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Deoxyfluorination of (Hetero)aryl Aldehydes Using Tetramethylammonium Fluoride and Perfluorobutanesulfonyl Fluoride or Trifluoromethanesulfonyl Anhydride

Devin M. Ferguson,^[a] Patrick R. Melvin,^[a] and Melanie S. Sanford*^[a]

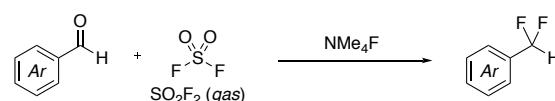
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Abstract: This Communication describes the conversion of (hetero)aryl aldehydes into the corresponding (hetero)aryl difluoromethyl products using anhydrous NMe₄F in combination with perfluorobutanesulfonyl fluoride or trifluoromethanesulfonyl anhydride.

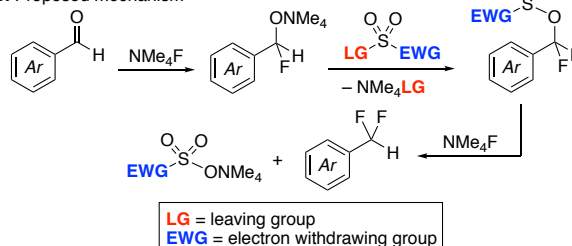
Keywords: difluoromethylation • deoxyfluorination • fluoroalkylation • fluorination • tetramethylammonium fluoride

(Hetero)aryl difluoromethyl substituents have become increasingly important targets for incorporation into bioactive molecules.¹ An attractive route to access these functional groups is the deoxyfluorination of (hetero)aryl aldehydes.² Our group recently reported the deoxyfluorination of (hetero)aryl aldehydes to afford the corresponding difluoromethyl (hetero)arenes using a combination of anhydrous tetramethylammonium fluoride (NMe₄F) and sulfonyl fluoride (SO₂F₂) (Figure 1A).³ Since SO₂F₂ is an inexpensive commodity chemical, this deoxyfluorination method has great potential for application on process scale. However, the laboratory scale use of SO₂F₂ can be hampered by safety concerns associated with using this toxic gas.³ In an effort to make this chemistry more accessible on a laboratory scale, we sought to identify an alternative method that employs NMe₄F in conjunction with a liquid sulfur(VI) electrophile to convert aryl aldehydes to difluoromethyl (hetero)arenes.⁴ Based on the proposed mechanism for this transformation, the liquid electrophile should have both a leaving group (LG in Figure 1B) as well as a strong electron withdrawing group (EWG in Figure 1B) attached to sulfur. Herein, we report two such methods that use either perfluorobutanesulfonyl fluoride (PBSF) or trifluoromethanesulfonyl anhydride (Tf₂O) in achieve this transformation under mild conditions (Figure 1C).

Our studies on the deoxyfluorination of (hetero)aryl aldehydes with NMe₄F/SO₂F₂ showed that *N,N*-dimethylformamide (DMF) was the optimal solvent.³ As such, we initially examined the reaction of 4-bromobenzaldehyde with 2 equiv NMe₄F and 1.2 equiv PBSF^{5,6} in DMF at room temperature for 24 h. This

A. Previous work (*Org. Lett.* 2019, 21, 1350)

B. Proposed mechanism



C. This work

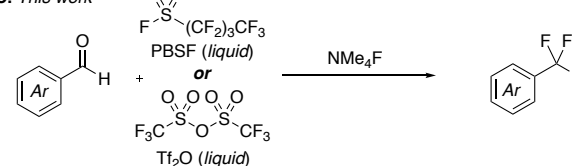


Figure 1 (A) Previous work: conversion of (hetero)aryl aldehydes to (hetero)aryl difluoromethyl products using NMe₄F and gaseous SO₂F₂. (B) Proposed mechanism. (C) This work: use of liquid reagents PBSF and Tf₂O for analogous transformations.

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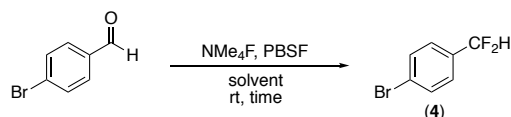


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transformation afforded 1-bromo-4-(difluoromethyl)benzene (**4**) in 63% yield as determined by ^{19}F NMR spectroscopy (Table 1, entry 1). Moving to 3 equiv of NMe_4F led to an increased yield of 84% (entry 2). A solvent screen showed that a variety of solvents can be used and that the highest yields are obtained in DMF (84%), dichloromethane (77%), and tetrahydrofuran (THF, 80%). Further optimization in THF showed that increasing the concentration from 0.20 M to 0.30 M resulted in a further enhancement in yield to 91% (entry 9).

