

IMPROVED PROCESS FOR THE PREPARATION OF 2-METHYL-3-TRIFLUOROMETHYLANILINE: A VERSATILE INTERMEDIATE FOR FLUNIXIN SYNTHESIS

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Abstract - A detailed new experimental investigation into the synthesis of Flunixin *via* 2-methyl-3-trifluoromethylaniline is described. The coupling process between 2-methyl-3-trifluoromethylaniline and 2-chloronicotinate was achieved stoichiometrically and in high yield, when ethylene glycol was used as reaction solvent at 160°C.

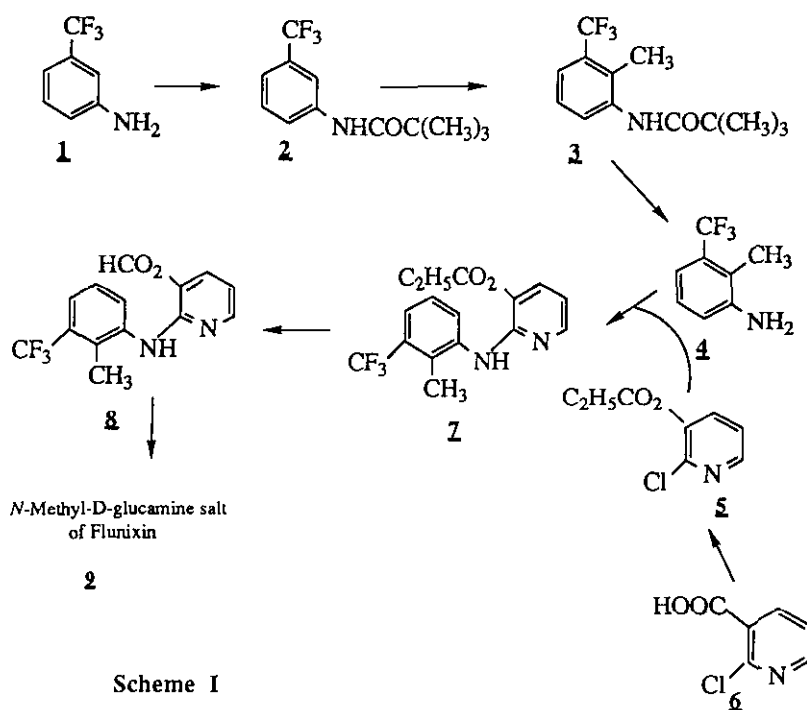
Flunixin, known as 2-[(2'-methyl-3'-trifluoromethyl)anilino]nicotinic acid] (**8**) is a potent analgesic, particularly suitable for parenteral administration¹ as well as an anti-inflammatory analgesic in horses.^{2,3} Its *N*-methyl-D-glucamine salt exhibits a unique parenteral activity with a potency comparable to that seen in potent narcotic analgesics such as morphine and the like.^{4,5}

2-Methyl-3-trifluoromethylaniline (**3**) is a versatile intermediate in the preparation of Flunixin. Its availability in the commercial market is very limited, and when existing, it is highly priced. Therefore the necessity to establish a reliable, cheap, new practical approach to the synthesis is very urgent. We investigated new experimental conditions for the methylation of the protected 3-trifluoromethylaniline (**2**) and its subsequent coupling with ethyl nicotinate (**5**) (Scheme I).

Treatment of 3-trifluoromethylpivaloylaniline (**2**) with 2 moles of butyllithium, and subsequently with methyl iodide directed predominantly a specific ortho substitution in position 2 of pivaloylaniline *via* the dilithio species.⁶ Removal of pivaloyl group in **3** is readily achieved with potassium hydroxide in ethylene glycol (160°C / 8 h) and 2-methyl-3-trifluoromethylaniline (**4**) of high purity was obtained.

