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Reactions of Trifluoromethylpyridines with Alkyllithium Reagents. Directing Effects of the Trifluoromethyl Groups

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Abstract: Reactions of eight trifluoromethyl substituted pyridines with alkyllithium reagents were examined. 3-Trifluoromethylpyridine, 3,4-, and 3,5-bis(trifluoromethyl)pyridines undergo regioselective lithiation at the 2-position thus providing an easy access to 2-functionalised trifluoromethylpyridines. The reactions of 2-trifluoromethylpyridine, 2,4-, 2,6-bis(trifluoromethyl)-pyridines and 2,4,6-tris(trifluoromethy)pyridine result exclusively by addition of RLi to the -N=C- bond. 2,5-Bis(trifluoromethylpyridine), depending on the reaction temperature, gives either 2-lithio derivative or an adduct.

INTRODUCTION

It is commonly known that treatment of pyridine with organometallic reagents does not result in formation of a C-metallated derivative. A well established general reaction is the addition to the formal azomethine link to form a 1-lithio-2-alkyl- or 1-lithio-2-aryl-1,2-dihydropyridine. On heating, the adduct may lose lithium hydride to give 2-alkyl- or 2-arylpyridine (Ziegler reaction) or alternatively it may react with an electrophile.[1,2] The only successful direct metallation of pyridine reported so far was achieved by using the kinetically very active combination of butyllithium and potassium *tert*-butoxide (LICKOR) and by working at -100°C; a mixture of 2- and 4-potassio derivatives was formed in a ratio depending on the polarity of the solvent used.[3]

In contrast, π-electron deficient pyridines containing a convenient *ortho*-directing group in the 3-position can be successfuly metallated at the 2- or 4-position, particularly when a poweful metallating agent and low temperature is applied. Substituents such as halogens, alkoxy and protected amino, keto or carboxylic groups effectively promote direct metallation of the pyridine ring.[4]

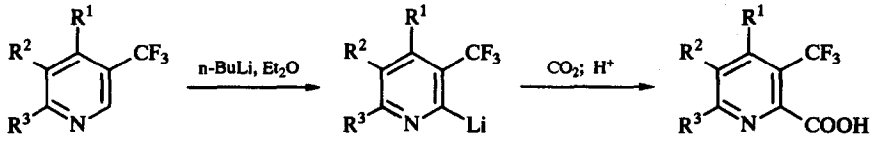
In the present paper we report the effects of trifluoromethyl groups, their number and positions in the pyridine ring, on the direction of reactions of various trifluoromethyl substituted pyridines with alkyllithium reagents.

RESULTS AND DISCUSSION

Eight trifluoromethyl substituted pyridines were synthesised by following the literature procedures[5] and their reactions with commercial n-butyllithium and/or *tert*-butyllithium reagents were examined. Isolable products were obtained by working at low temperatures, usually within the range of -78 to -60°C, and by using diethyl ether as a solvent. An increase of the reaction temperature over -50°C usually resulted in total charring or severely decreased yields. The yields of the products were also much lower when THF was used as a solvent.

The reactions of 3-trifluoromethylpyridine (**1a**), 3,4-bis(trifluoromethyl)pyridine (**1b**), 3,5-bis(trifluoromethyl)pyridine (**1c**) and 2,5-bis(trifluoromethyl)pyridine (**1d**) with n-butyllithium resulted in highly regioselective lithiation at the C-2 position. 2-Lithio derivatives were form exclusively which by treatment with carbon dioxide followed by acidification afforded the corresponding 2-pirydinecarboxylic acids **2a** - **2d** in 51-89% yields (Table 1).

Table 1. Reactions of trifluoromethylpyridines resulting in the C-2 lithiation.



1 **2**

Subst.No.	R^1	R^2	R^3	Temp.(°C)	Time(min.)	Prod.No.	Yield(%)[a]
1a	H	H	H	-78 to -60	40-60	2a	72-76
1b	CF_3	H	H	-78 to -40	40	2b	57
1c	H	CF_3	H	-78 to -10	3-15	2c	81-89
1d	H	H	CF_3	-78 to -40	40	2d	51-58

[a] isolated yields based on 1.