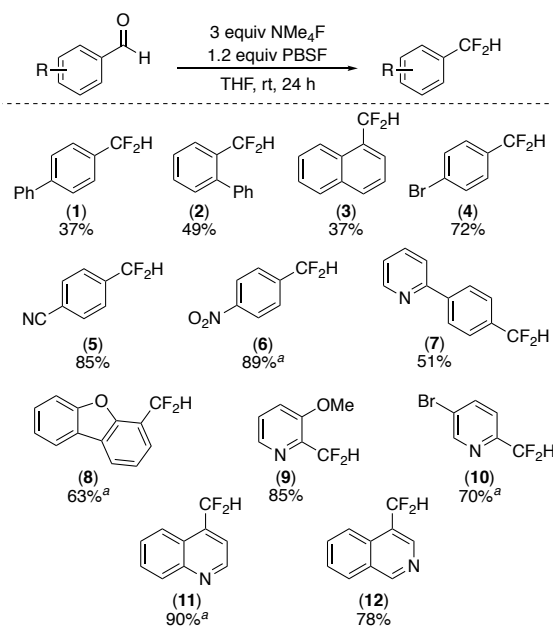
Table 1. Optimization of aryl difluoromethylation using NMe_4F and PBSF.



Entry	NMe_4F equiv	PBSF equiv	Solvent (conc)	Time	Yield (%) ^a
1	2.0	1.2	DMF (0.20 M)	24 h	63
2	3.0	1.2	DMF (0.20 M)	24 h	84
3	3.0	1.2	NMP ^b (0.20 M)	24 h	65
4	3.0	1.2	DMSO (0.20 M)	24 h	39
5	3.0	1.2	DCM (0.20 M)	24 h	77
6	3.0	1.2	EtOAc (0.20 M)	24 h	nd
7	3.0	1.2	Et_2O (0.20 M)	24 h	74
8	3.0	1.2	THF (0.20 M)	24 h	80
9	3.0	1.2	THF (0.30 M)	24 h	91 ^c

[a] Yields determined by ^{19}F NMR spectroscopy using (trifluoromethoxy)benzene as internal standard. nd = not detected. [b] NMP = *N*-methyl-2-pyrrolidone. [c] Average of two independent runs.

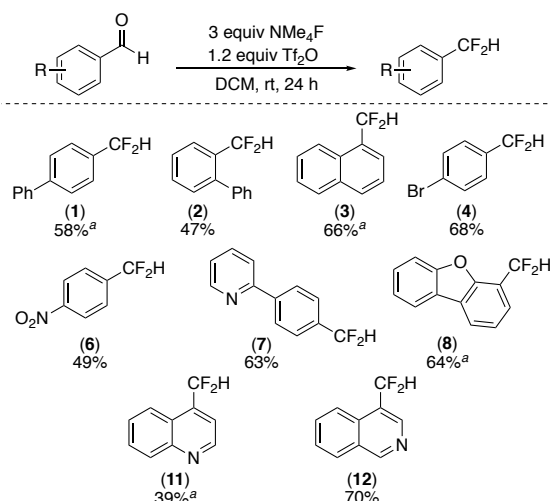
Using the optimal conditions (3 equiv of NMe_4F , 1.2 equiv PBSF, 0.30 M in THF, rt, 24 h), we next explored the substrate scope of this transformation (Scheme 1). Electron-neutral aryl aldehydes afforded the difluoromethylated products in moderate yields (**1-3**). Substrates bearing electron withdrawing substituents were well-tolerated, providing good to excellent yields of the desired products (**4-6**). Heteroarene functional groups proved compatible with these deoxyfluorination conditions, with 4-(2-pyridyl)benzaldehyde and dibenzofuran-4-carboxaldehyde producing the corresponding difluoromethylated products in 51% (**7**) and 63% (**8**) yield, respectively. Substrates containing pyridine, quinoline, and isoquinoline carboxaldehydes also afforded good to excellent yields (**9-12**). Additionally, aryl bromide functional groups are tolerated (**4** and **10**), providing a handle for further functionalization. Notably, employing THF as the solvent facilitates workup relative to DMF, due to its low boiling point. For instance, reactions that proceeded to complete conversion (e.g., those that form products **6** and **11**) could be worked up by simply filtering through a silica plug followed by removal of solvent to afford the pure difluoromethyl arene.



Scheme 1 Scope of aryl difluoromethylation with NMe_4F and PBSF. *Reagents and conditions:* (hetero)aryl aldehyde (0.20 mmol, 1.0 equiv), anhydrous NMe_4F (3.0 equiv), PBSF (1.2 equiv), THF (0.30 M), rt, 24 h. All yields are isolated yields. [a] Yield = average from two independent runs.

In parallel, we explored trifluoromethanesulfonic anhydride^{7,8} as a deoxyfluorinating reagent for the transformation of (hetero)aryl aldehydes into (hetero)aryl difluoromethyl products. Optimization studies showed that the use of dichloromethane (DCM) as solvent for this transformation results in higher yields than THF. Otherwise, analogous conditions were used to the PBSF reactions. As shown in Scheme 2, Tf_2O affords similar but somewhat complementary reactivity in comparison to PBSF. For instance, this system affords moderately higher yields with the electron-neutral aryl difluoromethyl products (**1** and **3**). In contrast, electron-deficient aryl and heteroaryl aldehydes reacted in lower yields in comparison to with PBSF (**6** and **11**).

