Regioselective Metalation of Pyridinylcarbamates and Pyridinecarboxamides with (2,2,6,6-Tetramethylpiperidino)magnesium Chloride†

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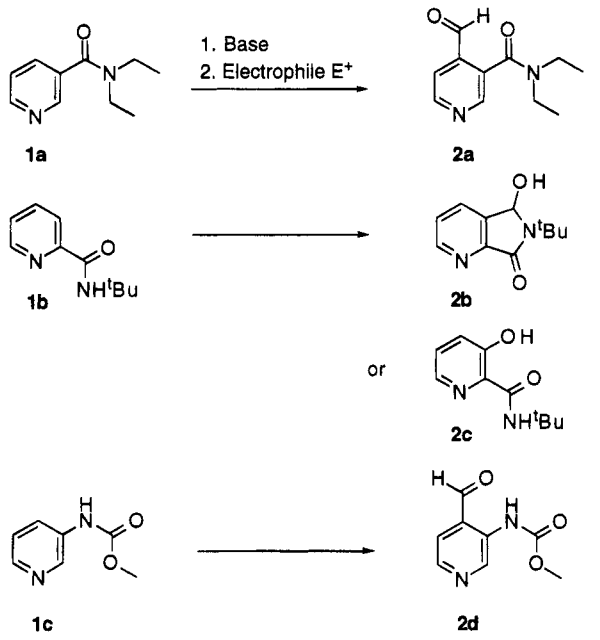
Received March 14, 1995 (Revised Manuscript Received September 27, 1995)

The difficulty in introducing functionality into π-deficient heterocycles by traditional electrophilic substitution renders directed ortho-metalation merely an attractive alternative.[1a-d] Most metalations have been performed with alkyllithium bases, whereas alkylmagnesium halides and Hauser bases ((dialkylamido)magnesium bromides) have been used in only a few cases.[2a-d] In 1989, Eaton and co-workers reported the directed ortho-metalation of *N,N*-diethylbenzamide with (diisopropylamido)-magnesium bromide (DAMgBr) and (2,2,6,6-tetramethylpiperidino)magnesium bromide (TMPMgBr).[3] In this paper, we describe the regioselective magnesiation of mono- and disubstituted pyridines exemplified by **1a-c**, **6**, **7**, and **9a,b**.

Metalation of Monosubstituted Pyridines. To find optimum conditions for the directed ortho-magnesiation of pyridinecarboxamides and carbamates compounds **1a-c** were used for model studies. The results are summarized in Scheme 1 and Table 1. When amide **1a** was treated with TMPMgBr[3] and the anion was formylated with *N*-formylpiperidine, 4-formylpyridine **2a** was formed in approximately 15% yield. To improve the discouragingly low yield the novel base (2,2,6,6-tetramethylpiperidino)magnesium chloride (TMPMgCl) was used. The base was conveniently prepared from strictly equivalent amounts of *n*-butylmagnesium chloride and 2,2,6,6-tetramethylpiperidine in refluxing THF.[4] Metalation of **1a** with TMPMgCl gave **2a** in 50% yield, comparable to the metalation of **1a** with LTMP.[5,6] However, the reaction of *N,N*-diethyl-2-pyridinecarboxamide with TMPMgCl and *N*-formylamines gave 3-formyl-*N,N*-diethyl-2-pyridinecarboxamide in only approximately 5% yield due to the lability of the tertiary amide under the metalation conditions.[6] For this reason the secondary amide **1b** was tried, as Epsztajn had demonstrated the powerful ortho-directing effect of N-monolithiated amide groups and their enhanced stability toward nucleophilic attacks.[7] Thus, **1b** was converted into the N,C-dimetalated species by metalation with TMPMgCl to give the 2,3-substituted pyridines **2b,c** in good yields after reaction with electrophiles. Suitable formyl donors are *N*-formylpiperidine or *N*-formyl-*N'*-methylpiperazine. The methyl carbamate group of commercially available **1c** served as a model for the 1,1-dimethylethyl carbamate group, which is frequently used as an activator for directed ortho-lithiation of arylamines.[8a-e] To our knowledge, this is the first time that a methyl carbamate group was used as an activator, and indeed, metalation of carbamate **1c** with TMPMgCl and formylation afforded the 4-formylpyridine **2d** in reasonably good yield. Attempts to improve the yield by raising the metalation temperature failed.

