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APPLICATION OF ORGANOLITHIUM AND RELATED REAGENTS IN SYNTHESIS; PART 20:[1] SYNTHESIS OF 4b-PHENYLAZAISOINDOLO[2,1-a]QUINOLINE DERIVATIVES

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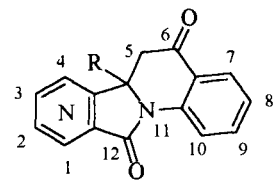
Abstract: The synthesis of hydroxyazaisoindolinones **3** and **4** and their successive conversion into azaisoindoleaceic acids **7** and **8** as effective precursors of the corresponding 4b-phenyldihydroazaisoindol[2,1-a]quinolinediones **9** and **10** are described.

The current interest in derivatives of isoindoles, i.e. type **A** as key starting materials for the preparation of numerous poly-heterocyclic compounds[2] including selective non-nucleoside HIV-1 reverse transcriptase inhibitors[3] and protective effect against N_2-induced hypoxia agents,[4] has led us to examine the methods for the synthesis of these systems. The available methods for the regiospecific preparation of type **A** isoinsoles generally require multistep



A

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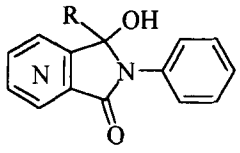
reactions.[2, 5] However, they appeared to be unsatisfactory both in yield and generality. A number of alternative methods have been attempted. One of the approaches involves Friedel-Crafts cyclization of 3-carboxymethylazaphthalimides



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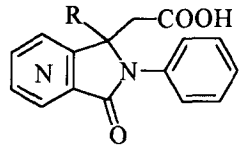
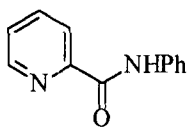


C

C into **A**. Thereby, the general strategy for the preparation of the desired systems **A** depends upon the synthesis of azaphthalimidines **C**. The most frequently travelled synthetic route to systems **C** involves fhe condensation of diverse Wittig reagents[5, 8] with 3-hydroxyisoindolinones **B** as a masked *ortho* carbonyloamides. On the other hand, as it will be demonstrated below it seems to us that this reaction is limited to the cases in which R = H. Alternative routes of their preparation require the conversion of 3-hydroxyazaisoindolones **B** into the corresponding *N*-acyliminium cation and then reactions with the appropriate nucleophiles.[6]

In this article we wish to describe a novel efficient and regiospecific synthetic sequence as a general strategy for the transformation of the picolin- and isonicotin anilides into the corresponding 4b-phenylazaisoindol[2,1-a]quinoline **A**.



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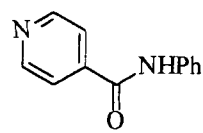

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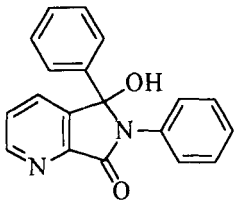

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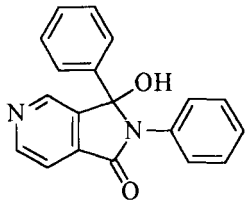

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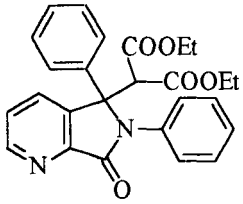

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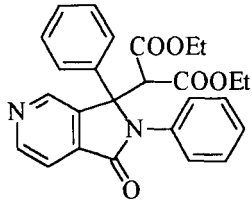

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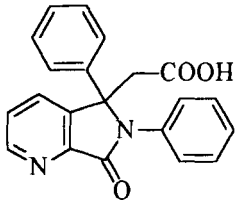

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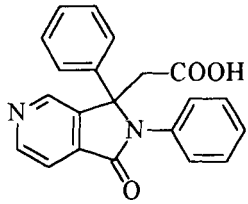

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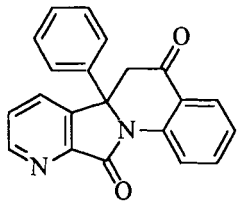

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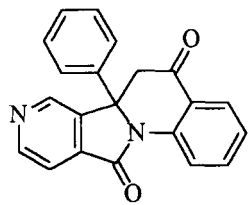