The lithiations preceeded rather slowly such that 40-60 minutes was required to complete the reaction. The exception was compound 1c in which the presence of another CF_3 group at the 5-position evidently increases the 2-hydrogen acidity and stabilises the resulting lithiated intermediate. The lithiation of 1c was completed in 10-15 minutes at -60°C and in only 2-3 minutes at -10°C without serious tar formation.

Lithiation of trifluoromethylpyridines **1a - 1d** followed by carboxylation provides an easy access to hitherto unknown mono- and bis(trifluoromethyl)-2-pyridinecarboxylic acids **2a - 2d**. The acids were obtained in high purity as evidenced by elemental analyses and their structures have been proven by the ^1H and ^{19}F NMR data (Table 2). The ^1H NMR spectra of the acids have shown the absence of protons at the 2-position, which appeared in the starting pyridines as singlets at 8.9 - 9.1 p.p.m., thus confirming the lithiation and carboxylation position. Other signals in both ^1H and ^{19}F spectra of acids **2a - 4d** appeared within the range of the corresponding signals of the starting pyridines **1a - 1d** with a slight downfield shift due to introduction of an strongly electron-withdrawing substituent which is a carboxylic group.

Table 2. ^1H and ^{19}F NMR data of trifluoromethyl-2-pyridine carboxylic acids **2a - 2d**.

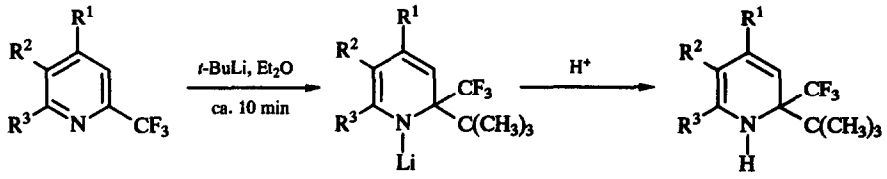
Compd. No.	Chemical shift, δ (p.p.m.)[a] H4	H5	H6	$CO_2H(H_2O)$	CF_3[b]	Coupling constant J (Hz)
2a	8.01 (d)	7.94 (dd)	8.90 (d)	3.4 (br)	63.3 (s)	H4H5 = 7.9; H5H6 = 5.6
2b	-	7.98 (dm)	8.90 (d)	3.4 (br)	59.6 (s); 62.4 (s)	H5H6 = 5.6
2c	8.32 (d)	-	9.24 (s)	3.5 (br)	60.0 (s); 63.3 (s)	
2d	8.22 (d)	7.96 (d)	-	3.5 (br)	64.0 (s); 69.0 (s)	H4H5 = 8.2

[a] In wet DMSO-d_6; [b] Related to $CFCl_3$.

Pyridines having no trifluoromethyl group in the 3-position do not undergo C-lithiation. Thus, 2-trifluoromethylpyridine (**3a**), 2,4-bis(trifluoromethyl)pyridine (**3b**) and 2,6-bis(trifluoromethyl)pyridine (**3c**) reacted rapidly with n-butyllithium forming brown polymeric tar, even at -76°C. Treatment of the reaction mixtures with carbon dioxide followed by acidification gave neither isolable products nor a trace of the staring material was recovered. However, pyridines **3a - 3c** react in a more controlable manner with *tert*-butyllithium such that within the temperature range of -78 to -50°C products of the addition of a *tert*-BuLi molecule across the carbon-nitrogen bond of the pyridine ring were formed. After acidification of the red-coloured reaction mixtures, 2-*tert*-butyl-trifluoromethyl-1,2-dihydropyridines **4a - 4c** were isolated in 22- 36% yields (Table 3). Interestingly, 2,5-bis(trifluoromethyl)pyridine (**1d**), which reacted at -70°C with n-BuLi (and also with *tert*-BuLi) to give the correponding 2-lithiopyridine in an appreciable yield (Table 1), with *tert*-butyllithium at -50°C afforded 2-*tert*-butyl-2,5-bis(trifluoromethyl)-1,2-dihydropyridine (**4d**) as the only product albeit in low yield (Table 3). The reaction of 2,4,6-tris(trifluoromethyl)pyridine (**5**) with *tert*-BuLi gave a 1 : 3.5 mixture of 2-*tert*-butyl-2,4,6-tris(trifluoromethyl)-1,2-dihydropyridine (**6a**) and 4-*tert*-

butyl-2,4,6-tris(trifluoromethyl)-1,4-dihydropyridine (**6b**) in a 56% total yield (Scheme).

