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Application of Organolithium and Related Reagents in Synthesis. Part 14[1]. Synthetic Strategies Based on Aromatic Metallation. A Concise Regiospecific Conversion of Benzoic Acids into Their *ortho*-Pyridoyl Derivatives

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Dedicated with admiration and affection, to Alan R. Katritzky on his 65th birthday

Abstract: *The synthesis of the 3-hydroxy-3-pyridyl-isoindolin-1-ones (5) and (6) via metallation (n-BuLi) of the benzanilides (1), and then the reaction of the generated bis lithiated anilides (2) with N,N-dimethylamides or methyl esters of pyridinecarboxylic acids (benzoylation reagents), and subsequent acidic hydrolysis of (5) and (6) as a way (general synthetic strategy) of regiospecific transformation of benzoic acids into their ortho-benzoylated derivatives, is described.*

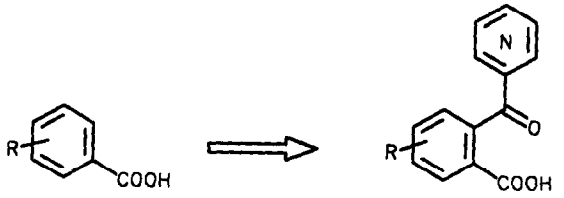
The current interest in *ortho*-benzoylated aromatic carboxylic acids as key starting materials for the preparation of numerous poly-heterocyclic compounds including important physiologically active products[2] has led us to examine methods for the synthesis of these systems.

Available methods for the preparation of *ortho*-benzoylated aromatic carboxylic acids generally require one of the following techniques: The most common approach involves the Friedel-Crafts reaction which is usually effected under harsh conditions and often does not proceed with desired positional specificity[3]. Alternatively, the desired compounds are synthesised *via* hydroxylation of phthalides at the 3-position by bromination with N-bromosuccinimide and subsequent hydrolysis[2a, 2b, 4]. However, this method is unsuccessful in some cases[2b, 5]. The most attractive route so far reported to ortho- benzoylated aromatic carboxylic acids is the directed lithiation of the amides[6-8, 10-16] or (4,4-dimethyloxazolin-2-yl)-aromatic derivatives[9] (masked carboxylic acids) followed by reaction with electrophiles such as chlorides, esters or N,N-dimethylamides of aromatic carboxylic acids. However, most cases relate only to specific instances.

In a series of recent studies, we have reported[13-16] that the secondary carboxamide moiety provides an excellent possibility for the regiospecific *ortho*-lithiation and subsequent electrophilic substitution of the benzene ring of N,N-dimethyl-aromatic amides (source of the benzoyl group), as a way of transforming the aromatic carboxylic acids into their *ortho*- benzoylated derivatives. We have now studied the lithiation

of aromatic benzamides and the effect of the position of the substituent upon the reaction of the generated bis-(N-and C-*ortho*)- lithiated species with N,N-dimethylpyridinecarboxamides as an extension of the scope of our benzoylation methodology.

We describe herein a novel efficient synthetic sequence, as a general strategy, for the transformation of the benzoic acids (**A**) into their *ortho*-pyridoylated derivatives (**B**)



