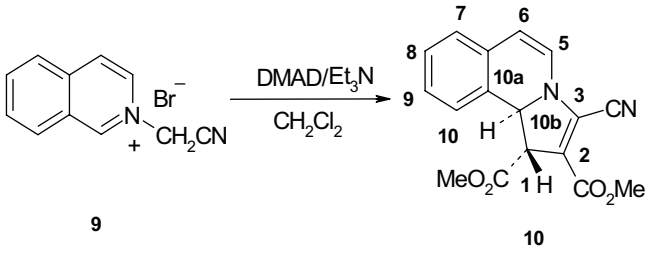
alkoxy carbonyl group. The ^{13}C NMR spectra present as main characteristics the signals of C-1 and C-6, which appear strongly shielded at ~110 ppm and ~116 ppm, respectively.

Both one-pot procedures avoid the formation of the dihydro intermediates leading to the desired aromatic compounds. By comparison, if no oxidizing agents were used, it was observed that in different solvents (CH_2Cl_2, benzene, DMF, MeCN) the reaction between the corresponding N-ylides and symmetrical acetylenic dipolarophiles leads to the formation of dihydro derivatives together with the aromatic compounds. These dihydro derivatives can be assigned as pyrrolo[2,1-*a*]phtalazines (type 4) [12] and pyrrolo[1,2-*a*][1,10]phenanthrolines (type 5) [13] (Scheme 1), which are important synthetic intermediates.

In the case of the dihydro derivatives obtained previously [6,7] from isoquinolinium N-ylides, some investigations were carried out in order to establish their stereochemistry [6,7]. Thus, the stereochemistry of the dihydro derivative **10** obtained by the reaction of isoquinolinium salt **9** with DMAD (dimethyl acetylenedicarboxylate) in the presence of triethylamine in methylene chloride as solvent (Scheme 3) was assigned on the basis of NMR spectroscopy [7].

The high coupling constant between protons from the pyrroline moiety H1 and H-10b, of magnitude 13–14 Hz was considered sufficiently large to ascertain a cis stereochemistry of the two hydrogen atoms under discussion. However, with the unexpected trans configuration observed for the dihydro pyrrolo[2,1-*a*]phthalazines [12] in mind, we reinvestigated the structure of the dihydro derivative **10** by single crystal X-ray analysis.

Figure 2 shows the molecular structure of **10** and the crystallographic numbering scheme. Crystal



9 **10**

SCHEME 3

data and details of the refinement appear in Table 2. The stereochemistry of the two H atoms in question is clearly *trans*. Although these H atoms were located unequivocally in a difference Fourier synthesis, they were added in idealized positions dependent on the local geometries. Because the five-membered ring adopts a twist conformation (twisted on C4–C5), the final calculated dihedral angle H4-C4-C5-H5 is in fact –145° for the *S*-, *S*- configurations at C4 and C5 shown in Fig. 1 and +145° for the inversion-related molecule in the crystal. The bond lengths C4–C5 and C2–C3 are 1.551(2) and 1.357(2) Å, respectively, in accordance with the formal bond orders indicated for **10** in Scheme 3.

The stereochemistry of the compound **10** was thus unambiguously assigned to be in reality *trans*, which is consistent with another structure discussed in the literature [9]. On the basis of the results highlighted in this paper and the reported literature [9,12,13], we can conclude that the primary cycloadducts of type **3** (Scheme 1) rearrange to the *trans* isomer of type **4** or **5**.

