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Fries rearrangement: scalable synthesis of key fluoro building blocks 3-fluoro-4-methoxybenzoyl chloride and 1,2-diethoxy-3-fluorobenzene

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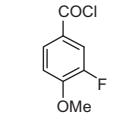
ABSTRACT

Lewis acid catalyzed Fries rearrangement of 2-fluorophenyl acetate (**3**) was performed on kg scale. The *ortho* **5** and *para* **4** isomers obtained were separated in an industrially feasible way. Compound **4** was then converted into fluorinated building block 3-fluoro-4-methoxybenzoyl chloride (**1**) while compound **5** was converted into 1,2-diethoxy-3-fluorobenzene (**2**) in high yields.

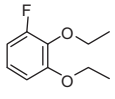
As many as 30% agrochemicals and 20% pharmaceuticals are estimated to contain fluorine, including half of the top ten drugs sold in 2005.[1] The applications of fluorinated molecules in pharmaceuticals and agrochemicals are continuously increasing owing to their metabolic stability and also due to their usefulness as bioisostere of the hydrogen atom. An estimated one fifth of pharmaceuticals contain fluorine, including several of the top drugs. Therefore there is a growing requirement of fluorinated building blocks.

Our literature search revealed that 3-fluoro-4-methoxybenzoyl chloride (**1**) and 1,2-diethoxy-3-fluorobenzene (**2**) (Fig. 1) are key fluorinated building blocks for the synthesis of several biologically active molecules.

Fluoro-4-methoxybenzoyl chloride (**1**) has been used as building blocks for preparing compounds which are active against various diseases. To cite a few examples (a) preparation of potent and selective agonist of estrogen receptor β ligand capable of treating inflammatory diseases.[2a] (b) preparation of inhibitors of heat shock protein 90, inhibition of which has shown beneficiary effects in the treatment of cancers and neurodegenerative diseases.[2b] (c) preparation of activators of SIRT1 which improves glucose metabolism in various skeletal muscles, and helps in treatment of type II diabetes and other metabolic disorders.[2c] 1,2-Diethoxy-3-fluorobenzene (**2**)



3-Fluoro-4-methoxy benzoyl chloride (**1**)



1,2-Diethoxy-3-fluoro-benzene (**2**)

Figure 1. 3-Fluoro-4-methoxybenzoyl chloride (**1**) and 1, 2-diethoxy-3-fluorobenzene (**2**).

is a building block in the preparation of 2-iminopyrrolidine derivatives which have shown promising antithrombotic activity.[3]

Hence we became interested in developing a process for synthesizing these important fluorinated building blocks. The literature search has revealed **1** and **2** have been prepared using various approaches. Starting form 3-fluoro-4-methoxybenzoic acid a number of synthetic approaches toward **1** has been reported in the literature. The key starting material 3-fluoro-4-methoxybenzoic acid is synthesized by chromate or permanganate oxidation of 3-fluoro-4-methoxytoluene,[4] carboxylation of 3-fluoro-4-methoxybromobenzene,[5] or by hydrolysis of 3-fluoro-4-methoxybenzonitrile.[6]

Hikal has reported a process for the synthesis of **2** via Claisen rearrangement of allyl-2-fluorophenyl ether followed by Dakin oxidation and ethylation.[7] Asahi and Charna have reported a

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process for the synthesis of **2** starting from commercially available 2-fluorophenol.[8] Another strategy of Asahi and Charna reports alkylation of 3-fluorocatechol (**8**).[8]

The key building block 3-fluorocatechol (**8**) is accessible via enzymatic oxidation of fluorobenzene followed by dehydrogenation of resultant fluoro-diol.[9] Corse et al. have reported the synthesis of 3-fluorocatechol (**8**) starting from 2,3-dimethoxynitrobenzene.[10]

We envisaged that compounds **1** and **2** can be prepared via Fries rearrangement of 2-fluoro-phenylacetate (**3**) (Scheme 1). The *ortho* isomer **5** and *para* isomer **4** can easily be converted into target compounds **1** and **2**.This communication summarizes our efforts to develop an improved, less expensive, simpler, safer, and easily scalable manufacturing process for synthesis of **1** and **2** starting from **4** and **5** respectively.

