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# Directed lithiation of unprotected pyridinecarboxylic acids: syntheses of halo derivatives

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**Abstract**—Deprotonation of all isomeric lithium pyridinecarboxylates and subsequent trapping with hexachloroethane or iodine afforded straightforward access to chloro- and iodopyridinecarboxylic acids, respectively. Starting from lithium 5-bromonicotinate, the introduction of an iodine atom at C4 and further halogen migration allowed the potential of this method to be extended to the synthesis of more elaborate derivatives. 

## 1. Introduction

Interest in pyridine natural products and pharmaceuticals, as well as pyridine building blocks for various applications such as materials science and supramolecular chemistry, has resulted in extensive efforts on synthesis methodologies.

Halo pyridinecarboxylic acids appear as particularly useful key intermediates for synthesis since the halogen substituent can be used in cross-coupling or nucleophilic substitution reactions whilst the carboxylic acid function can also undergo further transformations. The first syntheses of such substrates were effected either by oxidation or through diazotization;[1] however, these methods are only suitable when the starting halo methylpyridines and aminopyridinecarboxylic acids, respectively, are accessible. More recent syntheses use the lithiation reaction of halo pyridines[2,3] or pyridine carboxamides and oxazolines.[2] Nevertheless, the first method has proved to be unsuccessful starting from iodopyridines and the second one requires additional protection and deprotection steps for the carboxylic acid function.

Recently, our group found conditions for the deprotonation of lithium pyridinecarboxylates[4] and quinolinecarboxylates,[5] avoiding protection and deprotection steps. Herein, we describe the extension of this work to the synthesis of halo pyridinecarboxylic acids.

## 2. Results and discussion

Iodo and bromo aromatic substrates are largely used in cross-coupling reactions.[6] The use of chloro substrates is also developed, the reaction being particularly efficient in the π-deficient azaaromatics series.[7] We thus investigated the synthesis of chloro- and iodopyridinecarboxylic acids.

The metallation of picolinic acid (**1**) was effected using 3 equiv. of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in tetrahydrofuran (THF) at 0°C, after in situ formation of the lithium salt with 1 equiv. of BuLi at −75°C, as already described.[4] When the lithio derivative thus formed was treated at 0°C with a solution of hexachloroethane or iodine in THF, mixtures of halo and dihalo compounds were initially obtained. We suspected a metallation of lithium 3-halo picolinate during the quenching step and decided to modify the trapping procedure. Thus, the lithio derivative was transferred to a cooled (0°C) solution of the electrophile: the results could be largely improved since the $^1$H NMR spectra obtained after evaporation of the reaction mixtures showed carboxylates **2a**–**3a** as the only pyridinic compounds, the yields mainly depending on their isolation via column chromatography on silica gel. Since various attempts to precipitate the corresponding halo picolinic acids **2**–**3** were unsuccessful using aqueous solutions of mineral acids (HCl, HF, $H_2SO_4$, etc.) as already used for other electrophiles,[4] we turned to an ion-exchange resin in order to protonate the carboxylates. When an excess of Amberlyst® was used in methanol, the lithium salts could be converted to the corresponding carboxylic acids **2**–**3**, which were recovered after filtration and removal of the solvent (Scheme 1).

For isonicotinic acid (**4**), the metallation was carried out

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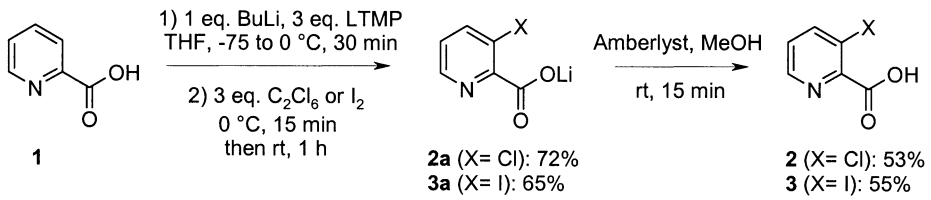
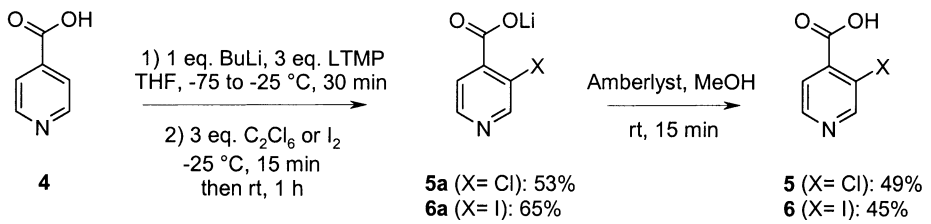