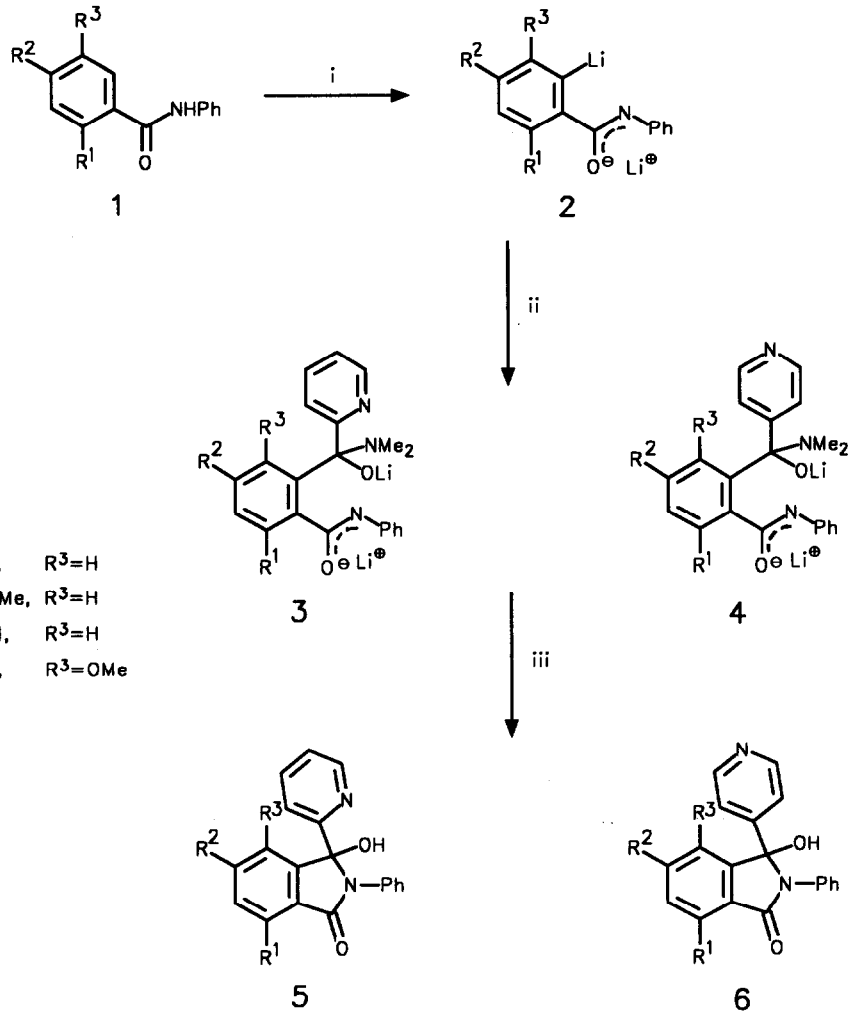
A B

It has been demonstrated[13, 17] that among the N-substituted carboxamides the N-phenylamides (anilides) are the most powerful directing group and that the anilide function should be considered the best choice for direct metallation of the masked carboxylic acids.

To this end, the anilides (**1**) were reacted in THF with 2.1 mol equivalents of *n*-BuLi (amide/-78°C/ *n*-BuLi/0.5 h → 0°C/2 h) and efficiently converted into the *bis* (N- and C-*ortho*) lithiated anilides (**2**). Treatment of the solution of the lithiated species with N,N-dimethyl- picolinic- or isonicotinic-amides afforded the corresponding adducts (**3**) and (**4**), which upon hydrolytic workup spontaneously cyclized into the 3-hydroxyisoindolin-1-ones (**5**) and (**6**). The bis-lithiated anilides (**2a**), (**2b**) and (**2c**) reacted with N,N-dimethylpyridinecarboxamides to give in good yields the desired isoindolin-1-ones (**5a**), (**5b**), (**5c**), (**6a**), (**6b**) and (**6c**). On the other hand, the *bis*-lithiated *m*-methoxyanilide (**2d**) when reacted with N,N-dimethyl-pyridinecarboxamides gave the products (**5d**) and (**6d**) in low yields (19%) and (6%) respectively. The yields were effectively increased after replacing the N,N-dimethylamides by methyl pyridincarboxylates.

Recently[13] it has been shown that the adducts (**3**) or (**4**) of the lithiated species, such as (**2**), across the carbonyl group of N,N-dimethylaromatic amides (formed via SET process[18]) are not stable and a slow retro cross-addition reaction has been observed. Therefore, the decreased output of the corresponding products, which would be derived *via* hydrolytic workup of the adducts (**3d**) and (**4d**), could be accounted for by their instability and/or impedance of their formation arising from steric hindrance caused by *meta* methoxy-substituent of the *bis*-lithiated anilide (**2d**).