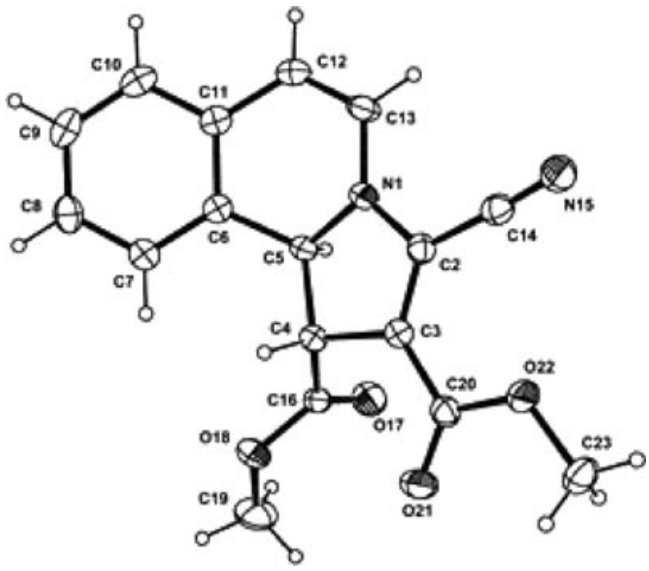


FIGURE 2 X-ray structure of **10** with thermal ellipsoids drawn at the 50% probability level.

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TABLE 2 Crystal Data and Refinement Data for **10**[a]

Molecular Formula	$C_{17}H_{14}N_2O_4$
M	310.30
Crystal system	Triclinic
Space group	P(-1)
a(Å)	8.5014(6)
b(Å)	8.8217(6)
c(Å)	10.3998(9)
α(°)	104.960(5)
β(°)	95.532(5)
γ(°)	101.455(4)
V_{cell} (Å^3)	729.47(10)
Z	2
T(K)	173(2)
Absorption coefficient (mm^{-1})	0.102
F(000)	324
θ-range (°)	2.72–27.48
Index ranges	$-11 \leq h \leq 11$, $-11 \leq k \leq 11$, $-13 \leq l \leq 13$
Reflections collected	21152
Unique reflections	3317
Observed reflections [$I > 2\sigma(I)$]	2794
Data/restraints/parameters	3317/0/210
Goodness-of-fit on F^2	1.033
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0409$, w$R_2 = 0.0906$
$\Delta\rho$(max., min.)/(e Å^{-3})	0.226, –0.216

[a]Full crystallographic data (CCDC 820337).

CONCLUSIONS

New pyrrolo[2,1-*a*]isoquinolines were obtained by two one-pot procedures via 1,3-dipolar cycloaddition between the isoquinolinium N-ylides and symmetrical acetylenic dipolarophiles, avoiding the formation of mixtures of dihydro derivatives. The compounds were fully characterized by standard techniques. The structure of the dihydro derivatives, of interest from a stereochemical viewpoint, was confirmed by the single crystal X-ray diffraction analysis of the representative dihydro derivative **10**. Furthermore, on the basis of the X-ray analysis, it can be concluded that the dihydro derivatives obtained together with the aromatic pyrroloazines possess a *trans* stereochemistry, no presence of the *cis* isomer being observed.

EXPERIMENTAL

Melting points were determined on a Boëtius hot plate microscope and are uncorrected. The elemental analysis was carried out on a COSTECH Instruments EAS32 apparatus. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Supplementary evidence was given by HETCOR and COSY experiments.

General Procedure for Synthesis of Pyrrolo[2,1-a]isoquinolines 8

Method A. Isoquinolinium bromide **7** (5 mmol) was suspended in dimethylformamide (25 mL) and then dimethyl (diethyl or diisopropyl) acetylenedicarboxylate (5.5 mmol) was added. Under stirring, triethylamine (5.5 mmol) and tetrakispyridinecobalt(II) dichromate (TPCD) (2 g, 3.2 mmol) were added to the reaction mixture. The reaction mixture was stirred at 80–90°C for 4 h and then cooled at room temperature and poured into a 5% aqueous HCl solution (100 mL). The solid product was filtered, washed with water, and purified either by crystallization or column chromatography on neutral Al_2O_3, using CH_2Cl_2 as eluent.

