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APPLICATION OF ORGANOLITHIUM AND RELATED REAGENTS IN SYNTHESIS. PART 15[1]. A CONCISE REGIOSPECIFIC CONVERSION OF PICOLINIC- AND ISONICOTINIC ACIDS INTO 2-BENZOYL- AND 4-BENZOYLNICOTINIC ACIDS.

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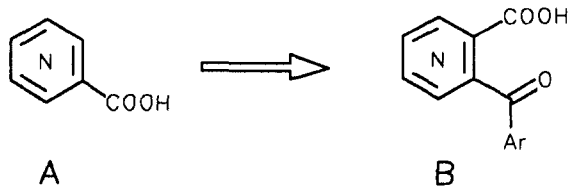
Dedicated with admiration and affection, to Alan R. Katritzky on his 65 birthday

Abstract: The synthesis of the azaphthalides (**7**) and (**8**) and their conversion into the corresponding 2- and 4-benzoyl-3-hydroxymethylpyridines (**9**) and (**10**), very useful precursors of the 2- and 4-benzoylated nicotinic acids (**11**) and (**12**), as a way of regiospecific transformation of the picolin- and isonicotinanilides (**1**) and (**2**) into nicotinic acid derivatives, is described.

As a part of our project centred around the preparation of polyheterocyclic compounds (biologically active)[2] an efficient synthetic route to benzoylnicotinic acids derivatives was required. Because of the importance of the nicotinic acid derivatives in the construction of physiologically active systems, they have long been targets of synthetic chemistry. Available methods of their preparation generally require total construction of the pyridine nucleus via multi-step

reactions[3]. A number of alternative methods have been attempted. The most common approach involves electrophilic substitution of benzene with quinolinic and cinchomeronic anhydrides, which is usually effected under harsh conditions and often does not proceed with the desired positional specificity[4]. Recently[5], the addition of aryllithiums to the carbonyl group of quinoline and cinchomeronic anhydrides has been tested. In these cases, a rather low regiospecificity has been observed.

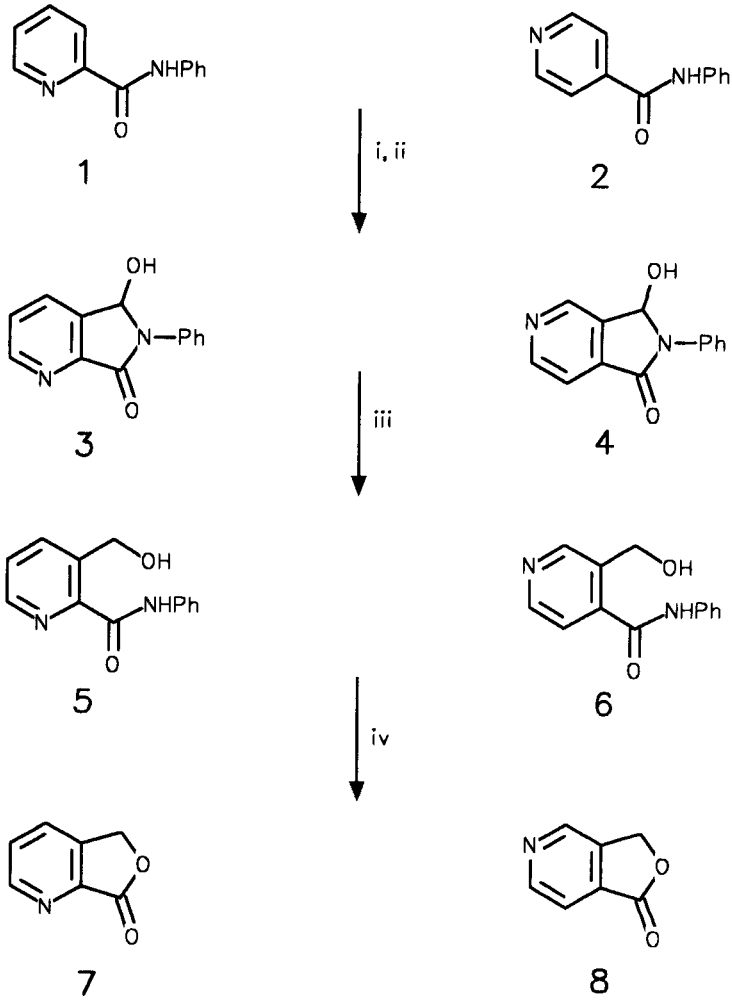
Herein we wish to report a five-step protocol starting from picolin- and isonicotinanilides for the efficient construction of *ortho*-benzoylated derivatives of nicotinic acid. For this purpose, we show a new specific methodology for the positional replacement of the carboxyl group with simultaneous introduction of the benzoyl substituent at the aromatic nucleus, as depicted in the Scheme **A** → **B**.