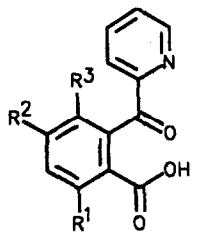
The observed methodology relating to the introduction of the aroyl group at the *ortho* position of the anilide function of aromatic acids shows a considerable versality for the regiospecific synthesis of the 3-hydroxy-3-pyridyl-2 phenylisoindolin-1-ones[19]. This, coupled with the quantitative removal



a: R^1=OMe, R^2=H, R^3=H
b: R^1=H, R^2=OMe, R^3=H
c: R^1=H, R^2=Cl, R^3=H
d: R^1=H, R^2=H, R^3=OMe

i, nBuLi in THF, −78°C (0.1 h) → 0°C (0.1 h)
ii, 2-$PyCONMe_2$ or 4-$PyCONMe_2$
iii, hydrolytic workup

of the anilide moiety on acid hydrolysis to the *ortho* benzoylated aromatic carboxylic acids should allow access to a wide variety of aromatic systems with two different electrophilc functions attached at the *ortho* positions.



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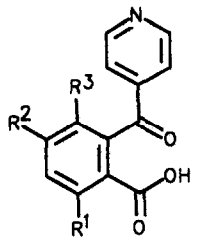

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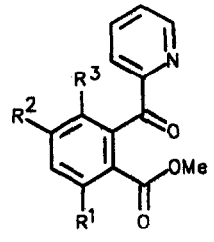

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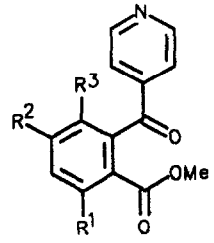

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Thus, the 3-hydroxyisoindolin-1-ones (**5**) and (**6**) upon reaction with boiling sulphuric acid (50% - H_2SO_4) afforded the *ortho*-pyridoylbenzoic acids (**7**) and (**8**), whose sodium salts reacted with MeI in DMF at 0°C to give the corresponding methyl esters (**9**) and (**10**). In all cases, MeI appeared to be inert towards N-alkylation of the pyridine nucleus (under the conditions used). The isolation of the compounds (**9a**) and (**10a**) as pure materials failed, although their formation has been observed by ^{1}H NMR of the reaction mixtures. All the other esters were successfully isolated and purified.

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 Tesla BS-467 (60 MHz) or a Varian-Gemini-200 (200 MHz) using TMS as an internal standard. *n*-Butyllithium (*n*-BuLi) (Aldrich) was used without further purification. Tetrahydrofuran (THF) was dried over calcium hydride and used directly after distillation. Benzanilides (**1**) were prepared by the standard methods.

Preparation of 3-hydroxy-2-phenyl-2,3-dihydro-1H-isoindol-1-ones (5) and (6)

To the anilide (0.01 mole) stirred in THF (30 ml) at -78°C *n*-BuLi (0.022 mole) was added. The solution was held at -78°C for 0.1 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 N,N-dimethylpicolinic or N,N-dimethylisonicotinic amide (0.01 mole) in THF (20 ml) was added respectively. The reaction after 0.2 h at -78°C was warmed up to room temperature, and kept for 24 h (in the case of compounds (**5a**), (**6a**) and (**6b**) for 1.5 h). Then, in the case of compounds (**5**) water (25 ml) was added and the whole lot was neutralised by addition of hydrochloric acid. The organic layer was separated and the water layer was extracted with a mixture of chloroform and THF - 1:1 (2 x 30 ml). The combined organic solutions were dried with magnesium sulfate, and the solvents were evaporated to give a solid residue. Compounds (**5d**) and (**5b**) were isolated by column chromatography (silica gel) and then were purified by crystallisation. The crude products (**5c**) and (**5a**) were washed with ethyl acetate (15 ml) and purified by crystallisation. In the case of compounds (**6**), methanol (20 ml) was added and the solvents were removed under reduced pressure. To the residue water (100 ml) was added and the whole lot was neutralised by addition of hydrochloric acid. The insoluble crude products were separated, washed with water and purified by crystallisation.

