Monatshefte für Chemie 121, 909–921 (1990)

Monatshefte für Chemie
Chemical Monthly

Application of Organolithium and Related Reagents in Synthesis, Part VI [1]. A General Study of the Lithiation of Secondary Picoline- and Isonicotine Amides

Jan Epsztajn*, Andrzej Jóźwiak*, Krzysztof Czech, and **Aleksandra K. Szcześniak**

Department of Organic Chemistry, Institute of Chemistry, University of Łódź, PL-90-136 Łódź, Poland

Summary. The lithiation of secondary picoline- (**1**) and isonicotine-amides (**2**) and the subsequent reaction of the corresponding (N- and 3-)lithiated amides (**3** and **4**) with N,N-dimethylbenzamide towards the synthesis of the C^3-benzoylated picoline (**12a**) and isonicotine acids (**13a**) has been investigated. The effect of the N-substituent upon the generation of the lithiated amides **3** and **4** has been studied. As a result it was found that the anilide function should be considered the best choice for direct metallation of the masked picoline- and isonicotinecarboxylic acids. The effects at various temperatures upon the generation of the lithiated reactive intermediates and the problems concerning their reactions with an acid (deuteriation) and an carbonyl electrophile are discussed.

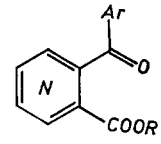
Keywords. Secondary picoline- and isonicotine amides; Lithiation; Lithiated reactive intermediates – dual behaviour; Protonation; Benzoylation.

Anwendungen von Organolithium und verwandten Reagenzien in organischen Synthesen, Teil VI [1]. Zur Metallierung von sekundären Picolinsäure- und Isonicotinsäureamiden

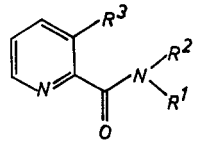
Zusammenfassung. Die Metallierung sekundärer Amide von Picolin- (**1**) und Isonicotinsäure (**2**) und nachfolgende Reaktion der entsprechenden (N- und 3-)metallierten Amide **3** und **4** mit N,N-Dimethylbenzamid – zur Synthese von C^3-benzoylierten Picolin- (**12a**) und Isonicotinsäuren (**13a**) – wurde untersucht. Der Einfluß des N-Substituenten auf die Bildung der metallierten Amide **3** und **4** wurde studiert und dabei festgestellt, daß der Anilidrest für eine direkte Metallierung der maskierten Picolin- und Isonicotinsäure gut geeignet ist. Der beobachtete Einfluß des Substituenten bei verschiedenen Temperaturen bei Bildung der metallierten Spezies und die Probleme ihrer Reaktivität gegen Säuren (*Me*OD) und Carbonyl-Elektrophilen wurden diskutiert.

Introduction

Extensive studies in the synthesis of podophylotoxin [2] have promoted interest in developing a synthetic route to their aza-analogues. We were particularly interested in the use of the directed *ortho*-lithiation (electrophilic substitution) of pyridine carboxylic acid amides as the first step towards the synthesis of the *ortho*-benzoyl derivatives (**A**) – compounds with two different regioselectively fixed electropholic centres [3] – being convenient starting materials in the construction of the desired



(A)



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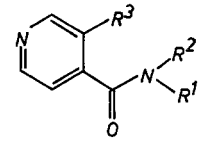


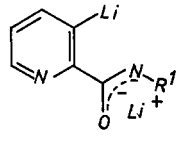
(2)

a, R^1 = Me; R^2 = R^3 = H

b, R^1 = Ph; R^2 = R^3 = H

c, R^1 = Me; R^2 = H; R^3 = D

d, R^1 = Ph; R^2 = H; R^3 = D



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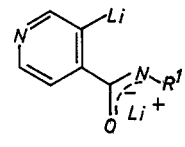

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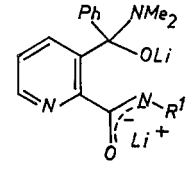

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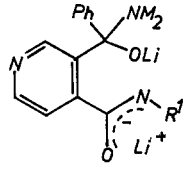

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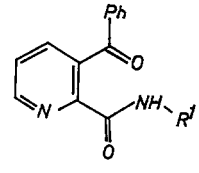

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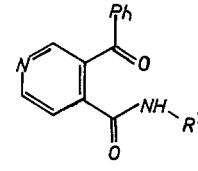

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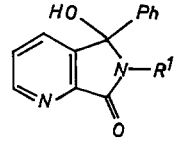

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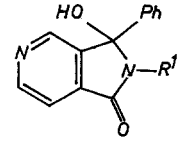

