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Site-Specific Preparation of 3-Fluoro-1-substituted-naphthalenes via a Novel Base-Catalyzed Cyclization Reaction from (*E*)-Monofluoroenynes§

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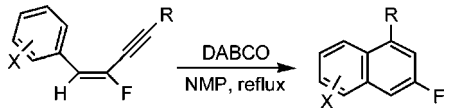
ABSTRACT



A novel cyclization reaction for the preparation of 3-fluoro-1-substituted-naphthalenes is reported. (*E*)-Monofluoroenynes, which are prepared by Sonogashira coupling reaction from (*Z*)-1-bromo-1-fluoroalkenes, undergo cyclization to afford 3-fluoro-1-substituted-naphthalenes in good to excellent yields when treated with DABCO or DBU in refluxing *N*-methyl-2-pyrrolidinone (NMP).

As fluorine is small (similar to oxygen in size) and the most electronegative among all elements, compounds in which hydrogen is strategically replaced by fluorine can modify biological activity by altering physicochemical properties of the fluorinated compounds.[1] Site-specific fluorination of organic compounds has received continued attention due to the unique properties of fluorine.[2] Recently fluoroaromatics, especially fluorinated naphthalenes, have been of interest to us because of the paucity of synthetic methodologies for these compounds although they are in growing demand as agricultural and pharmaceutical agents.[3−5]

There are limited methodologies for the preparation of monofluorinated naphthalenes. The Balz−Schiemann reaction[6] (thermolysis of arenediazonium salts) is the classical method to incorporate fluorine into a naphthalene ring, as demonstrated by the preparation of 2-fluoronaphthalene.[7] There are drawbacks to this method: the starting diazonium salts are hazardous; certain functional groups ortho to the diazonium group could not be tolerated; and the intermediate aryl cations produce various tarry byproducts.[8] The preparation of 2-fluoronaphthalene from 2-naphthylsilane by $Pb(OAc)_4$ and $BF_3{\cdot}Et_2O$,[3,8] or from 2-naphthylboronic acid by diethanolamine and $CsSO_4F$,[4] has also been reported. Direct electrophilic fluorination of naphthalene with use of N−F reagents, such as SelectFluor, has been successfully carried out to prepare monofluoronaphthalenes.[9] However, the isomeric products (1- and 2-fluoronaphthalenes) were formed with little regioselectivity and were difficult to separate.[9] The addition reaction of a fluorinated carbene : CFX (X = F, Cl, Br) to indene, followed by base-induced rearrangement, has also been utilized in the preparation of 2-fluoronaph-

§ This paper is dedicated to Professor Karl O. Christe on the occasion of his 70th birthday.

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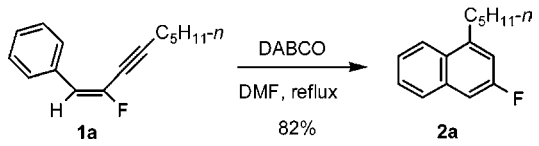
thalene.[10] However, this method has a limitation in the preparation of functionalized 2-fluoronaphthalenes due to the inconvenient preparation of the starting material. Schlosser and co-workers recently reported a synthetic route to fluoronaphthalenes via fluoroarynes. However, regioisomeric mixtures were found in their cases.[11] Herein, we wish to report the first base-catalyzed cyclization to site specifically prepare 3-fluoro-1-substitutued-naphthalenes via the cyclization reaction of (*E*)-monofluoroenynes.

Recently, we reported the preparation of monofluoroenynes (*E*)-RCH═CFC≡CR′ **1a** from (*Z*)-1-bromo-1-fluoroalkenes[12] by the Sonogashira coupling reaction.[13] Although photochemical 6π electron cycloaromatizations of aryl enynes have been reported,[14] no cyclization product was detected according to ^{19}F NMR analysis of the reaction mixture, when a solution of **1a** in DMF was photochemically irradiated at 254 nm overnight. Instead, 8% of the (*Z*)-isomer of **1a** was observed due to isomerization.

