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Two-Step Synthesis of Difluoromethyl-Substituted 2,3-Dihydrobenzoheteroles

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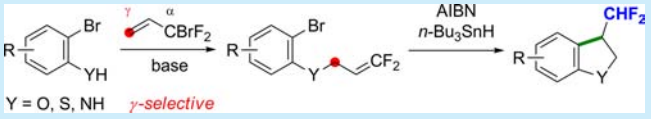
Supporting Information

ABSTRACT: 3-Difluoromethylated 2,3-dihydrobenzoheteroles, 2,3-dihydrobenzofurans, 2,3-dihydrobenzothiophenes, and indolines were readily synthesized from *ortho*-heterosubstituted bromobenzenes, 2-bromophenols, 2-bromobenzenethiols, and 2-bromoanilines, respectively, in two steps: (1) γ-selective allylic substitution of 3-bromo-3,3-difluoropropene with heteronucleophiles and (2) intramolecular radical cyclization of the resulting 3,3-difluoroallylic compounds.



The difluoromethyl (CHF_2) group occupies a significant position among fluorinated functional groups, exhibiting unique properties derived from the steric and electronic characteristics of fluorine.[1] In particular, the CHF_2 group has been regarded as a bioisostere of the hydroxy group,[2] and indeed difluoromethylated compounds are increasingly found in bioactive substances, particularly agrochemicals.[3] Furthermore, due to the electron-withdrawing effect of fluorine, the difluoromethyl group serves as a proton donor for hydrogen bonding, albeit with a hydrophobic nature.[4]

Despite the interesting potential of the CHF_2 group, conventional approaches to ring-difluoromethylated compounds have significant limitations; they require tedious reactions and toxic reagents such as diethylaminosulfur trifluoride (DAST).[5−8] Thus, building block approaches to difluoromethylated compounds that include effective transformation of a fluorine-containing functional group into a CHF_2 group have attracted increasing attention.[1c,9,10] Quite recently, a few methods for direct difluoromethylation have also been reported.[11]

In our previous study on the building block approach, we developed an intramolecular S_N2' reaction of 2-trifluoromethyl-1-alkenes bearing nucleophilic moieties for the regioselective synthesis of difluoromethylated heterocycles, such as indoles (Scheme 1A).[9] Herein, we describe a two-step synthesis of 3-difluoromethylated 2,3-dihydrobenzoheteroles **3** (Scheme 1B). The reaction proceeds via (i) the S_N2' allylic substitution of 3-bromo-3,3-difluoropropene with readily available 2-bromophenols **1a**, 2-bromobenzenethiols **1b**, and 2-bromoanilines **1c** under basic conditions[12] and (ii) the subsequent intramolecular radical cyclization of the intermediary 3,3-difluoroallylic compounds **2**.[13] It is noteworthy that both the installation of the CHF_2 substituent and construction of the dihydrobenzoheterole framework are simultaneously achieved in this process. Thus, this methodology ensures regio-defined introduction of a CHF_2 group on the heterocyclic ring.

First, we sought a base that was suitable for the S_N2' allylation with 3-bromo-3,3-difluoropropene using 2-bromophenol (**1aa**) as a model substrate (Table 1). While an amine and an organolithium reagent were practically ineffective (entries 1 and 2), alkali metal hydrides enhanced the formation of the allylation products **2aa** and **4aa** (entries 3 and 4). In comparison with sodium hydride, potassium hydride highly improved the **2aa**/**4aa** ratio. A similar trend was observed using carbonate salts (entries 5−7). In terms of both efficiency and selectivity, cesium carbonate was found to be the best among the bases examined (entry 7). The efficiency and selectivity of the formation of **2aa** in the reaction with cesium carbonate in *N*,*N*-dimethylformamide (DMF) was improved when 3-bromo-3,3-difluoropropene was increased to 2 equiv, affording a 56% yield of **2aa** with a 2:1 ratio of **2aa**/**4aa** (entry 8).[14] Moreover, this reaction was sensitive to the solvent used (entries 9−13). Thus, *N*-methyl-2-pyrrolidone provided better results than DMF (entries 12 and 7, respectively), and ultimately **2aa** was obtained in 79% yield with an approximately 5:1 ratio of **2aa**/**4aa** in the reaction using 2 equiv of 3-bromo-3,3-difluoropropene (entry 13).[14,15]

We believe that the size of the countercation may affect the selectivity because the **2aa**/**4aa** ratio was generally improved as

