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A novel general method for preparation of α-fluoro-α-arylcarboxylic acid. Direct fluorination of silyl ketene acetals with Selectfluor®

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Abstract—The reaction of an α-arylcarboxylic acid with TBSCl and LiHMDS in THF yielded bis-silyl ketene acetal, which was directly fluorinated with inexpensive Selectfluor® to produce the corresponding α-fluoro-α-arylcarboxylic acid in high yield. Application of the methodology to the synthesis of α-fluorocarboxylic ester from the corresponding carboxylic ester is also described.

1. Introduction

The α-fluoro-α-arylcarboxylic acid structural motif is the basis for a series of active pharmaceutical ingredients[1] as well as agrochemicals[2] and has been widely employed as a building block in organic synthesis. Conventionally, these targets were prepared from α-arylcarboxylic acids by fluorinating the corresponding metal enolates of acid derivatives with *N*-fluoro-*o*-benzenesulfonimide[3] or NFSI (*N*-fluorobenzenesulfonimide, $(PhSO_2)_2N$–F).[4] Despite the reported efficiency of those processes, the approaches were not practical for large scale production because of the high costs of those fluorinating reagents.[5] Additionally, this methodology is only applicable to acid derivatives such as esters. Because Selectfluor®[6] is an inexpensive fluorinating reagent[7] readily available in bulk,[5] the use of Selectfluor® as our choice of fluorinating reagent is highly desirable. To date, the preparation[8] of α-fluorocarbonyl compounds by the reaction of Selectfluor® with enol acetates or silyl enol ethers has been broadly present in the literature. Furthermore, the use of silyl ketene acetals as intermediates in the conversion of acids to α-chloro or bromo acids has also become widely practiced.[9] However, to the best of our knowledge, this methodology has not been extended to the fluorination reaction presumably because of the high reactivity of fluorinating reagents and complicated side reactions associated with fluorination.[10]

We now wish to report a practical method for accomplishing this transformation with high conversion and minimal side reactions. As a general procedure, bis-TBS ketene acetals can be conveniently prepared from free α-arylcarboxylic acids by reacting with TBSCl/LiHMDS and without purification, subsequent fluorination with Selectfluor® in MeCN provides α-fluoro-α-arylcarboxylic acids cleanly after an aqueous work-up.

The synthesis of bis-silyl ketene acetals from free acids[11] is usually achieved by deprotonating the free acids with either *n*-alkyllithium or amide bases followed by silylation and the process has been generally believed to proceed through the dianion intermediates.[12] In the application of this method to our synthesis, we observed that LiHMDS is the preferred base because *n*-BuLi or *n*-HexLi sometimes caused decomposition.[13] By adding 2.2 equiv of LiHMDS to the THF solution of α-arylcarboxylic acids and TBSCl at an ambient temperature, good conversions (>95%) from acids to bis-TBS ketene acetals were confirmed by ^{1}H NMR (Scheme 1).

Analogously, bis-TMS and TES silyl ketene acetals could also be prepared efficiently with the same protocol and excellent conversions were confirmed by NMR. However, fluorination reaction between Selectfluor® and bis-TMS silyl ketene acetal derived from 2-fluorophenylacetic acid gave the desired 2-fluoro-2-(2-fluorophenyl)-acetic acid in only ~70% conversion and

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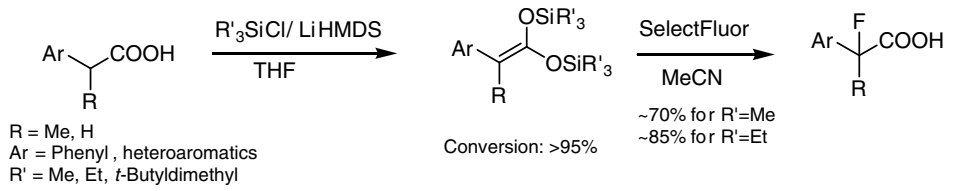


Scheme 1. The synthesis and fluorination of bis-silyl ketene acetals.

approximately 30% 2-fluorophenylacetic acid was detected by HPLC. Despite our efforts to exclude adventitious water in the reaction to achieve a higher conversion, the reaction consistently stalled at 70% and no further conversion was achieved even with the additional charge of Selectfluor®. With bis-TES silyl ketene acetal as the fluorination substrate, only a slightly improved conversion was obtained.

Considering the fact that a commercially available Selectfluor® is usually contaminated with variable amount of impurities such as F^- and inorganic acids, we suspected that the bis-TMS silyl ketene acetal might have already been hydrolyzed prior to the fluorination reaction with Selectfluor®. Based on our speculation, the performance of the reaction would then depend upon the relative stability of bis-silyl ketene acetals towards possible impurities in commercially available Selectfluor®.