3-Hydroxy-7-methoxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**5a**), (69%) m.p. 167-168°C (water : methanol - 5:8); (Found: N, 8.3. Calc. for $C_{20}H_{16}N_2O_3$: N, 8.43%); IR (KBr) 3600-3200 cm^{-1} (OH), 1690 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.39 (1H, d J 4.5 Hz, 6Py-H), 7.90-7.73 (2H, m, 3Py and 4Py-H), 7.70 (1H, s, exchanges with D_2O, OH-H), 7.60-7.46 (1H, m, 5-H), 7.40-7.02 (7H, m, Ph, 5Py and 4-H), 6.82 (1H, d J 7.5 Hz, 6-H), 3.97 (3H, s, OMe-H).

3-Hydroxy-5-methoxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**5b**), (63%), (eluent chloroform, R_f 0.10), m.p. 184-186°C (water : methanol - 1:3); (Found: C, 72.2; H, 4.9; N, 8.7. Calc. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43%); IR (KBr) 3600-3200 cm^{-1} (OH), 1710 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.36 (1H, d J 4.6 Hz, 6Py-H), 7.92-7.70 (4H, m, 3Py, 4Py, 7-H and exchanges with D_2O, OH-H), 7.42-7.03 (7H, m, Ph, 5Py and 6-H), 6.75 (1H, d J 2.2 Hz, 4-H), 3.77 (3H, s, OMe-H). The exact ^1H NMR assignment of the aromatic proton was extracted from the ^1H-^1H COSY plot.

5-Chlor-3-hydroxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**5c**), (71%) m.p. 213-214°C (benzene); (Found: C, 68.0; H, 3.9; Cl, 10.5; N, 8.3. Calc. for $C_{19}H_{13}ClN_2O_2$: C, 67.76; H, 3.89; Cl, 10.53; N, 8.32%); IR (KBr) 3600-3200 cm^{-1} (OH), 1710 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.47 (1H, d J 4.9 Hz, 6Py-H), 8.02 (1H, s, exchanges with D_2O, OH-H), 7.94-7.76 (3H, m, 3Py, 4-Py and 7-H), 7.65 (1H, dd J 8.0 and 1.7 Hz, 6-H), 7.44-7.10 (7H, m, Ph, 5Py-H and 4-H). The exact ^1H NMR assignment of the aromatic proton was extracted from the ^1H-^1H COSY plot.

3-Hydroxy-4-methoxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**5d**), (19%), (eluent ethyl acetate, R_f 0.57), m.p. 226-227°C (ethanol); (Found: C, 72.6; H, 4.8; N, 8.2. Calc. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43%); IR (KBr) 3600-3200 cm^{-1} (OH), 1710 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 60 MHz) 8.7-8.3 (1H, m, 6Py-H), 8.2-7.0 (11H, m, Ph, 3Py, 4Py, 5Py and 5, 6, 7-H), 3.7-3.6 (3H, two s, OMe-H), 3.4-3.0 (br. s, OH-H).

3-Hydroxy-7-methoxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**6a**), (85%) m.p. 282-284°C (decompose), (methanol); (Found: C, 72.5; H, 4.9; N, 8.4. Calc. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43%); IR (KBr) 3600-3200 cm^{-1} (OH), 1710 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.46 (2H, dd J 4.5 and 1.5 Hz, 2Py and 6Py-H), 7.81 (1H, s, exchanges with D_2O, OH-H), 7.64-7.52 (1H, m, 5-H), 7.52-7.40 (2H, m, 2Ph and 6Ph-H), 7.35 (2H, dd J 4.5 and 1.5 Hz, 3Py and 5Py-H), 7.32-7.06 (4H, m, 3Ph, 4Ph, 5Ph and 4-H), 6.82 (1H, d J 7.7 Hz, 6-H), 3.93 (3H,s, OMe-H). The exact ^1H-NMR assignment of the aromatic proton was extracted from the ^1H-^1H COSY plot.

