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Direct Synthesis of Diverse β-Fluoroethylamines by a Multicomponent Protocol

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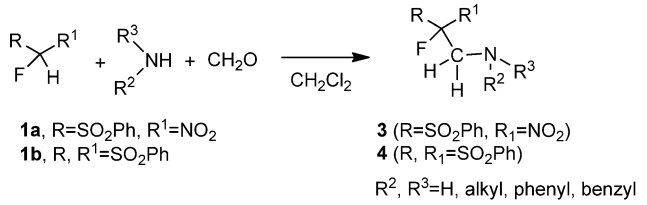
In Memory of Horst Prinzbach

Multicomponent reactions (MCRs) are synthetically highly efficient and economical as they offer high structural diversity and incorporate molecular units of all reaction components in a single step.[1] A well-known example of an MCR is the Mannich reaction, in which the educts formaldehyde, an amine, and a ketone or aldehyde are converted directly into the adduct bearing the molecular fragments of all components. It has been established as a powerful tool for C–C and C–N bond forming reactions.[2] In recent years, Mannich-type reactions of fluorinated substrates have actively been explored[3] because of the interesting properties imparted by the incorporation of a fluorine atom into a molecule. The presence of fluorine in organic compounds brings forth significant changes in their biological properties. Specifically, fluorine in drug molecules has a profound impact in their physicochemical, pharmacokinetic, and pharmacological properties.[4] For example, monofluoroacetic acid has been found to be a powerful inhibitor for the Krebs cycle.[5] Compounds with a monofluoromethyl moiety are of great importance with regards to isostere-based drug design.[6]

The classical intermolecular Mannich reaction, however, has a number of serious disadvantages.[2] Often, the harsh reaction conditions and the long reaction times lead to unwanted side reactions and products. With primary amines or ammonia as the amine component, the reaction can continue until all of the H atoms on the nitrogen are replaced. This has been avoided by the use of preformed electrophiles such as imines and iminium salts or nucleophiles such as enolates, enol ethers, and enamines. Preformed electrophilic Mannich reagents increase the concentration of the electrophile with significant reduction of reaction temperatures and times. Consequently, many undesired side reactions, which often cause problems in the Mannich reaction, are avoided, even with sensitive substrates.[2] Therefore, it is not surprising that direct Mannich reactions of fluorinated molecules involving three components are scarce.[3i] In most Mannich-type reactions of fluorinated substrates, preformed imines are used as Mannich reagents in combination with other nucleophiles.[3a–h]

Although the effectiveness of preformed electrophiles has been demonstrated extensively,[2] a fast and selective reaction with simple and basic molecular units in a Mannich-type reaction is highly desirable. Herein, we report a new protocol (Scheme 1) for the synthesis of fluoroethylated



Scheme 1. Preparation of β-fluoro(phenylsulfonyl)ethylamines from α-fluoro(phenylsulfonyl)methanes, formaldehyde, and amines.

amines by the Mannich-type three-component reaction of formalin, an amine (primary and secondary) and an activated fluoromethane, namely α-fluoro-α-nitro(phenylsulfonyl)-methane (FNSM, **1a**) or α-fluorobis(phenylsulfonyl)methane (FBSM, **1b**). To our knowledge, this is the first report of a three-component protocol involving an α-fluorocarbanion for the preparation of diverse *N*-alkyl and *N*,*N*-dialkyl fluoroethylamines from their molecular subunits. Furthermore, by introducing a proper fluoromethyl pronucleophile, the method avoids the use of corrosive or expensive fluorinating reagents such diethylaminosulfur trifluoride (DAST), morpholinosulfur trifluoride (Morpho-DAST), SF_4, and HF-amine complexes for selective fluorination. The reaction is simple and efficient with high yields.

