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Synthesis of aryl allylic fluorides by direct electrophilic fluorination of alkenes

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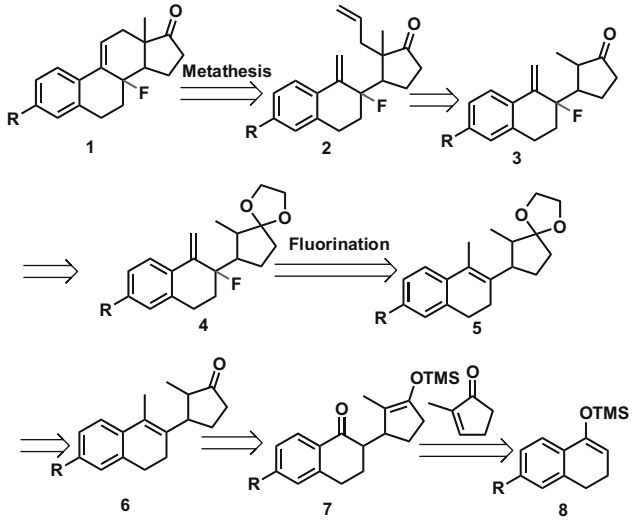
ABSTRACT

Aryl allylic fluorides were synthesized in 47–83% yields by using Selectfluor as the electrophilic reagent in DMF. The outcome of this reaction may be explained by electronic effects while the reactivity was controlled by the stabilization effect of the aryl group on the benzylic cationic intermediates.

There has been significant interest in fluorinated organic compounds especially in the fields of medicine, pharmaceuticals and material science. Introduction of a fluorine atom into organic molecules produces profound effects on the biological activity, metabolism, solubility, hydrophobicity and bulk properties of organofluorine compounds.[1,2] Therefore, much effort has been directed towards developing facile synthetic methods to introduce fluorine into useful intermediates or desired substrates.

In connection with our interest in the synthesis of fluorinated steroids (**1**, Scheme 1), we were interested in developing a method to obtain aryl allylic fluoride **4** (Scheme 1). Although there are methods for the synthesis of aryl allylic fluorides,[3,4] most of these fluorination reactions used allyltrimethylsilanes as starting materials. Previously, aryl alkenes have been shown to react with electrophilic fluorinating reagents. In these reactions, solvent systems were used as the nucleophiles to capture the fluorocarbocationic intermediates.[5] In our synthesis, we required a considerably more direct and efficient entry to aryl allylic fluorides using alkenes as starting materials.

In this Letter, we disclose our recent observations on electrophilic fluorination using aryl alkenes as starting materials for car-



Scheme 1. Designed route to synthesize fluorinated steroids.

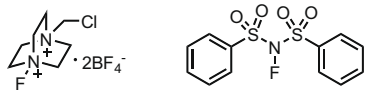
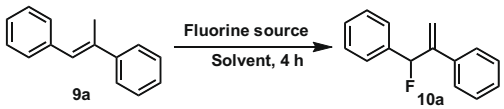


Figure 1. Sources of fluorine.

Table 1
Reaction of α-methylstilbene (**9a**) with fluorine sources[a]



Entry	Solvent	Fluorine Source	Reaction temperature (°C)	Conversion	Yield[b] (%)
1	DCM	NFSI	rt	No reaction	
2	THF	NFSI	rt	No reaction	
3	CH3CN	NFSI	75	No reaction	
4	DMSO	NFSI	75	No reaction	
5	DMF	NFSI	75	No reaction	
6	CH_3CN/H_2O 10:1	NFSI	75	No reaction	
7	CH_3CN/H_2O 10:1	Selectfluor	rt	>98%	8
8	CH_3CN	Selectfluor	rt	>98%	12
9	DMSO	Selectfluor	75	No reaction	
10	**DMF**	**Selectfluor**	**75**	**>95%**	**83**

[a] Conditions: α-Methylstilbene (0.50 mmol), fluorine source (0.525 mmol), reaction time 4 h.
[b] Isolated yield.