Our route leading to the *ortho*-benzoylated nicotinic acids (**11**) and (**12**) is outlined in Schemes **I** and **II.** It begins with successive C^3-formylation of the picolin- and isonicotinanilides (**1**) and (**2**).

The anilides (**1**) and (**2**) on reaction in THF with 2.1 mole equivalents of *n*-BuLi (amide/-78°C/*n*-BuLi/0.5 h → 0°C/2 h) were efficiently converted into the bis-(N- and C^3-) lithiated anilides. Treatment of the solutions

Scheme I



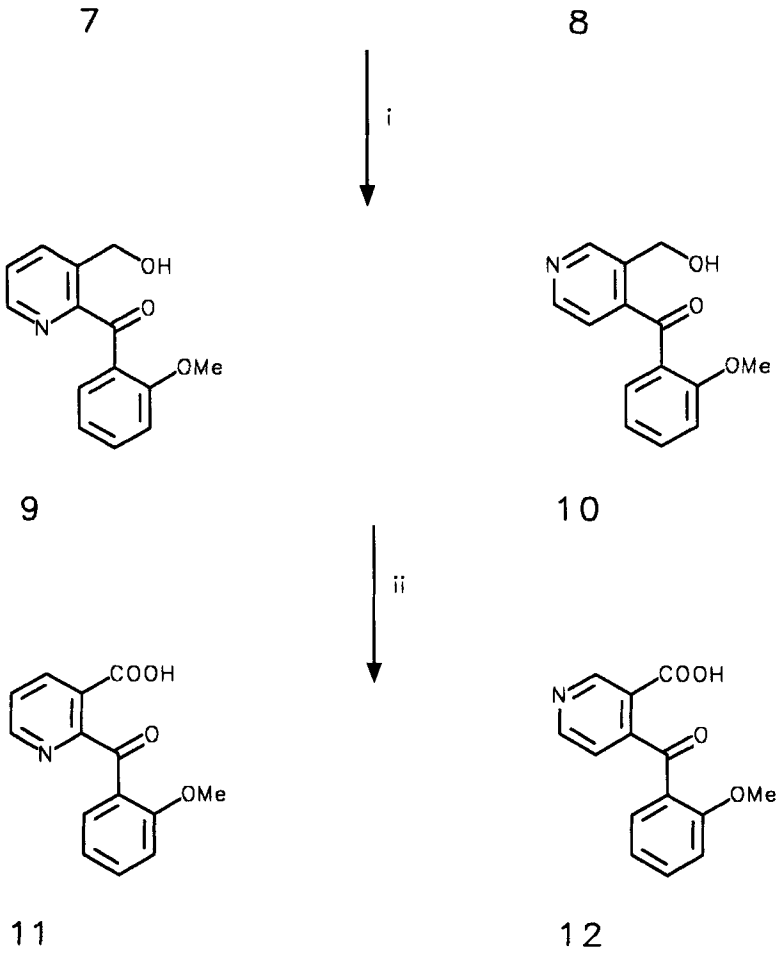
i, n–BuLi in THF, –78°C (0.5 h) → 0°C (0.1 h);

ii, Me_2NCHO, –78°C (1 h) → 0°C (1 h);

iii, KBH_4 in methanol, 20°C;

iv, HCl

Scheme II



i, o–$MeOC_6H_4$–Li in THF;

ii, $KMnO_4$ in water : acetone – 1 : 1

of the lithiated species with dimethylformamide (DMF) afforded the corresponding formylated derivatives, which upon hydrolytic workup spontaneously cyclized into the 3-hydroxyisoindolin-1-ones (**3**) and (**4**). Subsequent reduction of the 3-hydroxyisoindolin-1-ones (**3**) and (**4**) with KBH_4 in MeOH yielded the anilides (**5**) and (**6**), which upon acid-driven cyclization were converted into the corresponding phthalides (**7**) and (**8**).