Scheme 1. Synthetic Routes to Difluoromethylated Benzoheterole Derivatives

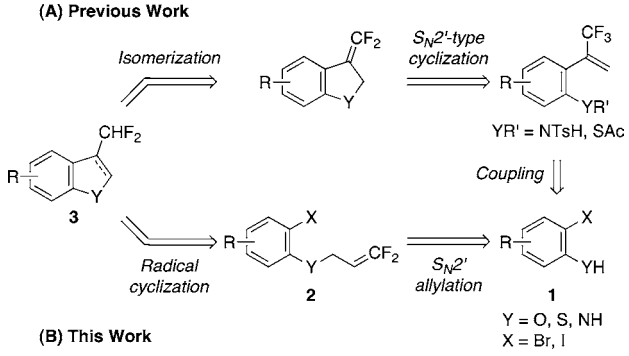


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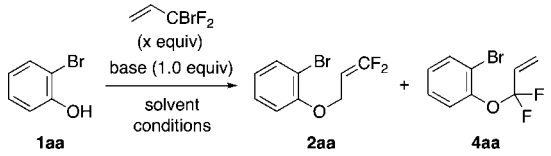
Table 1. Screening of Conditions for the S_N2'-Selective Reaction with Phenol 1aa



1aa 2aa 4aa

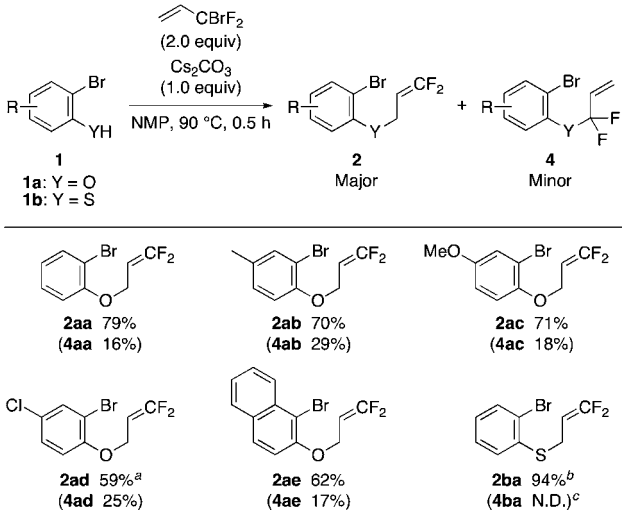
entry	x	base	solvent	conditions	2aa (%)[a]	4aa (%)[a]
1	1.0	DMAP	DMF	90 °C, 1.5 h	6	16
2	1.0	*n*-BuLi	THF	−78 to 80 °C, 4 h	1	1
3	1.0	NaH	DMF	100 °C, 1.5 h	29	48
4	1.0	KH	DMF	100 °C, 4 h	41	13
5	1.0	Na_2CO_3	DMF	100 °C, 2 h	16	27
6	1.0	K_2CO_3	DMF	100 °C, 2 h	37	37
7	1.0	Cs_2CO_3	DMF	100 °C, 17 h	42	28
8	2.0	Cs_2CO_3	DMF	100 °C, 4 h	56	28
9	1.0	Cs_2CO_3	EtOH	90 °C, 2 h	trace	trace
10	1.0	Cs_2CO_3	MeCN	90 °C, 2 h	55	23
11	1.0	Cs_2CO_3	DMSO	100 °C, 3 h	49	21
12	1.0	Cs_2CO_3	NMP	100 °C, 3 h	62	21
13	**2.0**	**Cs_2CO_3**	**NMP**	**90 °C, 0.5 h**	**79**	**16**

[a]Isolated yield.

the diameter of the countercation increased (Table 1, entries 3 and 4; entries 5−7). In the case of cesium carbonate, the intermediary cesium phenoxide formed in equilibrium could attack the carbon atom α or γ to the fluorine substituents of 3-bromo-3,3-difluoropropene. Under the optimal conditions, cesium phenoxide appears to predominantly attack the less hindered γ-carbon atom, avoiding the steric hindrance between the cesium core and the fluorine substituents on the α-carbon atom.