Valoti et al. reported the synthesis of 3-fluoro-4-hydroxyacetophenone (**4**) and 3-fluoro-2-hydroxy-acetophenone (**5**) using Lewis acid catalyzed Fries rearrangement of 2-fluorophenyl acetate (**3**).[11] We focused our attention on this approach with keeping a goal of carrying out this transformation on large scale and secondly, to avoid column chromatography used to separate both isomers **4**/**5** which would not be a practical proposition during large scale production.

The substrate for Fries rearrangement 2-fluorophenyl acetate (**3**) was synthesized in high yields from commercially available 2-fluorophenol using acetyl chloride and triethyl amine. In order to study the ratio of *ortho*/*para* isomer obtained during the Fries rearrangement we developed a HPLC method (see Supporting information) Fries rearrangement was carefully studied using different Lewis acid catalysts and temperatures. Thus, using $BF_3.OEt_2$ we did not observe any product formation while the use of $TiCl_4$ gave hydrolyzed product 2-fluorophenol in 75% yield. When 1.1 or 1.2 equiv of $AlCl_3$ was used, we observed product formation (**4**/**5**) in 50% yield.

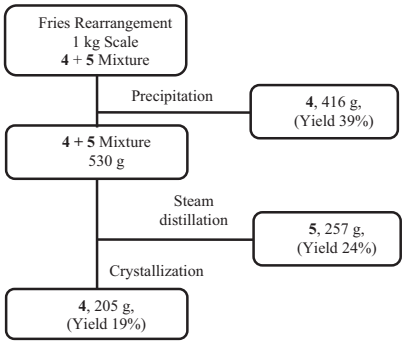
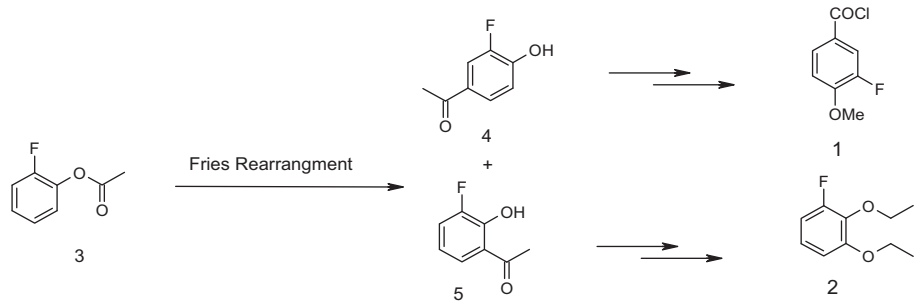


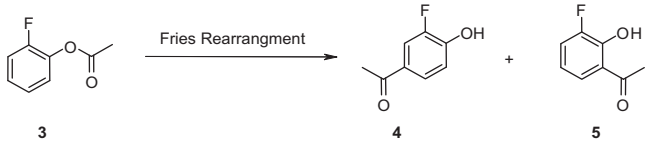
Figure 2. Flowchart for the separation of Fries rearrangement products.

Based on above results $AlCl_3$ was chosen as a Lewis acid to study the impact of temperature on the *ortho*/*para* selectivity observed during Fries rearrangement. Toward this goal, Fries rearrangement was performed at various temperatures ranging from 40 °C to 170 °C. The results are summarized in Table 1. Use of 1.5 equiv of $AlCl_3$ in the Fries rearrangement gave us consistent results; hence all the optimizations were carried out using 1.5 equiv of $AlCl_3$. It was also observed that when the temperature of reaction was increased from 40 °C to 80 °C the reaction rate as well as the percentage of conversion of **3** into the product **4**/**5** increased (entries 1–3). When the Fries rearrangement was carried out in monochlorobenzene at 100 °C, the formation of Fries rearranged products **4** and **5** was observed in the ratio of 3.03:1.0 (Table 1, entry 4). At 120 °C the reaction went to completion with 90% isolated crude yield



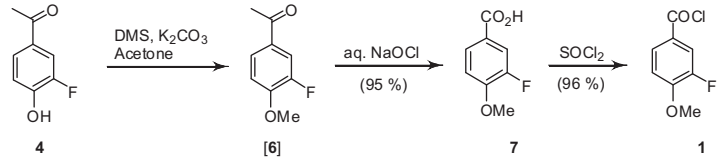
Scheme 1. Synthetic strategy toward 3-fluoro-4-methoxybenzoyl chloride (**1**) and 1,2-diethoxy-3-fluorobenzene (**2**).