(10)

For compounds (3), (4), (5), (6), (7), (8), (9) and (10)

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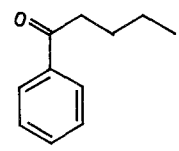
b, R^1 = Ph



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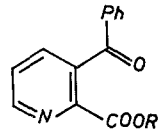

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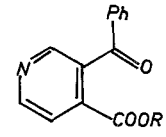


(13)

a, R = H

b, R = Me

systems. The picoline and isonicotine acids were selected to fulfill the requirements of the compounds (**A**). We could not find, however, corresponding general investigations in the literature. Only specific compounds and only the isolated yields of the major products have been reported. This was somewhat surprising not only because of the wide use of the carboxamide moiety as a directing group of the *ortho*-lithiation (first reported in Ref. [4]), which has been proved to be synthetically useful in the aromatic series [5–11], but also because of the large number of analogous studies reported for the aliphatic series. It could only be concluded that in the cases of picoline- and isonicotine carboxamides the anilides **1 b** and **2 b** should be expected to be the best choice for directed metallation of the masked picoline- and isonicotine-carboxylic acids [1]. For this reason we now investigated the lithiation (*Bu*^{n}Li/*THF*) of amides **1** and **2** towards their conversion into the bis(N- and 3-)lithiated amides **3** and **4**, and subsequently the reaction with an electrophile aiming at the synthesis of 3-benzoyl substituted amides **7** and **8**. We have attempted to establish the conditions necessary to obtain the maximum yields for the desired synthesis of the 3-benzoyl-picoline- (**12**) and 3-benzoyl-isonicotine- (**13**) acids. N,N-Dimethylbenzamide (*DMB*) was selected as an electrophile being the best source for the introduction of the aroyl-carbonyl group [5].

Results and Discussion

The results of the lithiation of the amides **1** and **2** and the subsequent reaction of the lithiated species with *DMB* are reported in Table 1: The data reveal the following:

1. The lithiation of the anilides **1 b** and **2 b** (amide/*THF* with or without *TMEDA*/ −78 °C/2.1 equivalents *Bu*^{n}Li/0.5 h) and the subsequent trapping of the lithiated species with *DMB* (−78 °C → 20 °C) give low yield of the corresponding 2-benzoyl-anilides (**7 b** and **8 b**) which spontaneously cyclized (on workup) to form stable aza-izoindolinones (**9 b** and **10 b**), respectively. In addition to the compounds **9 b** and **10 b** and starting materials, a large quantity of butyrophenone (**11**) was obtained. Its formation indicates that unreacted *Bu*^{n}Li adds to the carbonyl group of *DMB*.

Table 1. Reactions of the pyridinecarboxamides **1a**, **1b**, **2a**, and **2b** with Bu^nLi and subsequently generated lithiated reactivite intermediates with N,N-dimethylbenzamide (*DMB*)

Expt.	Products yields[a] (%)								
	Reaction conditions				Recovered			Overall yields[d] (%)	
	Pyridine carbox-amide	Lithiation[b] (°C/h)	Reaction with *DMB* (°C/h)	Benzoyl-ation[c]	Ketone (**11**)	Pyridine carbox-amide	*DMB*		
1	**1b**	−78/0.5	−78/0.5	**9b**					
			20/3	31.9	54.0	57.7	7.2	89.6	93.1
2	**1b**	−78/0.5	−78/0.5	**9b**					
			20/3	58.0	21.5	28.1	6.2	85.7	95.2
3	**1b**	−78/0.5	−78/2	**9b**					
		−23/0.5	20/3	66.1	e	17.6	29.1	85.7	95.2
4	**1b**	−78/0.5	−78/2	**9b**					
		−23/0.5	20/24	33.0	e	55.5	49.2	88.5	82.2
5	**1b**	−78/0.5	−78/2	**9b**					
		−23/0.5	20/96	12.1	e	75.8	73.5	87.9	85.6
6	**1b**	−78/0.5	−78/5	**9b**					
		−23/0.5		13.1	e	81.0	79.5	94.1	92.6
7	**1b**	−78/0.5	−78/2	**9b**					
		−23/0.5	0/1	70.1	e	16.3	19.2	86.4	89.3
8	**2b**	−78/0.5	−78/2	**10b**					
			20/3	11.7	76.2	81.2	4.2	92.9	92.1
9	**2b**	−78/0.5	−78/2	**10b**					
			20/3	23.7	45.3	65.7	15.2	89.4	84.2
10	**2b**	−78/0.5	−78/2	**10b**					
		−23/0.5	20/3	56.9	e	31.4	28.2	88.3	85.1
11	**2b**	−78/0.5	−78/2	**10b**					
		−23/0.5	20/72	42.2	e	43.1	41.3	85.3	83.5
12	**2b**	−78/0.5	−78/5	**10b**					
		−23/0.5		16.3	e	78.8	77.6	95.1	93.9
13	**2b**	−78/0.5	−78/2	**10b**					
		−23/0.5	0/1	74.2	e	15.3	14.1	89.5	88.3
14	**1a**	−78/0.5	−78/2	**9a**					
		−23/0.5	20/3	55.5	e	26.7	23.1	82.2	78.6
15	**2a**	−78/0.5	−78/2	**10a**					
		−23/0.5	0/1	8.7	e	83.7	73.2	92.4	81.9

