

# **DEVELOPMENT OF A BENCH-SCALE PHARMACEUTICAL SYNTHESIS**



By

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A thesis submitted for the degree of Master of Science

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at

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This thesis is dedicated to my parents, especially to my mother for her love throughout my life.

## Declaration

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of Master of Science is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Signed: Jing Li  
Jing Li

Date 15 Nov 1993.

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## Abstract

A straightforward synthesis of 2-methyl-3-trifluoromethyl-aniline has been developed from inexpensive 3-trifluoromethylaniline. Details of the synthetic steps are as follows:

- (1) conversion of 3-trifluoromethylaniline to pivalylamino-3-trifluoromethylbenzene,
- (2) conversion of pivalylamino-3-trifluoromethylbenzene to pivalylamino-2-methyl-3-trifluoromethylbenzene,
- (3) conversion of pivalylamino-2-methyl-3-trifluoromethylbenzene to 2-methyl-3-trifluoromethylaniline.

In attempting a one-step synthesis of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid from 2-methyl-3-trifluoromethylaniline and 2-chloronicotinic acid, we unexpectedly obtained N-(2-methyl-3-trifluoromethyl)phenyl-2-hydroxynicotinamide.

A feasible bench-scale synthetic route to 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid, involving reaction of the methyl ester of 2-chloronicotinic acid with 2-methyl-3-trifluoromethylaniline, has been successfully developed.

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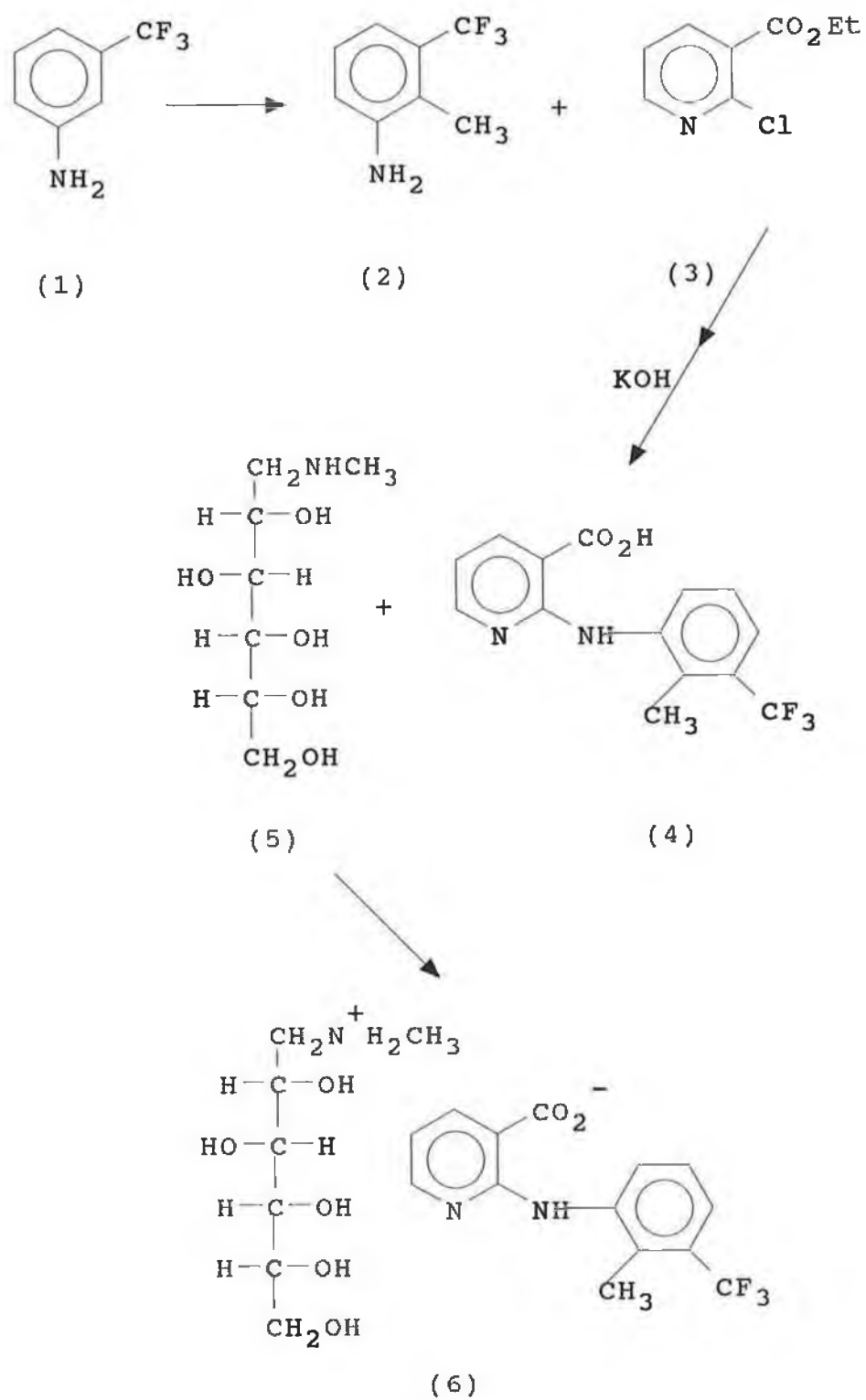


## INTRODUCTION

### Chapter 1. Background.

In this thesis the development of a feasible synthetic route to the N-methyl-D-glucamine salt of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (6) will be presented. The N-methyl-D-glucamine salt of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (6) was reported early in 1975<sup>[1]</sup>, as an anti-inflammatory and potent analgesic pharmaceutical

It was prepared from 2-methyl-3-trifluoromethylaniline (2) and ethyl 2-chloronicotinate (3) which were reacted together to give ethyl 2-(2-methyl-3-trifluoromethylanilino)nicotinate. The product was hydrolyzed with potassium hydroxide to give 2-(2-methyl-3-trifluoromethyl-anilino)nicotinic acid (4), which combined with N-methyl-D-glucamine (5) in ethanol to give the salt (6). <sup>[1]</sup> (Scheme 1.1.1).

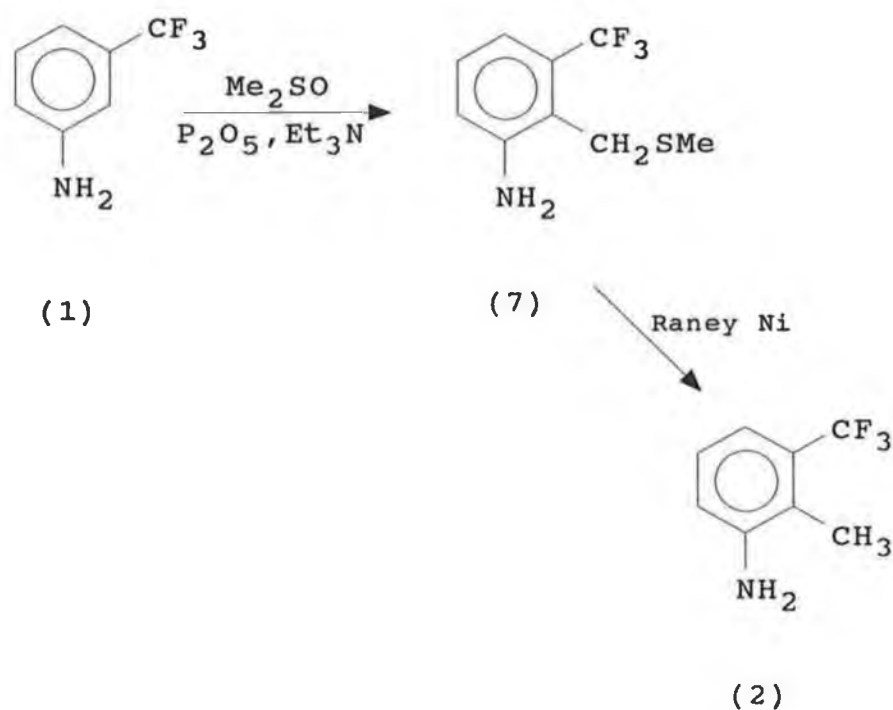


Scheme 1.1.1

## **1.1 Information Regarding the Preparation of 2-Methyl-3-trifluoromethylaniline (2)**

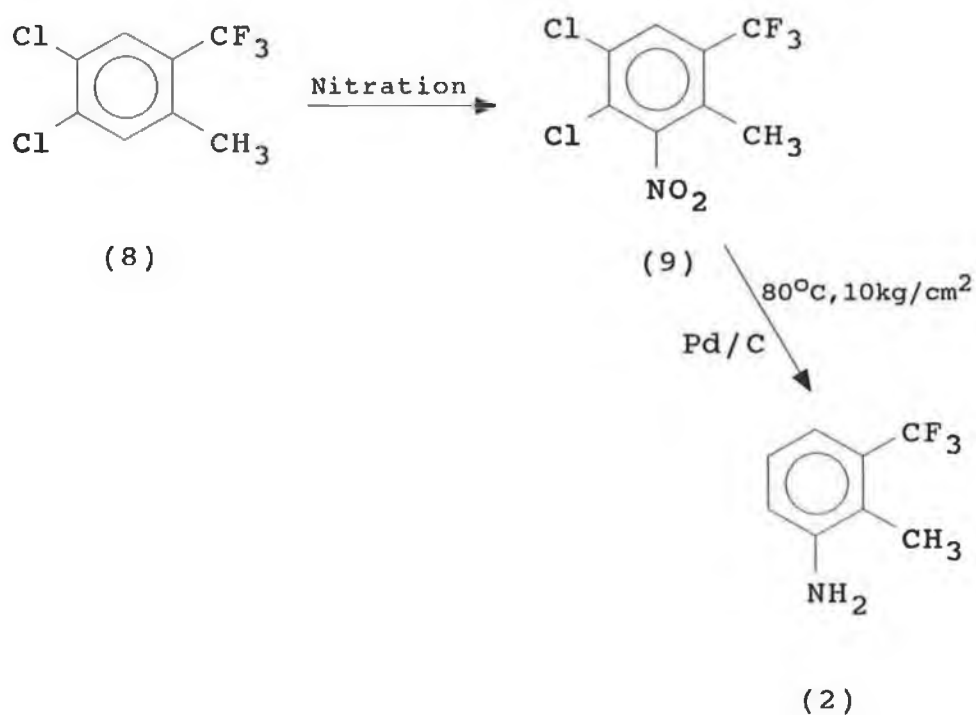
An efficient synthesis of 2-(2-methyl-3-trifluoromethyl-anilino)nicotinic acid (4) was required by a pharmaceutical company. We proposed to synthesise it using 3-trifluoromethylaniline (1) and 2-chloronicotinic acid (27) as commercially available starting materials. 3-Trifluoromethylaniline (1) is inexpensive and has the advantage of having amino and trifluoromethyl groups appropriately placed on the ring, merely requiring regioselective introduction of a methyl group at carbon-2 position.

Synthesis of 2-methyl-3-trifluoromethylaniline (2) had previously been reported from 3-trifluoromethylaniline (1).<sup>[2] [3]</sup> Condensation with dimethyl sulfoxide in the presence of phosphoric anhydride and triethylamine gave compound (7) which, on reaction with Raney nickel, gave 2-methyl-3-trifluoromethylaniline (2). (see Scheme 1.1.2)



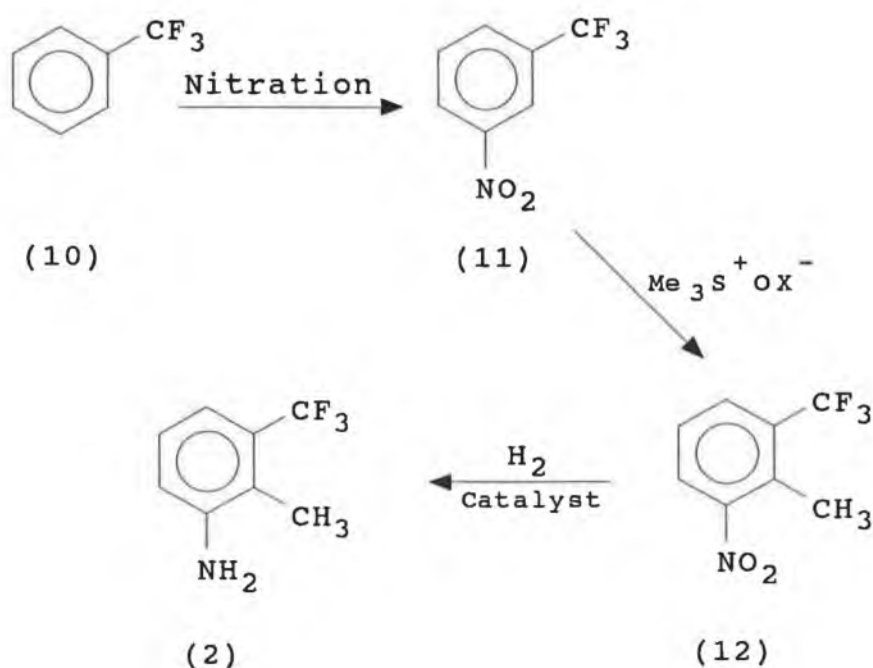
Scheme 1.1.2

An alternative method is nitration of 3,4-dichloro-6-(trifluoromethyl)toluene (8) to give 2-nitro-3,4-dichloro-6-(trifluoromethyl)toluene (9), which was hydrogenated over Pd/C at 80°C and 10 kg/cm<sup>2</sup> in 28% aq. sodium acetate to give 2-amino-6-(trifluoromethyl)toluene (2-methyl-3-trifluoromethylaniline) (2).<sup>[4]</sup> (see Scheme 1.1.3)



Scheme 1.1.3

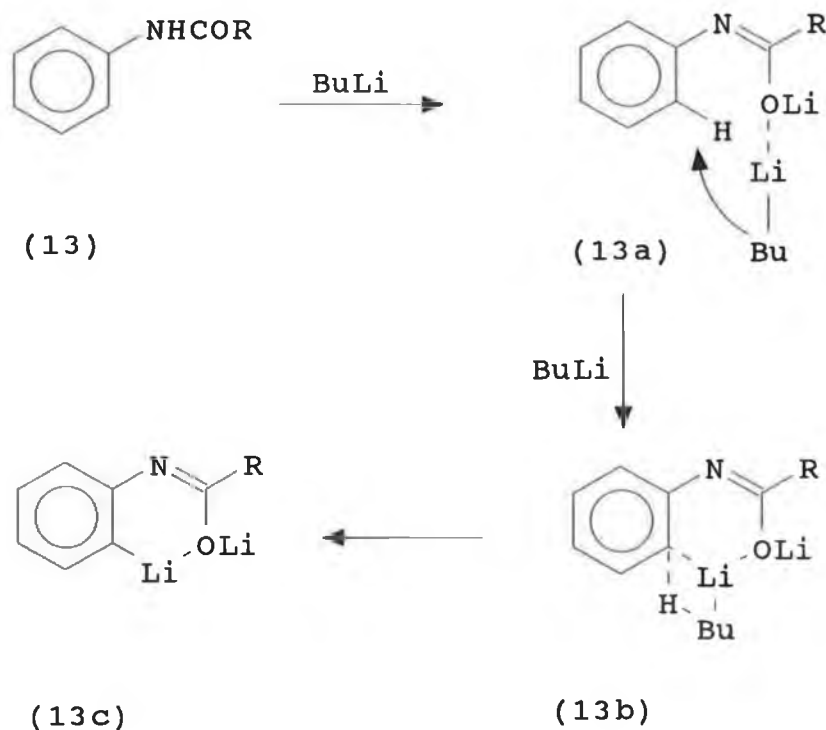
Another method is nitration of trifluoromethylbenzene (10) to give 3-nitro-trifluoromethylbenzene (11), methylation of the latter with  $\text{Me}_3\text{S}^+\text{OX}^-$  ( $\text{X}=\text{halo}$ ), and reduction of the resultant 2-methyl-3-nitro-trifluoromethylbenzene (12).<sup>[5]</sup> <sup>[6]</sup> (see Scheme 1.1.4)



Scheme 1.1.4

Although electrophilic substitution of anilines, in particular of N-acylated derivatives is feasible,[7] [8] the formation of isomers and the low yields obtained makes this synthetically unattractive. But more recently a regiospecific *ortho* alkylation of aromatic amines has been developed.[9]

In 1978, a method was described<sup>[10]</sup> to convert N-pivalylanilines (13) into their *o*-lithio derivative by treatment with *n*-butyl lithium. The oxygen (or nitrogen) atom in the initially deprotonated species (13a) serves as a ligand for a second equivalent of lithiating agent, thus facilitating a regiospecific protophilic attack on the *o*-hydrogen (13b) and formation of the dilithio intermediate (13c) (see Scheme 1.1.5).

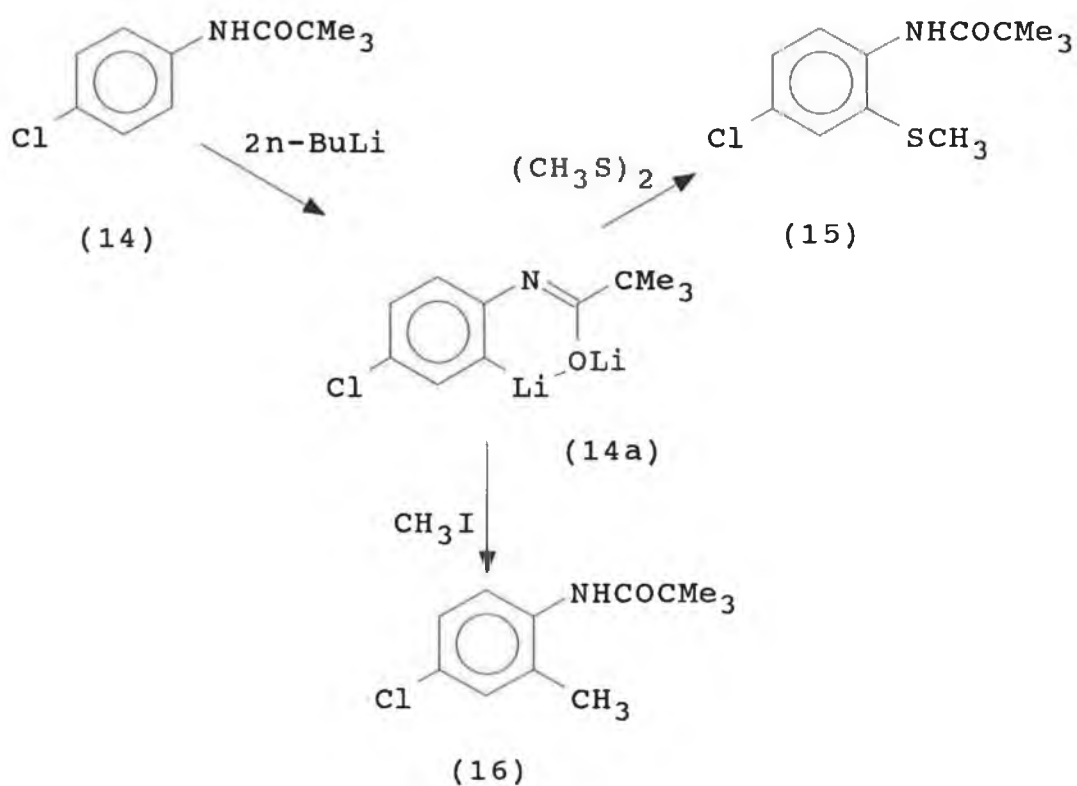


Scheme 1.1.5

It is evident that the nature of R has to be such that no deprotonation of the acyl group should occur. Since lithiation of benzanilide occurs exclusively in the position *ortho* to the carbonyl group, R cannot be aryl. Alkyl groups having a hydrogen  $\alpha$  to the carbonyl group have to be excluded as well, because of the acidic character of their  $\alpha$ -protons.

These lithiated species, in particular those derived from *p*-chloro-, *m*-methoxy-, and *o*-methylaniline, were reacted with a variety of electrophiles, for example dimethyl disulfide or methyl iodide, to give *ortho*-substituted derivatives in very good yield.<sup>[10]</sup>

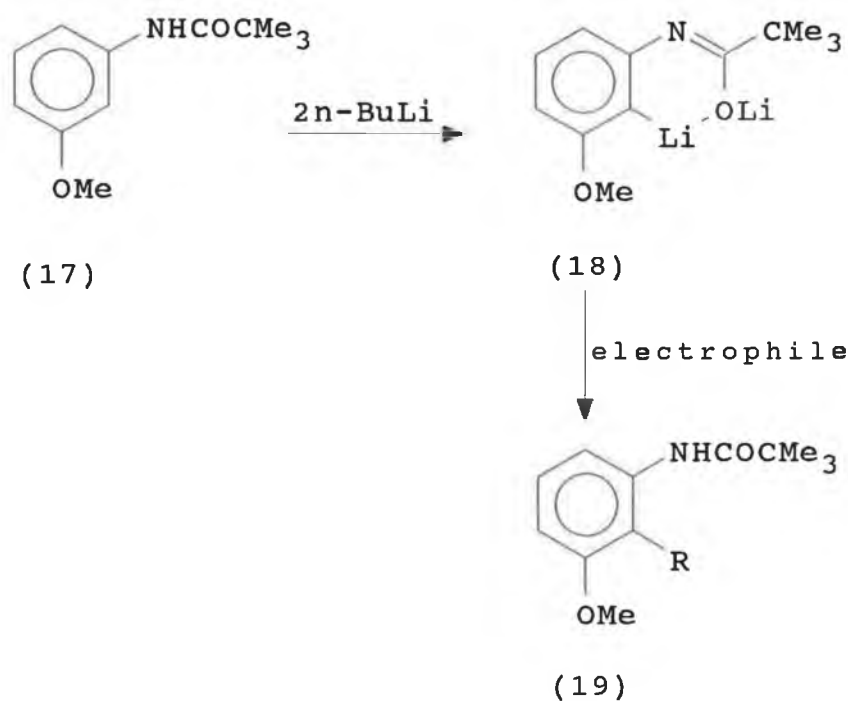
This may be illustrated<sup>[10]</sup> (see Scheme 1.1.6) by the lithiation of the 4-chloro derivative (14) with *n*-butyllithium in tetrahydrofuran at 0°C, as shown in Scheme 1.1.6. Reaction of the dilithio species (14a) with dimethyl disulfide results in an almost quantitative formation of the thioether (15) (93% by GC) which can be isolated in 79% yield by crystallization. Alkylation with 1 equiv of methyl iodide occurs selectively at the carbon-2 position, thus yielding the *o*-methyl derivative (16).



