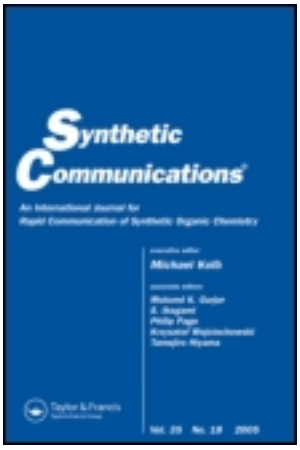

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Application of Organolithium Compounds in Organic Synthesis. XIX. Synthetic Strategies Based on Aromatic Metallation. A Concise Regiospecific Synthesis of 3-Halogenated Picolinic and Isonicotinic Acids

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APPLICATION OF ORGANOLITHIUM COMPOUNDS IN ORGANIC SYNTHESIS. PART 19.[1] SYNTHETIC STRATEGIES BASED ON AROMATIC METALLATION. A CONCISE REGIOSPECIFIC SYNTHESIS OF 3-HALOGENATED PICOLINIC AND ISONICOTINIC ACIDS.

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Abstract: The synthesis of the halogenated picolin- and isonicotinanilides (**3**) and (**4**) *via* metallation (*n*-BuLi) of the anilides (**1**) and (**2**) and then the reaction of the generated bis-lithiated anilides with halogenating agents (CCl_3-CCl_3, CH_2Br-CH_2Br, I_2) followed by subsequent acidic hydrolysis of (**3**) and (**4**), as a way of regiospecific transformation of picoline and isonicotine acids into their C^3-halogenated derivatives, is described.

As a part of our project centred around the preparation of poly-heterocyclic compounds, an efficient synthetic route to the C^3-halogenated picoline- (**5**) and isonicotine- acids (**6**) was required. Because of the importance of *ortho*-halogenated aromatic carboxylic acids in the construction of physiologically active systems, they have long been targets of synthetic chemistry.

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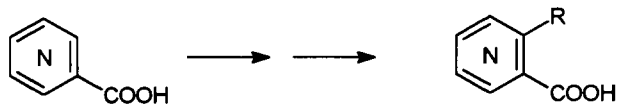
Available routes for their preparation generally require one of the following methods. The method based upon the Sandmeyer reaction[2] is one of the oldest and still applied methodologies[2]. Alternatively, the desired compounds can be synthetised *via* oxidation[3] of the *ortho*-halogenated alkyl-aromatic derivatives. A number of diverse specific methods have been attempted. One of approaches involves chlorination of the aromatic carboxylic acids.[4] This methodology often does not proceed with the desired positional specificity. The reaction of 1,2-dihalo-aromatics with magnesium and then quenching by carbon dioxide was applied as well.[5] Another specific route for the preparation of the desired acids appeared to be the hydrolysis of the *ortho*-cyanohalogeno derivatives.[6] For the reported methods the preparation of the necessary starting materials can involve multi-step procedures, which are often unsatisfactory both in yield and generality. The most attractive route so far reported to *ortho*- halogenated aromatic carboxylic acids is direct lithiation of masked carboxylic acids[7] such as amides or (4,4-dimethyl-oxazolinyl-2-yl) aromatic derivatives, followed by reaction with halogenating electrophiles as a straightforward procedure, or directed silylation and then ipso halo-desilylation.[8] However, in most cases these methods are related only to specific instances.

In a series of recent studies, we have reported[9] that the secondary carboxamide moiety- especially *N*-phenylamides (anilides) provides an excellent possibility for the regiospecific *ortho*-lithiation and subsequent electrophilic substitution of the aromatic ring.

Herein we wish to report a three-step protocol starting from picolin- and isonicotinanilides for an efficient preparation of *ortho*-halogenated picoline- and isonicotine carboxylic methyl esters, as depicted (below) in the perspective Scheme **A** → **B**.