Table 1
Optimization of reaction conditions for Fries rearrangement

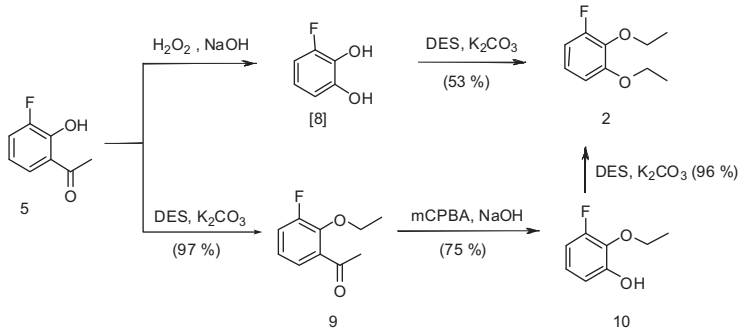


Entry	Solvent	Temp (°C)/time (h)	% Crudeyield	% Conversion[#]	O:P ratio (4:5)[§]
1	MCB	40/4	84	37.2	2.44:1.0
2	MCB	60/4	86	46.4	1.33:1.0
3	MCB	80/4	85	80.8	2.84:1.0
4	MCB	100/3	90	90.2	3.03:1.0
5	MCB	120/3	90	100	2.84:1.0
6	DCB	150/2	74	100	1.92:1.0
7	DCB	170/2	62	100	1.72:1.0

[#] In all the reaction $AlCl_3$ (1.5 equiv) was used as a Lewis acid. MCB = Monochlorobenzene, DCB = *o*-dichlorobenzene.
[§] O/P ratios were calculated on the basis of HPLC analysis of reaction mass.



Scheme 2. Synthesis of 3-fluoro-4-methoxybenzoyl chloride (**1**).



Scheme 3. Synthesis of 1, 2-diethoxy-3-fluorobenzene (**2**).

(entry 5). The *ortho*/*para* regioselectivity obtained was 2.84:1.0. This result is in line with the well known fact that the increase in the reaction temperature increases the *ortho*-selectivity in the Fries rearrangement. Taking a clue from these results we carried out Fries rearrangement in high boiling *o*-dichlorobenzene at an elevated temperature (entries 6 and 7). At 170 °C the *ortho* product formation was significantly increased (*ortho*/*para,* 1.72:1), however the isolated crude yield of the reaction was only 62% (entry 7). It can be noted from Table 1 that the reaction below 100 °C leads to incomplete conversion while above 150 °C leads to lower isolated yields due to significant formation of other side products. Based on the above study we chose to do Fries rearrangement in monochlorobenzene at 120 °C.

Our approach used for the separation of **4** and **5** is summarized in Figure 2. During the work-up of Fries rearrangement upon acidification of the reaction mass and cooling at 5–10 °C, the yellow product precipitated out (yield 38.8%). This precipitated product was filtered and found to be **4** after spectroscopic characterization. The HPLC purity of **4** was >98%. The mother liquor obtained after the filtration when analyzed by HPLC showed mixture of **4** and **5**. For the further purification and separation of **4** from **5**, at this stage it was anticipated that due to intramolecular hydrogen bonding, compound **5** could be steam volatile. This proved to be the case as we were able to efficiently separate **5** (yield 24%, >98% purity by HPLC) from **4** (remained in residue) by steam distillation. Thus steam distillation was found to be an efficient technique to separate pure **4** from **5**. The steam distillation residue when analyzed by HPLC showed compound **4** (92.7% HPLC Purity). This residue was further purified by recrystalization with a mixture of MTBE: Hexane to provide **4** (19.2%, >98% HPLC Purity). Thus the total yield of **4** was increased to 58%.

With sufficient quantity of pure **4** in hand we turned our attention for transforming it into **1** (Scheme 2). Toward this goal first phenolic hydroxyl group was methylated with dimethyl sulfate to obtain **6**. Compound **6** was subjected to hypochlorite oxidation to get the benzoic acid derivative **7** which upon refluxing in thionyl chloride gave targeted compound **1**. All these three steps were realized with high yields. Thus the synthesis of **1** was achieved starting from commercially available 2-fluorophenol in 5 steps avoiding any chromatographic purification.

The Fries product **5** obtained was transformed into **2** via two approaches (Scheme 3). In the first approach, compound **5** was first subjected to Dakin oxidation which resulted in the formation of fluorocatechol **8**; this unisolated intermediate was o-ethylated to furnish the target compound in 53% yield. The second approach involved o-ethylation of compound **5** by using diethyl sulfate in the presence of potassium carbonate to give compound **9**, which was then subjected to Baeyer–Villiger oxidation using *m*-CPBA to obtain fluorophenol **10**. Finally the synthesis of target compound **2** was achieved by ethylation of **10** in 96% yield in a chromatography free manner.

