

# Retro-Favorskii Reaction Employing Fluoride Sources

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## Abstract

In this study, we developed a novel and simple approach to perform retro-Favorskii type reactions comprising the use of a readily available fluoride source. Compared to the methods usually employed – which rely on the use of strong basic systems, such as KOH in toluene, at high temperatures and a reaction time of several hours – the one we propose employs milder conditions, shorter reaction times, is compatible with more solvents, and produces no appreciable amount of byproducts, thus allowing simple workup procedures. The reaction we describe is enabled by the strong basic character of the fluoride ion in absence of water. However, we observed that the reaction is remarkably tolerant to humidity and no anhydrous conditions are needed, making the reaction extremely straightforward to perform. The possibility of performing such reactions in a fast and reliable manner, without the appreciable formation of byproducts, can offer new interesting opportunities to efficiently employ propargyl alcohol derivatives as a masking group for carbonyls. The latter approach can be particularly interesting for the synthesis and derivatization of carbonyl-rich compounds – such as large, conjugated, electron-deficient systems or quinoid-based pigments – for which the limited solubility often precludes the synthesis of certain derivatives or their application in functional devices.

## Introduction

The retro-Favorskii reaction finds limited use in organic synthesis being performed in most cases to obtain terminal alkynes from propargyl alcohols.<sup>2-4</sup> The reaction requires the use of a strong base, high temperature (usually reflux temperature of toluene or *n*-butanol), and usually needs several hours, thus limiting its scope and often resulting in side reactions and degradation of the substrates.<sup>5,6</sup>

While most interest in the retro-Favorskii is focused on the alkyne, in our group we are currently investigating the possibility of employing this approach to synthesize suitable precursors for the preparation of conjugated compounds bearing carbonyl and quinone functionalities. These materials are usually characterized by a small band-gap and a low LUMO, making them appealing in the field of organic electronics to achieve *n*-type transport or as electrode material for organic batteries.<sup>7-10</sup> However, they are also often insoluble and prone to the formation of aggregates, limiting their processability in device fabrication and narrowing down the number of derivatives accessible. Synthetic methods based on precursors can circumvent these problems.<sup>11,12</sup>

In this sense, the role of the alkyne becomes to improve the solubility and tune the chemical properties of the precursor (provided that the retro-Favorskii reaction can occur rapidly, with high yield, and with a simple workup procedure).

In trying to find good reaction conditions and broaden the range of solvents one can use, we found that the fluoride ion can act as a base for the retro-Favorskii reaction.

The strong basic character of F<sup>-</sup> in anhydrous aprotic environments is known. It usually arises in systems where there is a weak interaction between the solvent/counterion and the fluoride anion, which drastically affect its reactivity.<sup>13-15</sup>

While most of fluoride sources, such as inorganic salts or tetramethylammonium fluoride (TMAF), are not soluble in common organic solvents,<sup>13</sup> higher tetralkylammonium cations are compatible with many solvents, including apolar ones.<sup>16</sup> They, however, suffer limited stability toward the Hoffmann degradation, especially at high temperatures.<sup>17</sup> Performing the reaction in a short time and at low temperatures becomes therefore of primary importance.

In this study, we report the use of TBAF as base in the retro-Favorskii reaction. For most of the substrates investigated, the reaction proceeds quantitatively in a broad range of solvents within 1 hour at 70 °C (or at room temperature if run for longer periods) limiting the effect of the degradation. Remarkably, we found the reaction to be tolerant to humidity.

## Results and Discussion

As an example for providing a general procedure for this reaction, we employed 9-ethynylfluoren-9-ol and a 1 M TBAF solution in tetrahydrofuran (THF), both commercially available. If a different solvent is needed, one can use TBAF trihydrate, also widely available. As an alternative, the commercial THF solution can be mixed with the desired solvent to form a mixture.

We summarize the different solvents tested in Table 1. No solvent was anhydrous nor we performed any drying procedure prior to the use.

**Table 1. Summary of solvent screening. Reactions were performed in a screw-cap vial containing 0.4 mmol of 9-ethynyl-fluoren-9-ol, 10 mL of solvent and TBAF\*3H<sub>2</sub>O.**

Entry	Solvent	TBAF equiv	T [°C]	Time [h]	Yield
1	THF	1.1	70	1	quant.
2	THF	0.1	70	1	26%
3	Acetone	2	70	1	33%
4	Acetone	2	70	2	quant.
5	Methylisobutyl ketone	2	70	1	quant.
6	Hexane	2	70	1	quant.
7	Diethyl ether	2	Boiling	1.5	quant.
8	Dimethylsulfoxide	2	70	1	-
9	Chloroform	2	Boiling	1	-
10	Acetonitrile	2	70	1	quant.
11	Ethanol	2	70	1	-
12	No solvent	1.5	70	0.08	-
13	THF + 25% H <sub>2</sub> O	2	70	3	-
14	THF + 20% H <sub>2</sub> O	80	100	4	-

Surprisingly, the reaction was successful in hexane and Et<sub>2</sub>O (Entry 6 and 7) even if the TBAF was not completely soluble in them. Entry 12 refers to the reaction performed in a mortar using solid TBAF trihydrate. The mixture was found very hygroscopic and no product was obtained. A detrimental role of water or other proton source is clear, even when a large excess of TBAF is used (Entry 11-14). The reaction in DMSO (Entry 8) yielded a very complex mixture; no reaction was observed in CHCl<sub>3</sub> (Entry 9), most likely as a result of the incompatibility of TBAF and halogenated solvents.<sup>18</sup> It is worth mentioning that the reaction performed as Entry 1 on a 2g scale produced benzophenone with a quantitative yield and 98% purity by HPLC-MS.