10

To this end, the anilides **1** and **2** were reacted in tetrahydrofuran (THF) with 2.1 mol equivalents of butyllithium (BuLi) (amide / -78°C / 0.5 h → 0°C / 0.1 h) and efficiently converted into the bis-(*N*- and C^3-) lithiated anilides. The treatment of the lithiated species with methyl benzoate afforded the corresponding benzoylated derivatives, which upon hydrolytic workup spontaneously cyclized into the azaisoindolinones **3** and **4**. With the compounds **3** and **4** in hand, ethoxycarbonylmethylenetriphenylphosphorane and triethyl phosphonoacetate were tested for their carbonylalkenation. The compounds **3** and **4** appeared to be inert toward the Wittig or Wittig-Horner reaction which is known in the literature for the carbonylalkenation of isoindolinones, which contain a masked aldehyde group.[4, 5, 8] This is probably due to the steric hindrance caused by the phenylsubstituant of the componds **B** (R = Ph). As the attempts at the preparation of acids **7** and **8** were unsuccessful, other possibility for their synthesis was investigated. The amidoalkilation reaction[6] was used for the synthesis of diethyl azaisoindolomalonates **5** and **6** by treating the 3-hydroxyazaisoindolinones **3** and **4** with diethyl malonate in anhydrous methaesulfonic acid in the presence of acetic acid anhydride. When the hydroxyazaisoindolinone **4** was reacted with diethyl malonate in commercially available methansulfonic acid (98%), the desired ester **5** (16%) and ethyl 3-benzoylisonicotinate (80%) were formed. This result suggests that the azaisoindolinon system was decomposed by water included in commercial methansulfonic acid. In the next step, the resulting esters **5** and **6** upon reaction of hydrodecarboxylation[7] with boiling hydrochloric acid (20% - HCl) gave the

azaisoindoleacetic acids **7** and **8**. The obtained compounds **7** and **8** after their treatment with oxalyl chloride were converted into the corresponding acyl chloride, which in the presence of aluminium chloride cyclized into azaisoindoloquinolines **9** and **10**.

In summary, we have shown a synthetic method for the preparation of azaisoindoloquinolines **9** and **10** with the economy of steps which involves: the successive conversion of the picolin- and isonicotinanilides **1** and **2** into the diethyl azaisoindolomalonates **5** and **6**, and then the formation of acids **7** and **8** as precursors of **9** and **10**.

Experimental Section

Melting points were determined using a Boetius hot-stage apparatus and they are uncorrected. IR spectra were recorded on a Zeiss-Jena Specord 71-IR. ^{1}H NMR spectra were determined on a Varian-Gemini-200 (200 MHz) using TMS as an internal standard. Analytical thin layer chromatography tests (TLC) were carried out on silica gel (Merck, $60F_{254}$, layer thickness 0.2 mm). Column chromatography separations were performed on silica gel (Macherey Nagel & Co. 0.075-0.150 mm/100-200 mesh ATSM). All reagents were commercially available materials used without purification unless otherwise stated. Tetrahydrofuran was dried over calcium hydride and used directly after distillation. Anilides **1** and **2** were prepared by means of standard methods.[9]

General Procedure for the Preparation of Aza-isoindolinones 3 and 4

To the anilide (0.025 mol) stirred in THF (100 mL) at -78°C BuLi (0.055 mol) was added. The solution was held at -78°C for 0.5 h, then allowed to rise to 0°C and kept at 0°C for 0.1 h. The whole lot was cooled to -78°C and methyl benzoate (0.03 mol) in THF (20 mL) was added. The reaction after 0.3 h at -78°C was warmed up to room temperature and kept for 1 h and then water (20 mL) was added. The water layer was separated and extracted with a mixture of chloroform in order to remove some amount of the starting anilide, then it was adjusted to pH ≈ 3.4 (by HCl) to precipitate products **3** and **4**. The crude products were separated, washed with water and purified by crystallisation.

6,7-Dihydro-5-hydroxy-5,6-diphenyl-5H-pyrrolo[3,4-b]pyridin-7-one (**3**):

yield: (74%), m.p. 167-168°C (acetone : hexane - 1 : 1), (lit.[10] m.p. 163-164°C).