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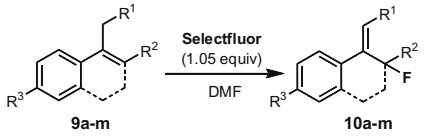
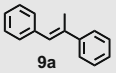
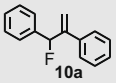
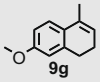
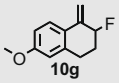
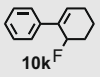
Table 2
Fluorination of various aryl alkenes with Selectfluor in DMF[a]



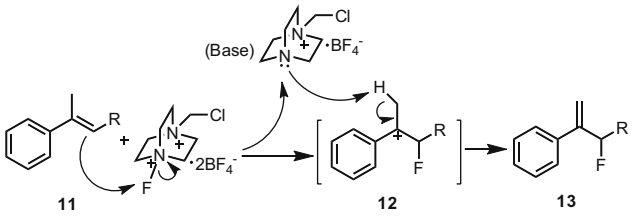
9a-m 10a-m

Entry	Aryl alkene	Reaction time (h)	Reaction temperature (°C)	Main product	Yield[b] (%)
1	 9a	4	75	 10a	83
2	 9b	4	75	 10b	65[c]
3	 9c	4	75	 10c	67[c]
4	 9d	4	75	 10d	82
5	 9e	4	75	 10e	80
6	 9f	6	45	 10f	59
7	 9g	4	75	 10g	81
8	 9h	6	45	 10h	68
9	 9i	5	70	 10i	78
10	 9j	5	70	 10j	71
11	 9k	6	40	 10k	47[c]
12	 9m	4	75	No reaction	

[a] Al reactions were performed in DMF under an N_2 atmosphere.
[b] Isolated yield.
[c] The isolated yield was low because the product is volatile and decomposes.

bon–fluorine bond formation, which provides a much more efficient way to synthesize aryl allylic fluorides.

Our initial studies focused on screening fluorine sources such as Selectfluor[6–8] (**S_1**, Fig. 1) and *N*-fluorobenzenesulfonimide (NFSi)[9,10] (**S_2**, Fig. 1) for the conversion of **9a** into **10a**. As shown in Table 1, no reaction was observed when NFSi was used as the fluorine source. However, the reaction proceeded smoothly to afford the desired product **10a** when Selectfluor was used as the fluorine source (entries 7, 8 and 10). The best conditions involved reaction in *N*,*N*-dimethylformamide (DMF) for 4 h at 75 °C (entry 10). In this reaction, dry DMF was required, as the yield of the



Scheme 2. Proposed fluorination mechanism.

product decreased substantially in the presence of water, with formation of a byproduct produced by capture of a fluorocarbocationic intermediate by water.[5]

Using the optimized conditions, we explored the scope of this reaction with various aryl alkenes. The results are summarized in Table 2. In all cases, the desired aryl allylic fluorides were obtained in moderate to good yields (Table 2, entries 1–11). Interestingly, a substrate without a 1-methyl group also gave the desired product **10k** in 47% yield at lower temperature. The tetra-substituted aryl alkenes (Table 2, entries 6 and 8) reacted at a lower temperature to afford aryl allylic fluorides as the main products.[3] Carbocation stabilization of the phenyl group is essential for clean reactions. No reaction was detected with allylic alkene **9m**.

The following mechanism is proposed to account for the observed fluorinated products. The fluorocarbocationic intermediate **12** (Scheme 2) was generated upon electrophilic addition of Selectfluor to the alkene **11**, which underwent loss of a proton to produce the aryl allylic fluoride **13**.

In summary, this Letter describes a direct entry into aryl allylic fluorides using simple alkenes. The application of this reaction to the synthesis of other fluorinated compounds is in progress.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.052.

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