[a] All yields represent isolated pure materials

[b] In the cases of experiments number 2–7 and 9–14 the lithiations were carried out in the presence of *TMEDA*. If the temperature of the lithiation was increased up to 0 °C no additional effect comparative to those at −23 °C were observed

[c] The benzoylation yields are represented by isolation of the corresponding pyrro[3,4-b]- and pyrro[3,4-c]-pyridinones **9** and **10**

[d] Yields based on used pyridinecarboxamide and N,N-dimethylbenzamide, respectively

[e] Ketone **11** 3–8%

This result is inconsistant with the deuteriation experiments which showed quantitative conversion of **1b** and **2b** into **3b** and **4b** (see below).

This may suggest that in the case of the deuteriation (*Me*OD quenching) base (*Me*OLi/*Me*OD) catalyzed hydrogen – deuterium exchange at the 3-position of the pyridine ring has taken place. Tests (*Me*OLi/*Me*OD/20 °C/1 h) (see Experimental), however, indicated no incorporation of the deuterium at the 3-position of the pyridine nucleus and as well as in other positions, thereby the hydrogen – deuterium exchange seems to be negligible.

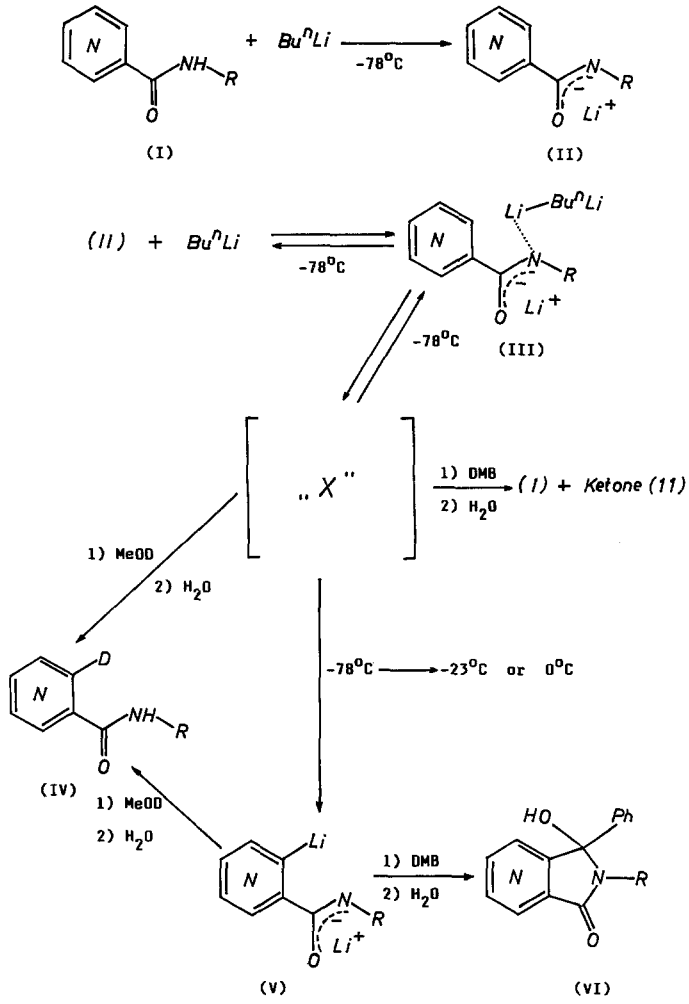
Addition of an equimolar amount of N,N,N′,N′-tetramethylendiamine [12, 13] (*TMEDA*) – with respect to *Bu*^{n}Li – afforded increase of the conversion of the anilides **1b** and **2b** into the products **9b** and **10b**. However, significant quantities of the ketone **11** were formed, higher than the amount derived from 0.1 mol excess of *Bu*^{n}Li used.