2,3-Dihydro-3-hydroxy-2,3-diphenyl-1H-pyrrolo[3,4-c]pyridin-1-one (**4**):

yield: (67%), m.p. 163-165°C (methanol : water - 1 :1), (lit.[10] m.p. 165-167°C).

Preparation of Diethyl Azaisoindolinone-malonate 5 and 6

Diethyl malonate (0.005 mole) and azaisoindolinone **3** or **4** (0.005 mol) were added to the mixture of methanesulfonic acid (5 mL) and acetic acid anhydride (0.005 mol). The whole lot was heated at 100 °C for 4 h and after cooling it was poured into water (50 mL). Then the mixture was neutralised ($NaHCO_3$) and extracted by $CHCl_3$ (4 x 10 mL). The products **5** or **6** was separated from the extract by column chromatography and purified by crystallisation.

Diethyl 6,7-dihydro-7-oxo-5,6-diphenyl-5H-pyrrolo[3,4-b]pyridine-5-malonate (**5**): yield: (54%), (eluent chloroform : THF - 4 : 1, R_f = 0.54), m.p. 179-181°C (heksan : ethyl acetate - 2 :1); (Found C, 69.9; H, 5.3; N, 6.3. Calc. for $C_{26}H_{24}N_2O_5$ C, 70.26; H, 5.44; N, 6.30%); IR (KBr) ν = 1750 and 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ = 8.92 (1H, dd J 4.8 and 1.5 Hz, 2-H), 8.63 (1H, dd J 8.0 and 1.5 Hz , 4-H), 7.57 (1H, dd J 8.0 and 4.8 Hz, 3-H), 7.43-7.11 (6H, m, Ph), 6.89-6.69 (4H, m, Ph), 4.76 (1H, s, CH), 4.12 (2H, q J 7.1 Hz, CH_2), 4.04-3.78 (2H, m, CH_2), 1.16 (3H , t J 7.1 Hz , Me), 0.98 (3H , t J 7.1 Hz , Me).

Diethyl 2,3-dihydro-1-oxo-2,3-diphenyl-1H-pyrrolo[3,4-c]pyridine-3-malonate (**6**): yield: (73%), (eluent chloroform : THF - 4 : 1, R_f = 0.42), m.p. 117-120°C (diisoprpyl ether); (Found C, 70.6; H, 5.5; N, 6.3. Calc. for $C_{26}H_{24}N_2O_5$ C, 70.26; H, 5.44; N, 6.30%); IR (KBr) ν = 1730 and 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ = 9.50 (1H, s, 4-H), 8.92 (1H, d J 4.9 Hz, 6-H), 7.87 and 7.86 (1H, two overlapping d J 4.9 Hz, 7-H), 7.46-7.14 (6H, m, Ph), 6.88-6.72 (4H, m, Ph), 4.71 (1H, s, CH), 4.13 (2H, q J 7.1 Hz, CH_2), 3.96-3.76 (2H, m, CH_2), 1.14 (3H , t J 7.1 Hz , Me), 0.92 (3H, t J 7.1 Hz , Me).

Preparation of Azaisoindolinone-acetic Acid 7 and 8

The mixture of the compounds **5** or **6** (0.001 mol) in 20% hydrochloric acid (5 mL) was heated till boiling for 4 h. Then the whole lot was poured into water (20 mL) and adjusted ($NaHCO_3$) to pH ≈ 3.4. The precipitated crude products were separated, washed with water and purified by crystalization.

6,7-Dihydro-7-oxo-5,6-diphenyl-5H-pyrrolo[3,4-b]pyridine-5-acetic Acid (7): yield: (75%); mp 252-257°C (methanol : water - 1 : 2, and dried under reduced pressure (1.0 mmHg) at 110°C); (Found C, 73.2; H, 4.6; N, 8.2. Calc. for $C_{21}H_{16}N_2O_3$ C, 73.24; H, 4.68; N, 8.13%); IR (KBr) ν = 1700 cm^{-1} (C=O); ^1H NMR (DMSO-d_6): δ = 12,3-12,1 (1H, br s, OH), 8.75 (1H, dd J 4.7 and 1.4 Hz, 2-H), 7.90 (1H, dd J 7.8 and 1.4 Hz , 4-H), 7.54 (1H, dd J 7.8 and 4.7 Hz, 3-H), 7.45-7.17 (8H, m, Ph), 7.05-6.94 (2H, m, Ph), 3.99 (1H, d J 16.5 Hz, CH_2), 3.25 (1H, d J 16.5 Hz, CH_2).