With the optimal conditions in hand, the substrate scope was then investigated (Scheme 2). Several functionalized (Me-, MeO-, and Cl-bearing) 2-bromophenols **1ab**−**1ad** and 1-bromo-2-naphthol (**1ae**) successfully underwent the S_N2'-selective reaction to afford the corresponding 3,3-difluoroallyl compounds **2ab**−**2ae** in good yields, whereas electron-withdrawing groups (e.g., CN) induced the selective formation of the undesired 1,1-difluoroallyl products **4a**.[16] Intriguingly, the reaction of 2-bromothiophenol (**1ba**) smoothly proceeded at room temperature to afford a high yield (94%) of the 3,3-difluoroallylated product **2ba** with exclusive selectivity, even when only 1 equiv of 3-bromo-3,3-difluoropropene was used.[17] This perfect selectivity may be the result of the ionic size effect of both sulfur and cesium.

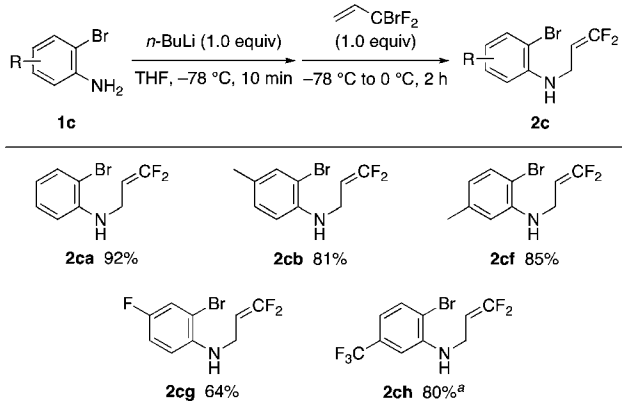
Scheme 2. 3,3-Difluoroallylation of Phenols 1a and Benzenethiols 1b via S_N2'-Selective Reaction



[a]3-Bromo-3,3-difluoropropene (5.0 equiv), DMF, 100 °C, 2 h. [b] 3-Bromo-3,3-difluoropropene (1.0 equiv), DMF, rt, 3 h. [c] N.D. = Not detected.

In contrast to phenols **1a**, the S_N2'-selective allylation of 2-bromoanilines **1c** with 3-bromo-3,3-difluoropropene was effectively promoted using butyllithium as the base, which resulted in the exclusive formation of 3,3-difluoroallyl products **2c** in good to high yields (Scheme 3). In addition, 2-bromoanilines bearing not only a methyl or fluorine substituent but also an electron-withdrawing substituent (CF_3) successfully participated in the S_N2' reaction. The exclusive formation of **2c** may be attributed to the steric hindrance caused by the N−H and N−Ar bonds on the nitrogen atom of the intermediary lithium amides, which leads to exclusive attack of lithium amide on the carbon atom γ to the fluorine substituents in 3-bromo-3,3-difluoropropene.

Scheme 3. 3,3-Difluoroallylation of Anilines 1c via S_N2'-Selective Reaction



[a]−78 to 80 °C, 8 h.

Next, the intramolecular radical cyclization was investigated with tributyltin hydride using **2aa** as a model substrate (Table 2). The choice of radical initiator and solvent was found to be critical for efficient cyclization. Triethylborane with oxygen (entry 1) and 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V70, entry 2) were inappropriate as initiators for this reaction. In contrast, 2,2′-azobis(isobutyronitrile) in hexane effectively promoted the radical cyclization in the 5-*exo* fashion to give the desired 3-difluoromethyl-2,3-dihydrobenzofuran (**3aa**) in 92% isolated yield (entry 7) without the formation of the 6-*endo* cyclization product.

The synthesis of 3-difluoromethylated 2,3-dihydrobenzoheteroles **3** was investigated under the conditions described above (Scheme 4). Regardless of the heteroatoms and substituents attached to the aromatic rings, the 3,3-difluoroallyl compounds **2** successfully underwent intramolecular radical cyclization to afford 3-difluoromethyl-2,3-dihydrobenzofurans **3a**, 3-difluoromethyl-2,3-dihydrobenzothiophenes **3b**, and 3-difluoromethylindolines **3c** in good to high yields (61%−96%).