2. Increasing the temperature up to −23 °C (amide/*THF*/−78 °C/−*Bu*^{n}Li/−78 °C/0.5 h/→ −23 °C or 0 °C/0.5 h) and subsequent reaction of the lithiated amides with *DMB* (−78 °C/2 h/→ 20 °C/3 h) enhanced the total yields of the products **9** and **10** and reduced the amount of **11**. At longer reaction time (24 h or more) of the lithiated amides **3b** and **4b** (generated at −23 °C or 0 °C) with *DMB* at room temperature a considerable decrease of the products **9b** and **10b** was observed (Table 1). Isolation of adequate amounts of starting *DMB* and **1b** or **2b** with regard to the desired products indicate the instability of the adducts **5b** and **6b**.

In an attempt to clarify the apparent dilemma between the reactions of the lithiated species with *Me*OD and *DMB*, we have investigated the lithiation – deuteriation experiments versus temperature and time variation; detailed results are summarized in Table 2. These data reveal that the anilides **1b** and **2b** appear to be the most active towards formation of the lithiated intermediate. In the both cases quantitative conversion into the corresponding C^3-deuteriated anilides **1d** and **2d** has been observed. In contrast to the anilides, the N-methylamides **1a** and **2a** – with regard to temperature and time of the reaction – varied in conversion to the deuteriated amides **1c** and **2c**. Thus, the N-methyl-picolinamide (**1a**) on increased temperature (−78 °C → 0 °C) showed enhanced incorporation of deuterium. In the case of the N-methyl-isonicotinamide (**2a**) at higher temperature a decrease of conversion into **2c** was found. Moreover, the conversion of **2a** into **2c** depends on the reaction time at 0 °C; at prolonged time the yield decreased to 0%. The results from the deuteriation experiments appeared to be parallel to the reactions of **1a** and **2a** via lithiated species with *DMB* (see Table 1) and iodine as electrophiles. Iodination [14] of **1a** furnished N-methyl-3-iodopicolinamide with 65% yield, but N-methyl-3-iodoisonicotinamide was formed from **2a** with ~10% yield as indicated by ^{1}H-NMR.

The methodology described for introducing a benzoyl group at the 3-position of the picoline- and isonicotine anilides shows considerable versatility for the regioselective synthesis of 2,3- and 3,4-disubstituted pyridines. This, together with the quantitative removal of the anilide moiety on acid hydrolysis (to give carboxylic acids) should allow access to a wide variety of pyridine derivatives. Thus, the azaisoindolinones (**9b** and **10b** gave the 3-benzoylated picoline (**12a**) and isonicotine (**13a**) acids, which via sodium salts reacting with *Me*I in *DMF* at 0 °C afford the corresponding methyl esters **12b** and **13b**.

Taking into account all results the whole process may be depicted by the equations as shown in Scheme 1.



Scheme 1

(i) Fraser and co-worker [15], have described the thermodynamic information with respect to the aromatic lithiation, especially *pKa* data of monosubstituted benzenes in *THF*, thereby providing a direct measure of the acidifying effect of a substituent on the *ortho* C−H bond using a method which involved a direct measurement of the equilibrium by means of ^{13}C-NMR.

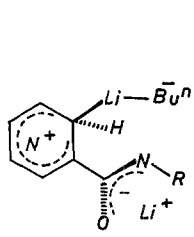
$$Ar-H + Li-NR_2 \rightleftarrows Ar-Li + H-NR_2 .$$

The fact that the observed effects (surprisingly little variation of the *pKa* values) differ significantly from those obtained during lithiation with lithium hydrocarbons [7–10], provides corroborative evidence for the importance of an intermediate complex (not defined) and it suggests that the lithiation does not depend upon the acidity of the appropriate C−H bond. Recently evidence for the irrespectiveness of the lithiation upon acidity has been provided [16]. Thus, *t*-butyl-3-(trifluoromethyl)phenyl carbamate on reaction with *Bu*^{n}Li in *THF* at −40 °C followed by the treatment of the lithiated compound with Me_3SiCl or *Ph*CHO gave the products at the weakest acidic 6-position instead of the expected 2-position [17]. Furthermore, use of the trimethylsilyl group as a blocking group [18] suggested that lithiation of *t*-butyl 3-(trifluoromethyl)-6-(trimethylsilyl)phenyl carbamate should be directed to the 2-position of the ring. However, sole attack of the $Si-CH_3$ group with the formation of $Si-CH_2-Li$, has been observed.