When **1a** was reacted with DABCO (6 equiv) in refluxing DMF, ^{19}F NMR spectroscopy of the reaction mixture showed that a new product, the fluorinated naphthalene derivative, **2a** was formed and isolated in 82% yield (Scheme 1). ^{19}F, ^{1}H, ^{13}C NMR, GC-MS, and HRMS analysis support the proposed structure.

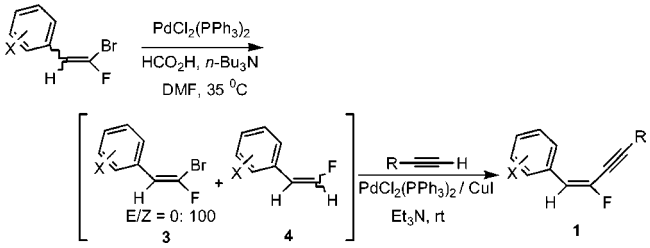
Scheme 1



Although Rolando and co-workers reported one example of the preparation of 2-bromo-4-fluoro-1-phenylnaphthalene from (*E*)-PhCF═CHC≡CPh via an electrophilic cyclization induced by "BrF",[15] to the best of our knowledge, our work is the first base-catalyzed cyclization reaction for the preparation of 3-fluoro-1-substituted-naphthalenes.

The starting enynes can be prepared via the Sonogashira reaction of terminal alkynes with pure (*Z*)-monofluoroenynes, which were synthesized via carboxylation of a mixture of (*Z*)- and (*E*)-1-bromo-1-fluoroalkenes, followed by Br_2 addition and subsequent decarboxylation.[15] However, this method has limitations. For example, isomeric mixtures were obtained when strong electron-withdrawing or electron-donating groups were present on the aromatic ring. A kinetic separation method for the preparation of (*E*)-monofluoroenynes has been developed in our laboratory.[12] (*Z*)-1-Bromo-1-fluoroalkenes were recovered after the Sonogashira reaction of the more reactive (*E*)-isomers with terminal alkynes. So, with a slight modification of this procedure, the starting (*E*)-monofluoroenynes **1** were prepared as illustrated in Table 1. Instead of using pure (*Z*)-1-bromo-1-fluoroalkenes, a mixture of (*Z*)-1-bromo-1-fluoroalkenes **3** and the corresponding reduced products **4**, which were prepared via the kinetic reduction of the *E*/*Z* ≈ 1:1 mixture of 1-bromo-1-fluoroalkenes,[16] were used as the starting materials. Thus, a mixture of **3** and **4**, terminal acetylene, $PdCl_2(PPh_3)_2$ (4 mol %), and CuI (1 mol %) in Et_3N was reacted at room temperature and the (*E*)-monofluoroenynes **1** were successfully prepared. In entry 3, the product **1d** was not completely separated from the reduced products **4** and the mixture was directly used in the subsequent cyclization reaction.

Table 1. Preparation of (*E*)-Monofluoroenynes by the Sonogashira Reaction between **3** and Terminal Acetylenes



entry	X	*E*/*Z* of **3**	R	time (h)	*Z*/*E* of **1**	product	isolated yield (%)
1	*o*-Cl	0:100	*n*-C_5H_{11}	36	0:100	**1b**	92
2	*o*-Cl	0:100	*n*-$C_{10}H_{21}$	48	0:100	**1c**	72
3	*p*-MeO	0:100	*n*-C_5H_{11}	21	0:100	**1d**	(82)[a]

[a] The product was not separated from the reduced products; the number in parentheses is the conversion, which was calculated based on the amount of **3** in the starting mixture of **3** and **4**.

The cyclization reactions between these (*E*)-monofluoroenynes **1** and different bases in refluxing polar solvents were also successful and good to excellent isolated yields of the 3-fluoro-1-substituted-naphthalenes **2** were obtained (Table 2).