**Scheme 1.**



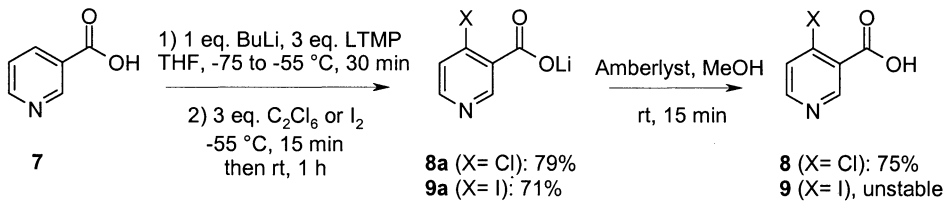

**Scheme 2.**

similarly at −25°C, after in situ formation of the lithium salt.[4] Subsequent reaction with hexachloroethane or iodine provided the halo lithium isonicotinates **5a**–**6a**, which were then converted to the corresponding acids **5**–**6**, as described above for the syntheses of the compounds **2**–**3** (Scheme 2).

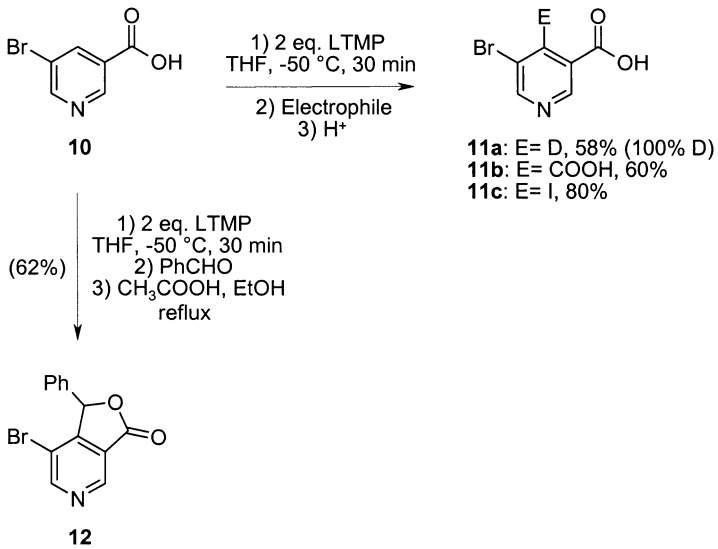
For nicotinic acid (**7**), treating the lithium salt with 3 equiv. of LTMP at −55°C allowed the deprotonation.[4] The lithium halo nicotinates **8a**–**9a** obtained after quenching were protonated to give the acids **8**–**9** (Scheme 3).

It should be pointed out that 3 equiv. of LTMP are necessary to obtain complete deprotonation of the pyridinecarboxylic acid **1**–**3** lithium salts. Since LTMP also reacts with hexachloroethane and iodine, 3 equiv. of electrophile were used to optimize the yields.

In order to study why an excess of the base was required to allow efficient metallation, the reaction was conducted starting from commercially available 5-bromonicotinic acid (**10**). Owing to the presence of the bromine atom at C5, which can act as a second directing group and stabilize a lithio derivative at C4,[2] one can predict milder conditions for deprotonation. Preliminary experiments showed that BuLi was not suitable to generate the lithium salt of **10**, because of the concurrent bromine-lithium exchange reaction; so, we turned to LTMP. Treating the lithium salt of **10** with a stoichiometric amount of base in THF at −50°C




**Scheme 3.**

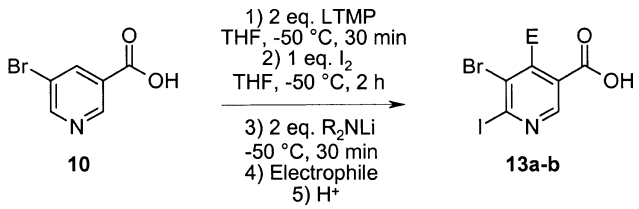



**Scheme 4.**

resulted in complete deprotonation at C4. Trapping the dilithio derivative with $D_2O$, dry ice or iodine afforded deuterated bromonicotinic acid **11a**, bromocinchomeronic acid **11b** and bromoiodonicotinic acid **11c** in medium to good yields. The use of benzaldehyde as an electrophile also afforded access to the lactone **12** after cyclization under acidic conditions. (Scheme 4).