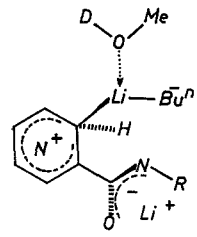
(ii) It has been observed that reactions of lithium hydrocarbons (e.g. *Bu*^{n}Li) with substituted pyridines depend upon the nature of the substituent and the position at which it is attached to the ring, and suggest that the pyridines may be divided into two groups: The first comprises derivatives

with the substituent attached at the 2- and 4-position of the ring. The second one consists of derivatives with the substituent at the 3-position. Generally compounds of the first group [1, 19–33] generate the *ortho*-lithiated pyridines at the 3-position. In contrast the compounds of the second group display significant dependence upon the nature of the substituent. Thus, derivatives with electron withdrawing ones (e.g. 4,4,-dimethyloxazolin-2-yl, CONHR, $CONR_2$), add the lithium hydrocarbons at the pyridine nucleus [21–23, 34]. The derivatives bearing electron donating groups (e.g. O*Me*, OCH_2OMe, NHCO*R*, $OCONR_2$) furnish lithiated pyridines at the 2- and/or 4-positions [22, 26, 29, 35–40]. All these data are entirely parallel to the well-known behaviour of pyridines in the electrophilic substitution reaction [41].

Although the behaviour of the amides (**I**) (Scheme 1) in the lithiation (*Bu*^{n}Li) electrophilic substitution sequence cannot be fully explained, it may be assumed that the species stable at low temperature (−78 °C), "**X**", which converts into lithiated amides (**V**) at increased temperature (−23 °C or 0 °C), has a structure similar to a σ-complex (**VII**) [1] (Scheme 2). We believe that the simple protophilic proton-transfer process is rather unlikely if the directing group is $CONR^-$ (similarly to COO^- in the aromatic electrophilic substitution [42], and/or another electron-donating group. The large isotopic effect found for the metallation of arenes [43] cannot be regarded as an unambiguous prove that the whole process cannot proceed



(VII)



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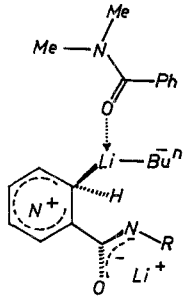
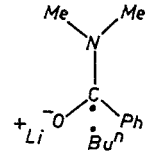
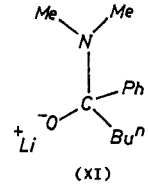


(IX)



(X)



(XI)

Scheme 2

[1] A number of examples for stable δ-complexes at low temperature (e.g. −78 °C), which on heating are converted into "normal" substitution products, are known [44]

via a σ-complex. In our case conversion of the species "**X**" ≡ σ-complex (**VII**) into the lithiated amide (**V**), being the slowest step in the process at −78 °C (Scheme 1), suggests that the intramolecular proton transfer [45] is the rate-determining step.

For the dual behaviour of the species "**X**" ≡ σ-complex (**VII**) towards a protonation and a reaction with carbonyl electrophiles, the following rationalization could be proposed: (i) In the case of the protonation (deuteriation), the coordination of an acid (*Me*OD) to the lithium atom of the (**VII**) forms (**VIII**) (Scheme 2), which causes release of a butyl anion with simultaneous protontransfer and subsequent deuteriation of the lithiated amide. (ii) Recently it has been demonstrated [46] that addition of the organolithium reagents across the carbonyl group was recognized as a SET process. It is then probable that (**VII**) by its nucleophilic part can act as an electron donor towards the carbonyl group of **DMB** and via complex **IX** forms the amide **I** and the radical anion radical cation pair **X**, which collapses rapidly within the solvent cage and affords the adduct **XI**, which on hydrolytic work-up converts into the ketone **11**.

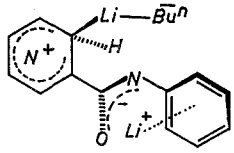
Table 2. Lithiation of the pyridinecarboxamides **1a**, **1b**, **2a**, and **2b** with *Bu*^{n}Li in *THF*

Expt. No.	Pyridine-carboxamide	Lithiation[a] (°C/time)	Isolated amide[b] (%)	Incorporation of deuteriated amide[c] (%)
1	**1a**	−78/0.5 h	85	**1c** 32
2	**1a**	−78/0.5 h 0/5 min	88	**1c** 45
3	**1a**	−78/0.5 h 0/5 min	86	**1c** 65
4	**2a**	−78/0.5 h	87	**2c** 28
5	**2a**	−78/0.5 h 0/5 min	85	**2c** 0
6	**2a**	−78/0.5 h 0/5 min	86	**2c** 0
7	**2a**	−78/0.5 h −23/0.5 h	86	**2c** 0
8	**2a**	−78/0.5 h 0/5 s	85	**2c** 25
9	**1b**	−78/0.5 h	94	**1d** 100
10	**1b**	−78/0.5 h	93	**1d** 100
11	**1b**	−78/0.5 h 0/5 min	93	**1d** 100
12	**2b**	−78/0.5 h	94	**2d** 100
13	**2b**	−78/0.5 h	95	**2d** 100
14	**2b**	−78/0.5 h 0/5 min	93	**2d** 100