Scheme 1



So far, the magnesiation of **1a-c** is comparable with respect to yield and regioselectivity to the lithiation of **1a,c** and the related 1,1-dimethylethyl 3-pyridinylcarbamate.[5-7,8e] The 4-position in **1a,c** is clearly favored over the 2-position, presumably due to the relative stability of the magnesiated species.

Synthesis and Metalation of Disubstituted Pyridines. To test the relative directing effects of a N-protected amino group vs a carboxamido group the compounds **6**, **7**, **9a**, and **9b** were prepared (Scheme 2). By offering the pyridine nitrogen as a preferred anchor site for aluminum, a selective one-step conversion of diester **3** to the methyl 6-carboxamido-3-pyridinecarbox-

† Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

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(4) Some 2,5-pyridinedicarboxamides undergo 1,4 addition with Grignard reagents. After metalation of these carboxamides with an 8-fold excess of TMPMgCl we have found no 4-butylpyridines or 4-butyl-1,4-dihydropyridines. Thus, the formation of TMPMgCl from *n*-BuMgCl is obviously almost quantitative within some minutes.

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Table 1. Metalation/Electrophilic Quench of Compounds 1a-c

substrate	base[a]/equiv/conditions/solvent	electrophile[b]/equiv/condns	product	yield, %
1a	TMPMgBr/2.2/1 h, 0 °C/THF	NFP/2.5/1.5 h, 0 °C	**2a**	15
1a	TMPMgCl/2.2/1 h, 0 °C/THF	NFP/2.5/1.5 h, 0 °C	**2a**	50
1b	*n*-BuLi/2.2/45 min, −78 °C, and then 0.5 h, −18 °C/THF	NFNMP/2.5/12 h, −78 °C to rt	**2b**	48
1b	*n*-BuLi/2.2/45 min, −78 °C, and then 0.5 h, −18 °C/Et_2O	NFNMP/2.5/12 h, −78 °C to rt	**2b**	60
1b	TMPMgCl/4.0/2 h, 65 °C/THF	NFNMP/4.5/12 h, rt	**2b**	64
1b	TMPMgCl/6.0/2 h, 65 °C/THF	NFNMP/6.8/12 h, rt	**2b**	86
1b	*n*-BuLi/2.2/45 min, −78 °C, and then 0.5 h, −18 °C/Et_2O	$B(OMe)_3$/2.5/1 h, −78 °C, and then 2 h, −78 °C to rt, and then H_2O_2/OH^-/2 h, 0 °C	**2c**	50
1b	TMPMgCl/6.0/2 h, 65 °C/THF	$B(OMe)_3$/6.8/2 h, rt, and then H_2O_2/OH^-/ 2 h, 0 °C	**2c**	70
1c	TMPMgCl/4.0/1.5 h, rt/THF	NFP/5.0/1.5 h, rt	**2d**	48