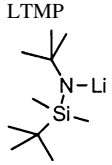
The excess of base necessary to achieve the complete deprotonation of the lithium salts of **1**, **4** and **7** allowed the equilibrium to be displaced to the dilithio derivative.

We now tried the halogen migration procedure on our halo pyridinecarboxylic acids.[2] The reaction was attempted on the lithium salt of the iodo derivative **11c**, generated in situ from 5-bromonicotinic acid (**10**). Various bases such as lithium diisopropylamide (LDA), LTMP and the less basic lithium *tert*-butyl(*tert*-butyldimethylsilyl)amide[8] were tested for this purpose. The latter proved to be more convenient; it promoted the smooth rearrangement of the 4-iodo-6-lithio intermediate to the more stable 4-lithio compound, flanked by bromine and carboxylate stabilizing groups, through the migration of the iodine atom from C4 to C6. Quenching the reaction mixture with water followed by acidification afforded the corresponding 6-iodonicotinic acid **13a**. It appeared that both LDA and LTMP, albeit to a lesser extent, gave after hydrolysis the deiodinated lithium salt (lithium salt of **10**) as the main reaction product. If one may invoke a hydride transfer mecanism (β-elimination) in the case of LDA,[9] this argument cannot be put forward for LTMP (no β-hydrogen atoms) and a single electron transfer from the base to the substrate remains the sole plausible assumption (Scheme 5, Table 1).[10]




**Scheme 5.**

**Table 1**. Metallation–isomerization of the lithium salt of **11c**

| Entry | $R_2NLi$ | Electrophile | Product (E) | Yield (%) |
|---|---|---|---|---|
| 1 | LTMP | $H_2O$ | **13a** (H) | 45 |
| 2 | LTMP | $D_2O$ | **13b** (D) | 47 (70% D) |
| 3 |  | $H_2O$ | **13a** (H) | 62 |



## 3. Conclusion

In conclusion, we have described the syntheses of chloro- and iodopyridinecarboxylic acids from the corresponding pyridinecarboxylic acids via deprotonation of the lithium salts and subsequent trapping with hexachloroethane or iodine.

The method can be compared with the metallation of halopyridines, which is the alternative direct method. Chloro- and bromopyridines can be used for the synthesis of the corresponding halo pyridinecarboxylic acids; nevertheless, the use of less stable 4-halo substrates complicates the procedure, and deprotonation of iodopyridines has proved to be unsuccessful. Metallation of 3-halo pyridines provides a route for the synthesis of 3-halo isonicotinic acids whereas 3-halo picolinic acids can be obtained via deprotonation of lithium picolinate. Moreover, our approach involves pyridinecarboxylic acids, which are more easily accessible than halo substrates. Conditions for a one pot iodine migration could be found.

Applications to the synthesis of biologically active compounds are currently underway.

## 4. Experimental

### 4.1. General

Melting points were measured on a Kofler apparatus. NMR spectra were recorded in $CDCl_3$ or DMSO-$d_6$ with a Bruker AM 300 spectrometer ($^1H$ at 300 MHz and $^{13}C$ at 75 MHz). Mass spectra were recorded with a Jeol JMS-AX500 spectrometer (electronic impact) and the molecular peak is given. IR spectra were taken on a Perkin–Elmer FT IR 205 spectrometer, and main IR absorptions are given in $cm^{-1}$. Elemental analyses were performed on a Carlo Erba 1106 apparatus. Satisfactory microanalyses were obtained for all new compounds: C±0.45, H±0.31, N±0.29. Deuterium incorporation was determined using $^1H$ NMR spectra integration.