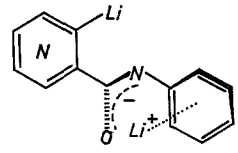
[a] In the cases of experiments number 3, 6, 7, 8, 10, 11, 13, 14 the lithianations were carried out in the presence of *TMEDA*

[b] All yields represent isolated pure materials

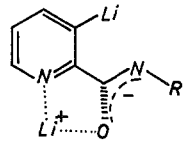
[c] Data represent yields identified by ^{1}H-NMR spectroscopy. Values are within ± 5% of the reported data



(XII)



(XIII)



(XIV)

Scheme 3

The effect of the N-substituent nature upon the generation of the lithiated reactive intermediates in the reaction of the amides **1** and **2** with *Bu*^{n}Li in *THF* (Table 2) remains to be discussed. The low extent of conversion of the N-methylamides **I** (*R*=*Me*) into the σ-complexes **VII** (*R*=*Me*) at −78 °C (deuteriation of the species "*X*") is probably due to their low stability caused by the electrostatic repulsion between the lithium atom at the 3-position of the ring and a lithium cation of the amide anionic moiety. On the other hand, the quantitative conversion of the anilides **I**(*R*=*Ph*) into the lithiated reactive intermediates (which appears to be independent on the temperature and time of the reaction) suggest that the repulsion ($Li^+ \cdots Li-C$) is sufficiently diminished by screening of the lithium cation by the N-phenyl substituent, as the π-type complexes [47, 48] (**XII**) and (**XIII**) may be formed (Scheme 3). The results: no differences between the N-methyl-picoline (**1a**) and N-methyl-isonicotinamides (**2a**) (deuteriation experiments) at −78 °C, and markedly increased conversion of **1a** into **3a** and decrease of **2a** to **4a** at 0 °C (Table 2) could be due to the 2-pyridyl nitrogen atom; this provides a strong bidentate ligand for the lithium cation by the formation of the chelate **XIV** (Scheme 3), which in turn minimizes the repulsion of the $Li^+ \cdots Li-C$.

Experimental

M.P.s. were determined using a Boetius hot-stage apparatus and are uncorrected. A Zeiss-Jena Specord 71-IR spectrometer was used for the IR spectra, and a Varian EM-360 or a Tesla BS-467 NMR spectrometer for the ^{1}H-NMR spectra. N,N,N′,N′-Tetramethylethylenediamine (*TMEDA*) was purified by the known method [49]. Compounds were purified until observed as single spots on TLC (Kieselgel GF-254 type 68). Tetrahydrofuran (*THF*) was used freshly distilled from sodium. The amides **1** and **2** were obtained by the known methods [1]. *n*-Butyllithium (Aldrich) was titrated before use.

General Procedure for the Metallation of Amides **1** *and* **2**.
Generation of the Lithiated Reactive Intermediates and Their Reactions with Electrophiles

To the amide (0.01 mol) with or without *TMEDA* (0.022 mol) stirred in *THF* (30 ml) at −78 °C *Bu*^{n}Li (0.022 mol) was added. The solution was stirred for appropriate time at −78 °C, then before addition

of an electrophile the reaction mixture was warmed up to −23 °C or 0 °C (appropriate time) and cooled down −78 °C before an electrophile was added.

(a) *Deuteriation.* To the solution (−78 °C) of the lithiated species *Me*OD (4 ml) was injected and the stirring continued for 15 min and then the reaction mixture was allowed to reach room temperature. The solvents were removed, $CHCl_3$ (50 ml) was added, the organic layer was separated, washed with water (20 ml), dried ($MgSO_4$), and evaporated till dryness. The residue was column chromatographed (silica gel, benzene−acetone = 1:9) to remove small quantities of polar contaminants before ^{1}H-NMR measurements. The yields of the deuteriated products and overall yields (summarized in Table 2) were determined by ^{1}H-NMR spectroscopy ($CDCl_3$ or *DMSO-*d_6, internal reference Me_4Si) utilizing the peak areas of the corresponding pyridine and methyl (N−CH_3) protons.