To further optimize the fluorination reaction, we chose TBS as the more robust silyl masking group. Consistent with our hypothesis, the fluorination reaction between Selectfluor® and bis-TBS silyl ketene acetals gave >95% conversion for all substrates screened, and hydrolysis back to α-arylcarboxylic acids was typically <4% (Scheme 2). In a further survey of a series of α-arylcarboxylic acids using our protocol, it was apparent that the complete conversion of free acids to bis-TBS silyl ketene acetals needed to be secured before fluorination because free acids are completely inert to Selectfluor®.

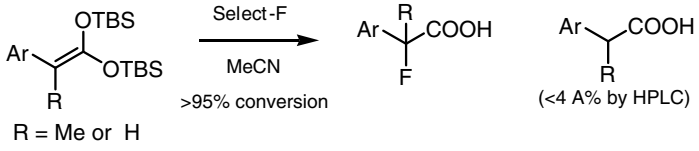
As a general procedure, bis-TBS silyl ketene acetals were treated with Selectfluor® in MeCN and instant fluorinations were observed with a slight exotherm. Typically within 5 min, excellent conversions were achieved and simple aqueous acid/base extraction produced the desired α-fluoro-α-arylcarboxylic acids,[14] which could be obtained in an analytical pure form by silica gel column chromatography. The chemistry works well for a number of electron-rich and poor aromatic substrates (Table 1). The method is also applicable to heteroaromatic substrates that are sensitive to electrophiles (entry 11) and α-alkyl-α-aryl disubstituted substrate (entry 9). The lower yields observed in entries 1 and 4 appear to be the result of the instability of the products.

To extend the application of this methodology, the reaction was briefly expanded to alkylsilyl ketene acetal other than bis-silyl ketene acetal (Scheme 3). The method proved to be applicable to both α-aryl and α-alkyl substituted carboxylic esters. For example, starting from methyl 2-fluorophenylacetate, the TBS silyl ketene acetal could be conveniently prepared as a mixture of *E* and *Z* isomers. The treatment of the mixture with Selectfluor® in MeCN afforded methyl 2-fluoro-2-(2-fluorophenyl)-acetate in a quantitative yield after aqueous work-up and column chromatography.

In conclusion, the reaction between Selectfluor® and a bis-TBS silyl ketene acetal provides a general method for the preparation of α-fluoro-α-arylcarboxylic acid from the corresponding α-arylcarboxylic acid. Additionally, extension of the methodology to esters without using the expensive NFSI will surely find its application in the synthesis of α-fluoroacid derivatives widely present in synthetic organic chemistry.

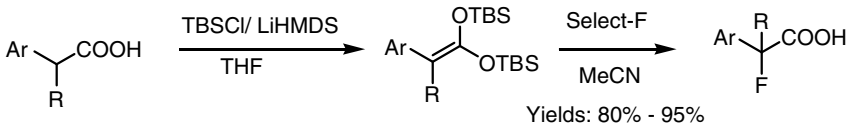
2. General procedure for the conversion of α-arylcarboxylic acids to α-fluoro-α-arylcarboxylic acids using Selectfluor®

Carboxylic acid (10 mmol) and TBSCl (23 mmol, 2.3 equiv) were dissolved in 10 mL THF at room temperature before cooling to 0 °C in an ice bath. LiHMDS (22 mL, 1 M in THF, 2.2 equiv) was introduced dropwise into the solution maintaining the batch temperature below 20 °C. The resulting reddish solution was stirred at ambient temperature for 2–16 h before concentrating in vacuum to dryness. The residual oil was re-dissolved into hexanes (LiCl quickly precipitated) and filtered before LiCl was washed with a minimum amount of hexanes (5–10 mL). The filtrates were collected and concentrated in vacuum to dryness to leave bis-TBS ketene acetal as a brown oil (^{1}H NMR in C_6D_6: olefinic



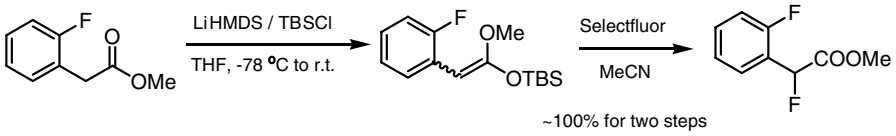
Scheme 2. Improved fluorination with Selectfluor® using bis-TBS silyl ketene acetals.