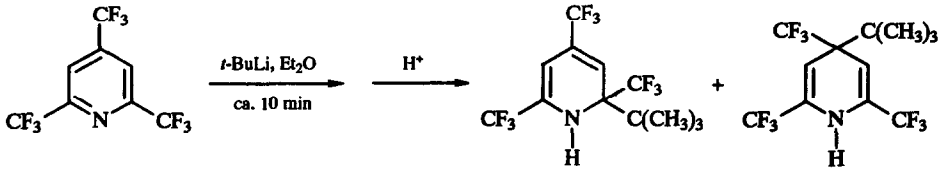
Table 3. Reactions of trifluoromethylpyridines resulting in addition of RLi.



3 **4**

Subst.No.	R^1	R^2	R^3	Temp.(°C)	Prod.No.	Yield(%)[a]
3a	H	H	H	-78 to -50	**4a**	26
3b	CF_3	H	H	-78 to -70	**4b**	22
3c	H	H	CF_3	-78 to -70	**4c**	36
1d	H	CF_3	H	-50	**4d**	18

[a] yields based on **3** and **1d** calculated from the GLC contents in enriched fractions isolated by column chromatography.



5 **6a** (12.5%) **6b** (43.5%)

Scheme

Trifluoromethyldihydropyridines **4a-4d**, **6a** and **6b** are rather unstable compounds. They slowly decompose on standing in a refrigerator and rapidly decomposed during attempted column chromatography isolation using commercial silica-gel. The isolation was achieved after neutralisation of the silica-gel with triethylamine. The dihydropyridines were also found to be unstable in $CDCl_3$ solutions, likely because of an acidity of the solvent, precluding obtaining their NMR spectra in this solvent.

The ^1H and ^{19}F NMR spectra of compounds **4** and **6** (Table 4) were successfuly obtained in C_6D_6 solutions and they unambiguously confirmed their structures. The ^1H spectrum of each

Table 4. ^{1}H and ^{19}F NMR data of dihydropyridines **4a - 4d, 6a and 6b.**

Compnd. No.	Chemical shift, δ (p.p.m.)[a] H3	H4	H5	H6	NH[b]	t-Bu[c]	CF_3[d]	Coupling constant J (Hz)
4a	4.68(dm)	5.62(dd)	4.90(dd)	4.82(d)	4.9	0.72	67.9	H3H4 = 7.1; H4H5 = 7.7 H5H6 = 7.2
4b	4.98(m)	-	4.94(dm)	4.83(d)	5.2	0.72	57.9 66.8	H5H6 = 7.6
4c	4.97(dm)	5.64(dd)	4.92(d)	-	3.8	0.74	71.3 74.2	H3H4 = 7.1; H4H5 = 12
4d	4.72(dm)	5.86(d)	-	4.93(s)	5.2	0.76	64.6 68.0	H3H4 =7.7
6a	5.01(m)	-	4.96(s)	-	5.3	0.78	64.7 67.5 68.2	
6b	5.20(s)	-	5.20(s)	-	5.7	1.08	62.2(3F) 64.7(6F)	

[a] in C_6D_6; [b] broad singlets; [c] quartets, $^{5}J_{HF}$ = 1.2 Hz; [d] related to $CFCl_3$, pseudo singlets: couplings to the *t*-Bu group protons are not resolved.

compound contains a signal of the *tert*-butyl group protons showing a coupling with the CF_3 group attached to the same ring carbon atom and a broad signal of the NH group. The chemical shifts and multiplicity of the ring protons cleanly determine their position. The ^{19}F spectra contain an appropriate number of the CF_3 group signals.