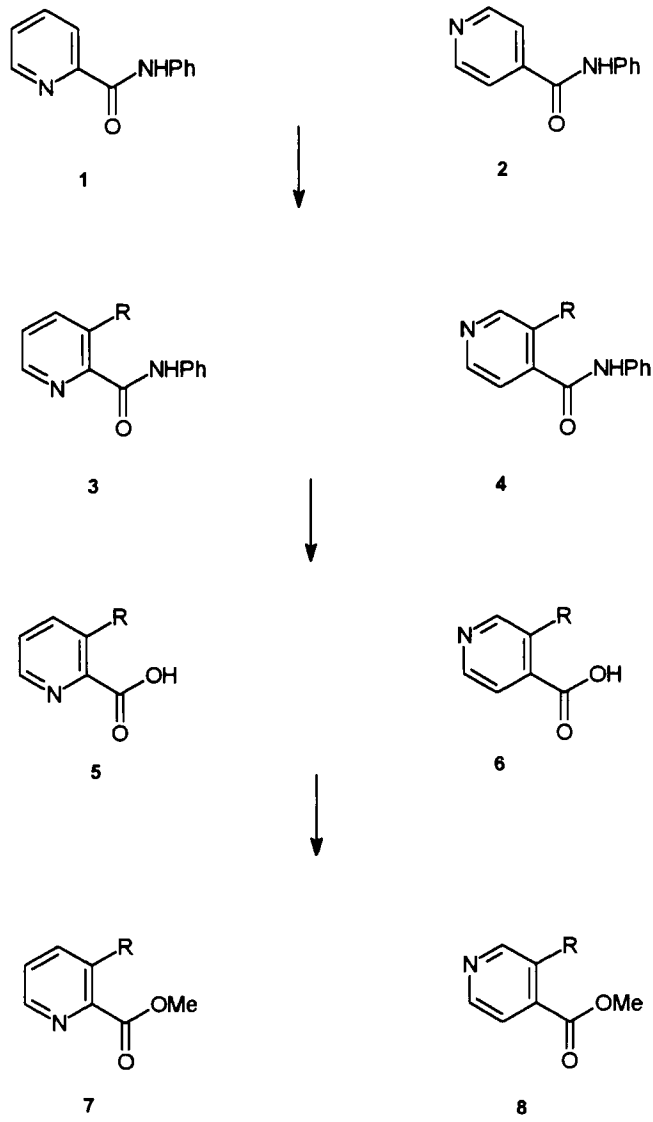


A **B**

R = -Cl, -Br, -I

Our route leading to the *ortho*-halogenated picoline- and isonicotine-methyl esters (**7**) and (**8**) is outlined in Scheme **I**. 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°/ 2h) were efficiently converted into the bis (*N*- and C^3-) lithiated anilides. Treatment of the solution of the lithiated species with halogenating agents (CCl_3-CCl_3, $CBrCl_2$-$CBrCl_2$, CH_2Br-CH_2Br, I_2) afforded the corresponding halogenated anilides (**3**) and (**4**). In the case of the isonicotinanilide (**2**), if $CBrCl_2$-$CBrCl_2$ was used for the bromination process, a mixture of chloro- and bromo- derivatives (**4a**) and (**4b**) in the ratio 1:2 was formed. That is why, for the selective preparation of bromo-isonicotinanilide (**4b**), 1,2-dibromoethane was employed as a brominating agent.

Scheme I



a: R = -Cl, **b**: R = -Br, **c**: R = -I

The subsequent hydrolysis of halogenated anilides (**3**) and (**4**) upon reaction with boiling hydrochloric acid (15%-HCl) afforded the corresponding carboxylic acids (**5**) and (**6**), whose sodium salts reacted with MeI in DMF at 0°C to give the desired picoline- and isonicotinecarboxylic methyl esters (**7**) and (**8**). In all cases, pyridine nucleus appeared to be inert towards *N*-methylation (under the conditions used).

