Journal of Fluorine Chemistry, 50 (1990) 243–249

Received June 25, 1990, accepted July 20, 1990

PREPARATIVE FLOW TECHNIQUES 2. GRIGNARD ADDITION REACTION ON FLUOROACETONITRILE: SYNTHESIS OF 2-AMINO-2-FLUOROMETHYL-3-PENTENENITRILE

FRITZ GERHART, JEAN-PAUL FRANÇOIS
Merrell Dow Research Institute, Strasbourg Center, 16, rue d'Ankara, F-67084 Strasbourg, Cedex (France)

MICHAEL KOLB*, MARK LASKOVICS
Merrell Dow Research Institute, 2110 East Galbraith Road, Cincinnati, Ohio 45215 (U.S.A.)

and JEAN-FRANÇOIS LE BORGNE
Gruppo Lepetit S.P.A., Zona Ex Punto Franco, Casella Postale 199, 72100 Brindisi (Italy)

SUMMARY

A convenient methodology for the use of fluoroacetonitrile in organic synthesis is described. The method, a low-temperature flow technique, is suitable for small scale as well as for large scale applications.

INTRODUCTION

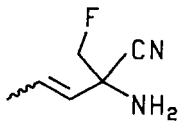
Readily available starting materials for the synthesis of functionalized fluoromethyl compounds, are rare [1]. For that reason the synthesis of these derivatives most often implies a fluorine-introducing step in the reaction scheme [2]. Usually on scale-up this then leads to inconveniences arising from toxicity, corrosiveness and stability of the reagents, along with having to deal with the hazards involved in their handling.

Fluoroacetonitrile is an attractive starting material for the preparation of fluoromethyl derivatives from a synthetic point of view. However, its potential toxicity [3] forbids its general use in reaction schemes for compounds to be scaled up.

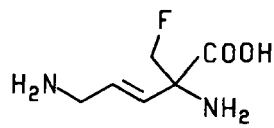
0022-1139/90/$3 50

SYNTHESES

Here we describe a methodology, which allows the use of fluoroacetonitrile in a convenient, however also secure manner, in the scale-up of 2-amino-2-fluoromethyl-3-pentenenitrile (1), a key intermediate in the synthesis of 2,5-diamino-2-fluoromethyl-3(E)-pentenoic acid (2) [4], an enzyme-activated inhibitor of ornithine decarboxylase activity.

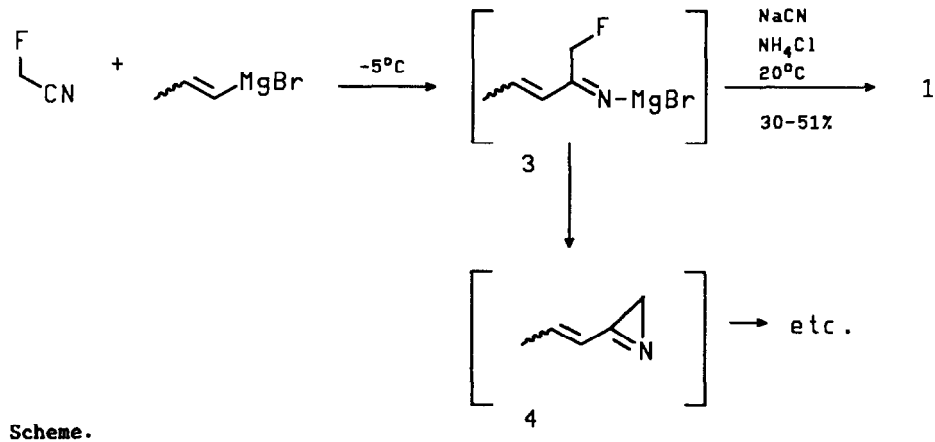


1



2

Originally the fluoromethyl pentenenitrile 1 was prepared in a batch process, adding 1-propenylmagnesium bromide to 0.85 equivalents of fluoroacetonitrile in tetrahydrofuran at -40°C to -50°C, (estimated $\Delta G \simeq$ -110 kcal/mol) followed by quenching the excess Grignard reagent and treatment of the iminomagnesium salt 3 with sodium cyanide and ammonium chloride in water (-35°C to 10°C; Scheme). At a 10 mol scale, several hours are required for the addition step at the required reaction temperature. The imino magnesium salt 3 slowly escapes over this period of time the desired reaction pathway even at -50°C, presumably towards the azirine 4 and further to unidentified by-products. Also, the risk in handling large quantities of fluoroacetonitrile in a reactor over this time period was a primary concern for us.