*Starting materials*. THF was distilled from benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[11] Reactions were carried out under dry $N_2$. Silica gel (Geduran Si 60, 0.063–0.200 mm) was purchased from Merck. BuLi (2.5 M) in hexane was purchased from Aldrich. Amberlyst® IR-120 was supplied by Fluka. *tert*-Butyl(*tert*-butyldimethylsilyl)amine was synthesized by literature method.[12]

### 4.2. General procedure 1: metallation of picolinic acid (1)

A solution of BuLi (40 mmol) in hexane (16 mL) and, 15 min later, picolinic acid (1.2 g, 10 mmol) were added at −75°C to a solution of 2,2,6,6-tetramethylpiperidine (5.1 mL, 30 mmol) in THF (50 mL). After 10 min at −75°C, the mixture was stirred for 30 min at 0°C and transferred dropwise to a cooled (0°C) solution of the required electrophile (30 mmol) in THF (50 mL). After 15 min at 0°C, the mixture was allowed to reach rt before hydrolysis (5 mL), 1 h later, and removal of the solvents under vacuum. The residue was dissolved in water (20 mL) and the resulting solution washed with $CH_2Cl_2$ (30 mL) and $Et_2O$ (2×30 mL). The aqueous phase was then evaporated to dryness and the residue chromatographed on a silica gel column (eluent: $CH_2Cl_2$ and then $CH_2Cl_2$/MeOH 70:30) to give the corresponding lithium picolinate. It was dissolved in MeOH (30 mL) and treated with Amberlyst® IR-120

(25 g). The resin was removed by filtration 15 min later; the solvents were evaporated and the residue washed with acetone (20 mL) to give after drying the pure halo picolinic acid.

**4.2.1. 3-Chloropicolinic acid (2).**[13] The general procedure 1, using $C_2Cl_6$, initially gave 72% of **2a**: $^1$H NMR (DMSO-$d_6$) $\delta$ 7.05 (dd, 1H, $J$=7.9, 4.5 Hz, $H_5$), 7.54 (dd, 1H, $J$=7.9, 1.5 Hz, $H_4$), 8.07 (dd, 1H, $J$=4.5, 1.5 Hz, $H_6$). The lithium salt was then converted in a 53% yield to **2**: beige powder; mp 150–154°C (dec.); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.42 (dd, 1H, $J$=7.9, 4.5 Hz, $H_5$), 7.92 (dd, 1H, $J$=7.9, 1.5 Hz, $H_4$), 8.41 (dd, 1H, $J$=4.5, 1.5 Hz, $H_6$) (the $^1$H NMR data are in accordance with those of the literature);[1d] $^{13}$C NMR (DMSO-$d_6$) $\delta$ 126.9 ($C_5$), 128.1 ($C_3$), 138.8 ($C_4$), 147.8 ($C_6$), 149.9 ($C_2$), 166.3 (CO); IR (KBr) $\nu$ 806, 1287, 1380, 1508, 1654, 1752, 3400 cm$^{-1}$; mass (EI): $m/z$ 157 ($M^{+\cdot}$).

**4.2.2. 3-Iodopicolinic acid (3).**[1a,13] The general procedure 1, using $I_2$, initially gave 65% of **3a**: $^1$H NMR (DMSO-$d_6$) $\delta$ 7.15 (dd, 1H, $J$=7.8, 4.5 Hz, $H_5$), 8.28 (dd, 1H, $J$=7.8, 1.5 Hz, $H_4$), 8.53 (dd, 1H, $J$=4.5, 1.5 Hz, $H_6$). The lithium salt was then converted in a 55% yield to **3**: beige powder; mp 210°C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.13 (dd, 1H, $J$=7.8, 4.5 Hz, $H_5$), 8.35 (dd, 1H, $J$=7.8, 1.5 Hz, $H_4$), 8.87 (dd, 1H, $J$=4.5, 1.5 Hz, $H_6$); IR (KBr) $\nu$ 630, 672, 1038, 1115, 1172, 1280, 1383, 1501, 1593, 1753, 2944 cm$^{-1}$; mass (EI): $m/z$ 249 ($M^{+\cdot}$).

### 4.3. General procedure 2: metallation of isonicotinic acid (4)

A solution of BuLi (40 mmol) in hexane (16 mL) and 15 min later, isonicotinic acid (1.2 g, 10 mmol) were added at −75°C to a solution of 2,2,6,6-tetramethylpiperidine (5.1 mL, 30 mmol) in THF (50 mL). After 10 min at −75°C, the mixture was stirred for 30 min at −20°C and transferred dropwise to a cooled (−20°C) solution of the required electrophile (30 mmol) in THF (50 mL). After 15 min at −20°C, the mixture was allowed to reach rt before hydrolysis (5 mL), 1 h later, and removal of the solvents under vacuum. The residue was dissolved in water (20 mL) and the resulting solution washed with $CH_2Cl_2$ (30 mL) and $Et_2O$ (2×30 mL). The aqueous phase was then evaporated to dryness and the residue chromatographed on a silica gel column (eluent: $CH_2Cl_2$ and then $CH_2Cl_2$/MeOH 70:30) to give the corresponding lithium isonicotinate. It was dissolved in MeOH (30 mL) and treated for 15 min with Amberlyst® IR-120 (25 g). The resin was removed by filtration; the solvents were evaporated and the residue washed with acetone (20 mL) to give after drying the pure halo isonicotinic acid.

