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Oxidative ring opening of 2,5-diarylfurans by Selectfluor®

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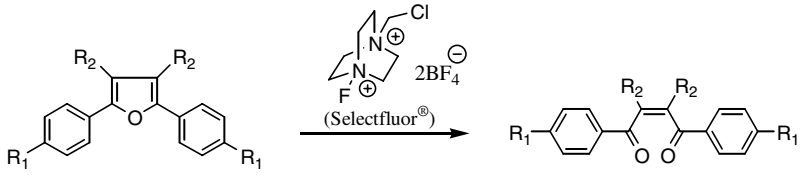
Abstract—Attempted fluorination of some 2,5-diarylfurans with the N–F reagent Selectfluor® has led instead to oxidative ring opening of the furan ring to give the *cis*-enedione, along with traces of the trans isomer, in good isolated yield.

1. Introduction

As part of a drug discovery effort, we were recently interested in preparing various 3-fluoro or 3,4-difluoro 2,5-diarylfurans by direct fluorination of the parent heterocycles. Our first attempt at this chemistry involved the reaction of furan **1a** with Selectfluor®, an N–F reagent that has seen much use in recent years for the fluorination of aromatics.[1–4] Instead of giving ring fluorination, the reaction led to oxidative ring opening of the furan to yield primarily the *cis*-enedione. Such ring opening of furans is known to occur with reagents such as nitric acid,[5] hydrogen peroxide,[6] lead tetraacetate,[7] meta-chloroperoxybenzoic acid (MCPBA),[8] magnesium monoperoxyphthalate (MMPP),[9] $Mo(CO)_6$/cumyl hydroperoxide,[10] MoO_5-HMPA,[11] and a urea hydrogen peroxide/methyltrioxorhenium combination (UHP/MTO)[12] and has been quite useful in the synthesis of some complex molecules.[8,13] The ring opening is also known to occur upon reaction with halogenating reagents such as Br_2 or NBS,[8,13] although the reaction of 2,5-diphenylfuran **1b** with NBS reportedly gives the 3,4-dibromofuran analog.[14] Furan ring opening by the Selectfluor® reagent has not been reported. In this letter we wish to describe our results with this reaction.



1a $R_1 = Br$, $R_2 = H$
1b $R_1 = R_2 = H$
1c $R_1 = Br$, $R_2 = CH_3$

2a-c
+ trace of trans isomer

2. Results

Our preliminary attempt at fluorinating furan **1a** involved reaction with Selectfluor® (2 equiv) in DMF at about 70–80 °C for a few hours. This led to complete consumption of starting material according to TLC, with formation of two products (one major, one very minor) in near quantitative yield. Separation of these two products by silica gel chromatography and characterization by ^1H NMR, IR, and mp showed that we had obtained *cis*-enedione **2a** as a major product, along with a trace amount of the trans isomer. Mechanistically, this most likely involves a 1,4-addition of HOF to the furan,

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followed by ring opening and elimination of fluoride. The water apparently came from traces present in the DMF solvent or the Selectfluor® reagent itself.

In an attempt to optimize this potentially useful reaction, we replaced the DMF solvent with aqueous THF. With this solvent, the reaction of furan **1a** with Selectfluor (2 equiv) at 60–70 °C for 3 h also gave complete/quantitative ring opening. Purification by chromatography to remove the traces of trans isomer (structure confirmed by TLC comparison with authentic sample and ^{1}H NMR of the crude sample) resulted in a 58% isolated yield of *cis*-enedione **2a**.

In a limited effort to examine the scope of this reaction, two other furans were subjected to the ring opening. The reaction of the parent 2,5-diphenylfuran **1b** with Selectfluor® was found to proceed fully at room temperature in just 2 h to give *cis*-enedione **2b** in 69% purified yield.[15] A similar reaction with the 3,4-dimethyl analog **1c** also gave complete ring opening (in essentially quantitative crude yield); however, we were unable to separate out the trace of trans product by chromatography, possibly due to isomerization between the two isomers on the column (which has been observed by others).[16]

3. Conclusion

In conclusion, attempted fluorination of some 2,5-diarylfurans with the N–F reagent Selectfluor® has led to oxidative ring opening of the furan ring to give predominantly the *cis*-enedione. Considering that many of the other reagents typically used for furan ring opening (i.e., HNO_3, MCPBA, UHP/MTO, etc.) are likely stronger oxidizers than Selectfluor®, this N–F reagent may represent a milder alternative for this conversion.

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15. *Representative procedure and notes*: To a solution of 2,5-diphenylfuran (**1b**) (Lancaster Synthesis) (0.22 g, 1.0 mmol) in tetrahydrofuran (THF) (4 ml) was added 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®) (0.71 g, 2.0 mmol) followed by 10 drops of water (Pasteur pipette) and the mixture was stirred at room temperature until the starting material was consumed by TLC (2 h). Aqueous extraction with EtOAc followed by silica gel column chromatography eluting with 1–2% EtOAc in hexanes gave the pure *cis*-enedione **2b** (*cis*-1,2-dibenzoylethylene) as an off white solid (0.163 g, 69% yield), mp 132–133.5 °C; lit. mp 131–132 °C[16] and 134 °C.[17] IR (cm^{-1}): 3086.2, 3065.5, 3021.6, 1664.1, 1599.1, 1232.2, 1015.1. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.15 (s, 2H), 7.45 (t, 4H), 7.55 (t, 4H), 7.95 (d, 2H). Dibromo *cis*-enedione **2a**, obtained as a white solid by heating as noted in the text, had mp 120–122 °C; lit. mp 122–123 °C.[18] Starting furans **1a** and **1c** were prepared according to the literature.[19]
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