Scheme.

Electronically controlled, short-stroke electromagnet, piston diaphragm dosing pumps ProMinent of the types B 25001 S and E 1002 S, purchased from Chemie und Filter GmbH (Heidelberg, West Germany), were used for the introduction of the reagents into the flow reactor.

Flow Reactor (Figure)

A cylindrical reactor (brass, 50 mL) is equipped with a stirring bar, 2 copper tubes (6 mm Ø) connected to the inlets, teflon tubing (6 mm Ø) at the lid outlet, and a thermocouple, introduced through the lid into the reactor. The bottom inlet copper tube is coiled around the reactor, the lid-inlet tube is kept at 30°C by use of a heat-exchange device. The system is kept tight by use of teflon seal gaskets in the lid, the in- and the outlet openings towards the reactor side, and by pressure screw/ferule joints towards the tubing. The inlet copper tubes are connected by teflon tubing (6 mm Ø, pressure screw/ferule connection) to the pumps, the pump inlets via teflon tubes (6 mm Ø) to either fluoroacetonitrile, THF or to the propenylmagnesium bromide solution (0.75M in THF), respectively. Positive N_2 pressure protects all the organomagnesium containing equipment.

Before the system is started, its integrity is checked by pumping hexane through both inlets. The entire flow reactor with the encoiled copper inlet tubing is immersed in a dry-ice/acetone bath (-78°C).

2-Amino-2-fluoromethyl-3-pentenenitrile p-toluene-sulfonate (1·PTS); Typical procedure

A 6 L, three-necked, round-bottomed flask is equipped with a pressure-equalizing addition funnel topped with a gas inlet, a condenser connected to a nujol-filled bubbler and a stirrer. The system is flushed with N_2 and the flask is then charged with Mg (70 g, 2.88 mol), THF (100 mL) and 1-bromo-1-propene (10 g, 0.08 mol). A slightly positive pressure of N_2 is maintained throughout the reaction. The mixture is warmed to 40°C to start

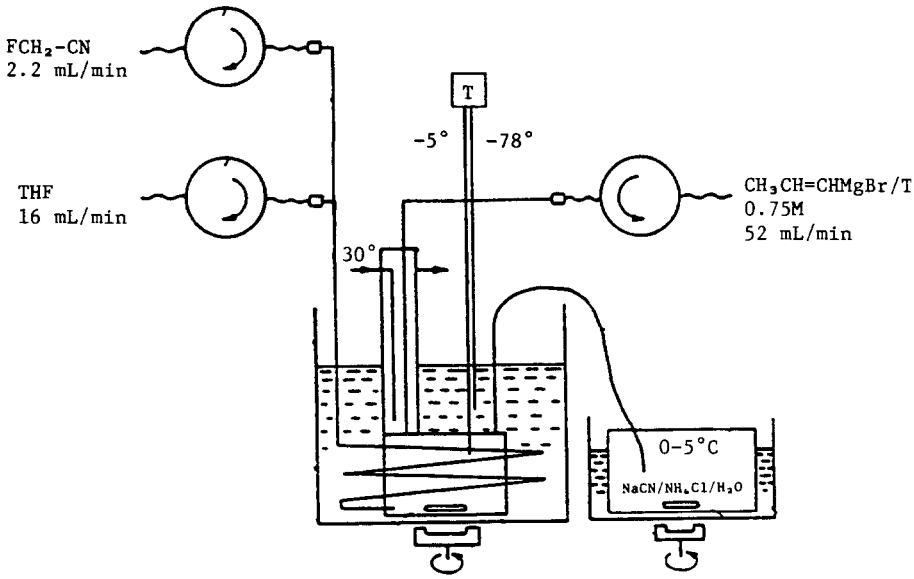


Fig. Flow-system device for the continuous 1-propenyl magnesium bromide addition to fluoroacetonitrile.

the reaction. A solution of 1-bromo-1-propene (350 g, 2.89 mol) in THF (3.5 L) is added over 2 h at 45-50°C. The reaction mixture is stirred for another hour at 40°C and then allowed to cool to room temperature to give 2.7 mol of an 0.75 M solution of the Grignard reagent in THF.