**4.3.1. 3-Chloroisonicotinic acid (5).**[13] The general procedure 2, using $C_2Cl_6$, initially gave 53% of **5a**: $^1$H NMR (DMSO-$d_6$) $\delta$ 7.39 (d, 1H, $J$=4.7 Hz, $H_5$), 8.52 (d, 1H, $J$=4.7 Hz, $H_6$), 8.61 (s, 1H, $H_2$). The lithium salt was then converted in a 49% yield to **5**: beige powder; mp 220°C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.55 (d, 1H, $J$=4.9 Hz, $H_5$), 8.47 (d, 1H, $J$=4.9 Hz, $H_6$), 8.61 (s, 1H, $H_2$) (the $^1$H NMR data are in accordance with those of the literature);[14] $^{13}$C NMR (DMSO-$d_6$) $\delta$ 124.1 ($C_5$), 128.5 ($C_3$), 139.3 ($C_4$), 148.7 ($C_2$), 150.4 ($C_6$), 165.6 (CO); IR (KBr) $\nu$ 1254, 1401, 1407, 1725, 2455, 2584, 2713, 3078 cm$^{-1}$; mass (EI): $m/z$ 157 ($M^{+\cdot}$).

**4.3.2. 3-Iodoisonicotinic acid (6).**[1b,13] The general procedure 2, using $I_2$, initially gave 65% of **6a**: $^1$H NMR (DMSO-$d_6$) $\delta$ 7.36 (d, 1H, $J$=4.5 Hz, $H_5$), 7.74 (d, 1H, $J$=4.5 Hz, $H_6$), 8.86 (s, 1H, $H_2$). The lithium salt was then converted in a 45% yield to **6**: beige powder; mp 205–210°C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.44 (d, 1H, $J$=4.5 Hz, $H_5$), 8.47 (d, 1H, $J$=4.5 Hz, $H_6$), 8.86 (s, 1H, $H_2$); IR (KBr) $\nu$ 810, 1267, 1382, 1405, 1634, 2844, 3050, 3264 cm$^{-1}$; mass (EI): $m/z$ 249 ($M^{+\cdot}$).

### 4.4. General procedure 3: metallation of nicotinic acid (7)

A solution of BuLi (40 mmol) in hexane (16 mL) and 15 min later, nicotinic acid (1.2 g, 10 mmol) were added at −75°C to a solution of 2,2,6,6-tetramethylpiperidine (5.1 mL, 30 mmol) in THF (50 mL). After 10 min at −75°C, the mixture was stirred for 30 min at −55°C and transferred dropwise to a cooled (−55°C) solution of the required electrophile (30 mmol) in THF (50 mL). After 15 min at −55°C, the mixture was allowed to reach rt before hydrolysis (5 mL), 1 h later, and removal of the solvents under vacuum. The residue was dissolved in water (20 mL) and the resulting solution washed with $CH_2Cl_2$ (30 mL) and $Et_2O$ (2×30 mL). The aqueous phase was then evaporated to dryness and the residue chromatographed on a silica gel column (eluent: $CH_2Cl_2$ and then $CH_2Cl_2$/MeOH 70:30) to give the corresponding lithium nicotinate. It was dissolved in MeOH (30 mL) and treated for 15 min with Amberlyst® IR-120 (25 g). The resin was removed by filtration; the solvents were evaporated and the residue washed with acetone (20 mL) to give after drying the pure halo nicotinic acid.