We attempted unsuccessfully to couple **4** with 2-chloronicotinic acid (**6**), since niflumic acid, known as 2-[3'-trifluoromethylanilinonicotinic acid], was prepared by direct coupling.⁷ The 2-chloronicotinic acid (**6**) was converted to the ester *via* the corresponding acid chloride quantitatively to the ester (**6**) which was coupled with **4** in ethylene glycol at 160°C for 5 h. The use of ethylene glycol improved the efficiency of the coupling process in two ways: (a) **4** and the nicotinate (**5**) were used in equimolecular ratio, while previously excess of **4** was used neat to achieve the coupling under drastic conditions.⁵ This is a much

more practical and economic process with respect to utilisation of the more expensive intermediate. (b): high yielding with purification easily achieved by distillation.



EXPERIMENTAL

Melting points were measured by using a Kofler apparatus and are uncorrected. ^1H Nmr spectra were recorded on a Bruker 300 spectrometer.

3- Pivalylaminobenzotrifluoride (2)

3-Aminobenzotrifluoride (**1**) (2580 g, 16 mol), anhydrous potassium carbonate (2500 g, 18.11 mol) and anhydrous acetone (12500 ml) were placed in a 20 l-vessel, fitted with a reflux condenser and a dropping funnel. Pivaloyl chloride (2114 g, 17.62 mol) was added dropwise with stirring over 4 h. As the reaction is exothermic, the rate of addition was controlled sufficiently to maintain gentle reflux. The reaction mixture was stirred under reflux for 6 h. On cooling, the mixture was filtered, and the filtrate evaporated to dryness. The residue was triturated with hexane (6 l), yielding a white solid which was recrystallised from ethanol (**2**) (3650 g, 93%) mp 109°C (lit., 1 mp $109.5\text{--}110^\circ\text{C}$).

2-Methyl-3- pivalylaminobenzotrifluoride (3)

3- Pivalylaminobenzotrifluoride (**2**) (1200 g, 4.89 mol) was dissolved in dry ether (12 l) in a 20 l vessel fitted with a reflux condenser, nitrogen inlet / outlet and a rubber septum. Through a cannular, butyllithium

(2.5 M in hexane) (4800 ml, 12 mol) was added and the rate of addition was controlled very carefully by removing the cannular from the butyllithium solution. After completion of the addition, the solution turned deep red and stirring continued for further 4 h. Methyl iodide (480 ml, 7.62 mol) was added dropwise over 3 h. (Caution: the reaction is very exothermic at one stage.) The reaction was stirred overnight. Ice water (1500 ml) was added dropwise, then the whole reaction mixture was poured into 8 l of water and filtered over super flow. The aqueous layer was then discarded and the ether layer dried (MgSO_4) and evaporated, affording a very viscous red oil. This was taken up with ethyl acetate and hexane was added until precipitation occurred and kept at 4°C for 48 h. The slightly yellowish solid was filtered off and dried (990 g, 78%). The purity as measured by nmr was above 86%) and used for the next step without further purification.

A sample recrystallised from ethyl acetate/hexane (1:1) yielded white crystals: mp 118-121°C (lit,¹ mp 123-124°C)

2-Methyl-3-trifluoromethylaniline (4)

2-Methyl-3-pivalylaminobenzotrifluoride (3) (420 g, 1.62 mol), potassium hydroxide (420 g, 7.5 mol) and ethylene glycol (4200ml) were placed in a 10 l-vessel, fitted with a reflux condenser and heated gradually to 160°C, with stirring. This temperature was maintained for 8 h. On cooling, the reaction mixture was poured into water (5 l) and extracted with dichloromethane (3x 3 l). The organic layer layer was washed with brine, dried (MgSO_4) and evaporated to dryness. The residue was distilled and the distillate suspended in hexane at -20°C, yielding a white solid (222 g, 78.3%) mp 38-40°C (identical to an authentic commercial sample from FLUOROCHEM Ltd)

Ethyl 2-Chloronicotinate (5)