In conclusion, trifluoromethyl groups in positions 3 and 5 of the pyridine ring effectively promote direct lithiation at the 2-position and stabilise the 2-lithio derivatives providing useful intermediates to various 2-functionalised 3-trifluoromethyl, 3,4-, 3,5- and 2,5-bis(trifluoromethyl)-pyridines. Trifluoromethyl groups in positions 2, 4 and 6 increase the reaction rates with alkyllithium reagents such that the reactions are hardly controlable but conventional addition of the RLi to the pyridine ring and polymerisation are the only observed reactions. It is worth to notify the contrast between the presently described reactions of trifluoromethylpyridines and reactions of 3-trichloro-methylpyridine and substituted 3-trichloromethylpyridines with sodium methoxide leading to a stepwise displacement of chlorine atoms from the trichloromethyl group.[6]

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Elemental analyses for C, H and N were done with a Perkin-Elmer 240 Elemental Analyzer. The fluorine was determined by a Rowley and Churchill method[7] after combustion of samples in an atmosphere of oxygen in a Schöniger flask.[8] The ^1H and ^{19}F NMR spectra were recorded in $CDCl_3$ with a Varian Gemini 200 spectrometer at 200 and 188 MHz, respectively; chemical shifts are in p.p.m. from internal TMS for protons and from internal $CFCl_3$ for fluorine nuclei (positive upfield). The GLC analyses were performed with a Shimadzu GC-144 chromatograph using a 3.5 m x 2 mm column packed with 3% Silicon Oil SE-52 on Chromosorb WAW.

Preparation of trifluoromethylpyridines

Mono- and bis(trifluoromethyl)pyridines **1a - 1d** and **3a - 3c** were obtained according to the described procedure by treatment of the corresponding pyridine mono- and dicarboxylic acids with sulphur tetrafluoride and hydrogen fluoride.[5] All compounds were over 99% pure (GLC estimated), they shown boiling or melting points within the reported ranges and gave satisfactory elemental analyses. ^1H and ^{19}F NMR ($CDCl_3$):

3-Trifluoromethylpyridine (**1a**): δ 7.45 (ddm, H5, ^3J = 4.9 Hz, ^4J = 0.7 Hz); 7.94 (dm, H4, ^3J = 8 Hz, ^4J = 0.8 Hz); 8.82 (d, H6, ^3J = 4.9 Hz); 8.92 (q, H1, ^4J = 0.8 Hz); 65.1 (s, CF_3).

3,4-Bis(trifluoromethyl)pyridine (**1b**): δ 7.54 (d, H5, ^3J = 5.4 Hz); 8.83 (d, H6, ^3J = 5.4 Hz); 9.10 (s, H2);

63.2 (s, CF_3); 65.5 (s, CF_3).

3,5-Bis(trifluoromethyl)pyridine (1c): δ (8.19 (sept, H4, ^4J = 0.7 Hz); 9.1 (q, 2H and 6H, ^4J = 0.7 Hz); 63.1 (s, $2CF_3$).

2,5-Bis(trifluoromethyl)pyridine (1d): δ 7.86 (d, H3, ^3J = 8.2 Hz); 8.17 (dq, H4, ^3J = 8.2 Hz); 9.02 (s, H6); 63.3 (s, CF_3); 68.9 (s, CF_3).

2-Trifluoromethylpyridine (3a): δ 7.86 (d, H3, ^3J = 8.2 Hz); 7.91 (dd, H4, ^3J = 7.7 and 8.2 Hz); 8.1 (dd, H5, ^3J = 5.2 and 7.7 Hz); 8.64 (d, H6, ^3J = 5.2 Hz); 68.7 (s, CF_3).

2,4-Bis(trifluoromethyl)pyridine (3b): 8.1 (d, H5, ^3J = 4.9 Hz); 8.14 (s, H3); 8.8 (d, H6, ^3J = 4.9 Hz); 65.4 (s, CF_3); 68.2 (s, CF_3).

2,6-Bis(trifluoromethyl)pyridine (3c): 7.91 (d, H3 and H5, ^3J = 7.7 Hz); 8.14 (t, H4, ^3J = 7.7 Hz); 68.6 (s, $2CF_3$).