Scheme 1.1.6



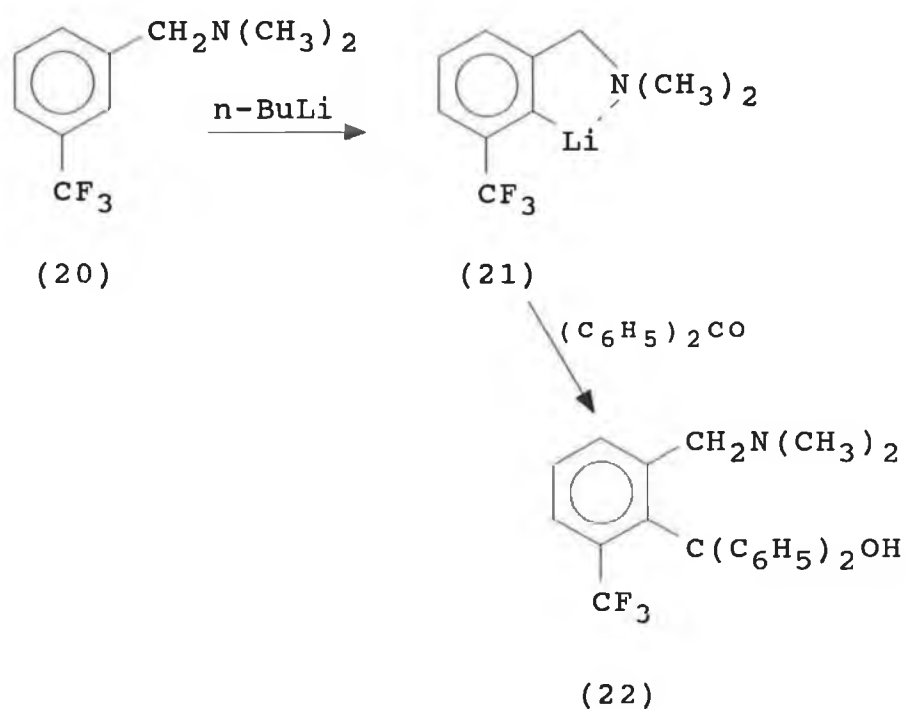
As a further example,<sup>[10]</sup> (see Scheme 1.1.7), N-pivaloyl-*m*-anisidine (17) can be functionalized regiospecifically in the 2-position of the ring to give (19). The pivalamido function is slightly superior to a methoxyl group as an *ortho* director.



Scheme 1.1.7

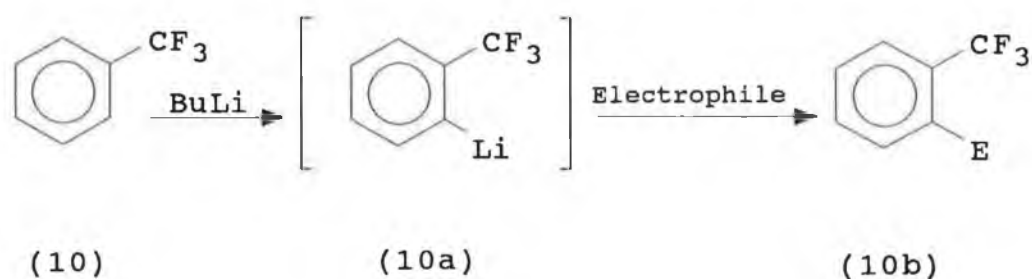
We have used directed *ortho* metalation of ring-substituted anilines as a key step for conversion of 3-trifluoromethylaniline (1) to 2-methyl-3-trifluoromethylaniline (2). We anticipated that 3-trifluoromethylaniline (1) could be lithiated in the 2-position via heteroatom-facilitated *ortho*-lithiation

of an appropriate acyl derivative, followed by metalation of the resulting aryllithium. The electron-withdrawing effect of the 3-trifluoromethyl group was expected to be advantageous to the introduction of a methyl group exclusively on carbon-2 position of ring. For example,<sup>[11]</sup> (see Scheme 1.1.8) when 3-trifluoromethyl-benzyl dimethyl-amine (20) was lithiated, the lithiation occurred preferentially at the position *ortho* to both the dimethylaminomethyl group and the ring substituent (21), and gave the compound (22) in a yield over 70%.



Scheme 1.1.8

The following substituent groups have been reported<sup>[12]</sup> to direct the lithium atom to the *ortho* position upon metalation with n-butyllithium: OMe, CF<sub>3</sub>, and F. For example, when trifluoromethylbenzene (10) was treated with n-butyllithium at 35°C in ether, exclusive metalation occurred at the position *ortho* to the substituent. (see Scheme 1.1.9).

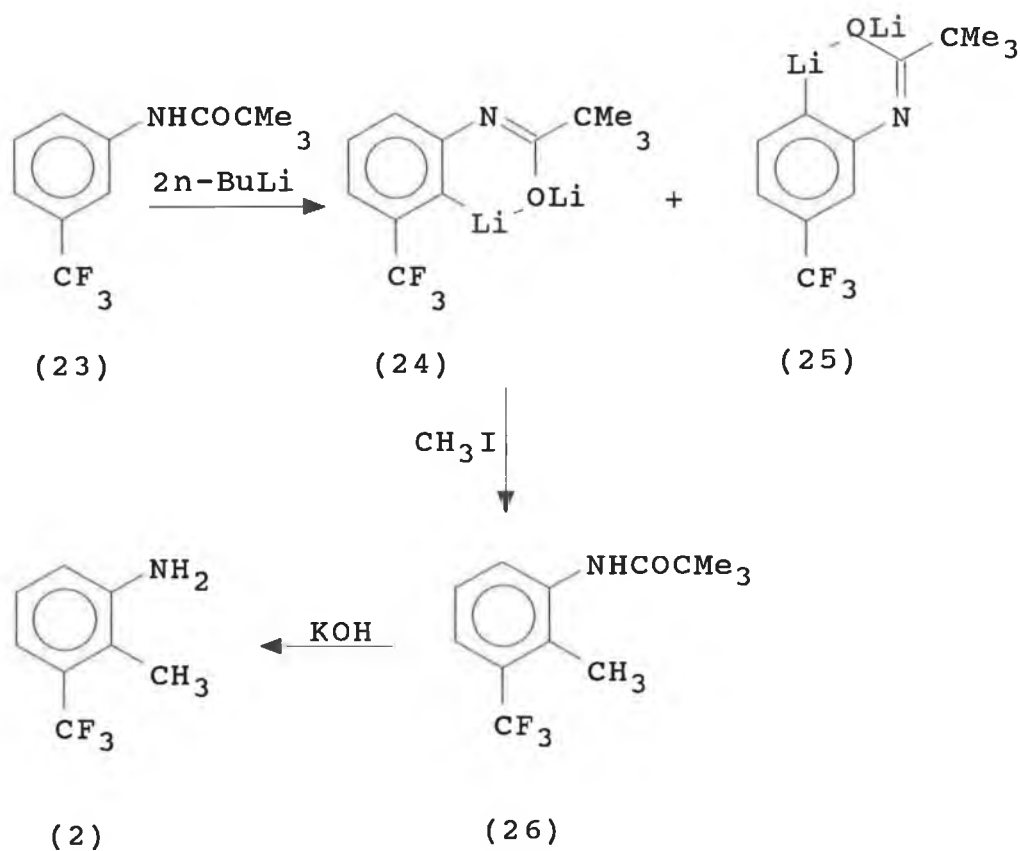


Scheme 1.1.9

Because electron-withdrawing groups greatly facilitate lithiation, presumably the relative ease of lithiation *ortho* to the acylamino group would parallel the anticipated relative acidities of the *ortho* hydrogens. In the metalation of 3-trifluoromethylaniline (1), lithiation of 3-trifluoromethylaniline (1) at carbon-2 rather than at carbon-6 might be expected since the electron-withdrawing effect of the trifluoromethyl group should considerably enhance the CH acidity at carbon-2 relative to that at carbon-6.

The proposed method for conversion of pivalylamino-3-trifluoromethylbenzene (23) to pivalylamino-2methyl-3-trifluoromethyl-

benzene (26) therefore is as shown in Scheme 1.1.10. Reaction of pivalylamino-3-trifluoromethylbenzene (23) with n-butyllithium might give conceivably two dilithiated isomers (24) and (25). However it would be anticipated that the major or single product would be (24), with lithiation being expected preferentially at the 2-position due to the electron-withdrawing effect of the 3-trifluoromethyl group. Subsequent methylation should then yield the required isomer (26) as the sole (or major) product.



Scheme 1.1.10

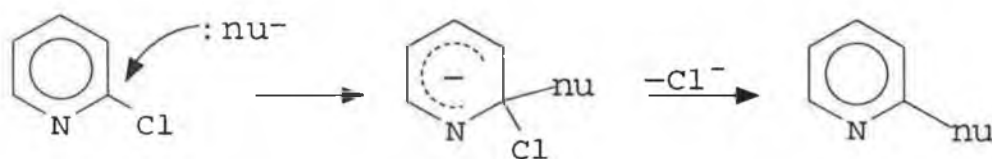
Finally the acyl group would be expected to be readily removed<sup>[13]</sup> by hydrolysis of pivalamino-2-methyl-3-trifluoromethylbenzene (26) to provide 2-methyl-3-trifluoromethylaniline (2).

## 1.2 Information of Regarding the Preparation of 2-(2-Methyl-3-trifluoromethyl-anilino)nicotinic Acid (4).

A second key problem in the synthesis of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) is the replacement of the 2-chloro group of 2-chloronicotinic acid (27) by the arylamino substituent.

2-Chloronicotinic acid (27) is a 2-chlorinated pyridine. Nucleophilic substitution takes place readily at the 2- and 4-positions of a pyridine ring particularly when substituted with an effective leaving group such as a chlorine atom.

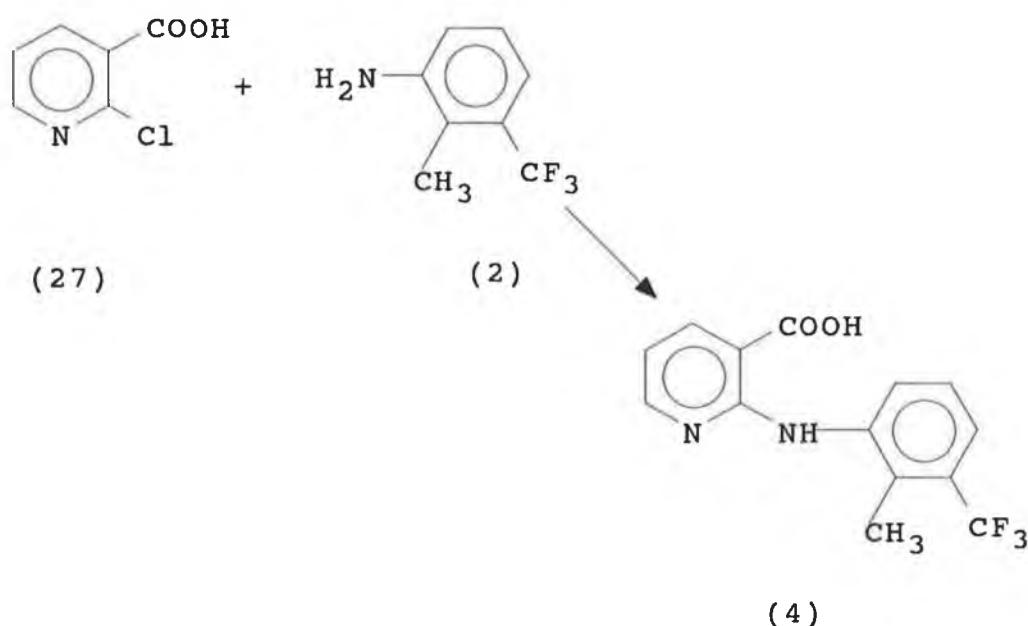
In nucleophilic substitution, the intermediate is negatively charged. The ability of the ring to accommodate the charge determines the stability of the intermediate and of the transition state leading to it, and hence determines the rate of the reaction. Nucleophilic attack at the 2-position yields a carbanion that is hybrid of structures.



Scheme 1.2.1

All the hybrid structures of the anionic intermediate are more stable than the corresponding ones for attack on a benzene derivative, because of electron withdrawal by the nitrogen atom. The structure is especially stable, since negative charge is located on the atom than can best accommodate it, the electronegative nitrogen atom. It is reasonable, therefore, that nucleophilic substitution occurs more rapidly on the pyridine ring than on the benzene ring, and more rapidly at the 2- and 4- positions than the 3-position.

Considering the effect of other substituents on the halogen, 2-chloronicotinic acid (27) contains a strongly electron-withdrawing group COOH. This would be expected to better activate the halogen located *ortho*-to it. (see Scheme 1.2.2)

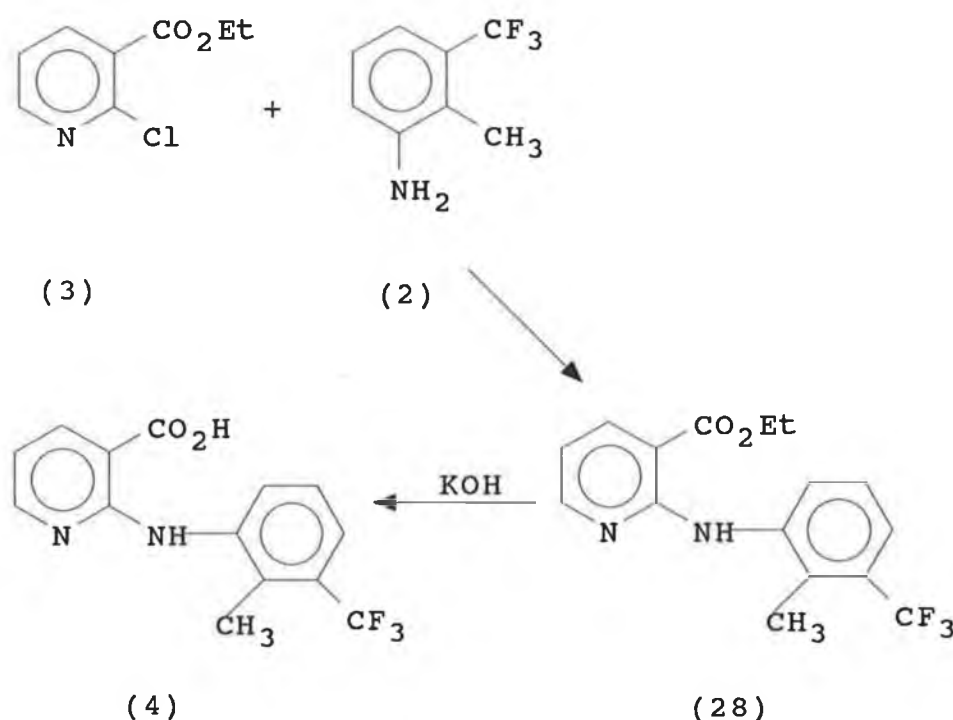


Scheme 1.2.2

2-Methyl-3-trifluoromethylaniline (2) is an aromatic amine and therefore a nucleophilic reagent. It should attack at the 2-position of 2-

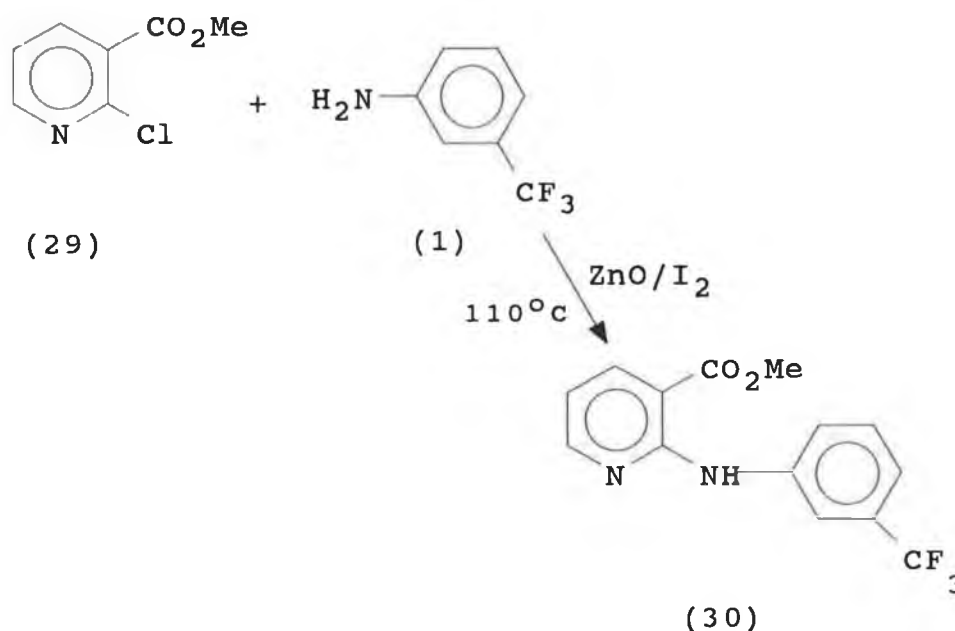
chloronicotinic acid (27) with formation of the required compound (4). This reaction and related ones have been reported in the literature and the aim was to develop a viable synthesis of (4) which could ultimately be scaled up for production purposes. High-yield reactions and mild reaction conditions would be required for this.

Synthesis of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) as an intermediate of anti-inflammatory agents had previously been reported. It had been prepared from ethyl 2-chloronicotinate (3) by reaction with 2-methyl-3-trifluoromethylaniline (2). This gave ethyl 2-(2-methyl-3-trifluoromethyl-anilino)nicotinate (28), which was then hydrolysed with potassium hydroxide to give 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4).<sup>[14]</sup> (see Scheme 1.2.3)



Scheme 1.2.3

An alternative process leading to methyl 2-(3-trifluoromethyl-anilino)nicotinate (30) involved reaction of methyl-2-chloronicotinate (29) with 3-trifluoromethylaniline (1) in xylene in the presence of zinc oxide and iodine at 110°C.[15] (see Scheme 1.2.4)

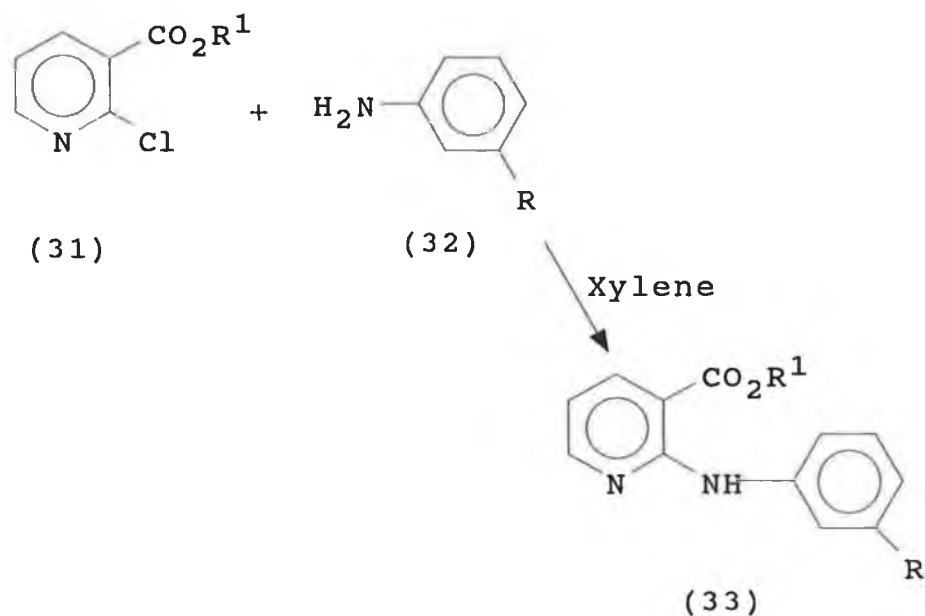


Scheme 1.2.4

Our interest was in attempting to develop an efficient single step synthesis of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) from 2-methyl-3-trifluoromethylaniline (2) using 2-chloronicotinic acid (27) rather than one of its esters. The prospect of success was supported by previously reported reactions in the literature.[16] [17] [18] [19] [20] and successfully modelled reactions which are also described.



Anilinonicotinic acid derivatives (33) were prepared [16] [17] [18] (see Scheme 1.2.5) by reaction of 2-chloronicotinic acid derivatives (31) with ring-substituted anilines (32) in xylene.