(b) *Reaction of the Lithiated Reactive Intermediates with N,N-Dimethylbenzamide.* To the solution (−78 °C) of the lithiated amides N,N-dimethylbenzamide (0.01 mol) in *THF* (10 ml) was added; the reaction was carried out at appropriate temperature and for required time (Table 1). Then water (30 ml) was added and the layers were separated and the aqueous one extracted with $CHCl_3$ (2 × 20 ml). The combined organic solutions were dried ($MgSO_4$) and the solvents removed to give a semi-solid residue. The residue triturated with acetone−hexane ≈ 2:3 gave a part of the products **9** or **10**. Then the filtrate was subjected to column chromatography on silica gel. Butyrophenone (**11**) was eluted with benzene, then starting materials and products were separated with benzene−ethyl acetate = 3:7 as eluant. An additional amount of the product **9** or **10** was obtained after adjusting the aqueous layer to *pH* = 3.5 (H_2SO_4). The yields of the reactions and overall yields are summarized in Table 1, the physical properties, the IR and ^{1}H-NMR data, and the analytical data are given below.

1-Hydroxy-2-methyl-1-phenyl-pyrro[3,4-b]pyridine-3(1H)-one (**9a**)

M.p. 214–216 °C (ethyl acetate−benzene) (Ref. [20], m.p. 214–216 °C). Calculated for $C_{14}H_{12}N_2O_2$: C 70.0, H 5.0, N 11.6. Found: C 69.7, H 5.2, N 11.6. IR (KBr, cm^{-1}): 3300 (O-H), 1700 (C=O). NMR (*DMSO-*d_6, δ): 8.7 (1H, dd, *J*=2 and 5 Hz, 5-H), 7.7 (1H, dd, *J*=2 and 8 Hz, 7-H), 7.6–6.8 (6H, m, 6-H and *Ph*-H), 2.7 (3H, s, *Me*-H).

3-Hydroxy-2-methyl-3-phenyl-pyrro[3,4-c]pyridine-1(3H)-one (**10a**)

M.p. 143–144 °C (ethyl acetate−heptane). Calculated for $C_{14}H_{12}N_2O_2$: C 70.0, H 5.0, N 11.6. Found: C 69.8, H 5.3, N 12.0. IR (KBr, cm^{-1}): 3290 (O-H), 1710 (C=O). NMR ($CDCl_3$, δ): 8.4–8.0 (2H, m, 4- and 6-H), 7.7−7.0 (6H, m, 7- and *Ph*-H), 6.9–6.4 (1H, m, O-H), 2.7 (3H, s, *Me*, H).

1,2-Diphenyl-1-hydroxy-pyrro[3,4-b]pyridine-3(1H)-one (**9b**)

M.p. 163–164 °C (acetone−hexane). Calculated for: $C_{19}H_{14}N_2O_2$: C 75.5, H 4.7, N 9.3. Found. C 75.8, H 4.8, N 9.4. IR (KBr, cm^{-1}): 3350 (O-H), 1680 (C=O). NMR ($CDCl_3$, δ): 9.9 (1H, br. s, O-H), 8.7 (1H, dd, *J*=2 and 5 Hz, 5-H), 8.0–6.8 (12H, m, 6-, 7- and *Ph*-H).

1,2-Diphenyl-3-hydroxy-pyrro[3,4-c]pyridine-1(3H)-one (**10b**)

M.p. 165–167 °C (*Me*OH). Calculated for $C_{19}H_{14}N_2O_2$: C 75.5, H 4.7, N 9.3. Found: C 75.5, H 4.8, N 9.3. IR (KBr, cm^{-1}): 3310 (O-H), 1690 (C=O). NMR (*DMSO-*d_6, δ): 8.6 (1H, d, *J*=5 Hz, 6-H), 8.4 (1H, s, 4-H), 7.7 (1H, s, O-H), 7.6 (1H, d, *J*=5 Hz, 7-H), 7.5–6.7 (10H, m, *Ph*-H).

Hydrolysis of the Compounds **9** *and* **10**. *Synthesis of the* C^3*-Benzoylated Picoline* **12a** *and Isonicotine* **13a** *Acids*

The mixure of the compounds **9** or **10** (0.02 mol) in 50% sulphuric acid (20 ml) was heated and boiled for 0.75 h. Then the whole lot was poured into water (50 ml) and after cooling made alkaline (K_2CO_3);

the obtained mixture was extracted with $CHCl_3$ (2 × 20 ml). The separated aqueous layer was adjusted (H_2SO_4) to $pH = 3.5$ to precipitate the acids **12a** or **13a**. In the case of **12a** the precipitated material was extracted with boiling benzene to separate it from some amount of sulphanilic acid (formed as a side effect of the hydrolysis). The additional amount of the corresponding acid **12a** or **13a** was obtained by evaporating till dryness of the filtrate and extraction of the solid residue with boiling benzene or absolute ethanol. The yields of the reactions, the physical properties, the IR and ^{1}H-NMR data, and the analytical data are given below.