Method B. To a suspension of 2.5 mmol of isoquinolinium bromide **7** in 25 mL 1,2-epoxybutane 3.5 mmol of acetylenic dipolarophile was added. The mixture was heated at reflux temperature for 40 h. A part of solvent was removed in vacuum, 5 mL of methanol was added, and the mixture was left overnight at room temperature. The solid was filtered, washed with a MeOH-Et2O 1:1 mixture, and recrystallized from $CHCl_3$/MeOH.

*Dimethyl 3-(2,4-dichlorobenzoyl)pyrrolo[2,1-a] isoquinoline-1,2-dicarboxylate (***8a***)*. Light yellow crystals; mp 212–214°C; Anal. Calcd. $C_{23}H_{15}Cl_2NO_5$: C 60.54; H 3.31; Cl 15.54; N 3.07. Found: C 60.89; H 3.08; Cl 15.74; N 3.21; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.30, 3.83 (2s, 6H, 2MeO); 7.20–7.31 (m, 3H, H-6, H-5′, H-6′); 7.41 (d, 1H, J = 1.9, H-3′); 7.56–7.62 (m, 2H, H-8, H-9); 7.69–7.72 (m, 1H, H-7); 9.06–9.10 (m, 1H, H-10); 9.45 (d, 1H, J = 7.4 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 14.1 (2Me); 61.6, 62.0 (CH_2); 110.3 (C-1); 116.9 (C-6); 121.1, 124.1, 130.6, 131.7, 133.7 (C-2, C-3, C-6a, C-10a, C-10b) 134.8, 137.1, 137.4 (C-1′, C-2′, C-4′); 124.4 (C-5); 126.7, 127.0, 127.2, 129.8, 130.0, 131.0 (C-7, C-8, C-9, C-3′, C-5′, C-6′); 128.4 (C-10); 164.5, 164.7 (COO); 183.4 (COAr).

*Dimethyl 3-(3-methoxybenzoyl)pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (***8b***)*. Light yellow crystals; mp 193–194°C; Anal. Calcd. $C_{24}H_{19}NO_6$: C 69.06; H 4.59; N 3.36. Found: C 69.21; H 4.27; N 3.52; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.30, 3.85, 3.94 (3s, 9H, 3MeO); 7.10–7.14 (m, 1H, H-4′); 7.17 (d, 1H, J = 7.4 Hz, H-6); 7.31–7.39 (m, 2H, H-2′, H-6′); 7.57–7.63 (m, 4H, H-8, H-9); 7.68–7.73 (m, 1H, H-7); 8.87–8.90 (m, 1H, H-10); 8.91 (d, 1H, J = 7.4 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.8, 52.4, 55.4 (4MeO); 109.6 (C-1); 112.9, 119.6, 121.7, 129.4 (C-2′, C-4′, C-5′, C-6′); 115.8 (C-6); 122.9, 124.4, 127.4, 129.5, 132.4 (C-2, C-3, C-6a, C-10a, C-10b); 125.7 (C-5); 127.1, 127.4, 129.0 (C-7, C-8, C-9); 128.3 (C-10); 142.0 (C-1′); 159.6 (C-4′); 164.6, 165.8 (2COO); 185.8 (COAr).

*Diethyl 3-(2,4-dichlorobenzoyl)pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (***8c***)*. Light yellow crystals; mp 160–162°C; Anal. Calcd. $C_{25}H_{19}Cl_2NO_5$: C 62.00; H 3.95; Cl 14.64; N 2.89. Found: C 62.32; H 4.11; Cl 14.97; N 2.99; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20, 1.34 (2t, 6H, J = 7.1 Hz, 2Me); 3.70, 4.38 (2q, 4H, J = 7.1 Hz, $2CH_2$); 7.26–7.32 (m, 2H, H-6, H-5′); 7.38 (d, 1H, J = 8.2, H-6′); 7.48 (d, 1H, J = 1.9, H-3′); 7.59–7.67 (m, 2H, H-8, H-9); 7.72–7.75 (m, 1H, H-7); 9.11–9.15 (m, 1H, H-10); 9.49 (d, 1H, J = 7.4 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 14.1 (2Me); 61.6, 62.0 (CH_2); 110.3 (C-1); 116.9 (C-6); 121.1, 124.1, 130.6, 131.7, 133.7 (C-2, C-3, C-6a, C-10a, C-10b) 134.7, 137.1, 137.7 (C-1′, C-2′, C-4′); 124.5 (C-5); 126.7, 126.9, 127.2, 129.8, 130.0, 131.0 (C-7, C-8, C-9, C-3′, C-5′, C-6′); 128.4 (C-10); 164.5, 164.7 (COO); 183.4 (COAr).