3-Hydroxy-5-methoxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**6b**), (77%) m.p. 283-285°C (acetic acid); (Found: C, 72.1; H, 5.0; N, 8.4. Calc. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43%); IR (KBr) 3600-3200 cm^{-1} (OH), 1710 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.49 (2H, d J 5.6 Hz, 2Py and 6Py-H), 7.95 (1H, s, exchanges with D_2O, OH-H), 7.81 (1H, d J 8.5 Hz, 7-H), 7.60-7.06 (8H, m, Ph, 3Py, 5Py, 6-H), 8.81 (1H, d J 2.1 Hz, 4-H), 3.80 (3H, s, OMe-H).

5-Chlor-3-hydroxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**6c**), (90%) m.p. 294-295°C (methanol); (Found: C, 68.0; H, 3.9; Cl, 10.4; N, 8.4. Calc. for $C_{19}H_{13}ClN_2O_2$: C, 67.76; H, 3.89; Cl, 10.53; N, 8.32%); IR (KBr) 3600-3200 cm^{-1} (OH), 1690 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.50 (2H, d J 5.4 Hz, 2Py and 6Py-H), 8.10 (1H, s, exchanges with D_2O, OH-H), 7.90 (1H, d J 8.1 Hz, 7-H), 7.69 (1H, dd J 8.1 and 1.6 Hz, 6-H), 7.56-7.10 (8H, m, Ph, 3Py, 5Py and 4-H).

3-Hydroxy-4-methoxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**6d**), (6%) m.p. 288-289°C (ethanol); (Found: C, 72.2; H, 5.0; N, 8.2. Calc. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43%); IR (KBr) 3600-3200 cm^{-1} (OH), 1710 cm^{-1} (C=O); ^1H NMR (DMSO-d_6 , 200 MHz) 8.44 (2H, d J 5.6 Hz, 2Py and 6Py-H), 7.75 (1H, s, exchanges with D_2O, OH-H), 7.68-7.56 (1H, m, 6-H), 7.54-7.30 (9H, m, Ph, 3Py, 5Py, 5-H and 7-H), 3.67 (3H, s, OMe).

Preparation of 3-hydroxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (5d) or (6d) in reaction with methyl picolinate or isonicotinate

To the anilide (**1d**) (0.01 mole) and TMEDA (0.022 mole) stirred in THF (30 ml) at -78°C *n*-BuLi (0.022 mole) was added. The solution was held at -78°C for 0.1 h, then allowed to rise to 0°C and the whole lot was cannulated into methyl picolinate or methyl isonicotinate (0.01 mole) in THF (30 ml) at -78°C. The reaction after 0.2 h at -78°C was warmed up to room temperature, and kept for 2 h. Then, in the case of compound (**5d**) water (20 ml) was added and the whole lot was neutralised by addition hydrochloric acid. The organic layer was separated and the water layer was extracted with a mixture of chloroform and THF - 1:1 (2 x 30 ml). The combined organic solutions were dried with magnesium sulfate, and the solvents and TMEDA were removed under reduced pressure. The residual crude product was washed with ethyl acetate (15 ml) and purified by crystallisation (76%, m.p. 225-227°C, ethanol). In the case of compound (**6d**), methanol (20 ml) was added. The solvents were evaporated and to the residue water (50 ml) was added. The whole lot was neutralised by addition of hydrochloric acid. The insoluble crude product was separated, washed with water and purified by crystallisation (73%, m.p. 288-289°C, ethanol).

Hydrolysis of the Compounds (5) and (6). Synthesis of the (7) and (8) Acids

The mixture of the compounds (**5**) or (**6**) (0.006 mole) in 50% sulphuric acid (20 ml) was heated till boiling for 1 h. Then the whole lot was poured into water (20 ml) and after cooling the solution was adjusted ($NaHCO_3$) to pH≈4 to precipitate acids (**7**) and (**8**). The crude products were separated, washed with water and purified by crystallisation.