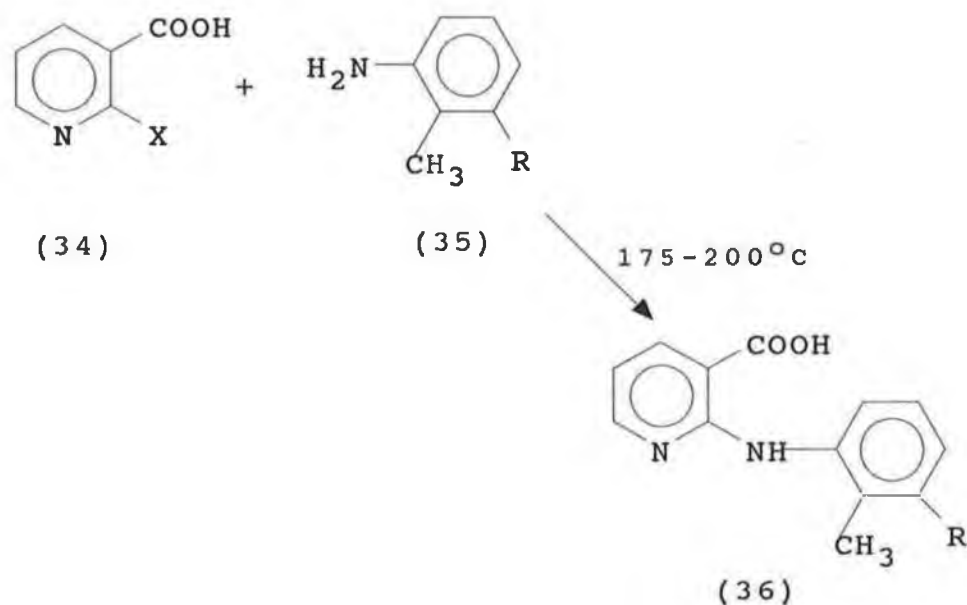


$R = \text{SCF}_3, \text{CF}_3, \text{Cl}, \text{CH}_3$

$R^1 = \text{H}, \text{Me}, \text{Ac}, \text{EtCO}.$

Scheme 1.2.5

Other reports[19] [20] of the synthesis of anilinonicotinic acids (36) as analgesic and antiinflammatory agents involved, for example, reaction of 2-substituted nicotinic acids (34) with ring-substituted anilines (35) at 175-200°C. (see Scheme 1.2.6)



$\text{X} = \text{Cl, OR, SR, SO}_3\text{R, NO}_2, \text{NH}_2, \text{or NHR}$

$\text{R} = \text{Cl or CF}_3$

Scheme 1.2.6

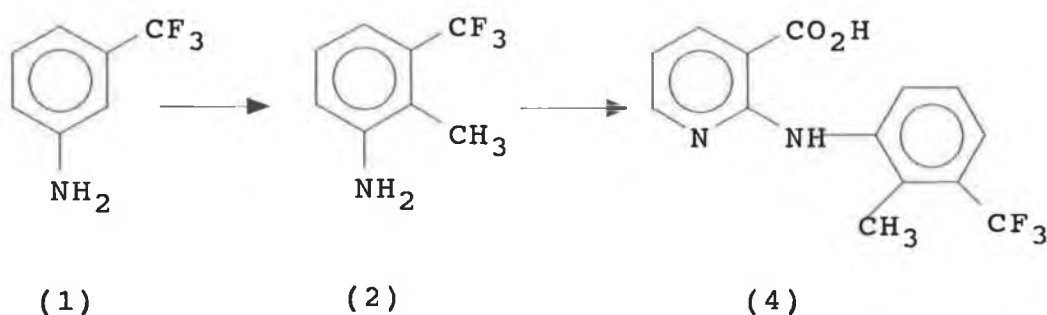
Finally, 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) would be treated with N-methyl-D-glucamine (5) to give the required N-methyl-D-glucamine salt (6) of 2-(2-methyl-3-trifluoromethyl-anilino)nicotinic acid (4). The literature reported that it was prepared by treatment of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) with N-methylglucamine and purified by recrystallisation.<sup>[1]</sup>

## **DISCUSSION**

### **Chapter 2. Successful Development of a Straightforward Synthesis of 2-Methyl-3-trifluoromethylaniline from Inexpensive 3-Trifluoromethylaniline.**

## 2.1 Introduction

The synthesis of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) is the main aim in this work. The proposed synthetic route is from inexpensive 3-trifluoromethylaniline (1), the formation of 2-methyl-3-trifluoromethylaniline (2) and ultimately 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4). (see Scheme 2.1.1)

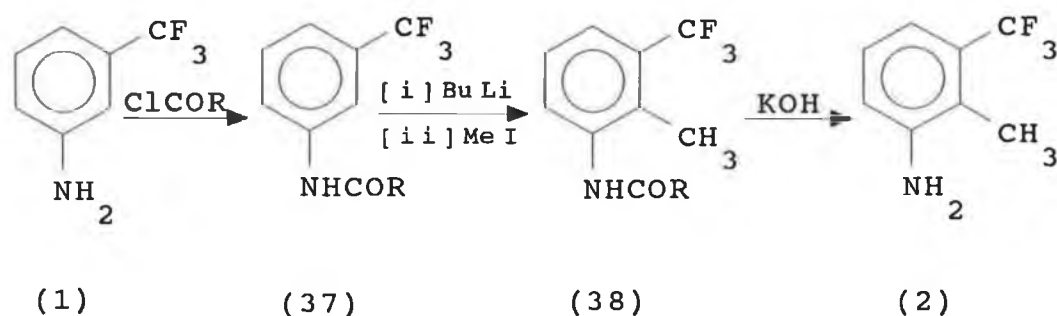


Scheme 2.1.1

As a theme to this chapter the synthesis and characterisation of 2-methyl-3-trifluoromethylaniline (2) and the intermediates in the step-wise reaction are reported and discussed.

It is convenient to divide the synthesis of (2) from (1) into two main steps. Step one is N-acylation, the acyl group being important in the subsequent step for *ortho* direction of methylation. Step two is the *ortho* direction of methylation of the N-acylaniline by regioselective *ortho*

alkylation of the aromatic amine. The facile and regioselective *ortho* lithiation of N-pivalylaniline, followed by methylation of the *o*-lithio derivative, is reported in this chapter, involving the application of the following reaction sequence (see Scheme 2.1.2).



Scheme 2.1.2

## 2.2 N-Acylation of 3-Trifluoromethylaniline (1).

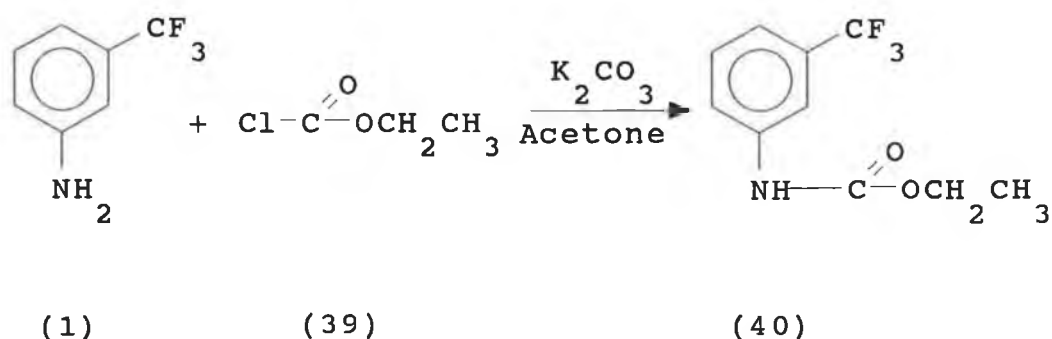
For the *ortho* metalation of aromatic amines a free aromatic amino group is ineffective, and the amino group is best protected by acylating it. As part of a search for synthetically useful aniline derivatives as *ortho*-directing group, we investigated the suitability of two acylated 3-trifluoromethylanilines.

In applying the reaction sequence of Scheme 2.1.2, it was evident that R can not be a simple alkyl group such as a methyl group because the presence of acidic carbon-hydrogen bond will lead to lithiation of the alkyl

group rather than aryl lithiation. Firstly ethyl chlorocarbonate was used as a protective reagent for the amino group, involving conversion of the  $\text{-NH}_2$  group to  $\text{-NHCO}_2\text{Et}$ . This was initially investigated because, while the amino group can be converted to  $\text{-NHCOCMe}_3$  by reaction with pivalylchloride, we were concerned that the tert butyl amide group, which is a much larger group, might affect the overall rate and yield of product, and there also might be difficulties in the removal of the bulky protecting group at a later stage.

### **2.2.1 N-carbethoxy-3-trifluoromethylaniline (40)**

Substituted aromatic amides are prepared by the Schotten-Baumann technique in which an acid chloride is added to an amine in the presence of a base.[21] [22] Ethylchlorocarbonate (39) was slowly added dropwise to 3-trifluoromethylaniline (1) at room temperature in acetone for 4hrs in the presence of potassium carbonate as base. N-Carbethoxy-3-trifluoromethylaniline (40), was obtained in 82% yield. (see Scheme 2.2.1).



Scheme 2.2.1

The product which was obtained from (1) was shown to be (40). The structure of product (40) was supported by its infrared spectrum which showed a very strong band at  $1698\text{ cm}^{-1}$ , ascribable to carbon-oxygen double bond stretching, and a very strong peak at  $1242\text{ cm}^{-1}$ , a carbon-oxygen-carbon stretch, as expected for the required product (40). The  $^1\text{H}$ -NMR spectrum of the product was also consistent with acylation having occurred. A three proton triplet ( $J=7\text{ Hz}$ ) at  $1.30\text{ ppm}$  and a two proton quartet ( $J=7\text{ Hz}$ ) at  $4.24\text{ ppm}$  were ascribable to the five ethyl protons of the carbethoxy group. Four aromatic proton absorptions were also present: a doublet ( $J=8\text{ Hz}$ ) at  $7.31$ , a triplet ( $J=8\text{ Hz}$ ) at  $7.39$ , a doublet ( $J=8\text{ Hz}$ ) at  $7.56\text{ ppm}$ , and a singlet at  $7.74\text{ ppm}$ , consistent with a 1,3-disubstituted aromatic ring. The amido proton absorption was at  $7.01\text{ ppm}$ . The  $^{13}\text{C}$ -NMR data for the product are listed, and the assignments made there are supported by the C-H correlations summarised in Table 2.1.

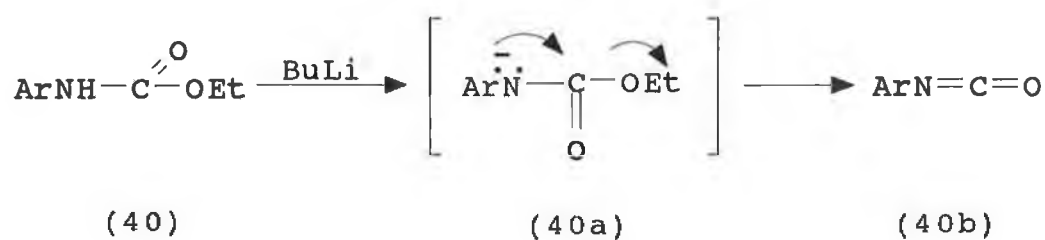
Table 2.1 The  $^{13}\text{C}$ -NMR data and C-H correlation couplings of N-carbethoxy-3-trifluoromethylaniline (40).

C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
1.30	14.48	positive	-Me
4.24	61.65	negative	-OCH <sub>2</sub> -
7.74	115.38	positive	-CH
7.31	119.90	positive	-CH
7.56	121.71	positive	-CH
	125.31	none	C
7.39	129.59	positive	-CH
	131.33*	none	CF <sub>3</sub>
	138.69	none	C
	153.63	none	C=O

\* multiplet due to carbon-fluorine coupling.

We used N-carbethoxy-3-trifluoromethylaniline (40) to continue to the next stage for the methylation. Attempted lithiation of (40), followed by methylation at room temperature gave an oil which was shown by TLC to be a mixture of four components. It seems probable that, when N-carbethoxy-3-trifluoromethylaniline (40) reacted with n-butyllithium to form the initial intermediate (40a), this intermediate was not stable but may have rapidly undergone an elimination with formation of (40b). (see Scheme 2.2.2)



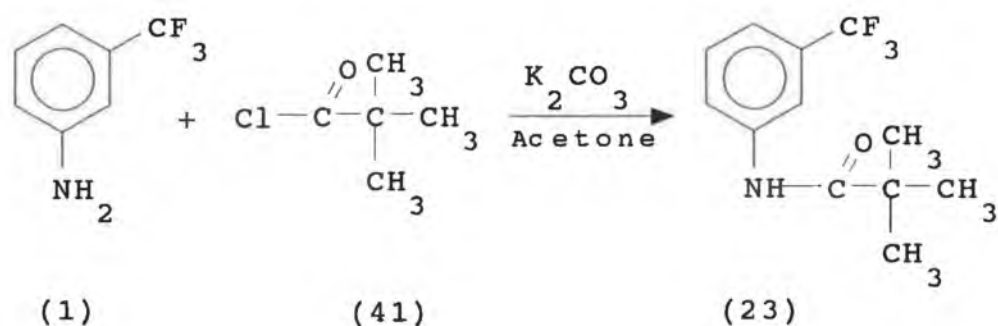


Scheme 2.2.2

The pivalyl residue ( $\text{R}=\text{C}_4\text{H}_9\text{-t}$ ), however, turned out to be ideal, and the desired reaction occurred readily and under relatively mild conditions.

### 2.2.2 Pivalylamino-3-trifluoromethylbenzene (23)

Pivalylchloride (41) was added at room temperature to 3-trifluoromethylaniline (1) and the reaction was completed under reflux for 4hrs, to give a very good yield (96%) of pivalylamino-3-trifluoromethylbenzene (23) (see Scheme 2.2.3).



Scheme 2.2.3

The structure of product (23) was supported by the infrared spectrum which showed peaks in the region 797 and 890  $\text{cm}^{-1}$ , indicating the three adjacent and one free aromatic hydrogen, respectively. The strong band at 1660  $\text{cm}^{-1}$  is the amide carbonyl stretch. In the  $^1\text{H}$ -NMR spectrum of (23), the nine proton singlet at 1.28 ppm is due to the nine protons of the tert-butyl group, consistent with acylation having occurred. A doublet ( $J=8$  Hz) at 7.33 ppm, a triplet ( $J=8$  Hz) at 7.40 ppm, a doublet ( $J=8$  Hz) at 7.68 ppm and a singlet at 7.88 ppm were assigned to the three adjacent and one free aromatic protons respectively, consistent with a 1,3-disubstituted aromatic ring. A singlet at 7.76 ppm was assigned to the proton of N-H group. The  $^{13}\text{C}$ -NMR spectrum of (23) is also clear and straightforward. The peaks at 27.25, and 39.50 ppm are ascribable to the carbons of the three methyls and the quaternary carbon of the tert-butyl group respectively. Those at 116.91, 120.52, 123.18, 125.96, 129.14, and 138.49 ppm are the six aromatic carbons. The multiplet at 131.20 ppm is the carbon of the  $\text{CF}_3$  group, and at 177.15 ppm is the carbon of carbonyl group. The infrared spectrum, the  $^1\text{H}$ -

NMR, and  $^{13}\text{C}$ -NMR spectrum are all consistent with amide (23) having been formed.

The  $^{13}\text{C}$ -NMR data are listed, and the assignments made there are supported by the C-H correlations summarised in Table 2.2.

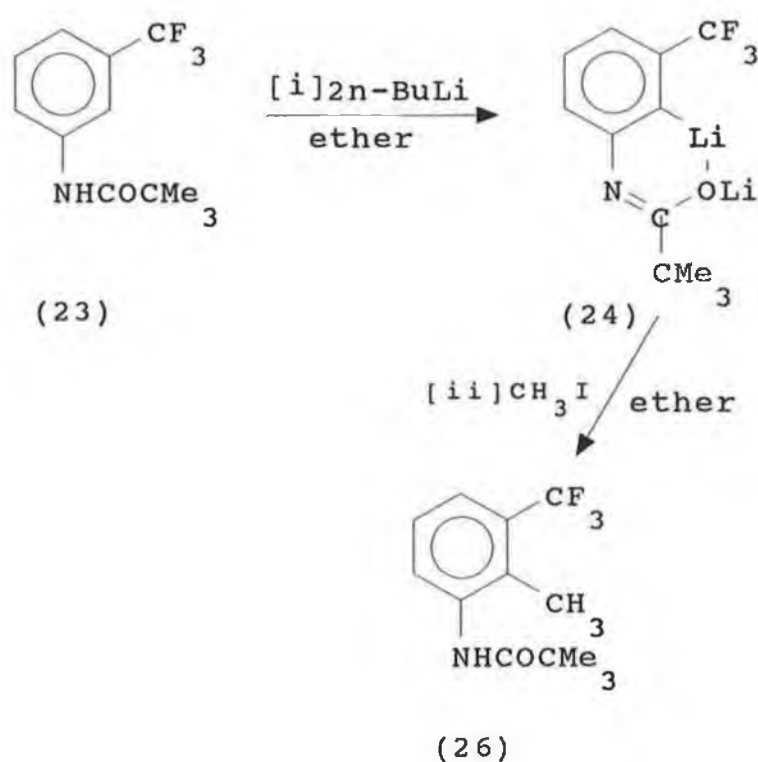
Table 2.2 The  $^{13}\text{C}$ -NMR spectrum and the C-H correlation of pivalamino-3-trifluoromethylbenzene (23)

C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
1.28	27.25	positive	-Me
	39.50	none	C
7.88	116.91	positive	-CH
7.33	120.52	positive	-CH
7.68	123.18	positive	-CH
	125.96	none	C
7.40	129.14	positive	-CH
	131.20*	none	$\text{CF}_3$
	138.49	none	C
	177.15	none	C=O

\*multiplet due to carbon-fluorine coupling.

### 2.3 Ortho Direction of Lithiation of N-pivaloylaniline.

Conversion of pivalylamino-3-trifluoromethylbenzene (23) into pivalylamino-2-methyl-3-trifluoromethylaniline (26) involves the introduction of a methyl group by an electrophilic substitution reaction on the aromatic ring (see Scheme 2.3.1).



Scheme 2.3.1

Pivalylamino-3-trifluoromethylbenzene (23) was treated with n-butyl lithium (2.5 equivalents) in dry diethyl ether at room temperature for 3hrs. Methyl iodide (1.5 equivalents) was then added and workup of the reaction mixture after a 2hrs methylation period yielded product. The crude methylated product included about 15% of the 6-methyl substituted product as indicated by examination of the aryl-CH<sub>3</sub> region of the NMR spectrum of the product, indicating that electronic effects predominated over steric effects, as had been anticipated. Pure pivalylamino-2-methyl-3-trifluoromethylbenzene (26) can be obtained in 72% yield after recrystallization (see Scheme 2.3.1). Some variation of reaction periods and of ratios of reactants was investigated but those reported seemed optimal.

The <sup>1</sup>H-NMR and the <sup>13</sup>C-NMR spectrum of the product (26) were consistent with methylation having occurred at carbon-2 on the ring. In the <sup>1</sup>H-NMR spectrum of (26) a singlet at 2.28 ppm is due to the methyl group and the tert-butyl group protons give rise to a singlet at 1.28 ppm. A triplet at 7.35 (J=8 Hz), a doublet at 7.48 (J=8 Hz), and a doublet at 7.90 ppm (J=8 Hz) are ascribable to the three adjacent aromatic protons, and the amide proton was at 7.35 ppm. If methylation had occurred at the 4-position or the 6-position, the aromatic proton pattern would have been expected to be two doublets (J=8 Hz approx.) and a singlet.

The <sup>13</sup>C-NMR data for the product (26) are consistent with the assigned structure (26) and the assignments made there are supported by the C-H correlations summarised in Table 2.3.

Table 2.3 The  $^{13}\text{C}$ -NMR spectrum and the C-H correlation of pivalylamino-2-methyl-3-trifluoromethylbenzene (26)

C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
2.28	13.28	positive	Me
1.28	27.60	positive	$\text{Me}_3$
	39.60	none	C- $\text{Me}_3$
	120.30	none	C
7.48	122.83	positive	-CH
	125.70	none	C
7.35	126.01	positive	-CH
7.90	127.94	positive	-CH
	129.60*	none	$\text{CF}_3$
	137.20	none	C
	177.10	none	C=O

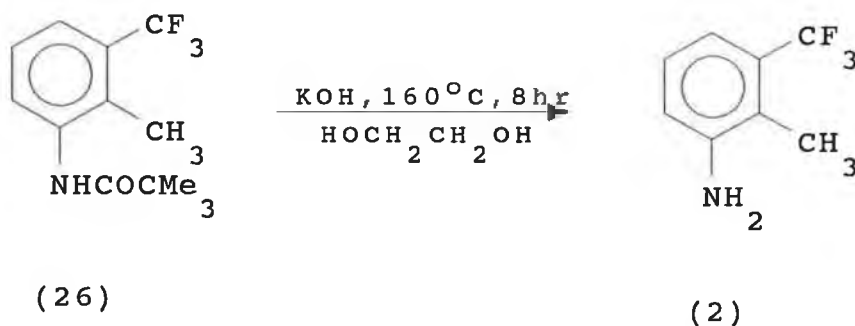
\*multiplet due to carbon-fluorine coupling.

The use of cheaper alternatives to methyl iodide (e.g. dimethyl sulphate and methyl-p-toluenesulphonate) was investigated though without any success. We have not investigated the use of methyl bromide because of its high volatility.

## 2.4 Conversion of Pivalylamino-2-methyl-3-trifluoromethylbenzene (26) to 2-Methyl-3-trifluoromethylaniline (2).

Removal of the pivalyl protecting group was achieved by alkaline hydrolysis. Initially potassium hydroxide in ethanol was used. However, even after a long reflux time of 24hrs a poor yield (44%) of the required 2-methyl-3-trifluoromethylaniline (2) was obtained. It was found that with ethylene glycol as solvent, the reaction could be carried out at 160°C using potassium hydroxide as base. This resulted in a shorter reaction time of 8hrs and a much better yield (93%) of 2-methyl-3-trifluoromethylaniline (2) (see Scheme 2.4.1).

In attempting to achieve a shorter reaction time, it was observed that the use of temperatures above 160°C leads to some carbonization. TLC was used to follow the reaction and it was observed that for reaction times less than 8hrs the reaction was not complete.



Scheme 2.4.1

The IR spectrum of product (2) showed the absence of the amide carbonyl group stretch at  $1660\text{cm}^{-1}$ , present in (26), as expected for the required product (2). The  $^1\text{H}$ -NMR spectrum of product (2) was also consistent with hydrolysis having occurred. There were no tert-butyl protons present. A three proton singlet at 2.22 ppm was ascribable to the methyl group, a doublet of doublets ( $J=7$  and 2 Hz) at 6.84 ppm, and a two proton multiplet at 7.08 ppm are consistent with structure (2) and arise from the three adjacent protons on a 1,2,3 trisubstituted aromatic ring. The  $^{13}\text{C}$ -NMR spectrum of the product (2) also showed the absence of the tert-butyl carbons at 27.6 and 39.6ppm, and the carbonyl carbon at 177.1ppm, present in the structure (26). The  $^{13}\text{C}$ -NMR data and the assignments made there are supported by the C-H correlations summarised in Table 2.4.

Table 2.4 The  $^{13}\text{C}$ -NMR spectrum and the C-H correlation of 2-methyl-3-trifluoromethylaniline (2).

C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-45	carbons
2.22	12.97	positive	Me
7.08	116.06	positive	-CH
6.84	118.34	positive	-CH
	120.20	none	C
	123.35	none	C
7.08	126.29	positive	-CH
	129.50*	none	$\text{CF}_3$
	145.80	none	C-N

\*multiplet due to carbon-fluorine coupling.