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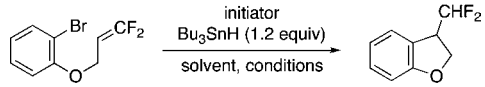
Table 2. Effect of Reaction Conditions on the Radical Cyclization of 3,3-Difluoroallyl Compound 2aa

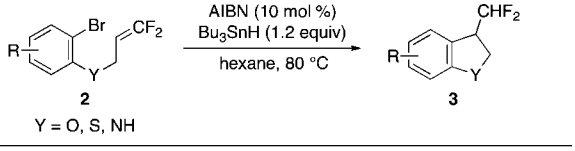


2aa 3aa

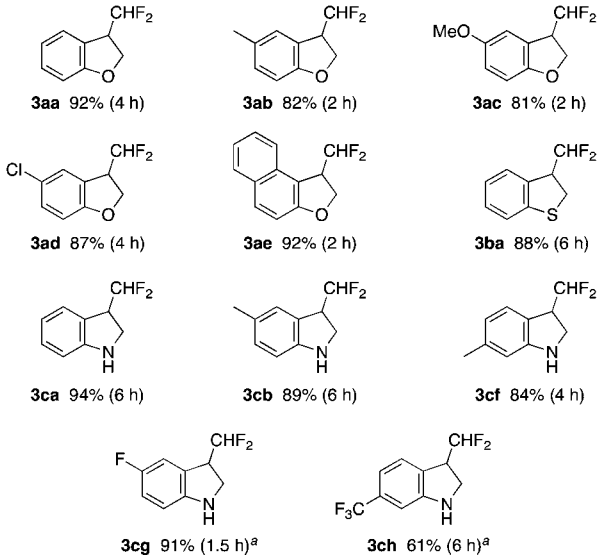
entry	initiator (mol %)	solvent	conditions	3aa (%)[a]
1	Et_3B(200) + O_2 (1 atm)	toluene	−78 °C, 9 h	35
2	V70 (20)	benzene	rt, 8 h	2
3	AIBN (50)	benzene	80 °C, 24 h	20
4	AIBN (20)	toluene	100 °C, 8 h	8
5	AIBN (10)	MeCN	80 °C, 12 h	trace
6	AIBN (10)	DCE	80 °C, 12 h	30
7	AIBN (10)	hexane	80 °C, 4 h	92[b]

[a]^{19}F NMR yield using $PhCF_3$ as an internal standard. [b]Isolated yield.

Scheme 4. Synthesis of 3-Difluoromethylated Dihydrobenzoheteroles 3 via Radical Cyclization of 3,3-Difluoroallyl Compounds 2



2 Y = O, S, NH 3



[a]Bu_3SnH (1.0 equiv).

In summary, we disclosed a facile approach to the synthesis of difluoromethyl-substituted dihydrobenzoheteroles starting from readily available bromoarenes and 3-bromo-3,3-difluoropropene. This sequence provides a powerful protocol for the regioselective introduction of CHF_2 substituents, which has attracted increasing attention.[18]

The 2,3-dihydrobenzoheterole frameworks thus formed have been recognized as enormously important structures in pharmaceutical science; e.g., this structure can be found in a diuretic[19] and a putative entactogen drug.[20] Because difluoromethylated dihydrobenzoheteroles are hybrids of two pharmaceutically important components, the CHF_2 group and the dihydrobenzoheterole framework, they are expected to serve as new bioactive compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H, ^{13}C, and ^{19}F NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) Unreacted **1aa** assisted the 1,3-allylic rearrangement of **2aa** to **4aa**. To suppress this undesired process, the reaction time should be shortened by the addition of an excess of 3-bromo-3,3-difluoropropene.

(15) When the reaction of 2-bromophenol **1aa** was quenched at an early stage (1 min), a 16% yield of the desired product **2aa** and a 4% yield of the side product **4aa** were obtained. The **2aa**/**4aa** ratio of this reaction (80/20) was similar to that of the reaction quenched after 30 min (83/17). This result suggests that the side product **4aa** can be formed directly via the reaction of bromophenol **1aa** with 3-bromo-3,3-difluoropropene.

(16) Reactions of 3-bromo-4-hydroxybenzonitrile with 3-bromo-3,3-difluoropropene afforded a 79% yield of the corresponding 1,1-difluoroallyl product with exclusive selectivity.

(17) Alternatively, thioethers **2b** were also prepared via the reaction with 1,1-difluoroallene. Treatment of **1ba** with 5 equiv of 1,1-difluoropropa-1,2-diene in the presence of 0.5 equiv of KOH (THF, 60 °C, 12 h) exclusively afforded **2ba** in 79% yield. In contrast, the reaction of bromophenols **1a** with 1,1-difluoropropa-1,2-diene selectively provided undesirably allylated products **4a**.

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