6-Methoxy-2-(2-pyridinecarbonyl)benzoic acid (**7a**),
existed in cyclic form as *3-hydroxy-7-methoxy-3-(2-pyridyl)phthalide*, (92%) m.p. 183-187°C, (benzene); (Found: C, 65.1; H, 4.3; N, 5.3. Calc. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44%); IR (KBr) 3600-2900 cm^{-1} (OH), 1750 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.70 (1H, s, exchanges with D_2O, OH-H), 8.53 (1H, d J 4.2 Hz, 6Py-H), 8.08-7.88 (2H, m, 3Py and 4Py-H), 7.80-7.66 (1H, m,5-H), 7.52-7.40 (1H, m, 5Py-H), 7.23 (1H, d J 8.4 Hz, 4-H), 7.02 (1H, d J 7.6 Hz, 6-H), 4.03 (3H, s, OMe-H).

4-Methoxy-2-(2-pyridinecarbonyl)benzoic acid (**7b**),
(85%) m.p. 198-207°C (decompose), (ethanol); (Found: C, 65.4; H, 4.3; N, 5.3. Calc. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44%); IR (KBr) 3600-2400 cm^{-1} (OH), 1690 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 60 MHz) 13.2-12.3 (br. s, OH-H), 8.6 (1H, d J 4 Hz, 6Py-H), 8.3-7.8 (3H, m, 3Py, 4Py and 6Ar-H), 7.7-7.4 (1H, m, 5Py-H), 7.3-6.9 (2H, m, 3Ar and 5Ar-H), 3.8 (3H, s, OMe-H).

4-Chlor-2-(2-pyridinecarbonyl)benzoic acid (**7c**),
(91%) m.p. 202-205°C (water : ethanol - 1:1); (Found: C, 59.7; H, 3.1; Cl, 13.6; N, 5.4. Calc. for $C_{13}H_8ClNO_3$: C, 59.67; H, 3.08; Cl, 13.55; N, 5.35%); IR (KBr) 3600-2400 cm^{-1} (OH), 1690 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 12.90-12.20 (1H, br. s, OH-H), 8.56 (1H, d J 4.2 Hz, 6Py-H), 8.20-7.90 (3H, m, 4Py, 5Ar and 6Ar-H), 7.78-7.56 (3H, m, 3Py, 5Py and 3Ar-H).

3-Methoxy-2-(2-pyridinecarbonyl)benzoic acid (**7d**),
(95%) m.p. 211-213°C (ethanol); (Found: N, 5.2. Calc. for $C_{14}H_{11}NO_4$: N, 5.44%); IR (KBr) 3500-2500 cm^{-1} (OH), 1685 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.53 (1H, d J 4.1 Hz, 6Py-H), 8.20-7.80 (2H, m, 4Py and 6Ar-H), 7.70-7.20 (4H, m, 3Py, 5Py, 4Ar and 5Ar-H), 3.67 (3H, s, OMe-H), 3.60-3.00 (br. s, OH-H).

6-Methoxy-2-(4-pyridinecarbonyl)benzoic acid (**8a**),
existed in cyclic form as *3-hydroxy-7-methoxy-3-(4-pyridyl)phthalide*, (89%) m.p. 263-267°C (decompose), (acetic acid); (Found: C, 65.2; H, 4.3; N, 5.1. Calc. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44%); IR (KBr) 3600-2400 cm^{-1} (OH), 1770 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.70 (1H, s, exchanges with D_2O, OH-H), 8.66 (2H, d J 5.0 Hz, 2Py and 6Py-H), 7.80-7.66 (1H, m, 5-H), 7.49 (2H, d J 5.0 Hz, 3Py and 5Py-H), 7.23 (1H, d J 8.3 Hz 4-H), 7.05 (1H, d J 7.7 Hz, 6-H), 3.95 (3H, s, OMe-H). Two small signals of acyclic form probably between 8.86-8.76 and 7.62-7.54 are also observed.

