Nitration of Benzoic Acids under Continuous Flow Conditions

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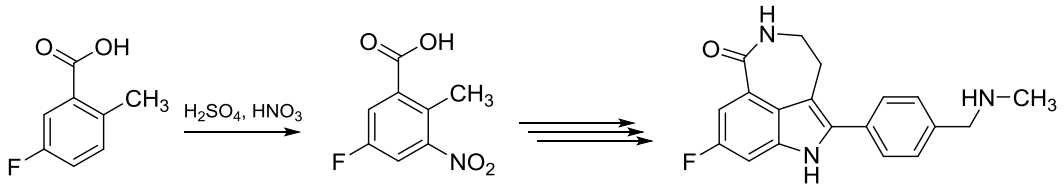
Objectives: Nitration is an extremely useful reaction for the functionalization of aromatic ring systems. Due to the exothermic nature of the reaction, especially on large scale, it has the potential to be very dangerous, especially when generating explosive nitro-species.[1] Some of the major benefits of flow chemistry, are fine control over reagent mixing, control of residence time in the reactor and very efficient heat transfer, because of this, continuous flow chemistry has been increasingly applied to large scale preparations of nitro-arenes.[2] However there have very few reports on the nitration of electron deficient arenes in under these conditions.[3]

The objective of this research was the preparation using flow chemistry, of sufficient quantities of the nitro intermediate (**2**) to allow production of Rucaparib (**3**).

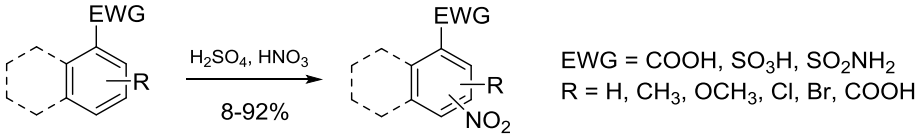


1 **2** **3**

Methods: Solutions of 5-fluoro-2-methylbenzoic acid (**1**) in concentrated sulfuric acid were reacted with nitric acid in sulfuric acid. The effect(s) of concentration, residence time, mixing, stoichiometry, nitric acid (fuming/glacial) and temperature on the reaction outcome were examined. Analysis of the by-product profile was also completed.

Results and Conclusions: Initial attempts with nitric acid in acetic acid gave no conversion (**1** to **2**).[4] As sulfuric acid is incompatible with components of the FlowSyn, e.g. certain plastics, namely PEEK. These components were upgraded to Hastalloy allowing direct translation of batch conditions (H_2SO_4/HNO_3). With these conditions we were able to achieve yields of up to 82% of **2** and scale this process up to batches of 25+ g, providing practical quantities of (**2**).

These optimised conditions were then applied to a range of electron deficient aromatic compounds to demonstrate the versatility of this process.



References:

1 A. Lunghi, P. Cardillo, Riv. Combust. **1997**, *51*, 1–2; b) J. Barton, R. Rogers, Chemical Reaction Hazards, IChemE, Trowbridge,1997.
2 a) C. E. Brocklehurst, H. Lehmann and L. La Vecchia *Org. Process Res. Dev.* **2011**, *15*, 1447–1453 b) J. Pelleter and F. Renaud Org. *Proc. Res. Dev* **2009,** *13,* 698–705
3 A. A. Kulkarni, V. S. Kalyani, R. A. Joshi and R. R. Joshi *Org. Proc. Res. Dev*. **2009,** *13,* 999–1002
4 www.uniqsis.com - FlowSyn™ Application Note 22: Flow Nitration