Application of FBSM as a monofluoromethide equivalent was independently reported by the groups of Hu and Shibata for nucleophilic fluoroalkylation of epoxides[7a] and asym-

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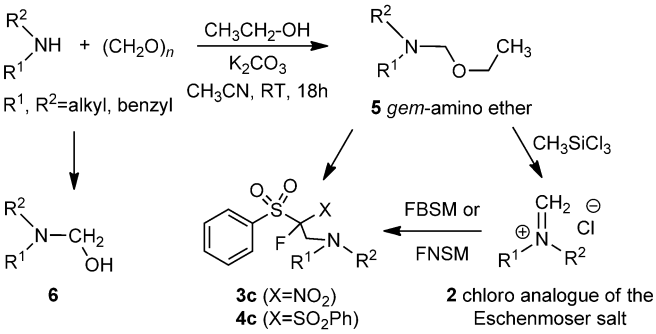
metric allylic fluorobis(phenylsulfonyl)methylation of allyl acetates, respectively.[7b] Highly electron-withdrawing groups, such as phenylsulfonyl, fluoro, nitro, cyano, and acetyl, activate the sp^3-hybridized C–H bond by significantly enhancing its acidity, making it an efficient fluoromethyl transfer agent.[8a] Since then, FBSM has been used by Prakash et al. and others efficiently for fluoromethide transfer in a variety of reactions.[8] Because the preparation of FBSM by electrophilic fluorination of bisphenylsulfonylmethane with Selectfluor is less atom economic,[8a] we recently discovered an efficient method for the high yield, multigram synthesis of FBSM from cheap and readily available potassium fluoride as the sole fluorinating source.[8b,c] On the other hand, the highly electrophilic nature of iminium salts makes them very reactive and attractive species in organic synthesis. Iminium salts are the most commonly used electrophilic Mannich reagents in the synthesis of a variety of molecules containing a C–N bond.[2,9a–j]

We began our exploration by testing the reactivity of dimethylmethylideneammonium chloride with α-fluorobis-(phenylsulfonyl)methane (FBSM, **1b**), which has a highly acidic C–H bond (the pK_a of bis(phenylsulfonyl)methane is 12.2 in DMSO).[10] In contrast to our expectation, FBSM showed no reactivity towards dimethylmethylideneammonium chloride in the absence of a base, even after stirring for 12 h at room temperature in CH_2Cl_2. However, with the addition of an equivalent amount of triethylamine, the reaction proceeded smoothly with 100% conversion (as shown by TLC and ^{19}F NMR spectroscopy) to give the desired product, 2-fluoro-*N*,*N*-dimethyl-2,2-bis(phenylsulfonyl)-ethanamine, **4a**. Under similar reaction conditions, the iminium salt dimethylmethylideneammonium chloride reacted with FNSM (the pK_a of α-nitro(phenylsulfonyl)methane is 7.1 in DMSO),[10] also giving the desired product, 2-fluoro-*N*,*N*-dimethyl-2-nitro-2-(phenylsulfonyl)ethanamine, **3a**, as the sole product. The higher reactivity displayed by FNSM, prompted us to continue our study with FNSM, which resulted in quantitative conversion to **3a** as expected.

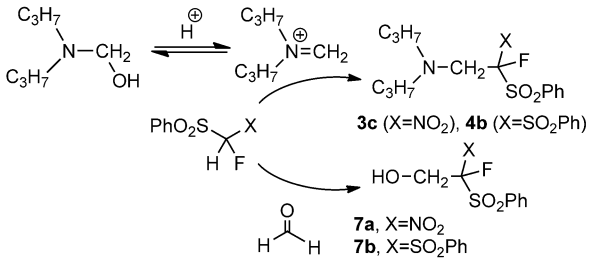
Due to their high electrophilicity, iminium salts are normally hygroscopic and prone to rapid hydrolysis. Particularly, salts with simple anions such as Cl^- are less stable and more sensitive to hydrolysis.[2] On the other hand, *gem*-amino ethers, which are the immediate precursors of the iminium salts,[11] have themselves been successfully utilized as effective electrophiles in various organic reactions.[12] Therefore, we were curious to determine the reactivity of a *gem*-amino ether towards FBSM or FNSM avoiding the difficulties with iminium salts. To our delight, when compound **5** ($R^1=R^2=$propyl) was reacted with FNSM under similar conditions to those described above, the reaction proceeded smoothly to give the corresponding product, *N*-(β-fluoro-β-nitroethyl)amine, **3c**, in high yield (Scheme 2).