2,4,6-Tris(trifluoromethyl)pyridine (5) (nc) was obtained likewise from 2,4,6-pyridinetricarboxylic acid; yield: 40.5%; GLC purity: 99.2%; b.p. 124-125°C; m.p. 19-20°C; ^1H NMR ($CDCl_3$): δ 8.14 (s); ^{19}F NMR ($CDCl_3$): δ 65.5 (s, CF_3); 68.7 (s, $2CF_3$).

Reactions of trifluoromethylpyridines 1a - 1d, 3a - 3c and 6 with alkyllithium reagents.

General procedure.

All reactions were conducted under a atmosphere of dry argon. n-Butyllithium or *tert*-butyllithium (6 mmoles, commercial 1.6M or 1.4M solution in hexane or pentane, respectively) was added with a syringe *via* a rubber septum to a pre-cooled (-78°C) stirred solution of a trifluoromethylpyridine (3 mmole) in diethyl ether (15 ml), at such a rate to keep the temperature within the range given in Table 1 and 3. After addition was complete, stirring was continued for the time and at a temperature close to the higher range shown in Table 1 and 3, then the reaction was cooled to -78 and quenched as described below.

Preparation of (trifluoromethyl)-2-pyridinecarboxylic acids 2a - 2d.

Solid carbon dioxide was added to cool reaction mixtures obtained from pyridines 1a - 1d and n-BuLi, then the mixtures were poored into 1% aqueous KOH (100 ml) and organic impurities were washed out with Et_2O. The alkaline solutions were acidified with hydrochloric acid, saturated with NaF and then extrated with Et_2O. Evaporation of the solvent gave solid residues which were recrystallised from water to give trifluoromethylpyridinecarboxylic acids as white solids. Yields of the acids are given in Table 1 and their ^1H and ^{19}F NMR data in Table 2.

3-(Trifluoromethyl)-2-pyridinecarboxylic acid (2a): m.p. 128-129°C (decomp.); found: C, 44.0; H, 2.15; F, 29.5; N, 7.25%; $C_7H_4F_3NO_2$ requires: C, 44.0; H, 2.1; F, 29.3; N, 7.3%.

3,4-Bis(trifluoromethyl)-2-pyridinecarboxylic acid (**2b**): m.p. 115-118°C (decomp.); found: C, 37.0; H, 1.2; F, 44.0; N, 5.3%; $C_8H_3F_6NO_2$ requires: C, 37.1; H, 1,2; F, 44.0; N, 5.4%.
3,5-Bis(trifluoromethyl)-2-pyridinecarboxylic acid (**2c**): m.p. 117-120°C (decomp.); found: C, 37.0; H, 1.2; F, 44.2, N, 5.25%. $C_8H_3F_6NO_2$ requires: C, 37.1; H, 1,2; F, 44.0; N, 5.4%.
3,6-Bis(trifluoromethyl)-2-pyridinecarboxylic acid (**2d**): m.p. 122-124°C (decomp.); found: C, 36.5; H, 1.1; F, 44.0, N, 5.4%. $C_8H_3F_6NO_2$ requires: C, 37.1; H, 1,2; F, 44.0; N, 5.4%.

Preparation of (trifluoromethyl)dihydropyridines 4a - 4d, 6a and 6b.

The reaction mixtures obtained from pyridines **1d**, **3a - 3c** and **5** and *tert*-BuLi were quenched by careful addition of a solution of acetic acid (1 ml) in tetrahydrofuran (3 ml) at -78°C. When warmed up to ambient temperature, the solutions were poured into water (100 ml) and extracted with diethyl ether (3 x 10 ml). The combined extracts were dried ($MgSO_4$), the solvent was removed under vacuum, and a brownish residues were subjected to chromatographic separation on silica-gel (230 - 400 mesh, 1 : 100 by weight, pre-treated with 1% solution of Et_3N in n-hexane) using n-hexane as eluent. Evaporation of the solvent gave colourless oils containing 80-85% (GLC estimate) of the dihydropyridines. Yields of compounds **4a - 4d** are given in Table 3 and those of compounds **6a** and **6b** in the Scheme. The ^1H and ^{19}F NMR data are shown in Table 4.

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