This and the observed unfavorable kinetics of this reaction scheme led us to investigate the possibility of using our previously described flow-system [5] as a safe methodology to handle large scale fluoroacetonitrile reactions. The features which are intrinsic to the flow-technique method, namely a small reaction volume and a short residence time of the reactants in the mixture, allowed us to minimize the hazard arising from the use of fluoroacetonitrile and also to improve on the described reaction kinetics.

Fluoroacetonitrile is pumped directly out of the container, mixed with tetrahydrofuran and run into the 50 mL reaction vessel together with the preformed Grignard reagent (Figure). Precaution has to be taken that the Grignard reagent is kept at 30°C before entering the reaction vessel (precipitation occurs at ~10°C). The outlet tube of the vessel then delivers the reaction mixture to a cooled Strecker solution. The amino nitrile 1 is extracted into toluene, and isolated on addition of p-toluene sulfonic acid, as the corresponding salt.

Under these conditions, which correspond to a feed rate of 37 mmol/min for the reagents to the reactor, the inside temperature stabilizes at -5°C (±5°C). The average yield obtained over 30 experiments ranging from a 2 to 4 mole scale, was 40% for isolated 2-amino-2-fluoromethyl-3-pentenenitrile 1 p-toluenesulfonic acid salt, of sufficient purity to be used as such in the synthesis of the amino acid derivative 2 [4].

Altogether about 100 mole of fluoroacetonitrile has been transformed to the aminonitrile 1 using the flow system. This corresponds to a reaction time of only 42 h using about 6 L of fluoroacetonitrile and a total reaction volume of 180 L. We strongly believe that these data demonstrate this methodology to be a convenient and safe technique and allows one to take advantage of fluoroacetonitrile, an attractive starting material for the synthesis of fluoromethyl compounds.

EXPERIMENTAL

^{1}H and ^{19}F NMR spectra were obtained with a Varian EM-390 (^{19}F: 84.6 MHz; reported in Ø down field from C_6F_6). Melting points were measured on a Kofler melting point apparatus. All reagents and solvents were used as obtained from the chemical supplier. Fluoroacetonitrile was bought from Columbia, Organic Chemicals Co., Inc. (Camden, SC, 29020, USA).

This Grignard solution in THF and fluoroacetonitrile (2.23 mol) together with THF are pumped at a rate of 52 mL/min and 18.2 mL/min (16.0 mL/min for THF, 2.2 mL/min for CH_2FCN), respectively, into the cooled flow-reactor system (-78°C, dry-ice/acetone; the lid-inlet tubing is kept at 30°C via a heat exchange device connected to a 30°C methanol bath). Stirring is started. The onset of the reaction in the reactor is marked by a rise of the inside temperature from -70°C to -5°C. During the reaction period the inside temperature varies around -5°C (±5°C). *The following operations should be done in a well ventilated hood and appropriate measures should be taken to avoid HCN intoxication.* The cold outflow is run into an ice-cooled stirred solution of NaCN (166 g, 3.39 mol) and NH_4Cl (500 g, 9.34 mol) in water (3 L). The mixture is stirred overnight at room temperature and toluene (3.6 L) is added. The layers are separated, the organic layer is washed with water (3 x 2 L) and then brine (2 L). The combined aqueous layers are treated with sodium hypochlorite before being stored in a special drum for destruction. To the organic layer is added a solution of p-toluenesulfonic acid (460 g, 2.42 mol) in THF (0.92 L). The solution is concentrated under reduced pressure (30-40°C, 20 torr), until crystallization commences. The mixture is stirred overnight, EtOAc (1 L) is added, the crystalline product is filtered off and washed with EtOAc (2 x 1 L). The solid is dried *in vacuo* and 269 g (40%) of 2-amino-2-fluoromethyl-3-pentenenitrile p-toluene-sulfonate (1·PTS) is isolated, almost exclusively (^1H NMR, >95%) as the Z-isomer; m.p. 125-135°C.

^1H-NMR (D_2O, DSS): δ = 1.96 (dd, 3H, J=2, 7 Hz, CH_3); 2.38 (s, 3H, CH_3); ABX centered at 4.83 (2H, J=11, 45 Hz, CH_2F); 5.33 (ddt, 1H, J=2, 2, 11 Hz, C=CH); 6.21 (dq, 1H, J=7, 12 Hz, CH-Me); 7.68, 7.65, 7.38 and 7.35 (4s, 1:1:1:1, 4H, aryl).