We presumed that if the methylene carbon α to both N and O in *gem*-amino ether **5** is sufficiently electrophilic to react with FNSM, then the hemiaminal **6**, which can be generated from formaldehyde and *N*,*N*-dipropylamine should



Scheme 2. Formation of β-fluoro(phenylsulfonyl)ethylamines from iminium salts and *gem*-amino ether precursors.

also react with FNSM. Therefore, the reaction of FNSM with an in situ generated hemiaminal would allow us to obtain α-fluoro-α-nitro(phenylsulfonyl)methyl derivatives from a simple three-component Mannich-type reaction. Intrigued by this approach, a series of reactions were carried out. *N*,*N*-Dipropylamine, paraformaldehyde, and potassium carbonate were stirred together to generate hemiaminal **6** in situ, followed by the addition of FNSM to the reaction mixture. The reaction was complete within 15 min of the addition of FNSM and the desired product **3c** was isolated in 65% yield (Scheme 3). The yield of **3c** was diminished due



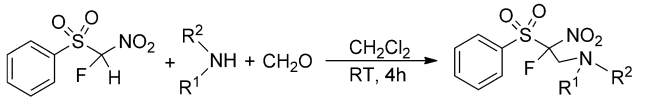
Scheme 3. Formation of fluoroethanol **7**, a competing pathway in the synthesis of β-fluoroethylamines **3** and **4**.

to the formation of the side product 2-fluoro-2-nitro-2-(phenylsulfonyl)ethanol, **7a**, isolated in 28% yield. It is clear that **7a** was formed from the direct addition of FNSM to formaldehyde, which was confirmed by conducting a separate reaction of FNSM with formaldehyde (formalin or paraformaldehyde) in dichloromethane, from which **7a** was isolated in 93% yield. Under similar conditions, **7b**, the adduct of FBSM and formaldehyde, was isolated in 90% yield (Scheme 3).

N,*N*-Dipropylamine itself is a good base; therefore, we decided to carry out this reaction without the addition of an additional base. However, to increase the yield of the product, the competing pathway, the formation of **7a**, should be suppressed (Scheme 3). To achieve this, the availability of formaldehyde in the reaction mixture for the formation of the aminal from the amine must be promoted to drive the reaction of FNSM in the desired direction during its addi-

tion. This was achieved by using formalin (37% aqueous solution) instead of solid polymeric paraformaldehyde. Indeed, the use of formalin was found to increase the selectivity as well as the yield of the product. The efficacy of the reaction could be further improved by initially stirring the amine and formalin to allow the formation of the aminal in ample concentration before the addition of FNSM (Table 1).

Table 1. Synthesis of β-fluoronitro(phenylsulfonyl)ethylamines by three-component reaction of α-fluoro-α-nitro(phenylsulfonyl)methane, an amine, and formalin without the addition of a base.



Entry	R^1	R^2	Product	Yield [%][a]
1	CH_3	CH_3	**3a**	92
2	CH_3CH_2	CH_3CH_2	**3b**	95
3	$CH_3(CH_2)_2$	$CH_3(CH_2)_2$	**3c**	95
4	$PhCH_2$	CH_3	**3d**	93
5	$-(CH_2)_4-$		**3e**	94
6	CH_3CH_2	CH_3	**3f**	91
7	$(CH_3)_2CH$	CH_3	**3g**	97
8	$(CH_3)_2CH$	$(CH_3)_2CH$	**3h**	95
9	$PhCH_2$	H	**3i**	92[b]
10	$CH_3(CH_2)_3$	H	**3j**	94
11	$(CH_3)_2CH$	H	**3k**	95
12	cyclopentyl	H	**3l**	96
13	$CH_3(CH_2)_5$	H	**3m**	93
14	Ph	H	**3n**	94[b]
15	p-CH_3O-C_6H_4	H	**3o**	93[b]

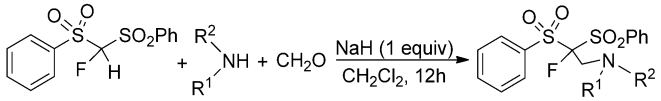
[a] Yield of the isolated product. [b] Reaction was carried out at 90°C.

Although the reaction was complete within 15 min of addition of FNSM in the case of *N*,*N*-dipropylamine, the required reaction time depended on the type of amine (e.g., primary or secondary amine) used in the reaction. In general, optimized conditions were found to be one equivalent of FNSM for 1.7 equivalents of secondary amine, and 1.5 equivalents of formaldehyde with a reaction time of 2 h before adding FNSM and 1 h after adding FNSM (Table 1). Secondary amines generally took longer than primary amines for the completion of the reaction. In terms of the selectivity for β-fluoro(phenylsulfonyl)ethylamines **3** (or **4**) over β-fluoro(phenylsulfonyl)ethyl alcohol **7a** (or **7b**), reactions with secondary amines were less selective than those with primary amines. This is reflected in the slightly higher yields of the products for reactions with primary amines. In addition to aliphatic amines, aromatic amines also underwent the reaction smoothly, giving the products in high yields (Table 1, entries 14, 15).