In conclusion, practical and scalable synthesis of fluorinated building blocks 3-fluoro-4-methyl benzoyl chloride (**1**) and 1,2-diethoxy-3-fluorobenzene (**2**) was achieved using $AlCl_3$ mediated Fries rearrangement starting from a common starting material 2-fluorophenol. Both the isomers **4**/**5** obtained from Fries rearrangement were separated efficiently using steam distillation and crystallization techniques. They were subsequently transformed into versatile fluorinated building blocks **1** and **2** in high yield.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.119.

References and notes

1. Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15–24. and references cited therein.
2. For the reference related to application of **1** refer (a) Malamas, Michael S.; Manas, Eric S.; McDevitt, Robert E.; IwanGunawan, Zhang B.; Xu, Michael D.; Collini, Chris P.; Miller; Tam Dinh, Ruth A.; Henderson, James C.; Keith, Heather A., Jr.; Harris *J. Med. Chem.* **2004**, *47*, 5021–5040; (b) Riccardo Baruchello; Daniele Simoni; GiuseppinaGrisolia; GiuseppinaBarbato; Paolo Marchetti; Riccardo Rondanin; StefaniaMangiola; Giuseppe Giannini; TizianaBrunetti; DomenicoAlloatti; Grazia Gallo; Andrea Ciacci; LoredanaVesci; Massimo Castorina, Ferdinando M.; Milazzo, Maria L.; Cervoni, Mario B.; Guglielmi; Marcella Barbarino; Rosanna Foderà; Claudio Pisano; Walter Cabri *J. Med. Chem.* **2011**, *54*, 8592–8604; (c) Vu, Chi B.; Bemis, Jean E.; Disch, Jeremy S.; Pui Yee Ng,

Joseph J.; Nunes, Jill C.; Milne, David P.; Carney, Amy V.; Lynch, Jesse J.; Smith; Siva Lavu, Philip D.; Lambert, David J.; Gagne, Michael R.; Jirousek; Simon Schenk, Jerrold M.; Olefsky, Robert B.; Perni *J. Med. Chem.* **2009**, *52*, 1275–1283.
3. MingjianQiu, Wei Zhang, Zhaohui Chen, Chunshan Zhang, Yali Zhang, US 20090227817 A1.
4. (a) Hansen, H. L. *J. Am. Chem. Soc.* **1937**, *59*, 280; (b) Schiemann, G.; Winkelmüller, W. *J. Prakt. Chem.* **1932**, *135*, 101–127.
5. Ziobro, D.; Dziaduszek, J.; Filipowicz, M.; Dabrowski, R.; Czu, J.; Urban, S. *Mol. Cryst. Liq. Cryst.* **2009**, *502*, 258–271.
6. Anne; D. S.; Brian, M. J.; Antonio, M. European Patent 623601, 1994.
7. Kuppuswamy, N.; Gupta, R. P.; Selven, A.; Chakraborty, D.; UlavathiShetter, S. S.; Malgi, C.; Kunte, S.; Reddy, R.; Avenkar, S. WO2011/64789 A1, 2011.
8. Qiu, M.; Zhang, W.; Chen, Z.; Zhang, C.; Zhang, Y. European Patent 2055692, 2009. (b) Qiu, M.; Zhang, W.; Chen, Z.; Zhang, C.; Zhang, Y. US Patent 0227817, 2009.
9. (a) Lynch, R. M.; Woodley, J. M.; Lilly, M. D. *J. Biotechnol.* **1997**, *58*, 167–175; (b) Schmid, A.; Kohler, H.-P. E.; Engesser, K.-H. *J. Mol. Catal B: Enzym.* **1998**, *5*, 311–316; (c) Berberian, V.; Allen, C. R. R.; Sharma, N. D.; Boyd, D. R.; Hardacre, C. *Adv. Synth. Catal.* **2007**, *349*, 727–739.
10. Corse, J.; Ingraham, L. L. *J. Org. Chem.* **1951**, *16*, 1345–1348.
11. Valoti, E.; Pallavicini, M.; Villa, L.; Pezzetta, D. *J. Org. Chem.* **2001**, *66*, 1018–1025.