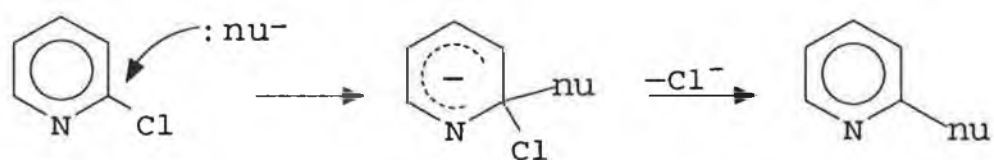
**Chapter 3. Attempted One-step Synthesis of 2-(2-Methyl-3-trifluoromethylanilino)nicotinic Acid from 2-Methyl-3-trifluoromethylaniline and 2-Chloronicotinic Acid.**

### 3.1 Background.

In this chapter, attempts at an efficient single step synthesis of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) from 2-methyl-3-trifluoromethylaniline (2) and 2-chloronicotinic acid (27) are reported. The prospect of success was supported by previously reported reactions in the literature and successfully modelled reactions which are also described.

2-Chloronicotinic acid (27) is a 2-chlorinated pyridine. Nucleophilic substitution takes place readily at the 2- and 4-positions of a pyridine ring particularly when substituted with an effective leaving group such as a chlorine.

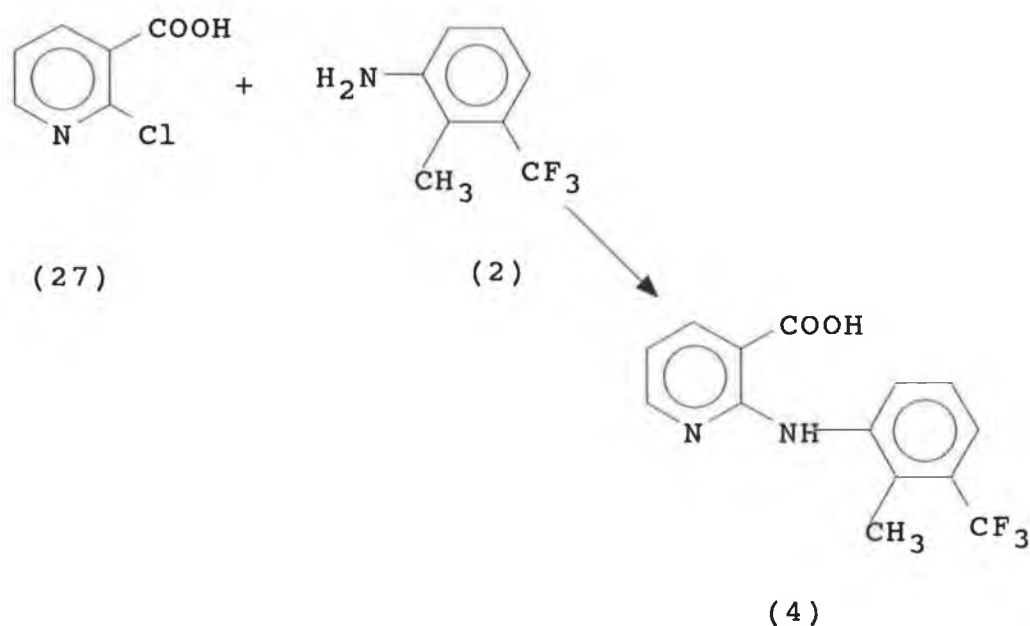
In nucleophilic substitution, the intermediate is negatively charged. The ability of the ring to accommodate the charge determines the stability of the intermediate and of the transition state leading to it, and hence determines the rate of the reaction. Nucleophilic attack at the 2-position yields a carbanion that is hybrid of structures. (see Scheme 3.1.1)



Scheme 3.1.1

All the hybrid structures of the anionic intermediate are more stable than the corresponding ones for attack on a benzene derivative, because of electron withdrawal by the nitrogen atom. The structure is especially stable, since negative charge is located on the atom that can best accommodate it, the electronegative nitrogen atom. It is reasonable, therefore, that nucleophilic substitution occurs more rapidly on the pyridine ring than on the benzene ring, and more rapidly at the 2- and 4- positions than the 3-position.

Considering the effect of other substituents on the halogen, 2-chloronicotinic acid (27) contains a strongly electron-withdrawing group -COOH. This would be expected to better activate the halogen located *ortho*-to it (see Scheme 3.1.2).



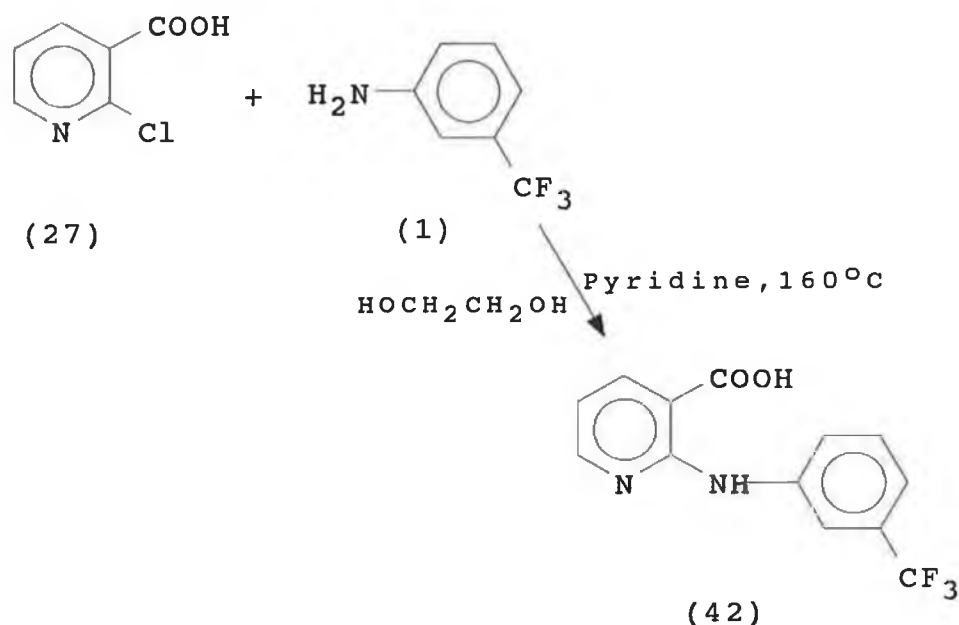
Scheme 3.1.2

2-Methyl-3-trifluoromethylaniline (2) is an aromatic amine and therefore a nucleophilic reagent. It should attack at the 2-position of 2-chloronicotinic acid (27) with formation of the required compound (4). This reaction and related ones have been reported<sup>[1] [14]</sup> in the literature and the aim was to develop a viable synthesis of (4) which could ultimately be scaled up for production purposes. High-yield reactions and mild reaction conditions would be required for this.

Attempts at an efficient single step synthesis of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) from 2-methyl-3-trifluoromethylaniline (2) and 2-chloronicotinic acid (27) are reported. The prospect of success was supported by previously reported reactions in the literature<sup>[16] [17] [18] [19] [20]</sup> and successfully modelled reactions which are also described. The properties of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) are reported in the literature.<sup>[23] [24] [25] [26]</sup>

### **3.2 Model Reactions.**

First, a model reaction between 3-aminobenzotrifluoride (1) and the readily available 2-chloronicotinic acid (27) was investigated. Reaction between these two components under nitrogen using an equimolar ratio at 160°C in ethylene glycol for 5hrs in the presence of pyridine as an organic base, gave the anticipated product, 2-(3-trifluoromethyl-anilino)nicotinic acid (42), in modest yields (43%). The product (42) obtained had a melting point identical to that reported in the literature<sup>[27]</sup>. Its spectra were also consistent with this structure (see Scheme 3.2.1).



Scheme 3.2.1

Another method was tried using 3-aminobenzotrifluoride (1) with 2-chloronicotinic acid (27) in equimolar ratios in the presence of pyridine as an organic base at 160°C in xylene for 5hrs. This method also gave product (42), but in lower yield (28%), identical with that obtained in ethylene glycol as solvent. Reaction between compounds (1) and (27) under reflux in ethylene glycol (bp: 194-199°C) led to carbonization of the reaction mixture.

The elemental microanalysis is consistent with the molecular formula of product (42) (C<sub>13</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub>). The nuclear magnetic resonance spectra of product (42) were also consistent with the nucleophilic substitution having occurred. The <sup>1</sup>H-NMR spectrum of product (42) shows a doublet of doublets (J=8 and 4 Hz) at 6.83, a doublet of doublets (J=8 and 2 Hz) at 8.26, and a doublet of doublets (J=4 and 2 Hz) at 8.37 ppm, which are the

three pyridyl protons of (42). A doublet ( $J=8$  Hz) at 7.20, a triplet ( $J=8$  Hz) at 7.41, a doublet ( $J=8$  Hz) at 7.79, and a singlet at 8.29 ppm are the four benzenoid protons of (42). A singlet at 10.52 ppm is ascribable to the amino proton. The  $^{13}\text{C}$ -NMR and DEPT-135 data for the product are listed, and the assignments made there are supported by the C-H correlations summarised in Table 3.1.

Table 3.1 the  $^{13}\text{C}$ -NMR and DEPT-135 spectrum and C-H correlations of 2-(3-trifluoromethylanilino)nicotinic acid (42).

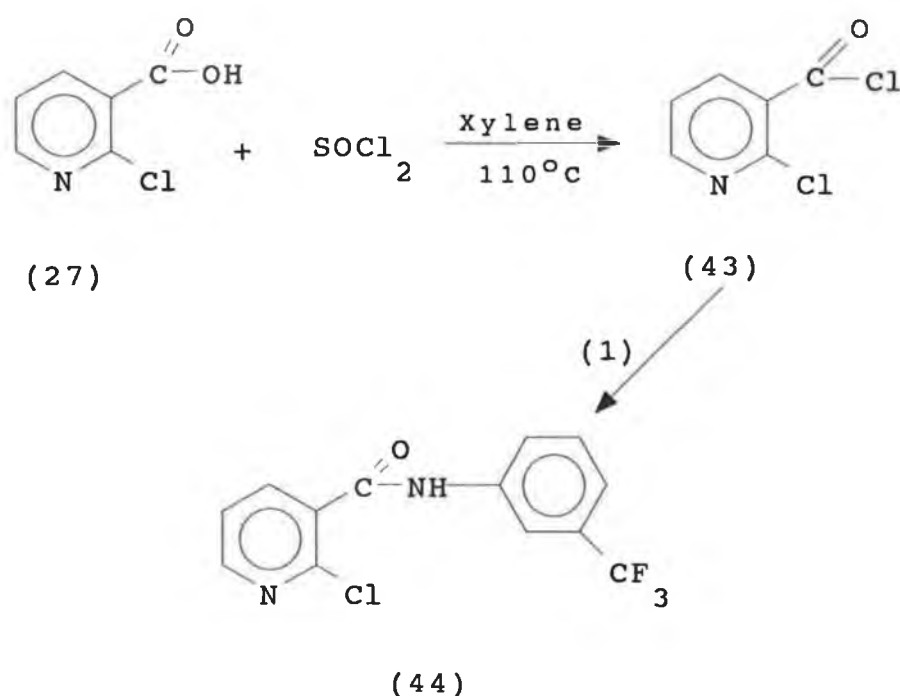
C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
	107.87	none	C
6.83	114.62	positive	-CH P
8.29	116.15	positive	-CH A
7.20	118.38	positive	-CH A
7.79	123.34	positive	-CH A
	125.99	none	C
7.41	129.65	positive	-CH A
	130.70*	none	$\text{CF}_3$
8.26	140.85	positive	-CH P
	141.18	none	C
8.37	152.96	positive	-CH P
	155.03	none	C
	168.87	none	C=O

\*multiplet due to carbon-fluorine coupling.

A: derived from 3-trifluoromethylaniline (1).

P: derived from 2-chloronicotinic acid (27).

The amide (44) was made from (27) via its acid chloride for comparison purpose (see Scheme 3.2.2). The acid chloride (43) was made by reaction of (27) with thionyl chloride. This was then reacted with trifluoromethylaniline (1). The product N-(3-trifluoromethyl)phenyl-2-chloronicotinamide (44) had different spectra and different melting point (112-114°C) those of compound (42).



Scheme 3.2.2

The IR spectrum of product (44) shows two strong bands in the 1672-1582 cm<sup>-1</sup> region, which were the carbonyl double bond stretching and the nitrogen-hydrogen bending in the amide.

The structure of product (44) was supported by its molecular formula. The  $^1\text{H}$ -NMR spectrum of product (44) showed a doublet ( $J=8$  Hz) at 7.52, a triplet ( $J=8$  Hz) at 7.65, a doublet ( $J=8$  Hz) at 7.98, and a singlet at 8.30 ppm, ascribable to the four benzenoid protons of (44). A doublet of doublets ( $J=7.5$  and 5 Hz) at 7.57, a doublet of doublets ( $J=7.5$  and 2 Hz) at 8.12, and a doublet of doublets ( $J=5$  and 2 Hz) at 8.53 ppm are the pyridyl protons of (44). At 10.10 ppm is the amide proton. The  $^{13}\text{C}$ -NMR and DEPT-135 data for product (44) are listed, and the assignments made there are supported by the C-H correlations summarised in Table 3.2.

Table 3.2.  $^{13}\text{C}$ -NMR and DEPT-135 spectrum and C-H correlations of N-(3-trifluoromethyl)phenyl-2-chloronicotinamide (44).

C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
8.30	115.92	positive	-CH A
	117.41	none	C
7.52	120.50	positive	-CH A
7.57	122.79	positive	-CH P
7.98	122.93	positive	-CH A
	125.59	none	C
7.65	129.87	positive	-CH A
	132.36*	none	$\text{CF}_3$
8.12	137.92	positive	-CH P
	139.09	none	C
	147.13	none	C
8.53	150.66	positive	-CH P
	164.23	none	$\text{C}=\text{O}$

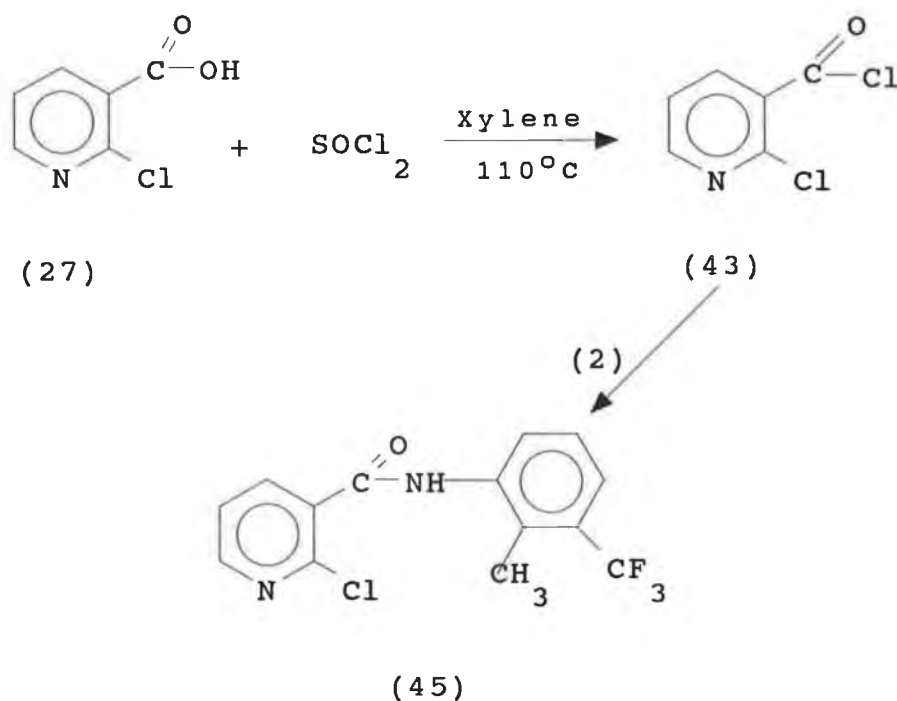
\*multiplet due to carbon-fluorine coupling.

A: derived from 3-trifluoromethylaniline (1).

P: derived from 2-chloronicotinic acid (27).



2-Methyl-3-trifluoromethylaniline (2) was also reacted with the acid chloride of 2-chloronicotinic acid (27) to give N-(2-methyl-3-trifluoromethyl)phenyl-2-chloronicotinamide (45) for later comparison with the required nicotinic acid derivative (4) (see Scheme 3.2.3).



Scheme 3.2.3

The infrared spectrum of product (45) showed at  $1662\text{ cm}^{-1}$  a strong band which is the carbonyl double bond stretching in the amide.

The structure of product (45), confirmed by its molecular formula, was supported by its nuclear magnetic resonance spectra. The  $^1\text{H}$ -NMR spectrum showed a three proton singlet at 2.55 ppm due to the methyl group

protons. A triplet ( $J=8$  Hz) at 7.34, a doublet ( $J=8$  Hz) at 7.50, and a doublet ( $J=8$  Hz) at 7.82 ppm are ascribable to the three benzenoid protons of (45). A doublet of doublets ( $J= 6$  and  $3$  Hz) at 7.41, a doublet of doublets ( $J= 8$  and  $6$  Hz) at 8.01, and a doublet of doublets ( $J= 8$  and  $3$  Hz) at 8.38 ppm are due to the pyridyl proton of (45) . The singlet at 9.4 ppm is amide proton. The  $^{13}\text{C}$ -NMR and DEPT-135 data for the product are listed, and the assignments made there are supported by the C-H correlations summarised in Table 3.3.

Table 3.3 the  $^{13}\text{C}$ -NMR and DEPT-135 spectrum and C-H correlation of N-(2-methyl-3-trifluoromethyl)phenyl-2-chloronicotinamide (45).

C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
2.55	13.57	positive	Me
	117.43	none	C
7.41 (or 7.50)	123.10	positive	-CH P
7.50 (or 7.41)	123.69	positive	-CH A
7.34	126.52	positive	-CH A
	129.23*	none	$\text{CF}_3$
7.82	129.82	positive	-CH A
	131.88	none	C
	132.60	none	C
	137.07	none	C
8.01	138.31	positive	-CH P
	147.08	none	C
8.38	150.82	positive	-CH P
	164.52	none	C=O

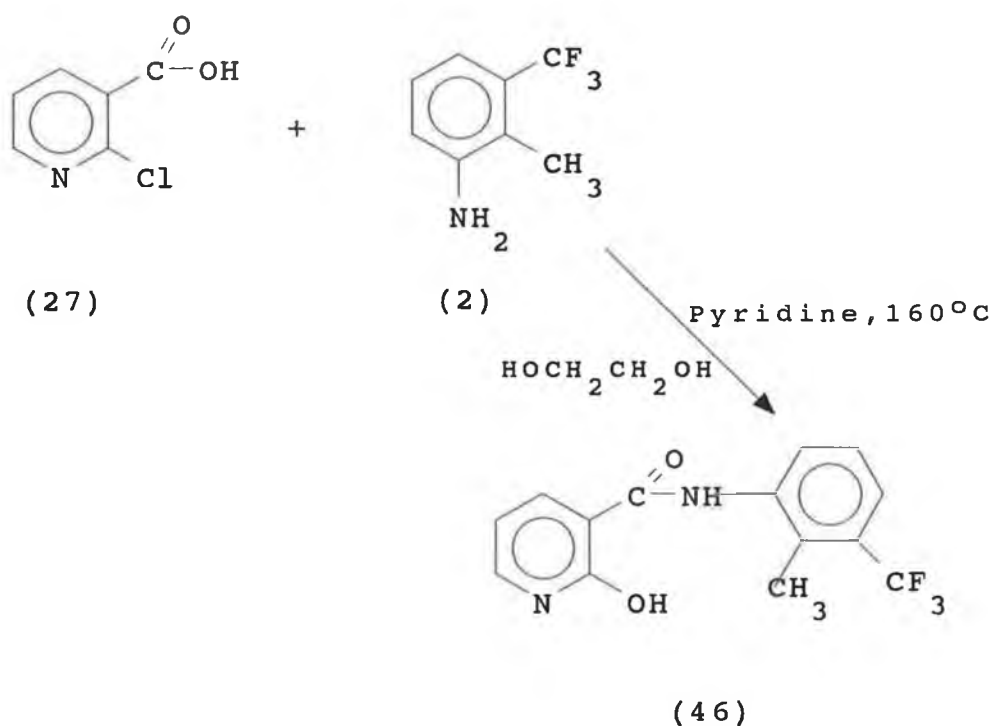
\*multiplet due to carbon-fluorine coupling.

A: derived from 2-methyl-3-trifluoromethylaniline (2).

P: derived from 2-chloronicotinic acid (27).

### 3.3 Reaction of 2-Chloronicotinic Acid (27) with 2-Methyl-3-trifluoromethylaniline (2)

When 2-chloronicotinic acid (27) and 2-methyl-3-trifluoromethylaniline (2) were heated together for 5hrs in an equimolar ratio at 160°C in ethylene glycol in the presence of pyridine, a pale pink crystalline material was obtained, yield about 21%. This compound, eventually assigned structure (46), had a melting point of 316°C, which was quite different from that of the required 2-(2-methyl-3-trifluoromethyl-anilino)nicotinic acid (4) (literature melting point: 225-228°C)<sup>[14]</sup>. This was in marked contrast to the closely related non-methylated compound 3-trifluoromethylaniline (1) which did react as expected with 2-chloronicotinic acid (27) to give the anticipated 2-(3-trifluoromethyl-anilino)nicotinic acid (42) under identical conditions (see Scheme 3.2.1). Mass spectrometry and elemental analysis showed that this compound was an isomer of the required 2-(2-methyl-3-trifluoromethyl-anilino)nicotinic acid (4). Its spectra are consistent with its assignment as N-(2-methyl-3-trifluoromethyl)phenyl-2-hydroxynicotinamide (46). (see Scheme 3.3.1).