Table 1. Preparation of α-fluoro-α-arylcarboxylic acids from α-arylcarboxylic acids using Selectfluor®



Entry	R	Ar	Yield (%)
1	H	*p*-Methoxyphenyl	<10[a]
2	H	*o*-Methoxyphenyl	87
3	H	*m*-Methoxyphenyl	87
4	H	*p*-Nitrophenyl	<10[a]
5	H	*o*-Nitrophenyl	80
6	H	*m*-Nitrophenyl	88
7	H	*o*-Fluorophenyl	95
8	H	Phenyl	92
9	Me	Phenyl	91
10	H	*o*-Methylphenyl	88
11	H	2-Thiophenyl	93

[a] Bis-TBS silyl ketene acetal formation was clean. However, a significant colour change and severe decomposition were observed during isolation and purification by column chromatography.



Scheme 3. Extension of the methodology to the synthesis of methyl 2-fluoro-2-(2-fluorophenyl)-acetate.

proton at 5–6 ppm and >95% conversion from the acid).

Selectfluor® (13 mmol) was suspended in MeCN (40 mL) and the solution of crude bis-TBS ketene acetal in 10 mL MeCN was introduced into the Selectfluor® solution[15] dropwise maintaining $T < 50$ °C (slight exotherm). The reaction was allowed to stand at ambient temperature for 15 min before it was poured into an 1 N aqueous HCl (100 mL) and extracted with MTBE (3×50 mL). The organic layers were combined and extracted with 0.5 N aqueous NaOH (3×50 mL). The residual silyl impurities were further removed by combining the aqueous NaOH layers and re-extraction with MTBE (3×50 mL). The organic layers were discarded and an aqueous NaOH solution was acidified with 5 N HCl until pH = 1.

The acidified aqueous solution was extracted with MTBE (3×50 mL), dried with $MgSO_4$, filtered and concentrated in vacuum to leave an oil which usually exhibited a clean ^1H NMR spectrum. If desired, the analytical samples can be obtained by silica gel chromatography with 1.5% or 2% MeOH in CH_2Cl_2 to give the corresponding α-fluoro-α-arylcarboxylic acid as a crystalline material.

Acknowledgements

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References and notes

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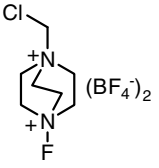
5. NFSI is available from Aldrich only in 5 g packages for ~$3000/mol and Selectfluor® is available from a number of vendors, for example, Scott Medical, in bulk for only ~$300/mol.
6. Structure of Selectfluor®:



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7. Another advantage that Selectfluor® offers for fluorination reaction is the easy aqueous workup because of water solubility of byproducts derived from Selectfluor®.
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9. For asymmetric version, see: Angibaud, P.; Chaumette, J. L.; Desmurs, J. R.; Duhamel, L.; Ple, G.; Valnot, J. Y.; Duhamel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1919–1932.

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13. For example: Treatment of 2-fluorophenylacetic acid in THF with 2 equiv of *n*-BuLi followed by D_2O quench did not give the recovered starting material in its full integrity and severe decomposition was detected by NMR.
14. Some representative spectral data: Entry 8: Yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.43–7.50 (m, 5H), 5.90 (br, 1H), 5.83 (d, $J = 47.5$ Hz, 1H); ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) -181.2; ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 174.1, 173.8, 133.6, 133.4, 130.00, 129.98, 129.0, 126.8, 126.7, 89.9, 87.9. IR (KBr, cm^{-1}) 2925.3 (br), 1697.7, 1231.5, 1047.3; HRMS (M−1) calculated: 153.0352, observed: 153.0350. Entry 11: Yield 93%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.1 (br, 1H), 7.5 (s, 1H), 7.39–7.40 (m, 1H), 7.20–7.21 (m, 1H), 5.99 (d, $J = 47.8$ Hz, 1H); ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) -177.53; ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.9, 173.6, 133.9, 133.7, 127.1, 125.59, 125.56, 125.3, 125.2, 86.0, 84.2. IR (KBr, cm^{-1}) 2987.9 (br), 1696.4, 1231.5, 1043.5; HRMS (M−1) calculated: 158.9916, observed: 158.9917.
15. Selectfluor has a reasonable solubility in MeCN at room temperature, but was not sufficiently soluble to form a homogeneous solution under the reaction condition and concentration. Furthermore, the 'reverse addition' procedure was adopted because it was more convenient to transfer ketene acetal solution into Selectfluor/MeCN suspension via a syringe pump while the temperature was maintained. No difluorination was observed because the product was totally inert to Selectfluor.