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Synthetic studies towards the antiviral pyrazine derivative T-705

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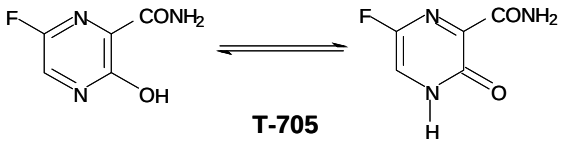
Abstract:

We report the improved synthesis of the antiviral 6-fluoro-3-hydroxy-pyrazine-2-carboxamide (T-705).

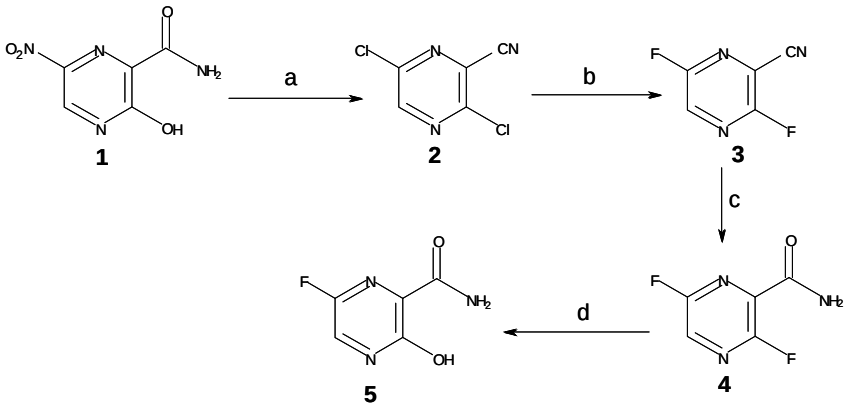
Introduction:



T-705, a fluorinated pyrazinone carboxamide, exhibits anti-influenza virus activity with a IC_{50} of 1 µM in vitro and in vivo[1]. In a promising new study T-705 prevented mortality in rodents infected with the normally fatal West Nile virus**2.** In an attempt to prepare this substance as a reference standard we encountered problems with the published procedures and thus optimised some of them.

Result and discussion:

The synthetic scheme described in patent was followed but the details were modified as described below.



***Reagents**: a) $POCl_3$, pyridine, 20-100 °C reflux; b) KF, BuN+Br-, DMSO, 55°C; c) 1:1 Conc. HCL:THF, 7 h; d) $NaHCO_3$, H_20, dioxane, 55 °C, 8h*

The synthesis started from the reaction of the nitro compound **1**[1] with $POCl_3$ in presence of pyridine to get 3,6 dichloropyrazine-2-carbonitrile (**2**). Initially the yield of this reaction was below 30% following the reported conditions at 55 ^oC. Raising the reaction temperature to 70^oC resulted in an initially homogeneous reaction mixture and **2** was finally isolated in 60% yield which is satisfactory considering the fact, that three different transformations are achieved in one pot. The exchange of chlorine against fluorine in the step leading to **3** was achieved using dry KF and BuN^+Br^- in DMSO. In this step, the recommended workup (Ref. 1, example II-3) asks for the isolation of the product by extraction of an acidic solution. In our hands this organic layer did not contain appreciable amounts of product, but **3** could be isolated by the extraction of the basic aqueous phase omitting the addition of HCl. While the nitrile hydrolysis of **3** to **4** proceeded without problems, the regioselective hydrolysis of the fluorine in the 3 position still is not a clean reaction, but we could isolate **5** by reverse phase chromatography.

Experimental:

3,6 dichloropyrazine-2-carbonitrile (2)

1 (8.00 g, 43 mmol) was added cautiously to $POCl_3$ (41 ml, 162 mmol) kept at 55-60 ^oC with magnetic stirring resulting in a suspension, heating this mixture to 70 ^oC for 15 min resulted in a homogenous solution. This was cooled to room temperature and pyridine (14 ml) was added dropwise with cooling keeping the temperature below 60 ^oC. The reaction mixture was stirred at 60 ^oC for 1 hr, then at 80 ^oC for 1 hr and finally at 100 ^oC for 4 hr. The cooled reaction mixture was added to crush ice (500g) with rapid stirring for 1 h. This solution was extracted with ethyl acetate (3x100ml), the organic phase washed with brine, dried over Na_2SO_4, and concentrated to dryness. The solid brown crude product was purified by Kugelrohr distillation at 65 $^oC/2.23x10^{-2}$ mbar to get the product as colourless crystals (4.5g, 60%).
mp: 89.7-89-8 ^oC
IR (KBr) cm^{-1}: 2241
^1H NMR ($CDCl_3$): 8.54 (1H, s)

3, 6-difluoropyrazine-2-carbonitrile (3)

To a solution of 3,6-dichloro pyrazine-2-carbonitrile (**2**) (5.00 g, 28 mmol) in DMSO (10 ml) was added vacuum dried KF (10.00 g, 172 mmol) and BuN^+Br^- (3.7 g, 11 mmol) was added and the mixture stirred at 50-55 ^oC for 3 h. Water (10 ml) was added to the cooled reaction mixture followed by extraction using ethyl acetate (4x20 ml) the combined organic layer were washed with brine, dried with Na_2SO_4 and concentrated to dryness to get crude product as an oil. The crude product was purified by Kugelrohr distillation at 55 $^oC/ 1.98x10^{-2}$ mbar as colourless crystals (2.6 g, 65%)
mp: 57.5-57.6 ^oC
IR (KBr) cm^{-1}: 2249
^1H NMR ($CDCl_3$) δ: 8.30(1H, dd, J=1.37, 8.04 Hz)

3, 6-difluoropyrazine-2-carboxamide (4)

3 was hydrolized to **4** following the published procedure[1] with no alterations.

6-fluoro-3-hydroxy-pyrazine-2-carboxamide (T-705) (5)

4 (50 mg, 0.31 mmol) was suspended to a mixture of dioxane (0.5 ml) and water (1 ml). Sodium hydrogen carbonate (0.132 g, 1.57 mmol) was added to above solution and the resulting mixture was stirred at 50 ^oC for 8.5 hrs. 6M HCl (0.5 ml) was added to the cooled solution to adjust to pH 1.0 and extracted with ethyl acetate (4x5 ml). The combined organic

layers were washed with brine, dried over Na_2SO_4 and concentrated to dryness to get the crude product that was purified on a Phenomenex Gemini reversed phase column using a gradient containing 0,1 %HCOOH of water / CH_3CN from 97:3 to 50:50. The fractions containing the product were lyophylized resulting in 12 mg of the product as a colorless, amorphous solid that in addition to showing the same IR and ^{1}H-NMR spectral data as reported, showed the expected molecular ion signal in the GC/MS.

Conclusion:

In summary we have successfully re-synthesised T-705 with some improvements to the experimental procedures.

References:

1. Furuta Y, Egawa H, Takahashi K, Tsutsui Y, Uehara S, Muratami M. Patent Application. International application number: PCT/JP2002/008250, International publication number: WO 2003/015798.
2. J.D. Morrey, B.S.Taro, V. Siddharthan, H. Wand, D.F. Smee, A.J. Christensen, Y. Furuta, Antiviral Res. 2008, 80, 377.