*Diethyl 3-(4-bromobenzoyl)pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (***8d***)*. Colorless crystals; mp 160–162°C; Anal. Calcd. $C_{25}H_{20}BrNO_5$: C 60.74; H 4.08; Br 16.16, N 2.83. Found: C 61.08; H 4.29; Br 16.31, N 3.01; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.01, 1.37 (2t, 6H, J = 7.1 Hz, 2Me); 3.75, 4.44 (2q, 4H, J = 7.1 Hz, $2CH_2$); 7.16 (d, 1H, J = 7.4 Hz, H-6); 7.58–7.66 (m, 4H, H-8, H-9, H-3′, H-5′); 7.68 (d, 2H, J = 8.2 Hz, H-2′, H-6′); 7.69–7.73 (m, 1H, H-7); 8.84 (d, 1H, J = 7.4 Hz, H-5); 8.85–8.88 (m, 1H, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6, 13.9 (2Me); 61.5, 61.6 (CH_2); 110.2 (C-1); 115.9 (C-6); 122.2, 124.3, 127.2, 129.5, 132.4 (C-2, C-3, C-6a, C-10a, C-10b); 123.5, 127.1, 129.0 (C-7, C-8, C-9); 125.7 (C-5); 127.6 (C-4′); 128.3 (C-10); 130.5, 131.8 (C-2′, C-3′, C-5′, C-6′); 138.5 (C-4′); 164.1, 165.4 (COO); 185.9 (COAr).

*Diisopropyl 3-benzoylpyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (***8e***)*. Light yellow crystals; mp 179–180°C; Anal. Calcd. $C_{27}H_{25}NO_5$: C 73.12; H 5.68; N 3.16. Found: C 73.44; H 5.29; N 3.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86, 1.42 (2d, 12H, J = 6.3 Hz, 4Me-isopropyl); 4.67, 5.40 (2 sept, 2H, J = 6.3 Hz, 2CH-isopropyl); 7.10 (d, 1H, J = 7.4 Hz, H-6); 7.43–7.49 (m, 2H, H-3′, H-5′); 7.55–7.61 (m, 3H, H-8, H-9, H-4′); 7.66–7.71 (m, 1H, H-7); 7.87–7.91 (m, 2H, H-2′, H-6′); 8.68 (d, 1H, J = 7.4 Hz, H-5); 8.71–8.75 (m, 1H, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2, 21.8 (4Me); 69.6 (2C**H**Me_2); 111.0 (C-1); 115.6 (C-6); 122.8, 124.6, 125.9, 129.4, 131.4 (C-2, C-3, C-6a, C-10a, C-10b); 125.4 (C-5); 123.6, 127.3, 128.8 (C-7, C-8, C-9); 128.3 (C-10); 128.7, 129.9 (C-2′, C-3′, C-5′, C-6′); 133.3 (C-4′); 139.6 (C-1′); 163.7, 165.6 (COO); 187.3 (COAr).