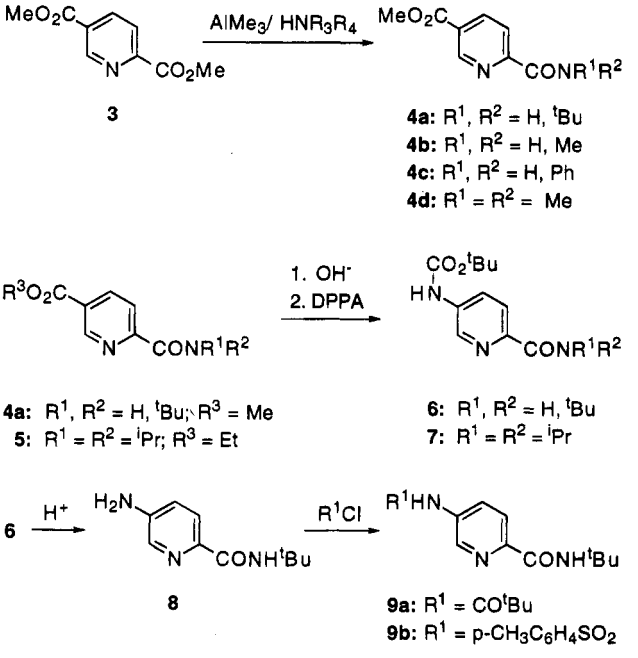
[a] *n*-BuLi was used with equimolar amounts of TMEDA as cosolvent (see Experimental Section). [b] NFP = *N*-formylpiperidine; NFNMP = *N*-formyl-*N'*-methylpiperazine.

Table 2. Metalation/Electrophilic Quench of Compounds 6 and 9a,b with TMPMgCl in THF

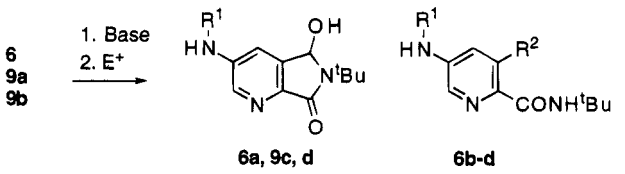
substrate	condns[a]	electrophile[b]/equiv/condns	product	R^1	R^2	yield, %
6	2 h, 55 °C	NFNMP/8.8/12 h, rt	**6a**	$CO_2{}^tBu$		84
6	1.5 h, 50 °C	$B(OMe)_3$/8.9/2 h, rt, and then H_2O_2/OH^-/2 h, 0 °C	**6b**	$CO_2{}^tBu$	OH	92
6	2 h, 70 °C	Me_2S_2/8.5/12 h, rt	**6c**[c]	$CO_2{}^tBu$	SMe	54
6	2 h, 70 °C	excess 3% DCl/D_2O/5 min, 0 °C	**6d**	$CO_2{}^tBu$	D	85
9a	1.5 h, 50 °C	NFNMP/9.5/4 h, rt	**9c**	CO^tBu		84
9b	1.5 h, 65 °C	NFNMP/8.7/12 h, rt	**9d**	tosyl		25

[a] Metalation was performed with 8 equiv of TMPMgCl in all cases. [b] NFNMP = *N*-formyl-*N'*-methylpiperazine. [c] Further methylthio compounds were isolated (see Experimental Section).

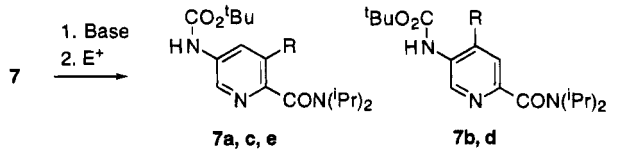
Scheme 2



Scheme 3



Scheme 4



ylates **4a-d** was achieved with aluminum amides.[9ab] Diisopropylamine failed completely; therefore, ethyl 6-[(diisopropylamino)carbonyl]-3-pyridinecarboxylate (**5**) was prepared by hydrolysis of diethyl 2,5-pyridinedicarboxylate[10ab] (approximately 8/1 mixtures of 2-/5-carboxylic acid were obtained) and subsequent reaction of the mixture with thionyl chloride and diisopropylamine. Saponification of esters **4a** and **5** to 3-pyridinecarboxylic acids and subsequent Curtius rearrangement provided carbamates **6** and **7**.[11] Hydrolysis of carbamate **6** led to aminopyridine **8**, which was acylated to give **9a,b**.