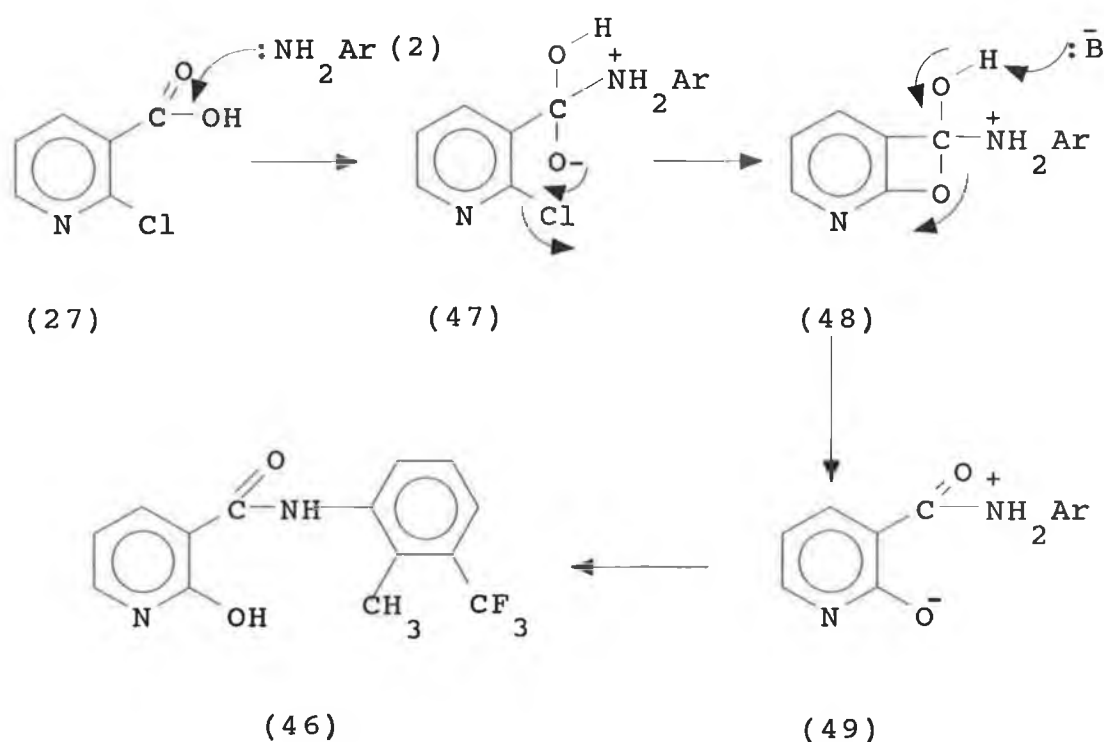
Scheme 3.3.1

The structure of the product (46) was indicated by its infrared spectrum which shows a hydroxyl stretch as a broad band in the 3419-3077  $\text{cm}^{-1}$  region, in addition to a strong carbonyl absorption at 1700  $\text{cm}^{-1}$ .

The nuclear magnetic resonance spectrum was also consistent with the suggested structure (46), an isomer of (4). The  $^1\text{H}$ -NMR spectrum of the product (46) gives the methyl protons as a singlet at 2.48 ppm. A triplet ( $J=7$  Hz) at 7.40, a doublet ( $J=7$  Hz) at 7.41, and a doublet ( $J=7$  Hz) at 8.41 ppm are ascribable to the three benzenoid protons of (46). A triplet ( $J=7$  Hz) at 6.57, a doublet of doublets ( $J=7$  and 2 Hz) at 7.76, and a doublet of doublets ( $J=7$  and 2 Hz) at 8.49 ppm are due to the three pyridyl protons of (46). These assignments were supported by the COSY spectrum of (46). A singlet

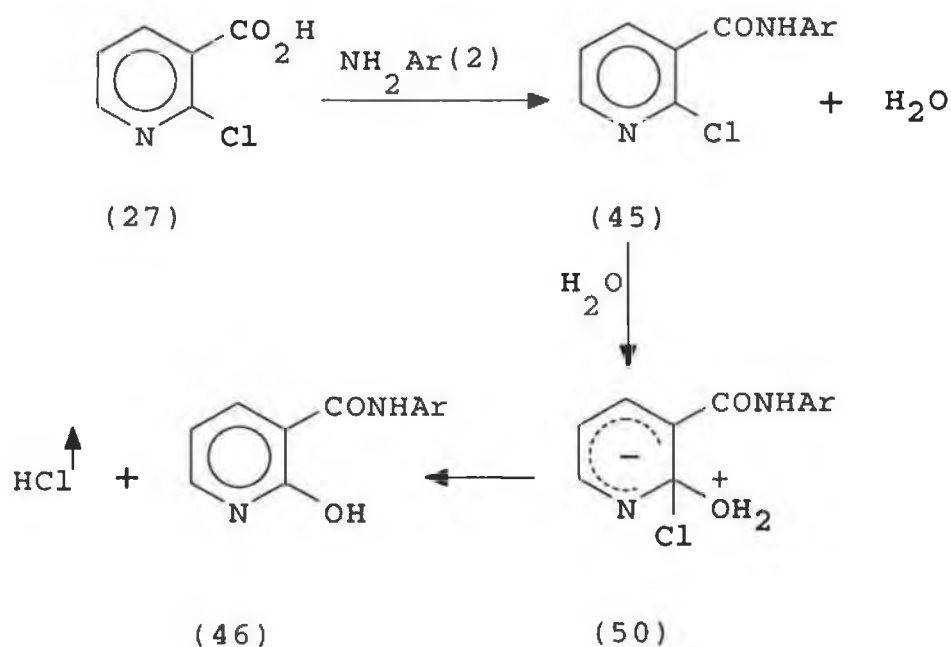
at 12.10 ppm is due to the amide group, and a broad singlet at 3.00 ppm due to the hydroxyl.

Knowing the structure of (46), we can propose a mechanism for the reaction. One possibility is outlined in Scheme 3.3.2, involving the amine (2), as a nucleophile, attacking the carboxyl group of (27) to form the intermediate (47). Attack by the alkoxide group of (47) on the neighboring 2-position carbon may result in the -Cl, as a leaving group, being lost, with formation of a cyclic intermediate (48). Subsequent ring-opening of (48), with cleavage of the carbon-oxygen bond, would form intermediate (49), product (46) being then formed by transfer of the proton from the amide group to the oxygen now present at carbon-2.



Scheme 3.3.2

An alternative possibility (see Scheme 3.3.3) is that formation of (46) occurs by a bimolecular displacement mechanism involving reaction of water, formed during an amide forming step, with amide (45) to form a carbanion intermediate (50). The expulsion of chloride ion from the carbanion would then yield the product (46).



Scheme 3.3.3

**Chapter 4. Development of a More Efficient Synthetic Route  
from 2-Chloronicotinic Acid to 2-(2-Methyl-3-  
trifluoromethylanilino)nicotinic Acid.**

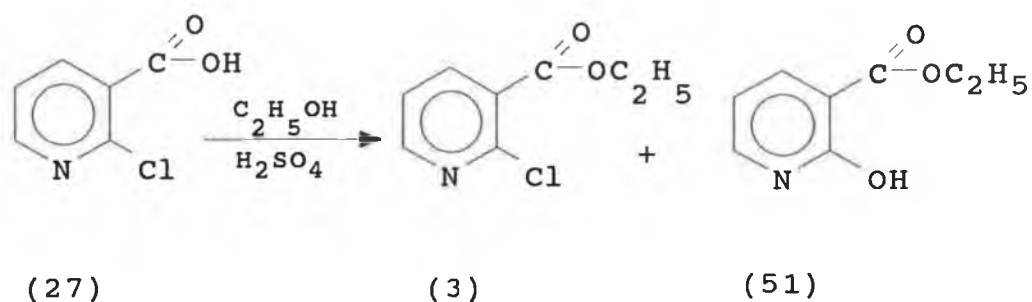
## 4.1 Background.

In the previous chapter, compound (46), an isomer of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4), was reported to be the product actually isolated as a result of attempted one-step synthesis of 2-(2-methyl-3-trifluoromethyl-anilino)nicotinic acid (4) from 2-methyl-3-trifluoromethylaniline (4) and 2-chloronicotinic acid (27). In this chapter the use of the methyl ester of the 2-chloronicotinic acid (27) to synthesise 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) is investigated.

## 4.2 Esterification of 2-Chloronicotinic Acid (27).

Previous work in an industrial laboratory, involving the reaction of (27) with ethanol in the presence of sulfuric acid, yielded ethyl ester (3). However, in addition to the required ethyl ester (3), a side-product ethyl 2-hydroxynicotinate (51) was produced. This could not be efficiently separated from (3)<sup>[15] [28]</sup> (see Scheme 4.2.1).

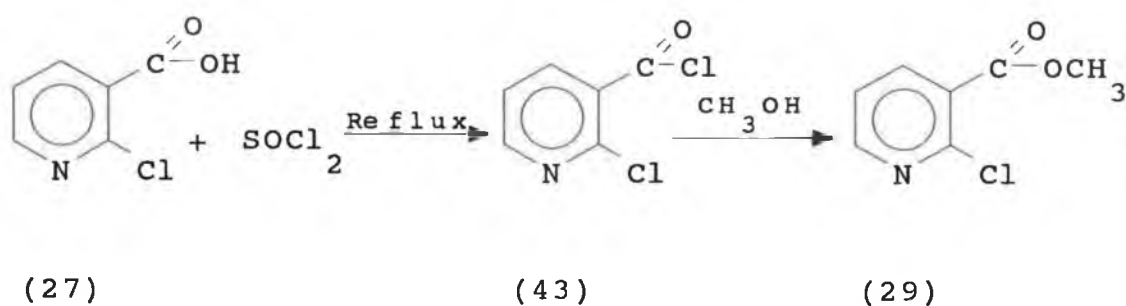




Scheme 4.2.1

We have now reinvestigated the esterification of 2-chloronicotinic acid (27) and have been able to carry out the esterification step to yield product which is free of this impurity.

2-Chloronicotinic acid (27) in thionyl chloride was heated under reflux until a clear solution was obtained. Then the mixture was reacted with methanol at room temperature for 30 minutes to yield high purity methyl 2-chloronicotinate (29). (see Scheme 4.2.2).



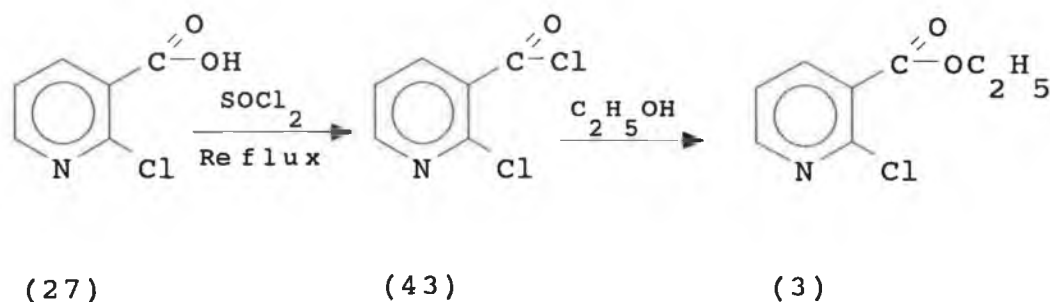
Scheme 4.2.2

The IR spectrum of the product (29) showed the carbon-hydrogen bond stretching of the O-methyl group as a sharp band at 2846  $\text{cm}^{-1}$ , the strong carbonyl stretch at 1740  $\text{cm}^{-1}$ , and a very strong broad band at 1277-1248  $\text{cm}^{-1}$ , assigned to the ester carbon-oxygen-carbon stretch. The  $^1\text{H}$ -NMR spectrum of the product (29) showed a three proton singlet at 3.45 ppm due to the methoxyl group, a doublet of doublets ( $J=7$  and 5 Hz approximately) at 6.92, a doublet of doublets ( $J=7$  and 3 Hz approximately) at 7.72, and a doublet of doublets ( $J=5$  and 3 Hz approximately) at 8.05 ppm due to the three protons of the pyridine ring. The  $^{13}\text{C}$ -NMR spectrum of product (29) was also consistent with esterification having occurred. The peak at 52.48 ppm is due to the carbon of the methoxyl. The C-H correlation spectrum assisted in the assignment of the additional peaks, and the  $^{13}\text{C}$ -NMR data for product are presented in Table 4.1.

Table 4.1 the  $^{13}\text{C}$ -NMR spectrum and the C-H correlation of methyl 2-chloronicotinate (29)

C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
3.45	52.48	positive	-OMe
6.92	122.19	positive	-CH
	126.25	none	C
7.72	140.12	positive	-CH
	149.19	none	C
8.05	151.67	positive	-CH
	164.24	none	C=O

The use of ethanol with the acid chloride of (27) at room temperature for 30 minutes yielded the ethyl ester of 2-chloronicotinic acid (3), free of compound (51). (see Scheme 4.2.3).



Scheme 4.2.3

The infrared spectrum of product (3) showed a very sharp peak, due to the saturated aliphatic carbon -hydrogen stretch, at  $3000\text{ cm}^{-1}$ , the strong carbonyl group stretch at  $1730\text{ cm}^{-1}$ , and several very strong narrow bands at  $1300\text{-}1240\text{ cm}^{-1}$  due to the ester carbon-oxygen-carbon stretch. The  $^1\text{H}$ -NMR spectrum of (3) showed a three proton triplet of doublets ( $J=7$  and  $4\text{ Hz}$ ) at  $0.80\text{ ppm}$ , and a two proton quartet of doublets ( $J=7$  and  $4\text{ Hz}$ ) at  $3.80\text{ ppm}$ , due to the ethoxy group, a multiplet ( $\text{C}=121.80\text{ ppm}$ ) at  $6.80$ , a doublet ( $J=8\text{ Hz}$ ) at  $7.55$ , and a singlet at  $7.90\text{ ppm}$  due to the three protons of pyridyl ring. The  $^{13}\text{C}$ -NMR and the C-H correlation data for the product are presented in Table 4.2.

Table 4.2 the  $^{13}\text{C}$ -NMR spectrum and the C-H correlation of ethyl 2-chloronicotinate (3)

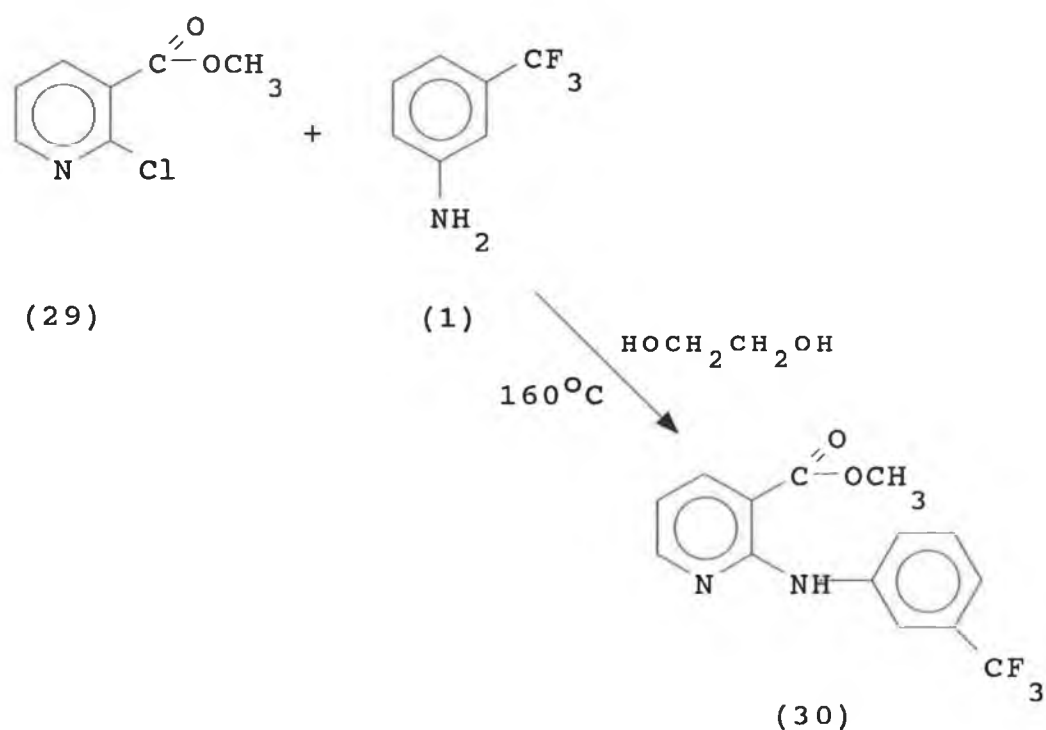
C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
0.80	13.45	positive	Me
3.80	61.24	negative	-OCH <sub>2</sub> -
6.80	121.80	positive	-CH
	126.87	none	C
7.55	139.55	positive	-CH
	148.72	none	C
7.90	151.13	positive	-CH
	163.49	none	C=O

### 4.3 Synthesis of 2-(2-Methyl-3-trifluoromethylanilino)nicotinic Acid (4) from Methyl 2-Chloronicotinate (29).

#### 4.3.1 Reaction of Methyl 2-Chloronicotinate (29) with Trifluoromethylaniline (1).

A model reaction between methyl 2-chloronicotinate (29) and trifluoromethylaniline (1) was first examined. Reaction between these two components using an equimolar ratio at 160°C in ethylene glycol for 6hrs in the presence of quinoline as an added organic basic gave the anticipated product methyl 2-(3-trifluoromethylanilino)nicotinate (30) in modest yield

(31%). (see Scheme 4.3.1). The product (30) has a melting point: (72-74°C) consistent with that reported in the literature (71.5-72.1°C).[15]



Scheme 4.3.1

The structure of the product (30) was supported by elemental microanalysis and by its IR spectrum which showed the carbon-oxygen double bond at  $1700\text{ cm}^{-1}$ . The  $^1\text{H}$ -NMR spectrum of product (30) was consistent with the assigned structure. There was a singlet at 3.95 ppm due to the three protons of the methoxyl group, doublets ( $J=8\text{ Hz}$ ) at 7.27 and 7.85 ppm, a triplet ( $J=8\text{ Hz}$ ) at 7.42 ppm, and a singlet at 8.10 ppm due to

the three adjacent and one isolated benzenoid protons of the structure (30) respectively. There were a doublet of doublets ( $J=8$  and  $4$  Hz) at  $6.75$ , a doublet of doublets ( $J=8$  and  $2$  Hz) at  $8.22$ , and a doublet of doublets ( $J=4$  and  $2$  Hz)  $8.38$  ppm respectively due to the three pyridyl protons of product (30). The proton of the NH group occurred at  $10.38$  ppm. The  $^{13}\text{C}$ -NMR spectrum of the product (30) showed a peak at  $52.22$  ppm which is the carbon of the methoxy group, the multiplet of the  $\text{CF}_3$  is at  $131.12$  ppm, and the carbon of the carbonyl at  $167.74$  ppm. The four benzenoid methine carbons were at  $117.02$ ,  $118.94$ ,  $123.40$ , and  $129.21$  ppm, and the three pyridyl methine carbons were at  $114.08$ ,  $140.23$ , and  $153.04$  ppm consistent with the required product (30). The C-H correlation and the  $^{13}\text{C}$ -NMR data for the product are presented in Table 4.3.

Table 4.3 The  $^{13}\text{C}$ -NMR spectrum and the C-H correlation of methyl 2-(3-trifluoromethylanilino)nicotinate (30)

C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
3.95	52.22	positive	-OMe
	107.25	none	C
6.75	114.08	positive	-CH P
8.10	117.02*	positive	-CH A
7.27	118.94*	positive	-CH A
7.85	123.40	positive	-CH A
	125.35	none	C
7.42	129.21	positive	-CH A
	131.12**	none	$\text{CF}_3$
	140.08	none	C
8.22	140.23	positive	-CH P
8.38	153.04	positive	-CH P
	155.56	none	C
	167.74	none	C=O

\*multiplet due to long range carbon-fluorine coupling.

\*\*multiplet due to carbon-fluorine coupling.

A: derived from 3-trifluoromethylaniline (1).

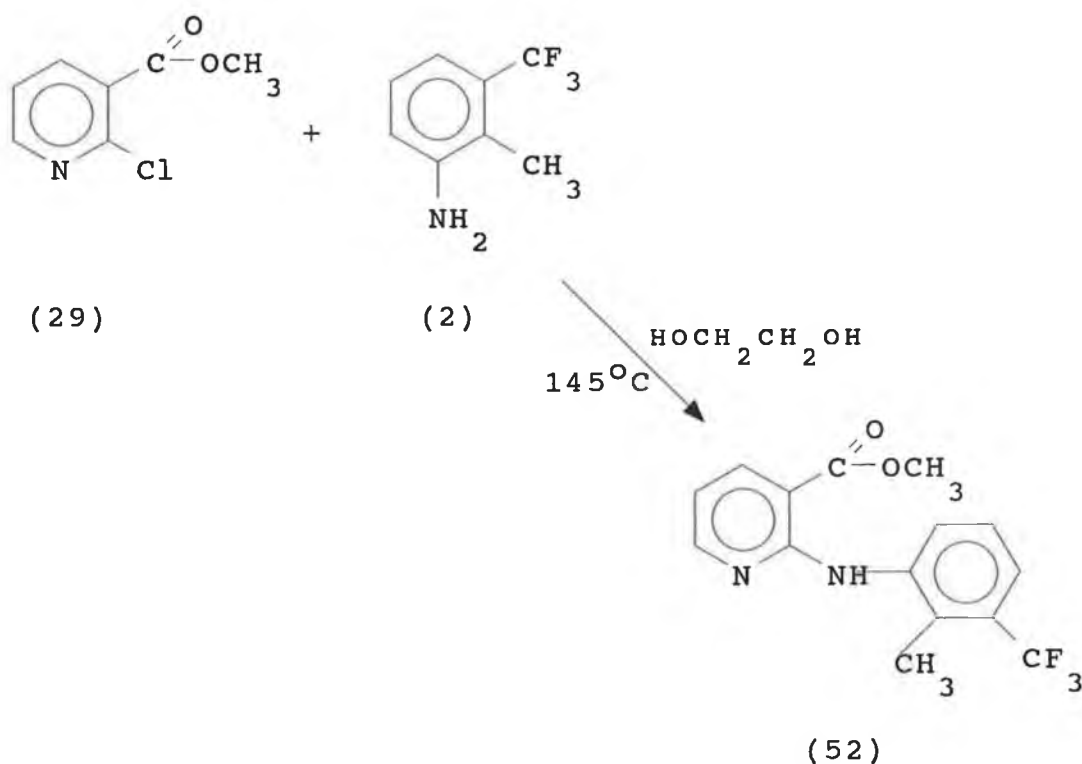
P: derived from methyl 2-chloronicotinate (29).

#### **4.3.2 Reaction of Methyl 2-Chloronicotinate (29) with 2-Methyl-3-trifluoromethylaniline (2).**

The preparation<sup>[1] [14]</sup> of ethyl 2-(2-methyl-3-trifluoromethyl-anilino)nicotinate involved heating ethyl 2-chloronicotinate (3) and 2-methyl-3-trifluoromethylaniline (2) together in a 1:1.5 molar ratio at 196-198°C (refluxed) with protection by a dry nitrogen atmosphere. For an industrial process, such high reaction temperatures are problematical and our aim was to find milder conditions for the reaction.