^{19}F NMR ($CDCl_3/C_6F_6$) Ø = -58.5 (t, J=45 Hz).

No correct CHN-analysis has been obtained for the amino nitrile **1**. Transformation to the corresponding crystalline phthalimido derivative [4] gave 98.4% pure material [HPLC, $MeCN/H_2O$ (70/3)] in 75% yield.

REFERENCES

1 I.L. Knunyants and G.G. Yakobson, 'Synthesis of Fluoroorganic Compounds', Springer-Verlag, Berlin, (1985).

2 Reagents used in this context are: DAST (Et_2NSF_3): L.N. Markovskij, V.E. Pashinnik and A.V. Kirsanov, Synthesis, (1973) 787; (1975) 801; P.J. Card, J. Org. Chem., 48 (1983) 393; P.J. Card and G.S. Reddy, J. Org. Chem., 48 (1983) 4734. $Et_2N(Me_2N)SF_2$: W.J. Middleton, J. Org. Chem., 40 (1975) 574. TASF $[(Me_2N)_3S^+ F_2Si\text{-}Me_3]$: J.E.G. Middleton, US Pat. 3 940 402; W.B. Farnham and R.L. Harlow, J. Am. Chem. Soc.,103 (1981) 4608; P.J. Card and W.D. Hitz, J. Am. Chem. Soc., 106 (1984) 5348. FAR $[Et_2NCF_2CHFCl]$: C.M. Sharts and W.A. Sheppard, Org. React. (N.Y.), 21 (1974) 125. XeF_2, HF: T.B. Patrick, K.K. Johri and D.H. White, J. Org. Chem., 43 (1983) 4158; AgF or HgF_2: J. San Filippe and L.J. Romano, J. Org. Chem., 40 (1975) 782; S.T. Purrington and J.H. Pittman, Tetrahedron Lett., 29 (1988) 6851. XeF_2: R. Filler, Isr. J. Chem., 17 (1978) 71. F_2: T. Tsushima, K. Kawada and T. Tsuji, J. Org. Chem., 47 (1982) 1107.
RSO_2NFR: E. Di Herding and R.W. Lang, Tetrahedron Lett., 29 (1988) 6087; W.E. Barnette, J. Am. Chem. Soc., 106 (1984) 452. $P\text{-}CH_2NMe_3F$: S. Colonna, A. Re, G. Gelbard and E. Cesarotti, J. Chem. Soc. Perkin I, (1979) 2248. CF_3OF: D.H.R. Barton, R.H. Hesse, G.P. Jackman, L. Ogunkoya and M.M. Pechet, J. Chem. Soc. Perkin I, (1974) 739.
$c[\text{-}CO\text{-}(CH{=}CH)_2\text{-}NF\text{-}]$: S.T. Purrington and W.A. Jones, J. Org. Chem., 48 (1983) 761; J. Fluorine Chem., 26 (1984) 43. HF/Pyridine: G.A. Olah and J. Welch, Synthesis, (1974) 652; G.A. Olah, J.T. Welch, Y.D. Vankar, M. Nojima, I. Kerekes and J.A. Olah, J. Org. Chem., 44 (1979) 3872. SF_4/HF: J. Kollonitsch, S. Marburg and L.M. Perkins, J. Org. Chem., 44 (1979) 771; ibid., 40 (1975) 3808. G.A. Boswell, Jr., W.C. Ripka, R.M. Scribner and C.W. Tullock, Org. React. (N.Y.), 21 (1974) 1.
$2,4,6\text{-}Me_3C_5H_2NF^+TfO^-$: I. Shimizu and A. Ishii, Chem. Lett., (1989) 577.

3 See also lit. 12 in reference 4.

4 P. Bey, F. Gerhart, V. Van Dorsselaer and C. Danzin, J. Med. Chem., 26 (1983) 1551.

5 For a view of the cross section of the reaction vessel, and more technical details on its design: M. Kolb, F. Gerhart and J.-P. François, Synthesis, (1988) 469; F. Gerhart and M. Kolb, US Pat. 4 847 401, July 11, 1989.