Earlier work in this field has shown that metalation of **6** and **9a** with *n*- and *t*-BuLi (MeI, DMF, Me_3SiCl, MOM-Cl as electrophiles) afforded 2,3,5-substituted pyridines (3,5,6-substitution for carbamate **6**) exclusively in moderate yields.[12] Similar product ratios were obtained from magnesiation and subsequent electrophilic quench (Scheme 3, Table 2) which demonstrates that the secondary carboxamide has a stronger directing effect than a carbamate, pivaloylamino, or (toluenesulfonyl)amino group.

To test the influence of the amide substitution, the tertiary carboxamide **7** was metalated with LTMP, TMPMgCl, and *t*-BuLi and quenched with bromine and formyl donors (Scheme 4, Table 3). Surprisingly, TMPMgCl effects regioselective proton abstraction with respect to C-4 whereas lithium bases generate 4-/5-mixtures.

Transmetalation of Lithiated vs Magnesiated Pyridine 7. To compare the relative extent to which a lithiated and a magnesiated pyridine **7** undergo transmetalation, the 5-bromo derivative **7a** was converted into the 5-deuterio derivate **7e** using a modified reduction protocol.[13] According to ^1H NMR analysis, the degree of 5-deuteration in **7e** was 95%. This material was meta-

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Table 3. Metalation/Electrophilic Quench of Compound 7 in THF

substrate	base/equiv/condns	electrophile[a]/equiv/condns	R	product	yield, %
7	*t*-BuLi/2.2/1 h, −78 °C	$C_2H_4Br_2$/1.3/12 h, −78 °C to rt	Br	**7a/7b**	75/14
7	TMPMgCl/6.0/2 h, 55 °C	Br_2/6.7/12 h, 0 °C to rt	Br	**7b**	58
7	LTMP/5.0/30 min, −78 °C, and then 40 min, 0 °C	NFNMP/5.6/3 h, −78 °C to rt	CHO	**7c/7d**	52/13
7	TMPMgCl/6.0/2 h, 55 °C	NFNMP/6.7/12 h, rt	CHO	**7d**	75

[a] NFNMP = *N*-formyl-*N'*-methylpiperazine.

lated alternatively with LTMP and TMPMgCl and quenched with aqueous citric acid. In the first case the 5-deuterium label was completely (>95%) replaced by hydrogen, whereas in the second case the deuterium was left essentially untouched (93% 5-*d*). This means that the lithium base initially metalates the 5-position and the magnesium base metalates the 4-position. The 5-lithiated pyridine undergoes partial 5-/4-translithiation, whereas the magnesiated pyridine is stable.

In conclusion, we have shown that TMPMgCl is an efficient base for achieving regioselective ortho-metalation of pyridinecarboxamides and carbamates. In contrast to the lithiated analogues, magnesiated pyridines obviously do not undergo transmetalation. They can be trapped with electrophiles to give a variety of synthetically useful pyridine derivatives.

Experimental Section

General Methods. Toluene and CH_2Cl_2 were dried over activated molecular sieves (4 Å). THF was distilled from sodium benzophenone ketyl. 2,2,6,6-Tetramethylpiperidine (TMPH) was distilled from CaH_2. Solutions of *n*-BuMgCl in THF were titrated according to the procedure of Watson and Eastham.[14] All reactions involving air-sensitive reagents were performed using syringe−septum cap techniques in oven-dried glassware under an argon atmosphere.