In summary, we have shown a versatile synthetic method for the preparation of C^3-halogenated picoline- and isonicotinecarboxylic methyl esters (**7**) and (**8**) with an economy of steps, which involves: (i) successive conversion of picolin- and isonicotinanilides (**1**) and (**2**) *via* direct lithiation-halogenation into halogenated anilides (**3**) and (**4**) and then (ii) their transformation into desired esters (**7**) and (**8**).

Experimental

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra are of solutions in $CHCl_3$ or KBr discs using a Zeiss-Jena Specord 71-IR. ^{1}H-NMR spectra were obtained with a Varian Gemini-200, or a Tesla BS-467 using Me_4Si as an internal standard. *n*-Butyllithium (*n*-BuLi - Aldrich) was used without further purification. Tetrahydrofuran (THF) was dried with calcium hydride and used directly after distillation under argon from sodium.

Anilides (**1**) and (**2**) were prepared by standard methods. Electrophiles were purified by standard methods before use.

General Procedure for the Preparation of Halogenated Anilides (3) and (4)

To the anilide (0.040 mole) stirred in THF (80 ml) at -78°C *n*-BuLi (0.084 mole) was added. The solution was held at -78°C for 0.5 h, then allowed to warm up to room temperature and kept at this temperature for 1 h. The whole was then cooled to -78°C and an electrophile (0.040 mole) in THF (100 ml) was added. The reaction mixture after 1 h at -78°C was warmed up to room temperature and kept at this temperature for 2 h. Then water (25 ml) was added. The organic layer was separated, and aqueous layer extracted with $CHCl_3$ (3×100 ml). In the case when iodine was used as an electrophile, the organic layer was washed with 10% aqueous sodium thiosulfate. The combined organic solutions were dried ($MgSO_4$) and the solvents removed to leave a semi-solid residue. This was subjected to column chromatography on silica gel with chloroform or benzene:acetone - 8:2 as eluent. This gave crude products (**3**) and (**4**), which were purified by crystallisation.

The yields of the reactions, the physical properties, the IR and ^{1}H-NMR data, and the analytical data are given below. In the case of the mixture concerning halo-anilides (**4a**) and (**4b**) in the ratio 1:2, they were determined by ^{1}H-NMR ($CDCl_3$; internal reference Me_4Si) spectroscopy utilizing the peak areas

of the amide (NH) and 2-pyridine protons. The chemical shifts of the amide and 2-pyridine protons are δ 8.50, 8.40 and 8.60, 8.70 respectively.

3-Chloropicolinanilide (**3a**)

(69%), m.p. 81 - 82°C (benzene : hexane - 1:9); (Found: C, 62.02; H, 4.22; N, 12.15; Cl, 15.13. Calc. for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04; Cl, 15.24%); IR (KBr) 1690 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 10.1-9.8 (1H, br. s, NH-H), 8.5 (1H, d J 5Hz, 6Py-H), 7.9 (1H, d J 8Hz, 4Py-H), 7.8-7.7 (2H, m, Ph-H), 7.5-7.3 (3H, m, 5Py-H and Ph-H), 7.2-7.1 (1H, m, Ph-H).

3-Bromopicolinanilide (**3b**)

(60%), m.p. 81 - 83°C (benzene : hexane - 5:95); (Found: C, 51.61; H, 3.25; N, 10.52; Br, 28.55. Calc. for $C_{12}H_9BrN_2O$: C, 52.01; H, 3.28; N 10.11, Br, 28.83%); IR (KBr) 1660 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 10.6 (1H, s, NH-H), 8.7 (1H, dd J 5 and 1Hz, 6Py-H), 8.2 (1H, dd J 8 and 1 Hz, 4Py-H), 7.8 (2H, m, Ph-H), 7.5 (1H, dd J 8 and 5 Hz, 5Py-H), 7.4-7.3 (2H, m, Ph-H), 7.2-7.1 (1H, m, Ph-H).