As mentioned earlier, we are interested in using this procedure for the synthesis of carbonyl- and quinone-rich compounds. We report a summary of substrates employed for this reaction in Table 2. This latter includes compounds bearing silicon protecting groups, which could be removed in the same procedure by using more TBAF equivalents.

As we show, the reaction was successful and high yielding in most cases. In particular, we tested several groups on the triple bond of the propargyl alcohol and they do not seem to affect the outcome of the reaction. In the view of a precursor approach, this observation indicates that it is indeed possible to employ a broad variety of terminal alkynes to meet the processability and fabrication requirements or simplify the purification procedures. In the case of the starting materials bearing a silicon protecting group on the hydroxyl group, the retro-Favorskii reaction in more common conditions (KOH, toluene, reflux) required several hours (at least 6) to run to completion.

On the contrary, methylation of the hydroxyl moiety (Entry 9), which cannot be cleaved in the reaction conditions, prevents the reaction from happening (in the case of Entry 9, we observed only the removal of the silicon protecting groups on the triple bonds). Also the substitution of at least one of the aromatic groups on the substrates affected the outcome of the reaction. For example, when a methyl group was introduced (employing 2-phenyl-3-butyn-2-ol as starting material, Entry 13), we obtained a complex mixture of products, probably as a consequence of the enolization of the  $\alpha$ -hydrogens in a basic environment. No expected product was observed in the case of 1-phenylpropargyl alcohol, for which one of the aryl groups is exchanged for an H (Entry 14).

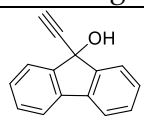
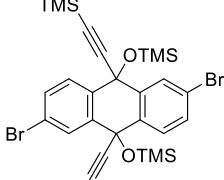
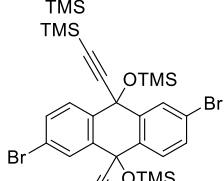
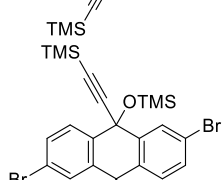
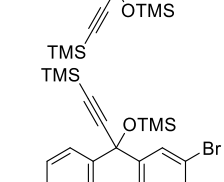
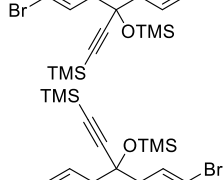
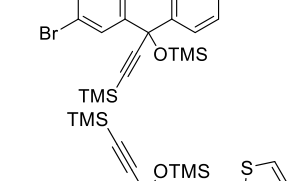
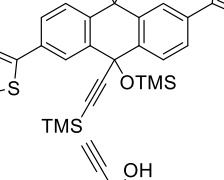
Surprisingly, in the case of Entry 4, less than the expected 6 equivalents of TBAF were necessary to bring the reaction to completion. While it could be interesting to study systematically the effect of different amounts of TBAF on the outcome of the reaction (even concerning the failed attempts just described), we did not investigate this aspect any further.

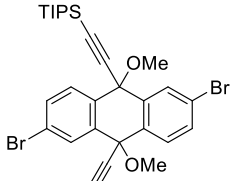
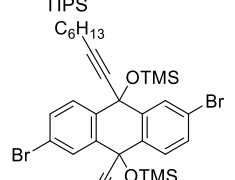
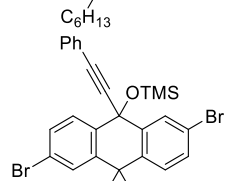
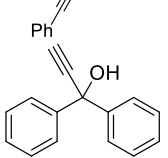
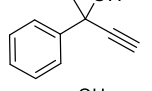
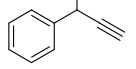
## Conclusions

To summarize, in this report we showed that it is possible to employ TBAF as a base in retro-Favorskii reactions. Compared to common procedures, this method allows users to perform the reaction at lower temperatures (even at room temperature) and for shorter periods of time. Moreover, TBAF expand the range of possible solvents and it can be easy to remove by washing.

We are currently employing the conditions reported here for the preparation of small molecules and conjugated polymers comprising a large fraction of keto and quinoid functionalities for applications as active layers in organic electronics and electrode materials in organic batteries.

**Table 2. Examples of retro-Favorskii reactions employing TBAF as base. All the reactions were carried in 20 mL screw-cap vials employing 10 mL of THF and 0.2 mmol of substrate. The final products consist in the starting materials bearing carbonyls in place of the propargyl alcohol groups. The yield was calculated from the <sup>1</sup>H-NMR by comparison with the amount of starting materials left. Starting materials in Entries 2-12 where synthesized previously.**

Entry	Starting	TBAF equiv	T [°C]	Time [h]	Yield
1		1.1	70	1	quant.
2		7	70	1	quant.
3		4	70	1	quant.
4		7	Rt	2	55%
5		7	Rt	18	quant.
6		2	70	1	71 %
7		6	70	1	quant.
8		2	70	1	91%

9		4	70	2	-
10		4	70	1	quant.
11		4	70	1	quant.
12		1.1	70	1	quant.
13		2	70	2	-
14		2	70	2	-

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