*Diisopropyl 3-(4-methylbenzoyl)pyrrolo[2,1-a] isoquinoline-1,2-dicarboxylate (***8f***)*. Light yellow crystals; mp 147–148°C; Anal. Calcd. $C_{28}H_{27}NO_5$: C 73.51; H 5.95; N 3.06. Found: C 73.88; H 5.71; N 3.31; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87, 1.41 (2d, 12H, J = 6.3 Hz, 4Me-isopropyl); 2.42 (s, 3H, 4′-Me); 4.70, 5.39 (2 sept, 2H, J = 6.3 Hz, 2CH-isopropyl); 7.06 (d, 1H, J = 7.4 Hz, H-6); 7.26 (d, 2H, J = 8.2 Hz, H-3′, H-5′); 7.54–7.60 (m, 2H, H-8, H-9); 7.65–7.71 (m, 1H, H-7); 7.78 (d, 2H, J = 8.2 Hz, H-2′, H-6′); 8.60 (d, 1H, J = 7.4 Hz, H-5); 8.70–8.75 (m, 1H, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2, 21.7 (4Me); 69.4, 69.5 (2C**H**Me_2); 110.7 (C-1); 115.4 (C-6); 123.2, 124.7, 125.4, 129.3, 131.1 (C-2, C-3, C-6a, C-10a, C-10b); 125.3 (C-5); 123.6, 127.3, 128.6 (C-7, C-8, C-9); 128.2 (C-10); 129.3, 130.0 (C-2′, C-3′, C-5′, C-6′); 136.9 (C-1′); 144.3 (C-4′); 163.7, 165.6 (COO); 187.0 (COAr).

*Diisopropyl 3-(4-phenylbenzoyl)pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (***8g***)*. Colorless crystals; mp 130–132°C; Anal. Calcd. $C_{33}H_{29}NO_5$: C 76.28; H 5.63; N 2.70. Found: C 76.56; H 5.71; N 3.04; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88, 1.42 (2d, 12H,

J = 6.3 Hz, 4Me-isopropyl); 4.73, 5.40 (2 sept, 2H, J = 6.3 Hz, 2CH-isopropyl); 7.11 (d, 1H, J = 7.4 Hz, H-6); 7.38–7.51 (m, 3H, H-3′, H-4′, H-5′); 7.57–7.64 (m, 3H, H-8, H-9, H-2′, H-6′); 7.67–7.71 (m, 3H, H-7, H-3″, H-5″); 7.96 (d, 2H, J = 8.6 Hz, H-2″, H-6″); 8.69 (d, 1H, J = 7.4 Hz, H-5); 8.71–8.73 (m, 1H, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.3, 21.8 (4Me); 69.6 (2C**H**Me_2); 111.0 (C-1); 115.6 (C-6); 123.0, 124.7, 125.8, 129.4, 131.4 (C-2, C-3, C-6a, C-10a, C-10b); 125.4 (C-5); 123.6, 127.4, 128.8 (C-7, C-8, C-9); 128.2 (C-10); 127.1, 129.1, 130.5 (9C, C-2′, C-3′, C-5′, C-6′, Ph); 138.3, 140.0, 146.1 (C-1′, C-4′, Cq-Ph); 163.8, 165.7 (COO); 186.8 (COAr).

*Diisopropyl 3-(3-nitrobenzoyl)pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (***8h***).* Colorless crystals; mp 170–172°C; Anal. Calcd. $C_{27}H_{24}N_2O_7$: C 66.39; H 4.95; N 5.73. Found: C 66.70; H 4.70; N 5.65; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90, 1.42 (2d, 12H, J = 6.3 Hz, 4Me-isopropyl); 4.65, 5.47 (2 sept, 2H, J = 6.3 Hz, 2CH-isopropyl); 7.16 (d, 1H, J = 7.4 Hz, H-6); 7.54–7.62 (m, 2H, H-8, H-9); 7.63 (t, 1H, J = 8.0 Hz, H-5′); 7.66–7.72 (m, 1H, H-7); 8.10–8.14, 8.37–8.41 (2m, 2H, H-4′, H-6′); 8.65–8.70 (m, 2H, H-10, H-2′); 8.81 (d, 1H, J = 7.4 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.3, 21.8 (4Me); 69.8, 69.9 (2C**H**Me_2); 111.6 (C-1); 116.2 (C-6); 121.6, 124.3, 127.0, 129.6, 132.2 (C-2, C-3, C-6a, C-10a, C-10b); 124.1 (C-4′); 125.4 (C-5); 123.5, 127.4, 129.2 (C-7, C-8, C-9); 126.2, 130.3 (C-2′, C-5′); 128.4 (C-10); 135.2 (C-6′) 141.3 (C-1′); 148.4 (C-3′); 163.4, 165.1 (COO); 184.5 (COAr).