The PBSF and Tf_2O conditions can also be compared to the analogous reactions using SO_2F_2 . In general, PBSF and SO_2F_2 afford comparable yields with electron-deficient (hetero)aryl aldehydes. For example, SO_2F_2 provides 96% yield of **11** while PBSF gives 90% yield. However, notably, SO_2F_2 excels with electron-neutral substrates providing 66% yield of **1**, whereas PBSF yields 37%. Tf_2O , on the other hand, affords 58% of **1** but gives **11** in 39% yield. Overall, PBSF and Tf_2O exhibit similar scope and reactivity to SO_2F_2 , but offer the convenience of liquid reagents.



Scheme 2 Scope of aryl difluoromethylation with NMe_4F and Tf_2O . *Reagents and conditions:* (hetero)aryl aldehyde (0.20 mmol, 1.0 equiv), anhydrous NMe_4F (3.0 equiv), Tf_2O (1.2 equiv), DCM (0.30 M), rt, 24 h. All yields are isolated yields. [a] Average of two independent runs.

In conclusion, this Communication demonstrates that perfluorobutanesulfonyl fluoride or trifluoromethanesulfonic anhydride and NMe_4F can be used to transform (hetero)aryl aldehydes into the corresponding (hetero)aryl difluoromethyl products in moderate to excellent yields. This work provides a practical laboratory scale alternative to SO_2F_2 for aldehyde deoxyfluorination.

Experimental Section

Optimization of the reaction in Table 1. In a nitrogen filled glovebox, a 4 mL scintillation vial containing a magnetic stirbar was charged with 4-bromobenzaldehyde (18.5 mg, 0.100 mmol, 1.00 equiv), anhydrous NMe_4F , and the appropriate solvent. The mixture was allowed to stir at room temperature for 30 s. Next, PBSF (22 μL , 0.120 mmol, 1.20 equiv) was added via syringe. The vial was sealed with a Teflon lined screw cap. The reaction was stirred vigorously at room temperature for the appropriate amount of time. Upon completion, (trifluoromethoxy)benzene (0.2 mL of 0.5 M stock solution in THF or acetonitrile, 1.0 equiv) was added as a standard. The reaction was analyzed by ^{19}F NMR spectroscopy.

General procedure for the deoxyfluorination of (hetero)aryl aldehydes using PBSF (Scheme 1). In a nitrogen filled glovebox, a 4 mL scintillation vial containing a magnetic stirbar was charged with aldehyde (0.200 mmol, 1.00 equiv), anhydrous NMe_4F (55.9 mg, 0.600 mmol, 3.00 equiv), and THF (0.67 mL, 0.30 M). The mixture was stirred at room temperature for 30 s. Next, PBSF (43 μL , 0.240 mmol, 1.20 equiv) was added via syringe. The vial was sealed with a Teflon-lined screw cap. The reaction was stirred vigorously at room temperature for 24 h. Periodically (approximately every 2 h), the vial was agitated to mix in insoluble material was stuck to the walls. Upon completion, the reaction was diluted with Et_2O (1 mL) and filtered through a pipette silica plug (approximately 3 cm), washing with Et_2O (5 mL). The resulting solution was concentrated and the product was purified using a Biotage 10 g SNAP column.

Representative example: synthesis of bromo-4-(difluoromethyl)benzene (4). The general procedure for Scheme 1 was performed using 4-bromobenzaldehyde as the substrate. Product **4** was obtained as a colorless oil (30 mg, 72% yield, $R_f = 0.46$ in 100% pentane). The NMR spectral data are consistent with those reported in the literature.⁹ HRMS calcd. for $\text{C}_7\text{H}_5\text{BrF}_2$: 205.9543; Found: 205.9552.

General procedure for the deoxyfluorination of (hetero)aryl aldehydes using Tf_2O (Scheme 2). In a nitrogen filled glovebox, a 4 mL scintillation vial containing a magnetic stirbar was charged with aldehyde (0.200 mmol, 1.00 equiv), anhydrous NMe_4F (55.9 mg, 0.600 mmol, 3.00 equiv), and DCM (0.67 mL, 0.30 M). The vial was capped with cap containing a pierceable Teflon/silicone septum. The mixture was stirred at room temperature for 30 s. Next, Tf_2O (40 μL , 0.240 mmol, 1.20 equiv) was added through the septum via syringe. The reaction was stirred vigorously at room temperature for 24 h. Periodically (approximately every 2 h), the vial was agitated to mix in insoluble material was stuck to the walls. Upon completion, the reaction was diluted with Et_2O (1 mL) and filtered through a pipette silica plug (approximately 3 cm), washing with Et_2O (5 mL). The resulting solution was concentrated and the product was purified using a Biotage 10 g SNAP column.

Representative example: synthesis of bromo-4-(difluoromethyl)benzene (4). The general procedure for Scheme 1 was performed using 4-bromobenzaldehyde as the substrate. Product **4** was obtained as a colorless oil (28 mg, 68% yield, $R_f = 0.46$ in 100% pentane). The NMR spectral data are consistent with those reported in the literature.⁹

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