Thionyl chloride (700 g, 6.14 mol) was added slowly to 2-chloronicotinic acid (6) (300 g, 1.90 mol) with stirring at room temperature. The reaction mixture was gradually heated to reflux, while the mixture became homogeneous after 1.5 h of reflux. Refluxing was continued for a further 1.5 h. On cooling, thionyl chloride was evaporated and benzene (100 ml) was added to the residue and evaporated. This operation was carried out twice. The oil obtained in quantitative yield was dried and its purity was checked by nmr and used for the next step without further purification. ¹H Nmr (CDCl_3 , 300 MHz): 8.48 (dd, J=3.2 and 4.5 Hz, 1H), 7.13 (dd, J=2 and 6.6 Hz, 1H), 7.32 (m, 1H), 4.22 (q, J=7.2 Hz, 2H), 1.38 (t, J=7.2 Hz, 3H)

Ethyl 2-(2-Methyl-3-trifluoromethylanilino)nicotinate (7)

Ethyl 2-chloronicotinate (5) (234 g, 1.265 mol) and 2-methyl-3-trifluoromethylaniline (4) (221.5 g, 1.265 mol) were dissolved in ethylene glycol (1300 ml) and heated up to 160°C with stirring. The reaction mixture was maintained at this temperature for 6 h. HCl gas was formed during the course the reaction. On cooling, the reaction mixture was poured into water (2 l) and extracted with ether (2x 1 l). The ether layer was dried (MgSO_4), evaporated and the residue distilled at 162-165°C/0.5 mmHg. Tlc (silica plate, chloroform) showed a major spot corresponding to the desired product (R_f 0.65) with minor impurities (less than 14%). This material was used for the next step without further purification (350 g, 86%). A sample for analytical

analytical data was purified by flash chromatography on silica (dichromethane as eluant) mp 43-45°C (lit,⁵ mp 44-46°C)

2-(2-Methyl-3-trifluoromethylanilino)nicotinic acid (8)

Ethyl 2-(2-methyl-3-trifluoromethylanilino)nicotinate (**7**) (157.1 g, 0.48 mol) and potassium hydroxide (55 g, 1 mol) were dissolved in a mixture of methanol (1450 ml) and water (120 ml) at room temperature. The mixture was then refluxed for 3 h, cooled and concentrated. The residue was dissolved in water (200 ml) and the aqueous solution was taken up with ether (500 ml). The ether layer was separated and to this was added 6N HCl slowly to pH 2-3 and white solid precipitated. The solid was filtered off, dried at 60°C in vacuum overnight and recrystallised from acetone. (130 g, 90%) mp 224-227°C (lit,⁵ mp 226-228°C)

N-Methyl-D-glucamine salt of 2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (9)

2-(2-methyl-3-trifluoromethylanilino)nicotinic acid (**8**) (127.1 g, 0.429 mol) and N-methyl-D-glucamine (88.75 g, 0.454 mol) were mixed with anhydrous acetonitrile (1250 ml) and refluxed for 10 min, then filtered whilst hot through a heated sintered filter. On cooling, the salt was crystallised as white crystals. This was filtered off, dried at 40°C under high vacuum and recrystallised from acetonitrile (201 g, 95.3%) mp 135-138°C (lit,⁵ mp 136-139°C)

REFERENCES

- 1 H J Doran, U S 07, 812, 183, (Chem Abstr, 1993, **119**, 249849k)
- 2 J W Houdeshell and P W Hennessey, *J Equine Med Surg*, 1977, **1**, 57
- 3 T. Tobin, *J. Equine Med. Surg*, 1979, **3**, 298
- 4 M H Sherlock and N. Sperber, U.S. 3,337,570 (Chem Abstr, 1970, **72**, 66829v)
- 5 M H Sherlock and N J. Bloomfield, U.S. 3,839,344 1974 (Chem. Abstr, 1975, **82**, 16705n)
- 6 H.W Gschwend and W. Fuhrer, *J. Org. Chem*, 1979, **44**, 1133
- 7 Laboratoires U P S.A., Neth, 6, 414, 717 (Chem. Abstr, 1966, **64**, 712h)

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