When methyl 2-chloronicotinate (29) and 2-methyl-3-trifluoromethylaniline (2) were heated to 160°C for 6hrs in a equimolar ratio in ethylene glycol, methyl 2-(2-methyl-3-trifluoromethyl-anilino)nicotinate (52) was obtained in 20% yield. (see Scheme 4.3.2)





Scheme 4.3.2

The structure of the product (52) was indicated by its IR, NMR, and microanalysis. A pure sample (melting point 69-71°C) was obtained by chromatography on a silica column. In the  $^1\text{H}$ -NMR spectrum of the product (52) a singlet at 2.35 ppm is due to the three protons of the methyl group, and a singlet at 3.95 ppm is due to the three protons of the methoxy group. A triplet ( $J=8$  Hz) at 7.25, a doublet ( $J=8$  Hz) at 7.38, and a doublet ( $J=8$  Hz) at 8.16 ppm are due to the three benzenoid protons of (52). There were a doublet of doublets ( $J=7$  and 4 Hz) at 6.62, a doublet of doublets ( $J=7$  and 2 Hz) at 8.22, and a doublet of doublets ( $J=4$  and 2 Hz) at 8.29 ppm due to the three pyridyl protons of (52). The  $^{13}\text{C}$ -NMR spectrum of the product

(52) has a peak at 13.98 ppm due to methyl group carbon, the methoxy group carbon was at 52.37 ppm. At 121.31, 125.85, and 126.85 ppm were the three benzenoid methine carbons of the product (52). At 113.73, 140.35, and 153.28 ppm were the three pyridyl methine carbons of the product (52). Table 4.4 presents the  $^{13}\text{C}$ -NMR, DEPT-135, and C-H correlation spectra.

Table 4.4 The  $^{13}\text{C}$ -NMR and DEPT-135, and C-H correlation of spectrum of methyl 2-(2-methyl-3-trifluoromethylanilino)nicotinate (52)

C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
2.35	13.98	positive	-Me
3.95	52.37	positive	-OMe
	107.25	none	C
6.62	113.73	positive	-CH P
	118.24	none	C
7.38	121.31	positive	-CH A
	123.12	none	C
7.25	125.85	positive	-CH A
8.16	126.85	positive	-CH A
	128.89*	none	$\text{CF}_3$
	139.38	none	C
8.22	140.35	positive	-CH P
8.29	153.28	positive	-CH P
	156.38	none	C
	168.06	none	C=O

\*multiplet due to carbon-fluorine coupling.

A: derived from 2-Methyl-3-trifluoromethylaniline (2).

P: derived from Methyl 2-chloronicotinate (29).

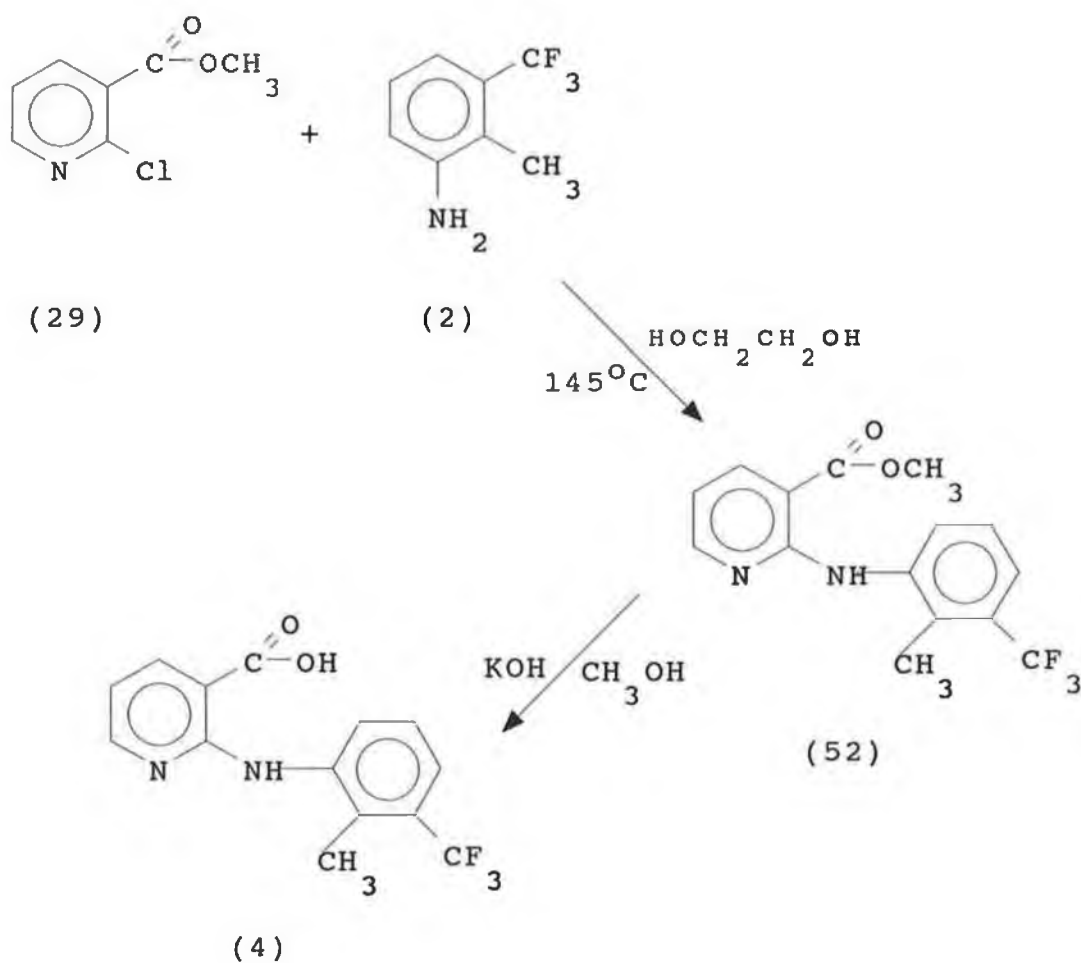
In order to obtain a higher yield of the product (52), we attempted to use sodium hydride or n-butyl lithium as catalyst in the reaction. However, this did not lead to any improvement in the reaction.

We further investigated the reaction temperature and the mole ratio of reactants to improve the product yield. Reactions of 2-methyl-3-trifluoromethylaniline (2) and methyl 2-chloronicotinate (29) were carried out in ethylene glycol in a 2:1 mole ratio at 160°C for 8hrs, in a 2:1.5 mole ratio at 150°C for 10hr, and in a 1:1 mole ratio at 145°C for 10hrs, respectively. The results of these investigations showed that the reaction involving a 1:1 mole ratio at 145°C for 10hrs gave the most satisfactory outcome, an isolated product with a melting point 69-71°C in 53% yield, purer than from the other reaction conditions. A final hydrolysis step then converted methyl 2-(2-methyl-3-trifluoromethylanilino)nicotinate (52) to 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) in good yield (82%), representing an overall modest yield of 43% (i.e. 53% x 82%) for conversion of (2) and (29) to (4).

#### **4.3.3 Improved Process for the Preparation of 2-(2-Methyl-3-trifluoromethylanilino)nicotinic Acid (4).**

When 2-methyl-3-trifluoromethylaniline (2) and methyl 2-chloronicotinate (29) were heated for 10hrs in a 1:1 mole ratio at 145°C in ethylene glycol, protected by a dry nitrogen atmosphere, and the crude product (52) hydrolysed without purification using potassium hydroxide under reflux in methanol for 3hr, 2-(2-methyl-3-

trifluoromethylanilino)nicotinic acid (4) was isolated in good yield (61%), with a crude melting point 210-212°C. The recrystallised product had mp 224-225°C, identical to the literature value 224-225°C.[1] (see Scheme 4.3.3).



Scheme 4.3.3

The structure of the product (4) was supported by the elemental analysis results and by the infrared spectrum which showed peaks at  $1700\text{ cm}^{-1}$ , and  $1600\text{ cm}^{-1}$  ascribable to the carbonyl and the nitrogen-hydrogen bond of the amine respectively. The NMR spectrum of the product (4) showed a singlet at 2.25 ppm, due to the three protons of the methyl group. A two proton multiplet at 7.22 ppm, and a doublet ( $J=8\text{ Hz}$ ) at 8.28 ppm were due to the three protons of the benzenoid portion of (4). Three doublet of doublets ( $J=8$  and  $4\text{ Hz}$ ) at 6.74, a doublet of doublets ( $J=8$  and  $2\text{ Hz}$ ) at 8.12, and a doublet of doublets ( $J=4$  and  $2\text{ Hz}$ ) at 8.21 ppm were ascribable to the three protons of the pyridine ring of (4). The proton of the amino group was at 10.30, and 13.51 (br, 1H, -COOH) ppm. The  $^{13}\text{C}$ -NMR data and the C-H correlation for compound (4) are listed in Table 4.5.

Table 4.5. The  $^{13}\text{C}$ -NMR spectrum and C-H correlation of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid. (4)

C-H (ppm)	$^{13}\text{C}$ -NMR (ppm)	DEPT-135	carbons
2.30	13.52	positive	-Me
	107.81	none	C
6.72	114.17	positive	-CH P
7.22	120.03	positive	-CH A
	123.10	none	C
7.22	125.89	positive	-CH A
8.28	126.45	positive	-CH A
	127.27	none	C
	128.22*	none	$\text{CF}_3$
	139.74	none	C
8.12	140.48	positive	-CH P
8.21	152.55	positive	-CH P
	155.68	none	C
	169.13	none	$\text{C}=\text{O}$

\*multiplet due to carbon-fluorine coupling.

A: derived from 2-methyl-3-trifluoromethylaniline (2).

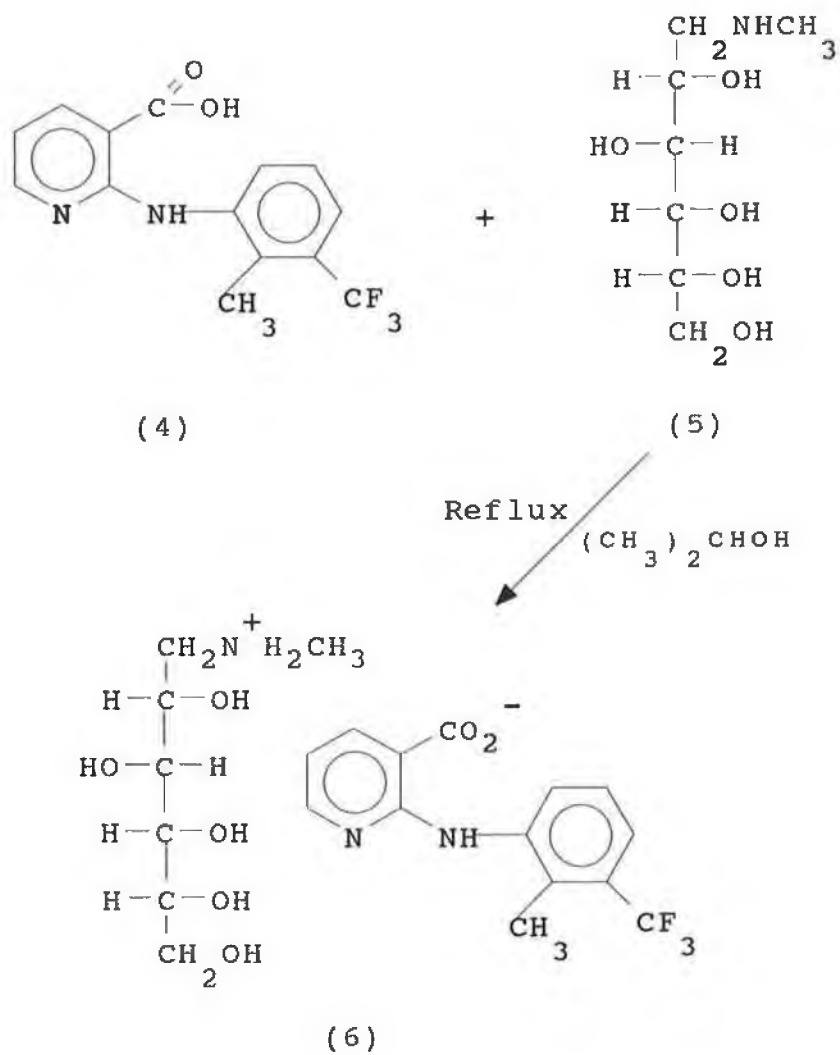
P: derived from 2-chloronicotinic acid (27).

#### **4.4 N-methyl-D-glucamine Salt of 2-(2-Methyl-3-trifluoromethyl-anilino)nicotinic Acid (6).**

In the final step, 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) was converted to its salt (6) with N-methyl-D-glucamine (5).

2-(2-Methyl-3-trifluoromethylanilino)nicotinic acid (4) and N-methyl-D-glucamine (5) were dissolved in propan-2-ol in a 1:1 mole ratio under reflux. On cooling, the salt (6) was obtained in 94% yield, melting point 129-130°C. The literature reported a melting point: 135-137°C.[1] [14] (see Scheme 4.4.1).

The composition of the salt (6) was supported by the  $^1\text{H}$ -NMR spectrum, the two methyl singlets integrating in a 1:1 ratio. The aromatic region showed six individual hydrogen multiplets as expected, also the ratio of aromatic hydrogens to total methyl hydrogens was 1:1. The  $^1\text{H}$ ,  $^{13}\text{C}$  and DEPT-135 spectra are shown on the following pages. The individual peaks in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are assigned in the experimental section.



Scheme 4.4.1



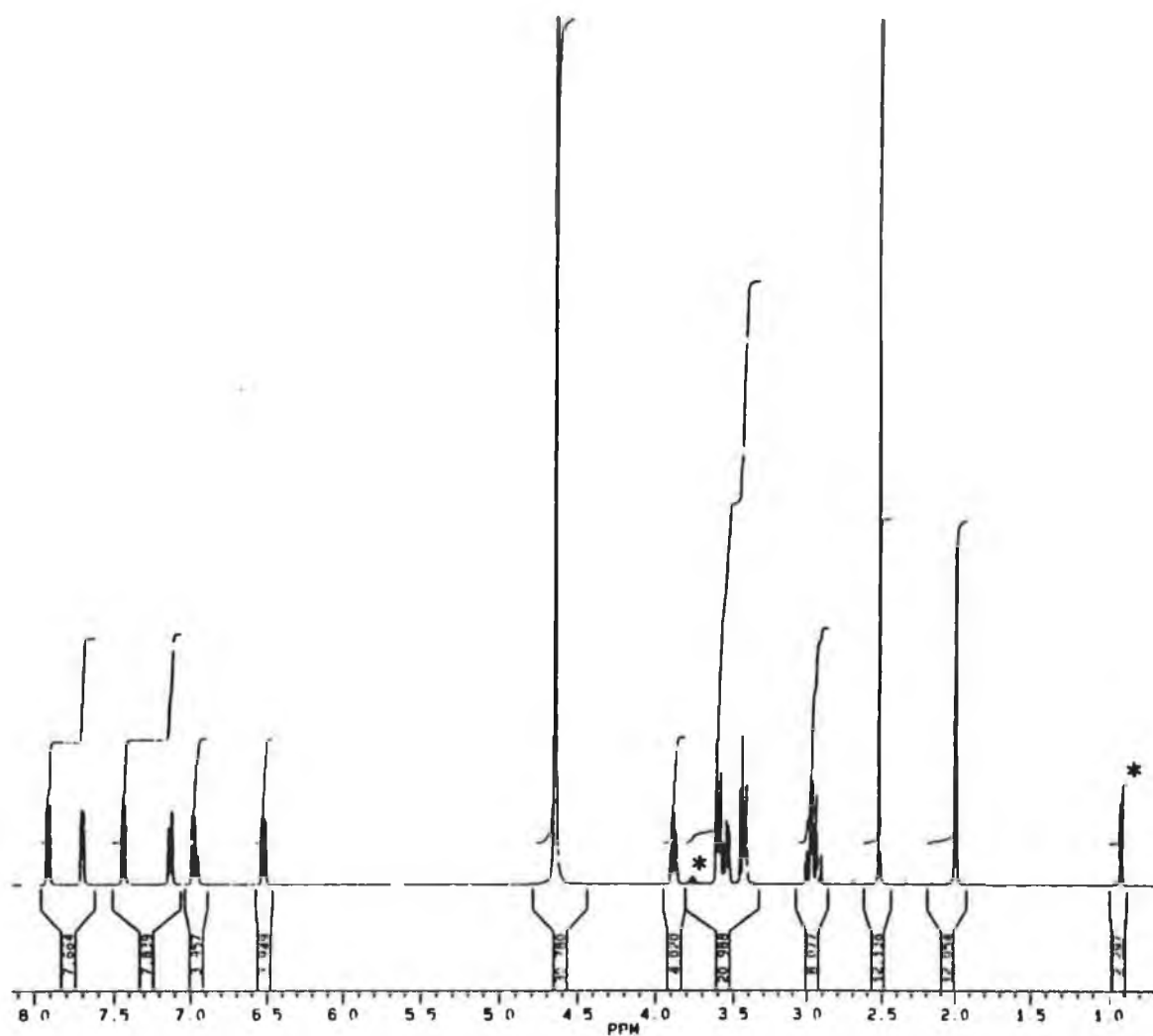


Figure 4.1 the  $^1\text{H}$ -NMR spectrum of the N-methyl-D-glucamine salt of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (6) in  $\text{D}_2\text{O}$ .

\*These peaks are due to traces of residual propan-2-ol.

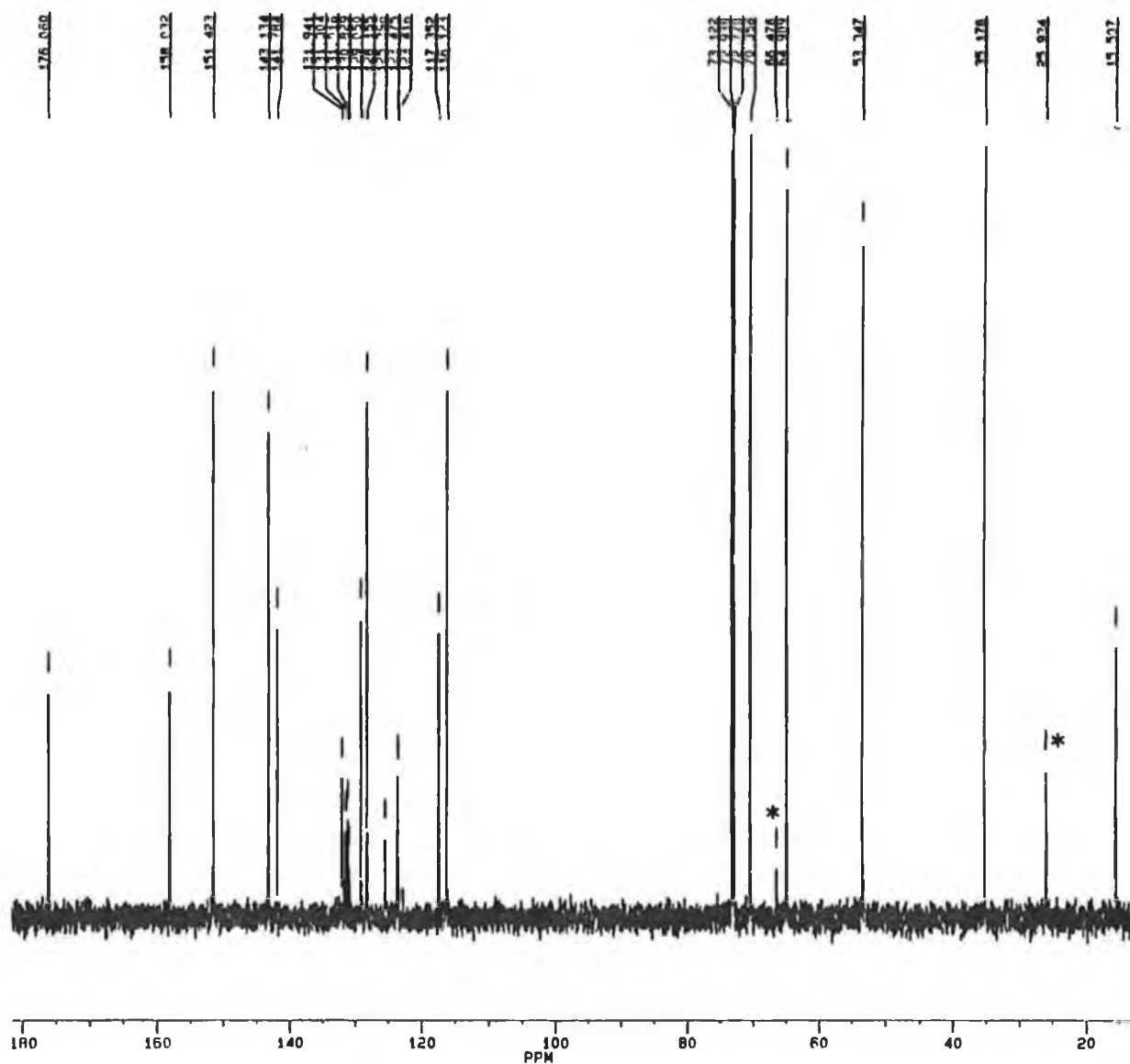


Figure 4.2 the  $^{13}\text{C}$ -NMR spectrum of the N-methyl-D-glucamine salt of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (6) in  $\text{D}_2\text{O}$ .

\*These peaks are due to traces of residual propan-2-ol.