3-Iodopicolinanilide (**3c**)

(74%), m.p. 106 - 107°C (benzene : hexane - 2:8); (Found: C, 44.57; H, 2.91; N, 9.05; I, 39.47. Calc. for $C_{12}H_9IN_2O$: C, 44.47; H, 2.80; N, 8.65; I, 39.15%); IR (KBr) 1690 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 10.1 (1H, s, NH-H), 8.6 (1H, dd J 5 and 2Hz, 6Py-H), 8.4 (1H, dd J 8 and 2Hz, 4Py-H), 7.8-7.7 (1H, m, Ph-H), 7.4-7.3 (2H, m, Ph-H), 7.2-7.1 (2H, m, 5Py-H and Ph-H).

3-Chloroisonicotinanilide (**4a**)

(71%), m.p. 133 - 134°C (benzene : hexane - 9:1); (Found: C, 62.05; H, 4.00; N, 11.93; Cl 15.24. Calc. for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90, N, 12.04, Cl 15.24%); IR (KBr) 1650 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) 10.7 (1H, s, NH-H), 8.8 (1H, s, 2Py-H), 8.7 (1H, d, J 5Hz, 6Py-H), 7.8-7.6 (3H, m, 5Py-H and Ph-H), 7.5-7.3 (2H, m, Ph-H), 7.2-7.1 (1H, m, Ph-H).

3-Bromoisonicotinanilide (**4b**)

(38%), m.p. 154 - 155°C (benzene : hexane - 1:1); (Found: C, 51.50; H, 3.38; N, 10.03; Br, 28.60. Calc. for $C_{12}H_9BrN_2O$: C, 52.01; H, 3.28; N, 10.11; Br, 28.83%); IR (KBr) 1650 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 8.7 (1H, s, 2Py-H), 8.6 (1H, d, J 5Hz, 6Py-H), 8.4-8.3 (1H, br. s, NH-H), 7.7-7.0 (6H, m, 5Py-H and Ph-H).

3-Iodoisonicotinanilide (**4c**)

(72%), m.p. 162 - 163°C (benzene : hexane - 8:2); (Found: C, 44.06; H, 2.95; N, 8.82; I, 39.24. Calc. for $C_{12}H_9IN_2O$: C, 44.47; H, 2.80; N, 8.65; I, 39.15%); IR (KBr) 1670 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) 10.6 (1H, s, NH-H), 9.0 (1H, s, 2Py-H), 8.7 (1H, d, J 4.8Hz, 6Py-H), 7.7-7.6 (2H, m, Ph-H), 7.5 (1H, dd, J 5 and 1 Hz, 5Py-H), 7.4-7.3 (2H, m, Ph-H), 7.2-7.1 (1H, m, Ph-H).

Preparation of 3-Halopicoline- and 3-Haloisonicotinecarboxylic Methyl Esters (7) and (8)

(i) Acidic Hydrolysis of 3-Haloanilides (3) and (4)

A solution of the haloanilides (**3**) and (**4**) (0.010 mole) in 15% hydrochloric

acid (60 ml) was heated under reflux for 15 h. The yellowish mixture was then made alkaline with 10% potassium hydroxide and extracted with benzene. The organic layer was separated and the aqueous phase was then adjusted to pH~3.4 (10% hydrochloric acid). If a colorless solid separated, it was filtered. Otherwise, water was removed under reduced pressure and the residual white solid was extracted with boiling ethanol. The 3-halopyridinecarboxylic acids (**5**) and (**6**) were separated and immediately converted into the methyl esters without purification.

(ii) Conversion of 3-Haloacids (5) and (6) into Methyl Esters (7) and (8)

To the suspension of the acid (0.004 mole) in water (30 ml) $NaHCO_3$ (0.005 mole) was added and the mixture was stirred until all solids had dissolved. The solvent was then removed under reduced pressure and the residue was dried under vacuum. The residue (sodium salt) was then subjected to reaction with iodomethane (0.004 mole) in DMF (15 ml) at 0°C for 4 h. Then the solvent was evaporated under reduced pressure and water (10 ml) was added to the residue. The product was extracted with $CHCl_3$ (3×15 ml) and purified by column chromatography (silica gel, chloroform).