**4.4.1. 4-Chloronicotinic acid (8).** The general procedure 3, using $C_2Cl_6$, initially gave 79% of **8a**: $^1$H NMR (DMSO-$d_6$) $\delta$ 7.33 (d, 1H, $J$=5.1 Hz, $H_5$), 8.27 (d, 1H, $J$=5.1 Hz, $H_6$), 8.51 (s, 1H, $H_2$). The lithium salt was then converted in a 75% yield to **8**: beige powder; mp 205–208°C (lit.[15] 207–210°C); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.52 (d, 1H, $J$=4.9 Hz, $H_5$), 8.46 (d, 1H, $J$=4.9 Hz, $H_6$), 8.71 (s, 1H, $H_2$) (the spectral data are in accordance with those of the literature).[1c]

**4.4.2. 4-Iodonicotinic acid (9).**[16] The general procedure 3, using $I_2$, initially gave 71% of **9a**: $^1$H NMR (DMSO-$d_6$) $\delta$ 7.55 (d, 1H, $J$=5.2 Hz, $H_5$), 7.74 (d, 1H, $J$=5.2 Hz, $H_6$), 8.22 (s, 1H, $H_2$). The lithium salt was then converted to **9**, which was found to be unstable.

### 4.5. General procedure 4: metallation of 5-bromonicotinic acid (10)

A solution of BuLi (4.4 mmol) in hexane (1.8 mL) and, 5 min later, 5-bromonicotinic acid (0.40 g, 2.0 mmol) were added at −50°C to a solution of 2,2,6,6-tetramethylpiperidine (0.81 mL, 4.8 mmol) in THF (10 mL). The mixture was stirred for 30 min at −50°C.

**4.5.1. 5-Bromo(4-D)nicotinic acid (11a).** The lithio

derivative obtained using the general procedure 4 was treated with $D_2O$ (0.2 mL). The mixture was stirred for 30 min at rt and evaporated to dryness. The residue was dissolved in water (10 mL); the aqueous layer thus obtained was washed with $Et_2O$ (3×10 mL) and acidified to pH 3 at 0°C, using a 1 M aqueous solution of hydrochloric acid. After filtration and drying under vacuum, compound **11a** was obtained as a pale yellow powder. Yield: 58% (100% *d*); the characteristics of this product were found to be identical to those of **10** except for $^1H$ and $^{13}C$ NMR spectra: $^1H$ NMR (DMSO-$d_6$) $\delta$ 8.68 (s, 1H, $H_6$), 8.98 (s, 1H, $H_2$); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 120.3 ($C_5$), 129.7 ($C_3$), 139.4 (t, $C_4$), 149.0 ($C_2$), 153.8 ($C_6$), 165.5 (CO).

**4.5.2. 5-Bromocinchomeronic acid (11b).** The lithio derivative obtained using the general procedure 4 was poured on an excess of freshly crushed dry ice. The solvents were evaporated and the residue dissolved in water (10 mL); the aqueous layer thus obtained was washed with $Et_2O$ (3×10 mL) and acidified to pH 3 using a 1 M aqueous solution of hydrochloric acid. After filtration and drying under vacuum, compound **11b** was obtained as a beige powder. Yield: 60%; mp 197–200°C (dec.); $^1H$ NMR (DMSO-$d_6$) $\delta$ 8.91 (s, 1H, $H_6$), 9.00 (s, 1H, $H_2$); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 117.3 ($C_5$), 127.6 ($C_3$), 147.8 ($C_4$), 149.7 ($C_2$), 153.5 ($C_6$), 166.0 (CO); IR (KBr) $\nu$ 1402, 1576, 1610, 3066, 3400 $cm^{-1}$.

**4.5.3. 5-Bromo-4-iodonicotinic acid (11c).** The lithio derivative obtained using the general procedure 4 was transferred onto a solution of $I_2$ (0.61 g, 2.4 mmol) in THF (5 mL) at −50°C. After 2 h at −50°C, the solvents were evaporated and the residue dissolved in water (10 mL); the aqueous layer thus obtained was washed with $Et_2O$ (3×10 mL) and acidified to pH 3 using a 1 M aqueous solution of hydrochloric acid. After filtration and drying under vacuum, compound **11c** was obtained as a beige powder. Yield: 80%; mp 178°C (dec.); $^1H$ NMR (DMSO-$d_6$) $\delta$ 8.48 (s, 1H, $H_6$), 8.74 (s, 1H, $H_2$); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 114.2 ($C_4$), 130.9 ($C_5$), 137.9 ($C_3$), 146.5 ($C_2$), 151.7 ($C_6$), 167.3 (CO); IR (KBr) $\nu$ 1557, 1714, 1910, 2449, 3418 $cm^{-1}$.