4-Methoxy-2-(4-pyridinecarbonyl)benzoic acid (**8b**),
(89%) m.p. 236-238°C (ethanol); (Found: C, 65.6; H, 4.4; N, 5.4. Calc. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44%); IR (KBr) 3600-2400 cm^{-1} (OH), 1690 cm^{-1} (C=O), ^1H NMR (DMSO-d_6, 200 MHz) 13.20-12.40 (br. s, OH-H), 8.74 (2H, d J 4.6 Hz, 2Py and 6Py-H), 7.97 (1H, d J 8.6 Hz, 6Ar-H), 7.49 (2H, d J 4.6 Hz, 3Py and 5Py-H), 7.22 (1H, dd J 8.6 and 2.3 Hz, 5Ar-H), 7.06 (1H, d J 2.3 Hz), 3.86 (3H, s, OMe-H).

4-Chlor-2-(4-pyridinecarbonyl)benzoic acid (**8c**),
(93%) m.p. 289-292°C (ethanol); (Found: C, 59.7; H, 3.2; Cl, 13.5; N, 5.4. Calc. for $C_{13}H_8ClNO_3$: C, 59.67; H, 3.08; Cl, 13.55; N, 5.35%); IR (KBr) 3600-2400 cm^{-1} (OH), 1690 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.75 (2H, d J 4.8 Hz, 2Py and 6Py-H), 8.02 (1H, d J 8.3 Hz, 6Ar-H), 7.73 (1H, dd J 8.3 and 2.0 Hz, 5Ar-H), 7.71 (1H, d J 2 Hz, 3Ar-H), 7.52 (2H, d J 4.8 Hz, 3Py and 5Py-H), 4.00-3.00 (br. s, OH-H).

3-Methoxy-2-(4-pyridinecarbonyl)benzoic acid (**8d**),
(95%) m.p. 226-228°C (ethanol); (Found: N, 5.4. Calc. for $C_{14}H_{11}NO_4$: N, 5.44%); IR (KBr) 3600-2500 cm^{-1} (OH), 1690 cm^{-1} (C=O), ^1H NMR (DMSO-d_6, 200 MHz) 8.85 (2H, d J 4.8 Hz, 2Py and 6Py-H), 8.10-7.30 (5H, m, 3Py, 5Py, and Ar-H), 5.10-4.20 (br. s, OH-H), 3.77 (3H, s, OMe-H).

Conversion of Acids (7) and (8) into the Corresponding Methyl Esters (9) and (10)

To the suspension of the acid (7) or (**8**) (0.004 mole) in water (30 ml), $NaHCO_3$ (0.005 mole) was added, and stirred until dissolved, then the solvent was removed under reduced pressure and the residue was dried under vacuum. The residue (sodium salt of the corresponding acid) was then subjected to react on with iodomethane (0.004 mole) in DMF (15 ml) at 0°C for 0.8 h in the case of compound (7) or for 4 h in the case of compound (**8**). Then the solvent was removed under reduced pressure and to the residue water (10 ml) was added. The product was extracted with $CHCl_3$ (3 x 15 ml) and separated by column chromatography (silica gel) and then purified by crystallisation.

Methyl 4-Methoxy-2-(2-pyridinecarbonyl)benzoate (**9b**),
(89%), (eluent ethyl acetate, R_f 0.53), m.p. 102-104°C (benzene : hexane - 1:1); (Found: C, 66.1; H, 4.9; N, 5.2. Calc. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.83; N, 5.16%); IR (KBr) 1730, 1705, and 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz) 8.6 (1H, d J 4 Hz, 6Py-H), 8.4-7.6 (3H, m, 3Py, 4Py and 6Ar-H), 7.5-7.2 (1H,m, 5Py-H), 7.1-6.8 (2H, m, 3Ar and 5Ar-H), 3.8 (3H, s, OMe-H), 3.5 (3H, s, OMe-H).