A general synthetic strategy for the transformation of the aromatic carboxylic acids (**A**) into the *ortho*-benzoylated derivatives (**B**) was exemplified by the preparation of the 2- and 4-benzoylnicotinic acids from the picolin- and isonicotinanilides respectively. To this end, at first the phthalides (**7**) and (**8**) were reacted with 2-methoxyphenyllithium[6] at -78°C to give the 2- and 4-benzoyl-3-hydroxymethylpyridines (**9**) and (**10**), which upon oxidation with potassium permanganate in water : acetone - 1 : 1 gave the benzoylated nicotinic acids (**11**) and (**12**).

In summary, we have shown a synthetic method for the preparation of 2-and 4-benzoylnicotinic acids (**11**) and (**12**) with an economy of steps which involves: (i) successive conversion of the picolin- and isonicotinanilides (**1**) and (**2**) into the phthalides (**7**) and (**8**), and then (ii) direct formation of 2- and 4-benzoyl-3-hydroxymethylpyridines (**9**) and (**10**) as precursors of (**11**) and (**12**).

Experimental

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on Zeiss-Jena Specord 71-IR, and ^{1}H-NMR spectra were determined on a Tesla BS-467 (60 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. Anilides (**1**) and (**2**) were prepared by standard methods.

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

To the anilide (0.01 mole) stirred in THF (60 ml) at –78°C *n*-BuLi (0.022 mole) 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 DMF (0.02 mole) was added. The reaction mixture after 1 h at -78°C was warmed up to 0°C and kept at 0°C for 1 h. Then water (20 ml) was added. The organic layer was separated, the water one extracted with $CHCl_3$ (2 x 20 ml). The combined organic solutions were dried ($MgSO_4$) and the solvents removed to give a semi-solid residue. The residue was subjected to column chromatography on silica gel with benzene : ethyl acetate - 3:7 as eluent. This gave a part of the products (**3**) and (**4**). The main amount of the products (**3**) and (**4**) was obtained after adjusting the aqueous layer to *pH*≈3.4 (HCl). The products were purified by crystallisation.

1-Hydroxy-2-phenyl-pyrro[3,4-b]pyridine-3(1H)-one (**3**)

(69%) m.p. 237-239°C (methanol); (Found: C, 69.0; H, 4.7; N, 12.3. Calc. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38%); IR (KBr) 3500-2600 cm^{-1} (OH), 1700 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) 8.9 (1H, dd J 5 and 2Hz, 5-H), 8.3 (1H, dd J 8 and 2Hz, 7-H), 8.2-7.0 (7H, m, 6-H, OH-H and Ph-H), 6,7 (1H, s, 1-H).

3-Hydroxy-2-phenyl-pyrro[3,4-c]pyridine-1(3H)-one (**4**)

(78%) m.p. 223-225°C (acetone); (Found: C, 69.2 H, 4.6; N, 12.4. Calc. for

$C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38%); IR (KBr) 3600-2600 cm^{-1} (OH), 1700 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) 8.8 (1H, s, 4-H), 8.7 (1H, d J 5Hz, 6-H), 7.7-6.8 (7H, m, 7-H, OH-H and Ph-H), 6.5 (1H, s, 3-H).

Preparation of Hydroxymethylpyridinanilides (5), (6) and Their Subsequent Cyclization into Phthalides (7) and (8)

a) Reduction of Aza-isoindolinones (3) and (4)

To the compound (**3**) or (**4**) (0.01 mole) in methanol (50 ml), potassium borohydride (0.02 mole) was added and the whole lot was stirred overnight at room temperature. Then methanol was evaporated in vacuum and to the residue water (20 ml) was added. The insoluble product was separated and purified by crystallisation.