*Diisopropyl 3-(4-fluorobenzoyl)pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (***8i***).* Colorless crystals; mp 156–158°C; Anal. Calcd. $C_{27}H_{24}FNO_5$: N 3.04. Found: N 3.26; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92, 1.42 (2d, 12H, J = 6.3 Hz, 4Me-isopropyl); 4.73, 5.40 (2 sept, 2H, J = 6.3 Hz, 2CH-isopropyl); 7.09 (d, 1H, J = 7.4 Hz, H-6); 7.14 (t, 2H, J = 8.5 Hz, H-3′, H-5′); 7.54–7.60 (m, 2H, H-8, H-9); 7.66–7.71 (m, 1H, H-7); 7.91 (dd, 2H, J = 8.5, 5.5 Hz, H-2′, H-6′); 8.63 (d, 1H, J = 7.4 Hz, H-5); 8.70–8.74 (m, 1H, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.3, 21.7 (4Me); 69.6 (2C**H**Me_2); 110.9 (C-1); 115.6 (C-6); 115.8 (d, J = 21.8 Hz, C-3′, C-5′); 122.5, 124.5, 125.7, 129.3, 131.4 (C-2, C-3, C-6a, C-10a, C-10b); 125.3 (C-5); 123.4, 127.3, 128.8 (C-7, C-8, C-9); 128.3 (C-10); 132.3 (d, J = 9.2 Hz, C-2′, C-6′); 136.2 (d, J = 2.9 Hz, C-1′); 163.6, 165.5 (COO); 165.1 (d, J = 252.2 Hz, C-4′); 185.6 (COAr).

*Diisopropyl 3-(4-chlorobenzoyl)pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (***8j***).* Light yellow crystals; mp 147–148°C; Anal. Calcd. $C_{27}H_{24}ClNO_5$: C 67.85; H 5.06; Cl 7.42, N 2.93. Found: C 68.01; H 5.35; Cl 7.78, N 3.03; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92, 1.42 (2d, 12H, J = 6.3 Hz, 4Me-isopropyl); 4.73, 5.40 (2 sept, 2H, J = 6.3 Hz, 2CH-isopropyl); 7.11 (d, 1H, J = 7.4 Hz, H-6); 7.44 (d, 2H, J = 8.4 Hz, H-3′, H-5′); 7.53–7.59 (m, 2H, H-8, H-9); 7.67–7.71 (m, 1H, H-7); 7.82 (d, 2H, J = 8.4 Hz, H-2′, H-6′); 8.68 (d, 1H, J = 7.4 Hz, H-5); 8.69–8.74 (m, 1H, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2, 21.7 (4Me); 69.6, 69.7 (2C**H**Me_2); 111.1 (C-1); 115.7 (C-6); 122.3, 124.5, 126.0, 129.4, 131.6 (C-2, C-3, C-6a, C-10a, C-10b); 125.4 (C-5); 123.5, 127.3, 128.9 (C-7, C-8, C-9); 128.3 (C-10); 128.9, 131.1 (C-2′, C-3′, C-5′, C-6′); 138.0, 139.7 (C-1′, C-4′); 144.3 (C-4′); 163.6, 165.4 (COO); 185.9 (COAr).