Methyl 4-Chlor-2-(2-pyridinecarbonyl)benzoate (**9c**),
(81%), (eluent benzene, R_f 0.24), m.p. 121-123°C (benzene : hexane - 1:1); (Found: C, 61.3; H, 3.7; Cl 12.9; N, 5.1. Calc. for $C_{14}H_{10}ClNO_3$: C, 60.99; H, 3.66; Cl, 12.86; N, 5.08%); IR (KBr) 1730 cm^{-1} and 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 8.57 (1H, d J 4.2 Hz, 6Py-H), 8.26 (1H, d J 7.9 Hz, 6Ar-H), 8.02-7.82 (2H, m, 4Py and 5Ar-H), 7.54 (1H, dd J 8.2 and 2.0 Hz, 3Py-H), 7.50-7.36 (2H, m, 5Py and 3Ar-H), 3.55 (3H, s, OMe). The exact ^1H NMR assignment of the aromatic proton was extracted from the ^1H-^1H COSY plot.

Methyl 3-Methoxy-2-(2-pyridinecarbonyl)benzoate (**9d**),
(93%), (eluent ethyl acetate, R_f 0.55), m.p. 153-154°C (benzene : hexane - 1:1); (Found: C, 66.5; H, 5.0; N, 4.9. Calc. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.83; N, 5.16%); IR (KBr) 1730 cm^{-1} and 1685 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz) 8.6 (1H, dd J 5 and 2 Hz, 6Py-H), 8.2 (1H, dd J 8 and 1 Hz, 6Ar-H), 8.0-7.0 (5H, m, 3Py, 4Py, 5Py, 4Ar and 5Ar-H), 3.6 and 3.5 (6H, two s, OMe-H).

Methyl 4-Methoxy-2-(4-pyridinecarbonyl)benzoate (**10b**),
(73%), (eluent ethyl acetate, R_f 0.31), m.p. 92-93°C (toluene : heptane - 1:1); (Found: C, 66.5; H, 4.9; N, 5.1. Calc. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.83; N, 5.16%); IR (KBr) 1710 cm^{-1} and 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 8.76 (2H, d J 4.8 Hz, 2Py and 6Py-H), 8.04 (1H, d J 8.0 Hz, 6Ar-H), 7.53 (2H, d J 4.8 Hz, 3Py and 5Py-H), 7.07 (1H, dd J 8.0 and 1.9 Hz, 5Ar-H), 6.86 (1H, d J 1.9 Hz, 3Ar-H), 3.86 (3H, s, OMe-H), 3.63 (3H, s, OMe-H).

Methyl 4-Chlor-2-(4-pyridinecarbonyl)benzoate (**10c**),
(63%), (eluent chloroform, R_f 0.36), m.p. 82-84°C (benzene : hexane - 1:1); (Found: C, 61.3; H, 3.6; Cl 12.8; N, 5.1. Calc. for $C_{14}H_{10}ClNO_3$: C, 60.99; H, 3.66; Cl, 12.86; N, 5.08%); IR (KBr) 1730 cm^{-1} and 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 8.80 (2H, d J 4.4 Hz, 2Py and 6Py-H), 8.05 (1H, d J 8.6 Hz, 6Ar-H), 7.65-7.32 (4H, m, 3Py, 5Py, 3Ar and 5Ar-H), 3.57 (3H, s, OMe-H).

Methyl 3-Methoxy-2-(4-pyridinecarbonyl)benzoate (**10d**),
(70%), (eluent ethyl acetate, R_f 0.40), m.p. 104-105°C (toluene : hexane - 1:1); (Found: C, 66.6; H, 5.0; N, 5.0. Calc. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.83; N, 5.16%); IR (KBr) 1730 cm^{-1} and 1695 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 8.76 (2H, dd J 4.4 and 1.6 Hz, 2Py and 6Py-H), 7.70 (1H, dd J 7.9 and 1 Hz, 6Ar-H), 7.63-7.40 (3H, m, 3Py, 5Py and 5Ar-H), 7.22 (1H, dd J 8.3 and 1.0 Hz, 4Ar-H), 3.75 and 3.71 (6H, two s, OMe-H).

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