3-Hydroxymethylpicolinanilide (**5**)

(88%) m.p. 110-112°C (hexane : acetone - 3:2); (Found: C, 68.6; H, 5.4; N, 12.1. Calc. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27%); IR (KBr) 3600-3200 cm^{-1} (NH and OH), 1670 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 10.3 (1H, br. s, NH-H), 8.5 (1H, dd J 5 and 2Hz, 6Py-H), 8.3-6.7 (7H, m, 4Py-H, 5Py-H and Ph-H), 5.2-4.3 (3H, s, CH_2-H and br.s OH-H).

3-Hydroxymethylisonicotinanilide (**6**)

(85%) m.p. 108-110°C (water : methanol - 9:1); (Found: C, 68.7; H, 5.3; N, 12.3. Calc. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27%); IR (KBr) 3400-3200 cm^{-1} (NH and OH), 1660 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$ and DMSO-d_6) 10.5 (1H, br. s, NH-H), 8.8-8.5 (2H, m, 2Py-H and 6Py-H), 8.0-7.0 (6H, m, 5Py-H and Ph-H), 5.1 (1H, s, OH-H), 4.7 (2H, s, CH_2-H).

b) Cyclization of compounds (5) and (6) into phthalides (7) and (8)

To hydrochloric acid (15%, 20 ml) the compound (**5**) or (**6**) (0.01 mole) was added and the whole lot was kept at room temperature for 3 days. Then the mixture was adjusted to *pH*≈3.4 ($NaHCO_3$). The obtained solution was continuously extracted with $CHCl_3$ and the extract was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by crystallisation.

Furo[3,4-b]pyridin-7(5H)-one (**7**)

(68%) m. p. 159-162°C (ethyl acetate), (lit.[7], m.p. 158-160°C)

Furo[3,4-c]pyridin-1(3H)-one (**8**)

(68%) m.p. 115-118°C (benzene), (lit.[7] m.p. 118°C).

Prepartion of 2- and 4-(o-Methoxybenzoyl)nicotinic Acids (11) and (12)

To the stirred THF (20 ml) solution of aza-phthalide (**7**) or (**8**) (0.01 mole) 2-methoxyphenyllithium[6] was added. The reaction mixture was kept at -78°C for 0.5 h, then allowed to rise to 20°C and held at ambient temperature for 0.5 h. The solvents were evaporated in vacuum and then water (30 ml) was added and the whole lot was extracted with CH_2Cl_2. The organic solution was dried ($MgSO_4$) and evaporated to give crude product (**9**) or (**10**) which was used without further purification for preparation of nicotinic acids (**11**) and (**12**). The crude product (**9**) or (**10**) was dissolved in the mixture of acetone : water - 1:1, 30 ml) and the water solution of potassium permanganate (0.014 mole, 30 ml) was added. The whole lot was heated under reflux for 1 h (until decolorization). Then the formed manganese(IV) oxide was filtered and washed with water and the filtrate was adjusted to *pH*≈3.4. The precipitated acid (**11**) or (**12**) was separated and purified by crystallisation.

2-(o-Methoxybenzoyl)nicotinic acid (**11**)

(40%) m.p. 181-184°C (benzene : ethyl acetate - 1:1), Found: C, 65.6; H, 4.4; N, 5.5. Calc. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.45%); IR (KBr) 3650-3300 cm^{-1} (OH), 1700 cm^{-1} and 1660 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) 8.6-8.5 (1H, dd J 5 and 2Hz, 6Py-H), 8,3-8,1 (1H, dd J 7Hz and 2, 4Py-H), 7.9-6.8 (5H, m, 5Py-H and Ar-H), 3.2 (3H, s, OMe-H).

4-(o-Methoxybenzoyl)nicotinic acid (**12**)

(70%) m.p. 240-242°C (ethyl acetate : ethanol - 3:2), (lit.[5]. m.p. 270-274°C) Found: C, 65.7; H, 4.3; N, 5.4. Calc. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.45%); IR (KBr) 3650-2500 cm^{-1} (OH), 1700 cm^{-1} and 1650 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) 9.0 (1H, s, 2Py-H), 8.7 (1H, d J 5Hz, 6Py-H), 7.9-6.8 (5H, m, Ar-H and 5Py-H), 3.3 (3H, s, OMe-H).

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