*Diisopropyl 3-(4-bromobenzoyl)pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (***8k***).* Colorless crystals; mp 146–147°C; Anal. Calcd. $C_{27}H_{24}BrNO_5$: C 62.08; H 4.63; Br 15.30, N 2.68. Found: C 62.29; H 4.82; Br 15.67, N 2.82; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92, 1.42 (2d, 12H, J = 6.3 Hz, 4Me-isopropyl); 4.73, 5.39 (2 sept, 2H, J = 6.3 Hz, 2CH-isopropyl); 7.11 (d, 1H, J = 7.4 Hz, H-6); 7.56–7.63 (m, 4H, H-8, H-9, H-3′, H-5′); 7.67–7.71 (m, 1H, H-7); 7.74 (d, 2H, J = 8.2 Hz, H-2′, H-6′); 8.68 (d, 1H, J = 7.4 Hz, H-5); 8.69–8.74 (m, 1H, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2, 21.7 (4Me); 69.6, 69.7 (2C**H**Me_2); 111.1 (C-1); 115.7 (C-6); 122.3, 124.4, 126.1, 129.4, 131.6 (C-2, C-3, C-6a, C-10a, C-10b); 123.5, 127.3, 128.9 (C-7, C-8, C-9); 125.4 (C-5); 126.6 (C-4′); 128.3 (C-10); 131.2, 131.9 (C-2′, C-3′, C-5′, C-6′); 138.4 (C-4′); 163.6, 165.4 (COO); 186.0 (COAr).

*Diisopropyl 3-(2,4-dichlorobenzoyl)pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (***8l***).* Light yellow crystals; mp 146–147°C; Anal. Calcd. $C_{27}H_{23}Cl_2NO_5$: C 63.29; H 4.52; Cl 13.84, N 2.73. Found: C 63.41; H 4.49; Cl 14.17, N 2.94; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.09, 1.40 (2d, 12H, J = 6.3 Hz, 4Me-isopropyl); 4.60, 5.35 (2 sept, 2H, J = 6.3 Hz, 2CH-isopropyl); 7.25–7.31 (m, 2H, H-6, H-5′); 7.43 (d, 1H, J = 8.2, H-6′); 7.48 (d, 1H, J = 1.9, H-3′); 7.58–7.68 (m, 2H, H-8, H-9); 7.75–7.78 (m, 1H, H-7); 8.80–8.84 (m, 1H, H-10); 9.36 (d, 1H, J = 7.4 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.5, 21.8 (4Me); 69.7, 70.5 (2C**H**Me_2); 111.5 (C-1); 116.5 (C-6); 121.3, 124.1, 130.0, 130.2, 133.3 (C-2, C-3, C-6a, C-10a, C-10b); 134.0, 137.3, 137.4 (C-1′, C-2′, C-4′); 124.3 (C-5); 126.1, 126.8, 127.3, 129.4, 130.5, 131.5 (C-7, C-8, C-9, C-3′, C-5′, C-6′); 128.1 (C-10); 163.8, 164.7 (COO); 183.4 (COAr).

X-Ray Analysis of Compound **10**

Intensity data from a specimen of **10** with dimensions 0.10 × 0.22 × 0.24 mm were collected on a Nonius Kappa CCD diffractometer. The crystal

temperature was maintained at 173(2) K by cooling it in a constant stream of nitrogen vapor. Data-collection strategy (Program COLLECT [15]) included ϕ- and ω-scans of 1.00–2.00° and program DENZO-SMN [16] was used for data-reduction and unit cell refinement. *Lp*-corrections were applied to the measured intensities and the structure was subsequently solved by direct methods (SHELXS-97) [17] and refined by full-matrix least-squares against F^2 (SHELXL-97) [18]. All H atoms were located in different electron density maps and were added in the idealized positions in a riding model with U_{iso} set at 1.2–1.5 times those of their parent atoms. All non-H atoms refined anisotropically. During refinement, least-squares weights of the form $w = [\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$ with $P = [\max(F_o^2, 0) + 2F_c^2]/3$ were employed.

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