2,3-Dihydro-1-oxo-2,3-diphenyl-1H-pyrrolo[3,4-c]pyridine-3-acetic Acid (**8**): yield: (74%); mp 217-221°C (methanol : water - 1 : 2, and dried under reduced pressure (1.0 mmHg) at 110°C); (Found C, 72.9; H, 4.6; N, 8.0. Calc. for $C_{21}H_{16}N_2O_3$ C, 73.24; H, 4.68; N, 8.13%); IR (KBr) ν = 1700 cm^{-1} (C=O); ^1H NMR (DMSO-d_6): δ = 12.7-12.1 (1H, br s , OH), 8.86-8.72 (2H, m, 4-H and 6-H), 7.88-7.80 (1H, m, 7-H), 7.46-7.18 (8H, m, Ph), 7.40-6.90 (2H, m, Ph), 4.02 (1H, d J 16.4 Hz, CH_2), 3.27 (1H, d J 16.4 Hz, CH_2).

Cyclization of Compounds 7 and 8 into Pyridoprrroloquinoline Systems 9 and 10

To azaisoindolilinoneacetic acid 7 or **8** (0.001 mol), oxalyl chloride (0.009 mol) and 1,2-dichloroethane (5 mL) were added. The mixture was stirred and gently refluxed for 0.2 h. The excess of oxalyl chloride was removed under reduced

pressure. Then 1,2-dichloroethane (5 mL) and aluminium chloride (0.003 mol) were added and the mixture was gently refluxed for 2 h. It next was cooled to r.t. and H_2O (5 mL) was added. The obtained mixture was adjusted ($NaHCO_3$) to pH ≈ 3.4, and the products and the starting materials were partially precipitated. The precipitates and the organic layer were separated. After evaporation of the organic layer, the residue and the precipitate were collected. The compounds **9** and **10** were isolated by column chromatography and then purified by crystallisation.

4b-Phenylo-4b,5-Dihydro-6H,12H-pyrido[3',2':3,4]pyrrolo[1,2-a]quinoline-6,12-dione (**9**): yield: (93%); (eluent ethyl acetate, R_f = 0.4), m.p. 273-278°C (methanol : ethyl acetate - 2 :1); (Found C, 76.9; H, 4.0; N, 8.4. Calc. for $C_{21}H_{14}N_2O_2$ C, 77.29; H, 4.32; N, 8.58%); IR (KBr) ν = 1730 and 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ = 8.87 (1H, dd J 4.7 and 1.5 Hz, 2-H), 8.57 (1H, d J 8.4 Hz, 10-H), 7.93 (1H, dd J 7.8 and 1.5 Hz, 7-H), 7.76-7.62 (2H, m, 4-H and 9-H), 7.48 (1H, dd J 7.8 and 4.7 Hz, 3-H), 7.36-7.14 (6H, m, Ph and 8-H), 4.02 (1H, d J 16.3 Hz, 5-H), 3.05 (1H, d J 16.3 Hz, 5-H).

4b-Phenylo-4b,5-Dihydro-6H,12H-pyrido[3',4':3,4]pyrrolo[1,2-a]quinoline-6,12-dione (**10**): yield: (54%); (eluent acetone, R_f = 0.6), m.p. 220-225°C (methanol : water - 1 : 2); (Found C, 77.2; H, 4.2; N, 8.6. Calc. for $C_{21}H_{14}N_2O_2$ C, 77.29; H, 4.32; N, 8.58%); IR (KBr) ν = 1730 and 1969 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ = 8.85 (1H, d J 4.9 Hz, 2-H), 8.73 (1H, s, 4-H), 8.48 (1H, d J 8.5 Hz, 10-H), 8.00-7.88 (2H, m, 1-H and 7-H), 7.75-7.63 (1H, m, 9-H), 7.32-7.18 (6H, m, Ph and 8-H), 4.19 (1H, d J 16.4 Hz, CH_2), 3.07 (1H, d J 16.4 Hz, CH_2).

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