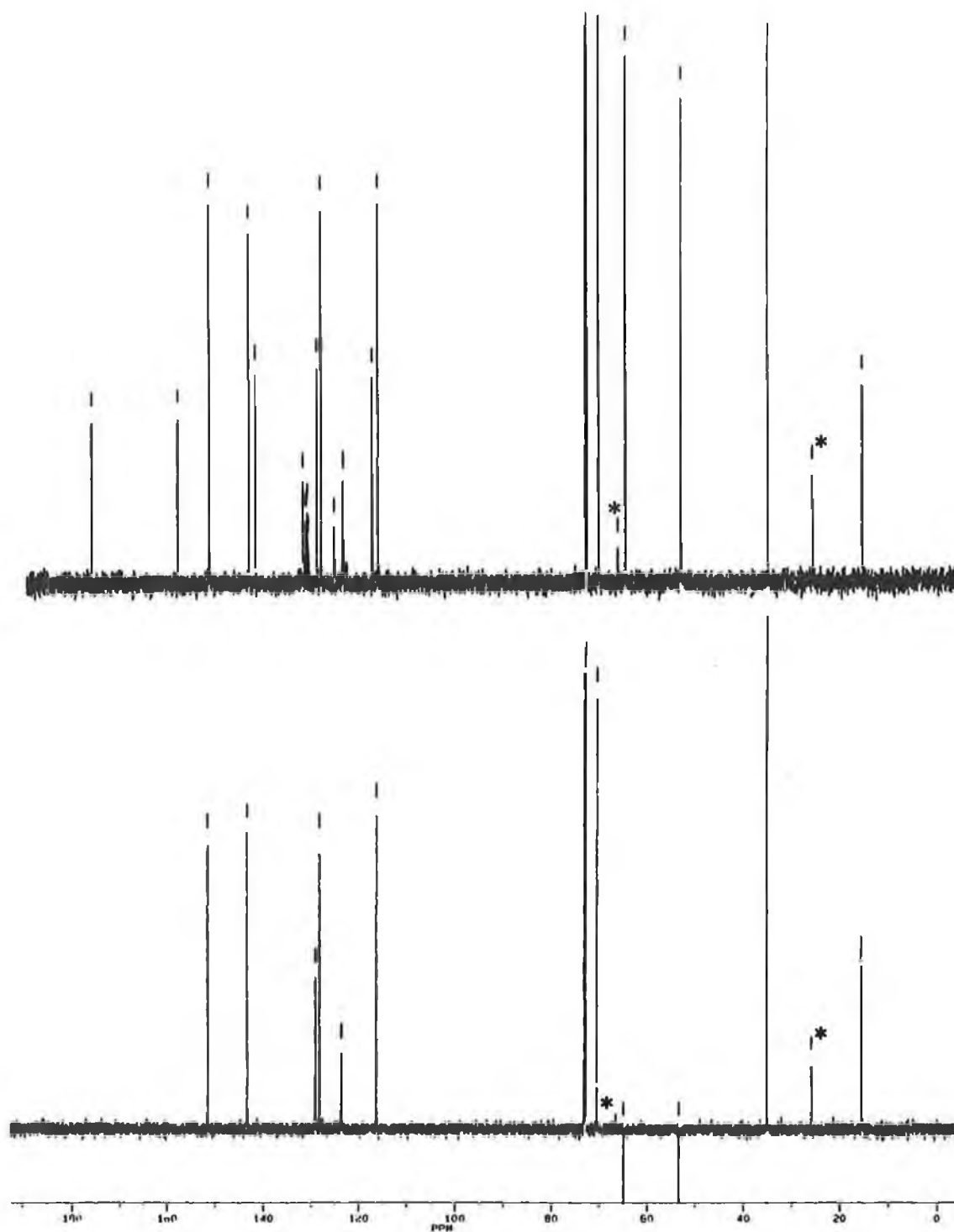


Figure 4.3 the  $^{13}\text{C}$ -NMR and DEPT-135 spectrum of the N-methyl-D-glucamine salt of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (6) in  $\text{D}_2\text{O}$ .

\*These peaks are due to traces of residual propan-2-ol.

## **EXPERIMENTAL SECTION**

### **Chapter 5.**

## 5.1 General

NMR spectra were recorded in deuteriochloroform (unless otherwise stated) on a Bruker AC-400 instrument operating at 400MHz for  $^1\text{H}$ -NMR, and 100MHz for  $^{13}\text{C}$ -NMR.

Infrared spectra were recorded on a Perkin-Elmer 983G infrared spectrophotometer. The compounds were mixed with potassium bromide, the mixture was subjected to compaction in a high pressure die and the resulting plate was used for measurement of the spectrum.

Chromatography was on silica using elution with dichloromethane/light petroleum (b.p.40-60°C) ratio 2:3.

Elemental analyses were carried out by the Microanalytical Laboratory of University College Dublin.

## 5.2 Synthesis of N-carbethoxy-3-trifluoromethylaniline (40)

### (a). Acetone as solvent.

3-Trifluoromethylaniline (1) (7.0g, 43.2mmol) and potassium carbonate (9.6g, 68.8mmol) in acetone (100cm<sup>3</sup>) were placed in a round-bottom flask fitted with a dropping funnel. Ethyl chlorocarbonate (6.5g, 57mmol) was slowly added dropwise with stirring at room temperature. The reaction mixture was heated with stirring under reflux for 4hrs. When cooled, the acetone solution was filtered. Removal of the solvent on the rotary evaporator yielded N-carbethoxy-3-trifluoromethylaniline (40) (9.45g,

82%), having m.p: 41-42°C. Recrystallisation from light petroleum (b.p. 40-60°C) give white crystals, m.p: 45-46°C. IR:  $\nu_{\text{max}}$  1698, 1242, 893, 806, and 701  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$ :  $\delta$  1.3 (t, 3H,  $J=7$  Hz,  $\text{CH}_3$ ), 4.24 (q, 2H,  $J=7$  Hz,  $-\text{OCH}_2-$ ), 7.31 (d, 1H,  $J=8$  Hz, arom-H), 7.39 (t, 1H,  $J=8$  Hz, arom-H), 7.56 (d, 1H,  $J=8$  Hz, arom-H), 7.74 (s, 1H, arom-H), 7.01 (s, 1H, NH) ppm.  $^{13}\text{C-NMR}$ : 14.48 (Me), 61.65 ( $-\text{OCH}_2-$ ), 115.38 (CH, arom-C), 119.90 (CH, arom-C), 121.71 (CH, arom-C), 125.31 (arom-C), 129.59 (CH, arom-C), 131.33 (multiplet,  $\text{CF}_3$ ), 138.69 (arom-C), 153.63 (carbonyl) ppm. (see: Chapter 2, Table 2.1). Microanalysis: Found: C: 51.39; H: 4.28; N: 5.93; F: 24.21%.  $\text{C}_{10}\text{H}_{10}\text{NO}_2\text{F}_3$  requires: C: 51.51; H: 4.32; N: 6.01; F: 24.44%.

#### **(b). Water as solvent.**

3-Trifluoromethylaniline (1) (20.0g, 120mmol) and ice water (25 $\text{cm}^3$ ) were mixed with stirring. Ethyl chlorocarbonate (6.7g, 60mmol) was slowly added dropwise with stirring at room temperature. Then ice water (25 $\text{cm}^3$ ) was added and a second portion of ethyl chlorocarbonate (6.7g, 60mmol) was introduced. Simultaneously with this, an ice-cold solution of sodium hydroxide (17 $\text{cm}^3$ ,  $c=0.3\text{g}/\text{cm}^3$ ) was added dropwise at such a rate that equal fractions of the ethyl chlorocarbonate and sodium hydroxide solutions were introduced over equal periods of time, with stirring at room temperature. Then the reaction mixture was stirred for 2hrs and filtered through a Buchner funnel. The solid product was washed with copious amounts of cold water and was air-dried to yield N-carbethoxy-3-trifluoromethylaniline (40) (19g, 66%), m.p: 41-42°C. Recrystallisation from light petroleum (b.p. 40-60°C) gave white crystals, m.p: 45-46°C.

### 5.3 Synthesis of Pivalylamino-3-trifluoromethylbenzene (23)

#### (a). Acetone as solvent.

3-Trifluoromethylaniline (1) (20cm<sup>3</sup>, 160mmol) and potassium carbonate (27.6g, 198mmol) in acetone (200cm<sup>3</sup>) were placed in a round-bottom flask fitted with a dropping funnel. Pivalylchloride (22cm<sup>3</sup>, 178.2mmol) was slowly added dropwise with stirring at room temperature. The reaction mixture was heated with stirring under reflux for 4hrs, then cooled and filtered. Removal of the solvent on the rotary evaporator yielded pivalylamino-3-trifluoromethylbenzene (23) (37.8g, 96%), m.p: 106-107°C. Recrystallisation from ethanol gave white crystals, m.p: 108-109°C; IR:  $\nu_{\text{max}}$  3324, 2973, 2913, 2876, 2087, 1945, 1777, 1660, 1603, 1548, 1474, 1444, 1401, 1332, 1297, 1267, 1240, 1182, 1161, 1126, 1072, 1025, 928, 890, 797, 699, and 661 cm<sup>-1</sup>. <sup>1</sup>H-NMR:  $\delta$  1.28 (s, 9H, t-Bu), 7.33 (d, 1H, J=8 Hz, arom-H), 7.40 (t, 1H, J=8 Hz, arom-H), 7.68 (d, 1H, J=8 Hz, arom-H), 7.88 (s, 1H, arom-H) 7.76 (s, 1H, NH) ppm. <sup>13</sup>C-NMR: 27.58 (Me), 39.6 (C-Me<sub>3</sub>), 117.15 (C-H, arom-C), 120.89 (C-H, arom-C), 123.46 (C-H, arom-C), 125.3 (arom-C), 129.48 (C-H, arom-C), 138.7 (arom-C), 131.1 (multiplet, CF<sub>3</sub>), and 177.5 (C=O) ppm. (see Chapter 2, Table 2.2). Microanalysis: Found: C: 58.85; H: 5.74; N: 5.55%. C<sub>12</sub>H<sub>14</sub>NOF<sub>3</sub> requires: C: 58.78; H: 5.71; N: 5.71%.

**(b). Water as solvent.**

3-Trifluoromethylaniline (1) (20cm<sup>3</sup>, 160mmol) and sodium hydroxide (7.1g, 178.2mmol) in water (150cm<sup>3</sup>) were placed in a round-bottom flask fitted with a dropping funnel and stirrer. Pivalylchloride (22cm<sup>3</sup>, 178.2mmol) was slowly added dropwise at room temperature over 20 minutes with stirring. The mixture was stirred for an additional 2hrs. Then the solid was filtered off, washed three times with water (300cm<sup>3</sup>), and dried overnight at 40°C under vacuum to yield pivalylamino-3-trifluoromethylbenzene (23) 23.4g (60% yield), m.p: 108-109°C. The product was recrystallized from ethanol to give white crystals, m.p: 109°C.

**5.4 Synthesis of Pivalylamino-2-methyl-3-trifluoromethylbenzene (26).**

Because of the reactivity of alkylolithium reagents, the apparatus in which they are used must be completely dry, and the ether used as solvent must be scrupulously dried over sodium. Also the reaction system must be protected from water vapor, oxygen, and carbon dioxide from the air. These are swept out of the system with dry nitrogen.

Pivalylamino-3-trifluoromethylbenzene (23) (20.0g, 82mmol) was dissolved in dry diethyl ether (250cm<sup>3</sup>) in a three-necked flask fitted with a rubber septum. The flask was flushed with dry nitrogen and during subsequent reaction a slow flow of dry nitrogen was maintained. Using a syringe, n-butyl lithium (in hexane; 2.5M; 80cm<sup>3</sup>, 200mmol) was added at room temperature. The mixture was then stirred at room temperature for



3hrs. A solution of methyl iodide (8cm<sup>3</sup>, 127mmol) in dry diethyl ether (24cm<sup>3</sup>) was then added slowly to the solution of the lithiated amide with stirring. The reaction mixture was stirred at room temperature for a further 2hrs, and was then hydrolyzed by cautious addition of icewater (400cm<sup>3</sup>). The ethereal solution was washed with saturated brine and dried over anhydrous magnesium sulphate. The solvent was removed by rotary evaporation, yielding a red-brown solid, m.p: 112-114°C, which was recrystallised from ethyl acetate/n-hexane (1:1) to give white crystals of pivalylamino-2-methyl-3-trifluoromethylbenzene (26) (15.2g, 72%), m.p: 115-116°C. IR:  $\nu_{\text{max}}$  3316, 2970, 1646, 1588, 1400, 1369, 1323, 1227, 1166, 1106, 1027, 947, 916, 887, 795, 725, 650, and 625 cm<sup>-1</sup>. <sup>1</sup>H-NMR:  $\delta$  1.28 (s, 9H, t-Bu), 2.28 (s, 3H, Me), 7.35 (t, 1H, J=8.0 Hz, arom-H), 7.48 (d, 1H, J=8.0 Hz, arom-H), 7.90 (d, 1H, J=8.0 Hz, arom-H), 8.26 (s, 1H, NH) ppm. <sup>13</sup>C-NMR: 13.28 (Me), 27.60 (-Me<sub>3</sub>), 39.60 (C-Me<sub>3</sub>), 120.3 (arom-C), 122.83 (C-H, arom-C), 125.7 (arom-C), 126.01 (C-H, arom-C), 127.94 (C-H, arom-C), 137.20 (arom-C), 129.60 (multiplet, CF<sub>3</sub>), 177.10 (C=O) ppm. (see Chapter 2, Table 2.3). Microanalysis: Found: C: 60.26; H: 6.24; N: 5.36%. C<sub>13</sub>H<sub>16</sub>NOF<sub>3</sub> requires: C: 60.22; H: 6.17; N: 5.40%.

## 5.5 Preparation of 2-Methyl-3-trifluoromethylaniline (2).

Pivalylamino-2-methyl-3-trifluoromethylbenzene (26) (10.0g, 39mmol) and potassium hydroxide (10.0g, 179mmol) in ethylene glycol (100cm<sup>3</sup>) was heated slowly with stirring to 160°C and the solution maintained at this temperature for 8hrs. The reaction mixture was then

cooled, water was added and the products were extracted with dichloromethane. The extract was washed with water, dried over magnesium sulphate and the dichloromethane removed by ambient pressure distillation\* to yield 2-methyl-3-trifluoromethylaniline (2) (6.3g, 93%), m.p: 35°C. Recrystallisation from light petroleum (b.p. 40-60°C) gave white crystals of 2-methyl-3-trifluoromethylaniline (2), having m.p: 37-38°C. (literature<sup>[3]</sup> m.p: 38°C). IR:  $\nu_{\text{max}}$  3399, 2932, 1626, 1477, 1328, 1294, 1217, 1202, 1169, 1122, 1020, 878, 793, 720, and 624  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$ :  $\delta$  2.22 (s, 3H,  $\text{CH}_3$ ), 6.84 (d of d, 1H,  $J=7$  and 2 Hz, arom-H), 7.08 (m, 2H, arom-H), 3.65 (s, 2H, NH) ppm.  $^{13}\text{C-NMR}$ : 12.97 (Me), 116.06 (CH, arom-C), 118.34 (CH, arom-C), 120.20 (arom-C), 123.35 (arom-C), 126.29 (CH, arom-C), 145.80 (arom-C), 129.50 (multiplet,  $\text{CF}_3$ ) ppm (see: Chapter 2, Table 2.4). Microanalysis: Found: C: 54.72; H: 4.58; N: 7.85%.  $\text{C}_8\text{H}_8\text{NF}_3$  requires: C: 54.86; H: 4.60; N: 7.99%.

\*Use of reduced pressure rotary evaporation results in significant loss of compound (2).

## 5.6 Synthesis of 2-(3-Trifluoromethylanilino)nicotinic Acid (42).

### (a). Ethylene glycol as solvent.

2-Chloronicotinic acid (27) (1.6g, 10mmol) and 3-trifluoromethylaniline (1) (1.6g, 10mmol) in ethylene glycol (10 $\text{cm}^3$ ) were heated with stirring to 100°C, and pyridine (0.5g, 10mmol) was added at this temperature. The reaction mixture was then heated with stirring at 160°C for 5hrs. It was then cooled, water was added and the product was extracted

with diethyl ether. The ether extract was washed with water, dried over magnesium sulphate and the solvent removed by rotary evaporator to yield 2-(3-trifluoromethylanilino)nicotinic acid (42) (12.0g, 43%), m.p: 190-192°C. The product was recrystallised from acetone to give yellow crystals, m.p: 199-201°C. (literature<sup>[27]</sup> m.p: 203-204°C). IR:  $\nu_{\text{max}}$  3320, 3099, 3014, 2915, 1666, 1611, 1583, 1531, 1483, 1448, 1427, 1362, 1329, 1286, 1242, 1210, 1149, 1111, 1069, 998, 934, 879, 793, 773, 698, and 663  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (acetone- $\text{d}_6$ ):  $\delta$  7.20 (d, 1H,  $J=8$  Hz, arom-H), 7.41 (t, 1H,  $J=8$  Hz, arom-H), 7.79 (d, 1H,  $J=8$  Hz, arom-H), 8.29 (s, 1H, arom-H), 6.83 (d of d, 1H,  $J=8$  and 4 Hz, pyrid-H), 8.26 (d of d, 1H,  $J=8$  and 2 Hz, pyrid-H), 8.37 (d of d, 1H,  $J=4$  and 2 Hz, pyrid-H), 10.52 (s, 1H, NH) ppm.  $^{13}\text{C-NMR}$ (acetone- $\text{d}_6$ ): 116.15 (C-H, arom-C), 118.38 (C-H, arom-C), 123.34 (C-H, arom-C), 129.65 (C-H, arom-C), 114.62 (C-H, pyrid-C), 140.85 (C-H, pyrid-C), 152.96 (C-H, pyrid-C), 107.87 (C), 125.99 (C), 141.18 (C), 155.03 (C), 130.70 (multiplet,  $\text{CF}_3$ ), 168.87 (C=O) ppm (see: Chapter 3, Table 3.1). Mass Spectrum: 43, 75, 93, 122, 145, 168, 186, 217, 236, 263, 282. Theory MW=282. Microanalysis: Found: C: 55.52; H: 3.22; N: 9.90%.  $\text{C}_{13}\text{H}_9\text{N}_2\text{O}_2\text{F}_3$  requires C: 55.33; H: 3.21; N: 9.93%.

**(b). Xylene as solvent.**

2-Chloronicotinic acid (27) (1.6g, 10mmol) and 3-trifluoromethylaniline (1) (1.6g, 10mmol) in xylene ( $30\text{cm}^3$ ) were heated with stirring to 40°C, and pyridine (0.79g, 10mmol) was added at this temperature. The reaction mixture was then heated with stirring under reflux for 5hr. The reaction mixture was cooled, water was added and the product was extracted with diethyl ether. The extract was washed with water, dried

over magnesium sulphate and the solvent removed by rotary evaporation to yield 2-(3-trifluoromethylanilino)nicotinic acid (42) (0.8g, 29%), m.p: 192-194°C. The product was recrystallised from acetone, to give yellow crystals having m.p:199-201°C (literature<sup>[27]</sup> m.p:203-204°C).

### **5.7 Synthesis of N-(3-trifluoromethyl)phenyl-2-chloronicotinamide (44).**

To 2-chloronicotinic acid (27) (4.0g, 25mmol) in xylene (30cm<sup>3</sup>), thionyl chloride (8.2g, 745mmol) was added with stirring at room temperature. The mixture was heated under reflux with stirring for 1hr, then cooled to room temperature. 3-Trifluoromethylaniline (1) (4.0g, 25mmol) was then added and the mixture was stirred at room temperature for 1hr. Triethylamine (1.8g, 18.3mmol) was then added and the mixture was heated under reflux for 1hr. When cold, water was added and the products were extracted with dichloromethane. The dichloromethane extract was washed with water to pH=7, dried over magnesium sulphate and the solvent was removed by rotary evaporation, to yield N-(3-trifluoromethyl)phenyl-2-chloronicotinamide (44) (6.5g, 88%), having m.p: 107-109°C. The product was recrystallised from ethanol to give white crystals, having m.p: 112-114°C. IR:  $\nu_{\text{max}}$  3410, 3257, 3084, 2994, 1672, 1600, 1483, 1450, 1406, 1327, 1308, 1260, 1153, 1127, 1068, 1000, 924, 894, 880, 806, 757, 699, and 663 cm<sup>-1</sup>. <sup>1</sup>H-NMR (acetone-d<sub>6</sub>):  $\delta$  7.52 (d, 1H, J=8 Hz, arom-H), 7.65 (t, 1H, J=8 Hz, arom-H), 7.98 (d, 1H, J=8 Hz, arom-H), 8.30 (s, 1H, arom-H), 7.57 (d of d, 1H, J=7.5 and 5 Hz, pyrid-H), 8.12 (d of d, 1H, J=7.5 and

2 Hz, pyrid-H), 8.53 (d of d, 1H,  $J=5$  and 2 Hz, pyrid-H), 10.10 (s, 1H, NH) ppm.  $^{13}\text{C}$ -NMR (acetone- $\text{d}_6$ ): 115.92 (C-H, arom-C), 120.50 (C-H, arom-C), 122.93 (C-H, arom-C), 129.87 (C-H, arom-C), 122.79 (C-H, pyrid-C), 137.92 (C-H, pyrid-C), 150.66 (C-H, pyrid-C), 117.41 (C), 125.59 (C), 139.09 (C), 147.13 (C), 132.36 (multiplet,  $\text{CF}_3$ ), 164.23 (C=O) ppm (see: Chapter 3, Table 3.2). Mass spectrum: 18, 28, 51, 76, 112, 114, 140, 142, 300. Theory MW=300. Microanalysis: Found: C: 50.98; H: 2.84; N: 9.10%.  $\text{C}_{13}\text{H}_8\text{N}_2\text{OF}_3\text{Cl}$  requires: C: 51.93; H: 2.68; N: 9.32%.