FBSM is an attractive reagent for monofluoroalkylation due to the susceptibility of the products to reductive desulfonylation to the corresponding monofluoroalkylated products in many cases. Reductive didesulfonylation of FBSM to use it as a monofluoromethide equivalent has been successfully carried out in similar systems by using Mg and MeOH by our group and others.[8b,k,13] Expecting similar results for FBSM in this reaction, the three-component strategy has also been extended to FBSM.

Longer reaction times were required for the complete and selective conversion of FBSM to the desired product. As in the case of reactions with FNSM, reactions with primary amines were faster and more selective than those with secondary amines. Although secondary amines did react with FBSM and formalin (formaldehyde) in the absence of a base, use of a base such as NaH, along with heating, promoted the selective and complete conversion of FBSM to the desired products (Table 2). A suspension of FBSM and

Table 2. Synthesis of β-fluorobis(phenylsulfonyl)ethylamines by three-component reactions of α-fluorobis(phenylsulfonyl)methane that require a base.



Entry	R^1	R^2	Product	Yield [%][a]
1	CH_3	CH_3	**4a**	67
2	$CH_3(CH_2)_2$	$CH_3(CH_2)_2$	**4b**	95[b]
3	$PhCH_2$	CH_3	**4c**	87
4	$-(CH_2)_4-$		**4d**	91[b]
5	CH_3CH_2	CH_3	**4e**	89[b]
6	$(CH_3)_2CH$	CH_3	**4f**	86
7	$PhCH_2$	H	**4g**	65
8	Ph	H	**4h**	41[b]
9	p-CH_3O-C_6H_4	H	**4i**	46[b,c]

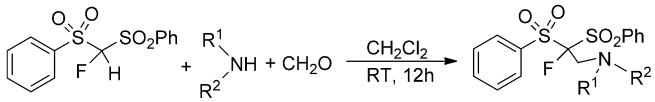
[a] Yield of the isolated product. [b] Reaction was carried out at 90°C. [c] Reaction time was 3 h.

NaH in CH_2Cl_2 was stirred separately in a vial for 5 min and subsequently added to the mixture of formalin and amine to avoid deactivation of NaH in the aqueous medium. As for FNSM, aromatic amines also participated in the three-component reaction with FBSM and formalin to give the expected products, albeit in low yields (Table 2, entries 9, 10). Neither base nor heating was required for the complete conversion of many primary amines to their respective products (Table 3, entries 1–7).

Dialkylation has been reported to occur during alkylation of primary amines. Therefore, alkylation of primary amines is usually carried out by prior protection and then deprotection after alkylation.[14] In our reactions with primary amines, no such dialkylation was observed. The validity of the three-component reaction was further confirmed by single-crystal X-ray crystallographic analysis of the product **4e** (Figure 1).

Fluorinated ethylamines can be prepared by many methods,[16] such as direct alkylation of amines,[16a–c] reaction of lithium amides with 2-fluoroethyl bromide[14] and alkylation of suitably protected aniline by 2-fluoroethyl 4-methylbenzenesulfonate.[16d] Fluoride exchange with anhydrous KF on *N*,*N*-bis(2-tosylethyl)anilines can also yield *N*,*N*-bis(2-fluoroethyl)anilines.[17a] Reductive amination of α-fluoroacetophenone with ammonia in EtOH in the presence of titanium isopropoxide followed by $NaBH_4$ reduction gives 1-aryl-2-

Table 3. Synthesis of β-fluorobis(phenylsulfonyl)ethylamines by three-component reaction of α-fluorobis(phenylsulfonyl)methane, amine, and formalin without the addition of a base.