Metalation of 1a-c, 6, 7, and 9a,b with TMPMgCl and Electrophilic Quench. General Procedure (Tables 1−3). To a stirred solution of *n*-BuMgCl in THF (approximately 0.2−0.7 M) under argon was added an equimolar amount of 2,2,6,6-tetramethylpiperidine, and the mixture was refluxed for 1.5 h. A pyridine derivative dissolved in THF was added dropwise to a 2.2−8.0-fold excess of TMPMgCl at 0 °C, and the mixture was stirred at 0−70 °C for 1−2 h. After addition of a slight excess of an electrophile at 0 °C, the mixture was allowed to react at 0 °C or ambient temperature for 1.5 −12 h. Workup consisted of quenching the cooled mixture with 20% aqueous citric acid, extraction of the aqueous layer with CH_2Cl_2, drying of the combined extracts with Na_2SO_4, filtration, and concentration in vacuo. The residue was purified by flash chromatography (FC) followed by recrystallization. For instance, **6-(1,1-Dimethylethyl)-6,7-dihydro-5-hydroxy-5*H*-pyrrolo[3,4-b]pyridin-7-one (2b)** was prepared using the magnesiation conditions described. In this case, the reaction was quenched with aqueous citric acid and stirred at rt overnight. FC (CH_2Cl_2/acetone 1:1) gave **2b** (86%) as colorless crystals, mp 156−158 °C (CH_2Cl_2/cyclohexane): ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 9 H), 4.32 (d, 1 H, *J* = 10.0 Hz), 6.12 (d, 1 H, *J* = 10.0 Hz), 7.35 (dd, 1 H, *J* = 8.0, 5.0 Hz), 7.90 (dd, 1 H, *J* = 8.0, 1.5 Hz), 8.55 (dd, 1 H, *J* = 5.0, 1.5 Hz); IR ($CHCl_3$) 3308, 1709 cm^{-1}; MS *m*/*z* (rel intensity) 206 (29, M$^+$), 191 (36), 149 (57), 134 (100), 106 (60). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.79; H, 6.80; N, 13.67.

Starting materials, amounts of base, conditions for metalation and electrophilic quench, electrophiles, products, and yields for all compounds prepared according to this method are listed in Tables 1−3. The analytical data of the products are described in the supporting information.

Amidodealkoxylation of Dimethyl 2,5-Pyridinedicarboxylate (3). General Procedure. To a stirred solution or suspension of amine (0.105 mol) or amine hydrochloride (0.105 mol) in toluene (250 mL) at 0 °C was slowly added trimethylaluminum (0.105 mol, 52.5 mL of 2 M solution in heptane). The reaction mixture was allowed to warm to rt, and after being stirred for 30 min the solution was added within 30 min to ester **3** (0.1 mol, 9.75 g) in dichloromethane (100 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 1 d. The mixture was slowly poured into cooled 20% aqueous citric acid and stirred until clear phase separation was obtained. The aqueous layer was extracted with THF/EtOAc (1:1; 7 × 100 mL), and the combined extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by FC followed by recrystallization. For instance, **methyl 6-[[*N*-(1,1-dimethylethyl)amino]carbonyl]-3-pyridinecarboxylate (4a)** was prepared according to the general procedure described. FC (cyclohexane/EtOAc 1:1) gave **4a** (98%) as colorless needles, mp 86−87 °C (diethyl ether/hexane): ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H), 3.98 (s, 3 H), 8.02 (s, 1H), 8.25 (dd, 1 H, *J* = 8.5, 1.0 Hz), 8.43 (dd, 1 H, *J* = 8.5, 2.0 Hz), 9.10 (dd, 1 H, *J* = 2.0, 1.0 Hz); IR ($CHCl_3$) 3375, 1728, 1677 cm^{-1}; MS *m*/*z* (rel intensity) 236 (30, M$^+$), 221 (100), 193 (11), 181 (14), 164 (40), 136 (49). Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.83; H, 6.80; N, 11.96.

The analytical data for esters **4b-d** are described in the supporting information.

Supporting Information Available: ^{1}H NMR, IR, and mass spectral data and elemental analyses of **1b**, **2a**, **c**, **d**, **4b-d**, **5**, **6**, **7**, **6a-d**, **7**, **7a-d**, **8**, and **9a-d**, preparation/lithiation procedures of **1b**, **2b**, **c**, **3**, **5**, **6**, **7**, **7a-e**, **8**, and **9a,b**, and copies of ^{1}H NMR spectra of those compounds lacking combustion analyses (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO950494W

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