## **5.8 Synthesis of N-(2-methyl-3-trifluoromethyl)phenyl-2-chloronicotinamide (45).**

To 2-chloronicotinic acid (27) (1.8g, 11.25mmol) in xylene (10cm<sup>3</sup>), thionyl chloride (3.0g, 25.22mmol) was added with stirring at room temperature. The mixture was heated with stirring to 110°C for 1hr, then cooled to room temperature. 2-Methyl-3-trifluoromethylaniline (2) (2.0g, 11.14mmol) was added, and the mixture with stirred at room temperature for 1hr. Then triethylamine (0.8g, 8.1mmol) was added, and the mixture was heated to 110°C for 30 minutes. It was cooled to room temperature, water was added, and the product was extracted with dichloromethane. The extract was washed with water to pH=7, dried over magnesium sulphate and the solvent removed by rotary evaporation, to yield N-(2-methyl-3-trifluoromethyl)phenyl-2-chloronicotinamide (45) (0.5g, 14%), m.p: 155°C. The product was recrystallized from ethanol to yield white crystals, m.p: 160-161°C. IR:  $\nu_{\text{max}}$  3499, 3240, 3032, 1662, 1582, 1560, 1524, 1479,

1455, 1407, 1325, 1175, 1152, 1112, 1087, 1067, 1022, 940, 910, 802, 763, 724, 693, and 624  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (acetone- $\text{d}_6$ ):  $\delta$  2.55 (s, 3H,  $\text{CH}_3$ ), 7.34 (t, 1H,  $J=8$  Hz, arom-H), 7.50 (d, 1H,  $J=8$  Hz, arom-H), 7.82 (d, 1H,  $J=8$  Hz, arom-H), 7.41 (d of d, 1H,  $J=6$  and 3 Hz, pyrid-H), 8.01 (d of d, 1H,  $J=8$  and 6 Hz, pyrid-H), 8.38 (d of d, 1H,  $J=8$  and 3 Hz, pyrid-H), 9.4 (s, 1H, NH) ppm.  $^{13}\text{C}$ -NMR (acetone- $\text{d}_6$ ): 13.57 (Me), 123.69 (C-H, arom-C), 126.52 (C-H, arom-C), 129.82 (C-H, arom-C), 123.10 (C-H, pyrid-C), 138.31 (C-H, pyrid-C), 150.82 (C-H, pyrid-C), 117.43 (C), 131.88 (C), 132.60 (C), 137.07 (C), 147.08 (C), 129.23 (multiplet,  $\text{CF}_3$ ), 164.52 (C=O) ppm (see Chapter 3, Table 3.3). Mass spectrum: 18, 51, 76, 77, 112, 114, 140, 142, 174, 314. Theory MW=314. Microanalysis: Found: C: 52.57; H: 3.37; N: 8.75%.  $\text{C}_{14}\text{H}_{10}\text{N}_2\text{OF}_3\text{Cl}$  requires: C:53.43; H: 3.20; N: 8.90%.

## 5.9 Synthesis of N-(2-methyl-3-trifluoromethyl)phenyl-2-hydroxynicotinamide (46).

2-Chloronicotinic acid (27) (0.90g, 5.7mmol) and 2-methyl-3-trifluoromethylaniline (2) (1.00g, 5.7mmol) in ethylene glycol (5 $\text{cm}^3$ ) were heated with stirring to 100°C, and pyridine (0.29g, 5.7mmol) was added at this temperature. The mixture was then heated with stirring at 160°C for 5hrs. The reaction mixture was cooled, and a solid precipitated from the solution. It was filtered off, and dried overnight at 60°C in vacuum to yield N-(2-methyl-3-trifluoromethyl)phenyl-2-hydroxynicotinamide (46) (0.36g, 21%), m.p: 312-314°C. The product was recrystallised from DMSO to give pale pink crystals, m.p: 316°C. IR:  $\nu_{\text{max}}$  3419, 3077, 2994, 2870, 1700,

1630, 1609, 1570, 1552, 1483, 1322, 1242, 1215, 1169, 1140, 1105, 1084, 1054, 1026, 963, 917, 808, 775, 711, and 619  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (DMSO):  $\delta$  2.48 (s, 3H,  $\text{CH}_3$ ), 3.00 (bs, 1H, hydroxyl-H), 7.40 (t, 1H,  $J=7$  Hz, arom-H), 7.41 (d, 1H,  $J=7$  Hz, arom-H), 8.41 (d, 1H,  $J=7$  Hz, arom-H), 6.57 (t, 1H,  $J=7$  Hz, pyrid-H), 7.76 (d of d, 1H,  $J=7$  and 2 Hz, pyrid-H), 8.49 (d of d, 1H,  $J=7$  and 2 Hz, pyrid-H), 12.25 (NH) ppm.  $^{13}\text{C}$ -NMR (DMSO): 13.35 (Me), 120.39, 121.10, 123.19, 125.95, 126.35, 126.86, 106.74, 138.74, 140.04, 144.73, 161.97, 128.64 (multiplet,  $\text{CF}_3$ ), 162.76 ( $\text{C}=\text{O}$ ) ppm. Mass spectrum: 39, 66, 94, 122, 175, 248, 278, 296. Theory MW=296. Microanalysis Found: C: 56.77; H: 3.76; N: 9.38%.  $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_2\text{F}_3$  requires: C: 56.76; H: 3.74; N: 9.45%.

### 5.10 Synthesis of Methyl 2-Chloronicotinate (29).

Thionyl chloride (23.6g, 198.3mmol) was slowly added to 2-chloronicotinic acid (27) (10.0g, 62.6mmol) with stirring at room temperature, and the mixture was then heated under reflux until a clear solution was obtained. Hydrogen chloride and sulphur dioxide were liberated during this stage. The resulting solution was allowed to cool to room temperature and methanol ( $80\text{cm}^3$ ) was slowly added and the resulting reaction mixture was stirred for 30 minutes. Aqueous sodium carbonate (10%, approx.  $100\text{cm}^3$ ) was then added to make the solution slightly alkaline ( $\text{pH}=8$ ) and stirring was continued for a further 30 minutes.

The reaction mixture was then extracted with diethyl ether. The combined extracts were washed with water ( $300\text{cm}^3$  aliquots), dried over

anhydrous magnesium sulphate, and the ether removed on the rotary evaporator. Methyl 2-chloronicotinate (29) (10.5g, 96%) was obtained as a clear yellow oil. This was of high purity (as determined by thin layer chromatography, proton and carbon NMR spectroscopy) and was used in subsequent reactions without further purification. (literature<sup>[15]</sup> b.p: 225-230°C).

IR:  $\nu_{\text{max}}$  3624, 3461, 3006, 2956, 1970, 1901, 1740, 1579, 1449, 1402, 1306, 1277, 1193, 1143, 1067, 959, 834, 766, 743, 693, and 645  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR:  $\delta$  3.45 (s, 3H,  $\text{OCH}_3$ ), 6.92 (d of d, 1H,  $J=7$  and 5 Hz, pyrid-H), 7.72 (d of d, 1H,  $J=7$  and 3 Hz, pyrid-H), 8.05 (d of d, 1H,  $J=5$  and 3 Hz, pyrid-H) ppm.  $^{13}\text{C}$ -NMR: 52.48 (OMe), 122.19 (CH, pyrid-C), 126.25 (pyrid-C), 140.12 (CH, pyrid-C), 149.19 (pyrid-C), 151.67 (CH, pyrid-C), 164.24 (C=O) ppm. (see: Chapter 4, Table 4.1).

### 5.11 Synthesis of Ethyl 2-Chloronicotinate (3).

Thionyl chloride (3.6g, 30mmol) was slowly added to 2-chloronicotinic acid (27) (1.6g, 10mmol) with stirring at room temperature, and the mixture was then heated under reflux until a clear solution was obtained. Hydrogen chloride and sulphur dioxide were liberated during this stage. The resulting solution was allowed to cool to room temperature and ethanol (10 $\text{cm}^3$ ) was slowly added and the resulting reaction mixture was stirred for 30 minutes. Aqueous sodium carbonate (10%, approx. 100 $\text{cm}^3$ ) was then added to make the solution slightly alkaline (pH=8) and stirring was continued for a further 30 minutes.



The reaction mixture was then extracted with diethyl ether. The combined extracts were washed with water, dried over magnesium sulphate, and the ether removed on the rotary evaporator. Ethyl 2-chloronicotinate (3) (1.3g, 69%) was obtained as a clear yellow oil. This was of high purity (as determined by thin layer chromatography, proton and carbon NMR spectroscopy) and was used in subsequent reactions without further purification.

IR:  $\nu_{\text{max}}$  2960, 2300, 1730, 1580, 1555, 1440, 1405, 1350, 1300, 1240, 1150, 1060, 1025, 860, 780, 750, and 650  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR:  $\delta$  0.80 (t of d, 3H,  $J=7$  and 4 Hz,  $\text{CH}_3$ ), 3.80 (q of d, 2H,  $J=7$  and 4 Hz,  $\text{OCH}_2$ ), 6.80 (m, 1H, pyrid-H), 7.55 (d, 1H,  $J=8$  Hz, pyrid-H), 7.90 (s, 1H, pyrid-H) ppm.  $^{13}\text{C}$ -NMR: 13.45 (Me), 61.24 ( $-\text{OCH}_2$ ), 121.80 (CH, pyrid-C), 126.87 (pyrid-C), 139.55 (CH, pyrid-C), 148.72 (pyrid-C), 151.13 (CH, pyrid-C), 163.49 ( $\text{C}=\text{O}$ ) ppm (see: Chapter 4, Table 4.2).

## **5.12 Synthesis of Methyl 2-(3-Trifluoromethylanilino)nicotinate (30).**

Methyl 2-chloronicotinate (29) (1.7g, 10mmol) and 3-trifluoromethylaniline (1) (1.6g, 10mmol) were added to ethylene glycol ( $10\text{cm}^3$ ) with stirring, then quinoline (1.3g, 10mmol) was added to the mixture with stirring at room temperature. The mixture was then heated to  $160^\circ\text{C}$  and stirring at this temperature was maintained for 6hrs. The solution was cooled to room temperature, then water was added and the solution made slightly alkaline ( $\text{pH}=8$ ) by slow addition of 10% aqueous sodium

carbonate solution. The resulting solution was extracted with diethyl ether. The extract was washed with water, dried over magnesium sulphate, concentrated on the rotary evaporator and the resulting residue purified by chromatography on silica using elution with dichloromethane/light petroleum (b.p.40-60°C) ratio 2:3. Methyl 2-(3-trifluoromethylanilino)nicotinate (30) (0.9g, 31%), m.p: 72-74°C, was obtained. (literature<sup>[15]</sup> m.p: 71.5-72.1°C).

IR:  $\nu_{\max}$  3248, 2900, 1700, 1650, 1590, 1540, 1450, 1410, 1325, 1280, 1255, 1230, 1175, 1125, 1060, 925, 890, 730, 700, and 650  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR:  $\delta$  3.95 (s, 3H, -OCH<sub>3</sub>), 7.27 (d, 1H, J=8 Hz, arom-H), 7.42 (t, 1H, J=8 Hz, arom-H), 7.85 (d, 1H, J=8 Hz, arom-H), 8.10 (s, 1H, arom-H), 6.75 (d of d, 1H, J=8 and 4 Hz, pyrid-H), 8.22 (d of d, 1H, J=8 and 2 Hz, pyrid-H), 8.38 (d of d, 1H, J=4 and 2 Hz, pyrid-H), 10.38 (s, 1H, NH) ppm.  $^{13}\text{C}$ -NMR: 52.22 (OMe), 117.02 (CH, arom-C), 118.94 (CH, arom-C), 123.40 (CH, arom-C), 129.21 (CH, arom-C), 114.08 (CH, pyrid-C), 140.23 (CH, pyrid-C), 153.04 (CH, pyrid-C), 107.25 (C), 125.35 (C), 140.08 (C), 155.56 (C), 131.12 (multiplet, CF<sub>3</sub>), 167.74 (C=O) ppm (see: Chapter 4, Table 4.3). Mass spectrum: 15, 39, 51, 65, 75, 93, 95, 125, 140, 145, 168, 236, 263, 295, 296. MW=296. Microanalysis: Found: C: 57.11; H: 3.96; N: 9.54%. C<sub>14</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub> requires: C: 56.76; H: 3.74; N: 9.46%.

### **5.13 Synthesis of Methyl 2-(2-Methyl-3-trifluoromethylanilino)nicotinate (52).**

2-Methyl-3-trifluoromethylaniline (2) (1.45g, 8.2mmol) and methyl 2-chloronicotinate (29) (1.42g, 8.2mmol) were dissolved in ethylene glycol

(4cm<sup>3</sup>) in a round-bottom flask at room temperature. The mixture was then slowly heated to 145°C with protection by a dry nitrogen atmosphere, and reacted for 10hrs with stirring at 145°C. The resulting solution was allowed to cool to room temperature and made slightly alkaline (pH=8) by slow addition of 10% aqueous sodium carbonate solution. The resulting solution was extracted with diethyl ether. The extract was washed with water until pH=7, dried over magnesium sulphate, and the solvent removed on the rotary evaporator. A thick oily residue was obtained. This was chromatographed on silica using elution with dichloromethane/light petroleum (b.p.40-60°C) (2:3). Methyl 2-(2-methyl-3-trifluoromethyl-anilino)nicotinate (52) (1.37g, 53%), m.p: 69-71°C, was obtained. IR:  $\nu_{\text{max}}$  3287, 2952, 1691, 1625, 1586, 1533, 1486, 1470, 1438, 1407, 1383, 1324, 1291, 1277, 1257, 1220, 1190, 1171, 1141, 1120, 1106, 1087, 1030, 926, 793, 773, 716, 682, and 666 cm<sup>-1</sup>. <sup>1</sup>H-NMR:  $\delta$  2.35 (s, 3H, CH<sub>3</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 7.25 (t, 1H, J=8 Hz, arom-H), 7.38 (d, 1H, J=8 Hz, arom-H), 8.16 (d, 1H, J=8 Hz, arom-H), 6.62 (d of d, 1H, J=7 and 4 Hz, pyrid-H), 8.22 (d of d, 1H, J=7 and 2 Hz, pyrid-H), 8.29 (d of d, 1H, J=4 and 2 Hz, pyrid-H), 9.98 (s, 1H, NH) ppm. <sup>13</sup>C-NMR: 13.98 (Me), 52.37 (OMe), 121.31 (C-H, arom-C), 125.85 (C-H, arom-C), 126.85 (C-H, arom-C), 113.73 (C-H, pyrid-C), 140.35 (C-H, pyrid-C), 153.28 (C-H, pyrid-C), 107.25 (C), 118.24 (C), 123.12 (C), 139.38 (C), 156.38 (C), 128.89 (multiplet, CF<sub>3</sub>), 168.06 (C=O) ppm (see: Chapter 4, Table 4.4). Microanalysis: Found: C: 57.98; H: 4.12; N: 8.90; F: 18.16%. C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub> requires: C: 58.07; H: 4.22; N: 9.03; F: 18.37%.

#### 5.14 Hydrolysis of Methyl 2-(2-Methyl-3-trifluoromethylanilino)nicotinate (52) to 2-(2-Methyl-3-trifluoromethylanilino)nicotinic Acid (4).

Methyl 2-(2-methyl-3-trifluoromethylanilino)nicotinate (52) (1.24g, 4.0mmol) and potassium hydroxide (0.54g, 0.97mmol) were dissolved in a mixture of methanol (12cm<sup>3</sup>) and water (1cm<sup>3</sup>) by stirring at room temperature. The mixture was then heated under reflux for 3hours, then cooled and concentrated on the rotary evaporator. Water (3.5cm<sup>3</sup>) was added to the residue which was then acidified (pH=5) by addition of dilute hydrochloric acid (hydrochloric acid 37% : water, 1:5). The cream coloured solid which precipitated was filtered off, and dried at 40°C in vacuo overnight. The crude 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) (1.03g, 87%), m.p: 220-222°C. Recrystallisation from acetone yielded a white crystalline product (0.97g, 82%), m.p: 225-227°C. (literature<sup>[1]</sup> m.p: 226-228°C).

IR:  $\nu_{\max}$  3250, 2950, 2850, 2800, 2460, 1675, 1575, 1510, 1450, 1325, 1240, 1175, 1125, 1075, 1025, 825, 800, 775, 720, 670, and 630 cm<sup>-1</sup>. <sup>1</sup>H-NMR (acetone-d<sub>6</sub>):  $\delta$  2.30 (s, 3H, CH<sub>3</sub>), 7.22-7.27 (m, 2H, arom-H), 8.28 (d, 1H, J=8 Hz, arom-H), 6.72 (d of d, 1H, J=8 and 4 Hz, pyrid-H), 8.12 (d of d, 1H, J=8 and 2 Hz, pyrid-H), 8.21 (d of d, 1H, J=4 and 2 Hz, pyrid-H), 10.30 (s, 1H, NH) and 13.51 (brs, 1H, COOH) ppm. <sup>13</sup>C-NMR (acetone-d<sub>6</sub>): 13.52 (Me), 120.03 (C-H, arom-C), 125.89 (C-H, arom-C), 126.45 (C-H, arom-C), 114.17 (C-H, pyrid-C), 140.48 (C-H, pyrid-C), 152.55 (C-H, pyrid-C), 107.81 (C), 123.10 (C), 127.27 (C), 139.74 (C), 155.68 (C), 128.22 (multiplet, CF<sub>3</sub>), 169.13 (C=O) ppm. (see: Chapter 4,

Table 4.5). Microanalysis: Found: C: 56.84; H: 3.88; N: 9.41; F: 19.39%.  $C_{14}H_{11}N_2OF_3$  requires: C: 56.76; H: 3.74; N: 9.45; F: 19.24%.

### **5.15 Hydrolysis of Methyl 2-(3-Trifluoromethyl-anilino)nicotinate (30) to 2-(3-Trifluoromethylanilino)nicotinic Acid (42).**

Methyl 2-(3-trifluoromethylanilino)nicotinate (30) (1.62g, 5.0mmol) and potassium hydroxide (0.68g, 1.21mmol) were dissolved in a mixture of methanol (15cm<sup>3</sup>) and water (1.5cm<sup>3</sup>) by stirring at room temperature. The mixture was then heated under reflux for 3hours, then cooled and concentrated on the rotary evaporator. Water (4cm<sup>3</sup>) was added to the residue which was then acidified (pH=5) by addition of dilute hydrochloric acid (hydrochloric acid 37% : water, 1:5). The cream coloured solid which precipitated was filtered off, and dried at 40°C in vacuo overnight. The crude 2-(3-trifluoromethylanilino)nicotinic acid (42) (1.40g, 91%), m.p: 197-199°C. Recrystallisation from acetone yielded a light yellow crystalline product, m.p: 200-202°C. (literature<sup>[27]</sup> m.p: 203-204°C), whose spectra were identical with those reported in Section 5.6, see also Chapter 3, Table 3.1.

### 5.16 One-step Synthesis of 2-(2-Methyl-3-trifluoromethyl-anilino)nicotinic Acid (4)

2-Methyl-3-trifluoromethylaniline (2) (3.5g, 20mmol) and methyl 2-chloronicotinate (29) (3.4g, 20mmol) were dissolved in ethyleneglycol (5cm<sup>3</sup>) in a round-bottom flask at room temperature. The mixture was slowly heated to 145°C and under a dry nitrogen atmosphere the mixture was then stirred at 145°C for 10hrs. The resulting solution was cooled to room temperature and 10% aqueous sodium carbonate added to make the solution slightly alkaline (pH=8).

The solution was extracted with diethyl ether, and the ether extract was washed with water until pH=7. The ethereal solution was dried over magnesium sulphate, and the solvent was removed. A thick oil (4.81g) was obtained.

The thick oil (4.8g), potassium hydroxide (2.1g, 3.77mmol) and water (3.8cm<sup>3</sup>) were dissolved in methanol (46cm<sup>3</sup>), and the mixture was heated under reflux with stirring for 3hrs. Then the mixture was cooled and concentrated under vacuum to remove the methanol.

Water (12cm<sup>3</sup>) was added to the residue which was then acidified (pH=5) by addition of dilute hydrochloric acid (hydrochloric acid 37% : water, 1:5). The cream coloured solid which precipitated from the solution was filtered off and dried overnight at 40°C in vacuum. 2-(2-Methyl-3-trifluoromethylanilino)nicotinic acid (4) (3.6g, 61%), m.p 210-212°C, was obtained.

The product was recrystallized from acetone to obtain white crystals (2.05g); m.p 224-225°C (literature<sup>[1]</sup> m.p: 226-228°C), whose spectra were identical with those reported in Section 5.14, see also Chapter 4 Table 4.5.

### 5.17 Preparation of the N-methyl-D-glucamine Salt (6) of 2-(2-Methyl-3-trifluoromethylanilino)nicotinic Acid (4).

N-methyl-D-glucamine (5) (0.98g, 5mmol) and 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (4) (1.48g, 5mmol) were mixed, and propan-2-ol (10cm<sup>3</sup>) was added to the round-bottom flask at room temperature. The mixture was heated to reflux to dissolve all the solid material. Then the solution was allowed to cool to room temperature and a mobile oil settled out. Diethyl ether (70cm<sup>3</sup>) was then added and the mixture was stirred to give a white solid. The solid was filtered off and dried to yield the salt (6) (2.3g, 94%), mp: 129-130°C. The solid recrystallised from propan-2-ol to give salt (6) (2.05g, 84%), mp: 130-131°C. (literature<sup>[1]</sup> mp: 135-137°C). IR:  $\nu_{\max}$  3200-3400, 1600, 1150-1080 cm<sup>-1</sup>. <sup>1</sup>H-NMR (D<sub>2</sub>O):  $\delta$  2.08 (s, 3H, arom-CH<sub>3</sub>), 6.53 (d of d, 1H, J=7 and 5 Hz, arom-H), 6.98 (t, 1H, J=8 Hz, arom-H), 7.12 (d, 1H, J=8 Hz, arom-H), 7.43 (d, 1H, J=8 Hz, arom-H), 7.70 (d of d, 1H, J=5 and 2 Hz, arom-H), 7.91 (d of d, 1H, J=7 and 2 Hz, arom-H), 2.50 (s, 3H, -NCH<sub>3</sub>), 2.97 (m, 2H, glucam-H), 3.40 (m, 2H, glucam-H), 3.53 (m, 1H, glucam-H), 3.62 (m, 2H, glucam-H), 3.87 (m, 1H, glucam-H) ppm. <sup>13</sup>C-NMR (D<sub>2</sub>O): 15.51 (Me, arom-Me), 35.18 (Me, -NHMe), 53.35 (C-H, glucam-C), 64.91 (C-H, glucam-C), 70.36 (C-H, glucam-C), 72.77 (C-H, glucam-C), 72.94 (C-H, glucam-C), 73.12 (C-H,

glucam-C), 116.12 (C-H, arom-C), 117.35 (arom-C), 123.42 (C-H, arom-C), 125.40 (arom-C), 128.16 (C-H, arom-C), 129.05 (C-H, arom-C), 130.83 (multiplet, CF<sub>3</sub>), 131.94 (arom-C), 141.78 (arom-C), 143.13 (C-H, arom-C), 151.42 (C-H, arom-C), 158.03 (arom-C), 176.06 (C=O) ppm. Microanalysis: Found: C: 49.07, H: 5.80, N: 7.81; F: 10.66% C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>7</sub>F<sub>3</sub> requires: C: 51.32, H: 5.74, N: 8.55; F: 11.60%.



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