**4.5.4. 7-Bromo-1-phenyl-1*H*-furo[3,4-*c*]pyridin-5-one (12).** The lithio derivative obtained using the general procedure 4 was treated with PhCHO (0.28 mL, 2.6 mmol) and allowed to react overnight. The solvents were evaporated and the residue dissolved in water (10 mL). The aqueous layer thus obtained was washed with $Et_2O$ (3×10 mL), acidified to pH 4 using a 1 M aqueous solution of hydrochloric acid, washed with $Et_2O$ (3×10 mL), acidified to pH 2 using a 1 M aqueous solution of hydrochloric acid and finally evaporated to dryness. To the residue were added EtOH (30 mL) and acetic acid (2 mL). The mixture was then heated under reflux for 3 h, evaporated and the residue chromatographed on a silica gel column (eluent: $CH_2Cl_2$) to afford **12** as a white powder. Yield: 62%; mp 116°C; $^1H$ NMR ($CDCl_3$) $\delta$ 6.55 (s, 1H, CH), 7.2 (m, 5H, Ph), 8.80 (s, 1H, $H_6$), 8.95 (s, 1H, $H_2$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 83.5, 116.4 ($C_5$), 124.6 ($C_3$), 128.8, 129.5, 130.6, 132.6, 146.7 ($C_2$), 156.1 ($C_6$), 156.6 ($C_4$), 168.0 (CO); IR (KBr) $\nu$ 1598, 1767, 2927, 3054 $cm^{-1}$.

### 4.6. General procedure 5: metallation–iodination–isomerization of 5-bromonicotinic acid (10)

A solution of BuLi (4.4 mmol) in hexane (1.8 mL) and, 5 min later, 5-bromonicotinic acid (0.40 g, 2.0 mmol) were added at −50°C to a solution of 2,2,6,6-tetramethylpiperidine (0.81 mL, 4.8 mmol) in THF (10 mL). The mixture was stirred for 30 min at −50°C. The lithio derivative was then transferred onto a solution of $I_2$ (0.61 g, 2.4 mmol) in THF (5 mL) at −50°C. After 2 h at −50°C, the mixture was treated at the same temperature with a solution prepared by adding BuLi (4.4 mmol) in hexane (1.8 mL) to 2,2,6,6-tetramethylpiperidine (0.81 mL, 4.8 mmol) in THF (5 mL) at 0°C. The mixture was stirred for 30 min at −50°C.

**4.6.1. 5-Bromo-6-iodonicotinic acid (13a).** The lithio derivative obtained using the general procedure 5 was treated with water (0.2 mL). The mixture was stirred for 30 min at rt and evaporated to dryness. The residue was dissolved in water (10 mL); the aqueous layer thus obtained was washed with $Et_2O$ (3×10 mL) and acidified to pH 3, using a 1 M aqueous solution of hydrochloric acid. After filtration and drying under vacuum, compound **13a** was obtained. Yield: 45% (62% when *tert*-butyl(*tert*-butyldimethylsilyl)amine[12] was used instead of 2,2,6,6-tetramethylpiperidine); mp 173°C (lit.[17] 173–174°C); $^1H$ NMR (DMSO-$d_6$) $\delta$ 8.17 (d, 1H, $J$=2.0 Hz, $H_4$), 8.60 (d, 1H, $J$=2.0 Hz, $H_2$); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 127.6 ($C_6$), 129.7 ($C_3$), 130.8 ($C_5$), 140.1 ($C_4$), 149.3 ($C_2$), 165.2 (CO); IR (KBr) $\nu$ 1570, 1721, 1919, 2928, 3476 $cm^{-1}$.

**4.6.2. 5-Bromo-6-iodo(4-D)nicotinic acid (13b).** The lithio derivative obtained using the general procedure 5 was treated with $D_2O$ (0.2 mL). The mixture was stirred for 30 min at rt and evaporated to dryness. The residue was dissolved in water (10 mL); the aqueous layer thus obtained was washed with $Et_2O$ (3×10 mL) and acidified to pH 3 at 0°C, using a 1 M aqueous solution of hydrochloric acid. After filtration and drying under vacuum, compound **13b** was obtained. Yield: 47% (70% *d*); the characteristics of this product were found to be identical to those of **13a** except for $^1H$ and $^{13}C$ NMR spectra: $^1H$ NMR (DMSO-$d_6$) $\delta$ 8.61 (s, 1H, $H_2$); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 127.6 ($C_6$), 129.7 ($C_3$), 130.8 ($C_5$), 140.1 (t, $C_4$), 149.3 ($C_2$), 165.2 (CO).

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