Entry	R^1	R^2	Product	Yield [%][a]
1	$CH_3(CH_2)_3$	H	**4j**	85
2	$(CH_3)_2CH$	H	**4k**	78
3	cyclopentyl	H	**4l**	97
4	$CH_3(CH_2)_4CH(CH_3)$	H	**4m**	88
5	(cyclohexyl)$CH(CH_3)$	H	**4n**	86
6	1-adamantyl	H	**4o**	94
7	$CH_3(CH_2)_9$	$CH_3(CH_2)_9$	**4p**	87[b]
8	$Ph(CH_2)_2$	H	**4q**	89[c]
9	$(C_6H_5)CH(CH_3)$	H	**4r**	93[c]
10	1-naphthylmethyl	CH_3	**4s**	68[c]

[a] Yield of the isolated product. [b] Solvent was EtOH. [c] When the reaction mixture was heated to 90 °C after the addition of FBSM, the reaction was complete after 1 h.

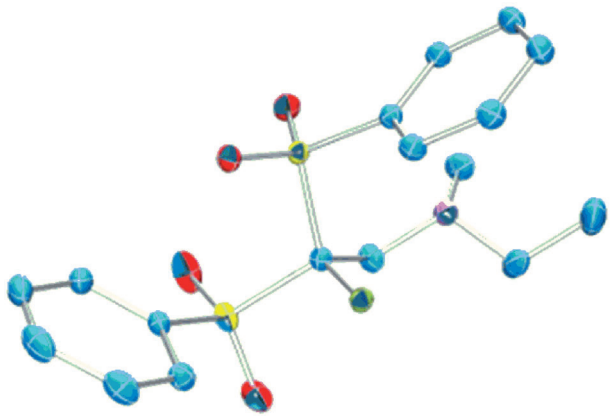
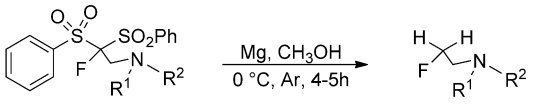


Figure 1. X-ray crystal structure of the three-component reaction product **4e** from FBSM, formalin, and ethyl methyl amine.[15]

fluoroethylamines.[17b] Recently reported stereoselective nucleophilic monofluoromethylation of (*R*)-(*tert*-butanesulfinyl)imines by Hu et al.[18] and enantioselective monofluoromethylation of in situ generated prochiral imines by Shibata et al.[3 h] are also efficient methods. However, in both cases, preformed imines or imines formed in situ from protected α-amidosulfones and strong bases in equimolar or greater amounts were always required. To our knowledge, the present method is the only direct method that utilizes the simple molecular units, namely, amine, formaldehyde (formalin) and FBSM for the formation of fluorinated ethylamines and therefore increases the scope for making the reaction more diverse. Further, a few β-fluorobis(phenylsulfonyl)ethylamines **4** were subjected to reductive didesulfonylation with Mg in MeOH at 0 °C under Ar to obtain monofluoroethylamines **8** (Table 4).

Mechanistically, both the iminium salt and the hemiaminal are possible reactive intermediates as manifested from the reactivity of both with FNSM. However, under the present reaction conditions, hemiaminals can be considered as most viable because the formation of significant amounts of the iminium salt is less likely (due to the absence of acid) and its stability is rather low (due to the presence of water).

Table 4. Synthesis of β-fluoroethylamines by reductive didesulfonylation of β-fluorobis(phenylsulfonyl)-*N*,*N*-dialkylethylamines.



Entry	R^1	R^2	Product	Yield [%][a]
1	$CH_3(CH_2)_4CH(CH_3)$	H	**8m**	35
2	(cyclohexyl)$CH(CH_3)$	H	**8n**	72
3	1-adamantyl	H	**8o**	55
4	$(C_6H_5)CH(CH_3)$	H	**8r**	81
5	1-naphthylmethyl	CH_3	**8s**	76

[a] Yield of the isolated product.

In conclusion, we have developed a direct Mannich-type reaction for the facile synthesis of β-fluoro(phenylsulfonyl)ethylamines by using fluorinated carbon pronucleophiles, FNSM and FBSM. The reaction is performed under mild conditions, is highly feasible for both primary and secondary amines, and no base is required in many cases. More importantly, the reaction adheres to the classical Mannich reaction conditions, bringing all three components, formaldehyde, amine, and the activated fluoromethane, together in one pot to form a fluorinated ethylamine in high yields. These β-fluoro(phenylsulfonyl)ethylamines may be candidates for further studies on their biological effects and therapeutic activities.

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Keywords: desulfonylation · fluoromethylation · formalin · Mannich reaction · multicomponent reactions · pronucleophiles · synthetic methods

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