The yields of the reactions, the physical properties, the IR and ^{1}H-NMR data, and the analytical data are given below.

3-Chloromethylpicolinate (**7a**)

(68%), m.p. 27-28°C; (Found: C, 48.30; H, 3.64; N, 7.94; Cl, 20.46. Calc. for $C_7H_6ClNO_2$: C, 49.00; H, 3.53; N, 8.16; Cl, 20.66%); IR (KBr) 1730 cm^{-1}

(C=O); ^{1}H-NMR ($CDCl_3$) 8.6 (1H, dd J 5 and 2 Hz, 6Py-H), 7.8 (1H, dd J 8 and 2 Hz, 4Py-H), 7.4 (1H, dd J 8 and 5Hz, 5Py-H), 4.0 (3H, s, OMe-H).

3-Bromomethylpicolinate (**7b**)

(46%), m.p. 35-36°C; (Found: C, 39.20; H, 3.03; N, 6.44; Br, 37.03. Calc. for $C_7H_6BrNO_2$: C, 38.32; H, 2.80; N, 6.48; Br, 36.99%); IR (KBr) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 8.6 (1H, dd J 5 and 1Hz, 6Py-H), 8.0 (1H, dd J 8 and 1Hz, 4Py-H), 7.2 (1H, dd J 8 and 5 Hz, 5Py-H), 4.0 (3H, s, OMe-H).

3-Iodomethylpicolinate (**7c**)

(75%), m.p. 38-40°C; (Found: C, 31.95; H, 2.37; N, 5.29; I, 47.80. Calc. for $C_7H_6INO_2$: C, 31.95; H, 2.30; N, 5.33; I, 48.25%); IR (KBr) 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 8.6 (1H, dd J 5 and 2 Hz, 6Py-H), 8.3 (1H, dd J 8 and 2 Hz, 4Py-H), 7.3 (1H, dd J 8 and 5 Hz, 5Py-H), 4.0 (3H, s, OMe-H).

3-Chloromethylisonicotinate (**8a**)

(56%), b.p. 122-127°C / 8 hPa (Kugelrohr); (Found: C, 48.88; H, 3.60; N, 8.23; Cl, 20.32. Calc. for $C_7H_6ClNO_2$: C, 49.00; H, 3.53; N, 8.16; Cl, 20.66%); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 8.8 (1H, s, 2Py-H), 8.6 (1H, d, J 5 Hz, 6Py-H), 7.7 (1H, d, J 5Hz, 5Py-H), 4.0 (3H, s, OMe-H).

3-Bromomethylisonicotinate (**8b**)

(78%), m.p. 18-20°C; (Found: C, 39.26; H, 3.05; N, 6.38; Br, 37.18. Calc. for $C_7H_6BrNO_2$: C, 38.92; H, 2.80; N, 6.48; Br, 36.99%); IR (KBr) 1740 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 8.8 (1H, s, 2Py-H), 8.6 (1H, d, J 6 Hz, 6Py-H), 7.6 (1H, d, J 6 Hz, 5Py-H), 3.9 (3H, s, OMe-H).

3-Iodomethylisonicotinate (**8c**)

(66%), m.p. 41-42°C; (Found: C, 32.11; H, 2.43; N, 5.37; I, 48.16. Calc. for $C_7H_6INO_2$: C, 31.95; H, 2.30; N, 5.33; I, 48.25%); IR (KBr) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 9.2 (1H, s, 2Py-H), 8.6 (1H, d, J 5 Hz, 6Py-H), 7.6 (1H, d, J 5 Hz, 5Py-H), 4.0 (3H, s, OMe-H).

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