3-Benzoylpicolinic acide (**12a**)

Yield 95%; m.p. 151–153 °C (*Me*OH) (Ref. [50], m.p. 148 °C). IR (KBr, cm^{-1}): 1 670 (C=O). NMR (*DMSO-d*$_6$, δ) 8.7 (1 H, dd, $J = 2$ and 5 Hz, 6-H), 8.4–6.8 (8 H, m, 4-, 5-, *Ph*- and O-H).

3-Benzoylisonicotinic acid (**13a**)

Yield 92%; m.p. 277–279 °C (*Me*OH) (Ref. [51], m.p. 277–279 °C). IR (KBr, cm^{-1}): 1 720 (C=O). NMR (*DMSO-d*$_6$, δ): 9.0 (1 H, d, $J = 5$ Hz, 6-H), 8.8 (1 H, s, 2-H), 7.9 (1 H, d, $J = 5$ Hz, 5-H), 7.8–7.4 (6 H, m, *Ph*- and O-H).

Conversion of the Acids **12a** *and* **13a** *into the Corresponding Methyl Esters* **12b** *and* **13b**

To the suspension of the acid **12a** or **13a** (0.01 mol) in water (40 ml), $NaHCO_3$ (0.011 mol) was added, then the solvent was removed under reduced pressure and the solid residue was dried under vacuum. The solid residue (sodium salt of the corresponding acid) was then subjected to react with *Me*I (0.01 mol) in *DMF* (10 ml) at 0 °C for 5 h. Then the solvent was removed under reduced pressure to give an oily residue. To the residue water (30 ml) was added and the product extracted with CH_2Cl_2 (30 ml) and purified by column chromatography (silica gel, eluent ethyl acetate) and then by distillation or crystallization. The yields of the reactions, the physical properties, the IR and ^{1}H-NMR data, and the analytical data are given below.

3-Benzoyl-methylpicolinate (**12b**)

Yield 89%; m.p. 91–93 °C (benzene – heptane) (Ref. [50], m.p. 91 °C). IR (KBr, cm^{-1}): 1 740 (C=O), 1 6890 (C=O). NMR ($CDCl_3$, δ) 8.8 (1 H, dd, $J = 2$ and 5 Hz, 6-H), 8.0–7.1 (7 H, m, 4-, 5- and *Ph*-H), 3.7 (3 H, s, *Me*-H).

*3-Benzoyl-methylisonicotinate 1 (***13b**)

Yield 76%; b.p. 165–175 °C at 0.8 mm Hg (bulb to bulb). Calculated for $C_{14}H_{11}NO_3$: C 69.7, H 4.6, NH 5.8. Found: C 69.4, H 4.7, N 5.9. IR (KBr, cm^{-1}): 1 730 (C=O), 1 670 (C=O). NMR ($CDCl_3$, δ): 8.8 (1 H, d, $J = 5$ Hz, 6-H), 8.6 (1 H, s, 2-H), 7.9–7.1 (6 H, m, 5- and *Ph*-H), 3.7 (3 H, s, *Me*-H).

Blank Tests; Base-Catalyzed Hydrogen – Deuterium Exchange of the Anilides **1b** *and* **2b**

(a) To the anilide **1b** or **2b** (0.002 mol) in *THF* (20 ml) a solution of *Me*OLi in *Me*OD prepared by addition of *Bu*^{n}Li (0.0042 mol) to *Me*OD (1 ml) in *THF* (5 ml) was added and stirred for 1 h. The usual work-up gave anilide (95% of yield), which subjected to ^{1}H-NMR ($CDCl_3$, Me_4Si) and utilizing the peak areas of the appropriate pyridine protons showed no incorporation of deuterium.

(b) To the anilide (0.005 mol) in *THF* (25 ml) *Bu*^{n}Li (0.005 mol) was added and then the solution of *Me*OLi in *Me*OD was added and stirred for 1 h. The usual work-up gave anilide (95% of yield). In this case likewise no incorporation of deuterium were observed.

Acknowledgement

We are grateful to the Polish Academy of Sciences for support of this work (Grant CPBP 01.13).

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Received January 15, 1990. Accepted February 1, 1990