The use of NMP as the solvent was important in these reactions. Most reactions could be completed within 10 h in NMP, compared to 87 h in DMF (entry 1), presumably due to the difference of their boiling points. In the above reaction conditions, 6.0 equiv of DABCO was used due to the sublimation of DABCO at the reflux temperature of NMP. A catalytic amount (20 mol %) of alternative bases, DBU and *n*-Bu_3N, was investigated, respectively, with **1b** in NMP at reflux temperature. The reaction was smooth and com-

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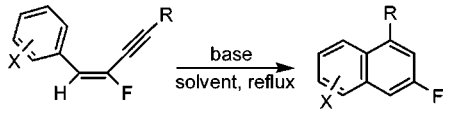
Table 2. Preparation of 3-Fluoro-1-substituted-naphthalenes by the Cyclization of (*E*)-Monofluoroenyenes **1**



1 **2**

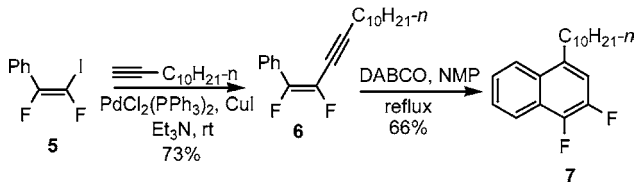
entry	X	R	base	solvent	time (h)	product	yield (%)[a]
1	H	*n*-C_5H_{11}	DABCO	DMF	87	**2a**	82
2	*o*-Cl	*n*-C_5H_{11}	DABCO	NMP	6	**2b**	93
3	*o*-Cl	*n*-C_5H_{11}	DBU	NMP	7	**2b**	80
4	*o*-Cl	*n*-C_5H_{11}	*n*-Bu_3N	NMP	7	**2b**	~8[c]
5	o-Cl	*n*-$C_{10}H_{21}$	DABCO	NMP	6	**2c**	94
6	*p*-MeO	*n*-C_5H_{11}	DABCO	NMP	11	**2d**	86
7	*p*-MeO	Ph	DABCO	NMP	43	N.R.[b]	0
8	*p*-MeO	*t*-Bu	DABCO	NMP	5	N.R.	0

[a] Isolated yield of **2**. All products gave satisfactory ^{19}F, ^{1}H, ^{13}C NMR, GC-MS, and HRMS data. [b] No reaction. [c] Determined by ^{19}F NMR.

pleted within 7 h when DBU was utilized (entry 3) and the desired product was successfully isolated in 80% yield. However, when *n*-Bu_3N was employed as the base (entry 4), the reaction was very slow. After 7 h, only $^1/_6$ of the starting **1b** was consumed and a considerable amount of unidentified side products was detected by ^{19}F NMR analysis of the reaction mixture. Therefore this cyclization reaction could be carried out with a catalytic amount of an alternative base (20 mol % of DBU). Note that when R is Ph or *t*-Bu (entries 7 and 8), no desired product was observed in either case. The products **2** showed a consistent F−H coupling pattern (triplet with a coupling constant of 9.5−10.0 Hz) in the ^{19}F NMR spectrum. The structure of **2c** was also confirmed by an X-ray crystal structure.[17]

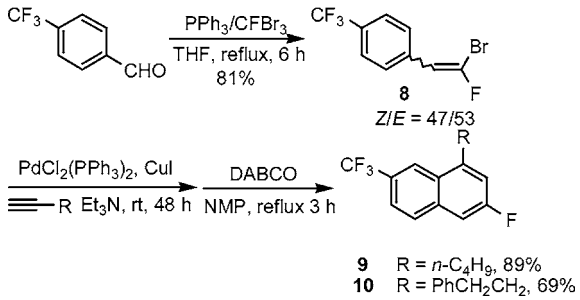
After the successful cyclization of monofluoroenynes, we extended the reaction to difluoroenynes. Difluoroenyne **6** was prepared from (*E*)-1,2-difluoro-1-iodo-2-phenylethene **5**[18] via a Sonogashira reaction with 1-decyne. Cyclization under similar reaction conditions afforded the difluorinated naphthalene **7** (Scheme 2).

Scheme 2



Since only (*E*)-enynes undergo cyclization to give the cyclized product, to simplify the synthetic route, we investigated the possibility of utilizing the mixture of (*Z*)- and (*E*)-enynes as the substrate for cyclization (Scheme 3). An *E*/*Z* mixture of **8** was prepared from the reaction of

Scheme 3



4-(trifluoromethyl)benzaldehyde, $CFBr_3$, and PPh_3 in refluxing THF.[19] The Sonogashira reaction of the *E*/*Z* mixture of **8** with 1-hexyne or 4-phenyl-1-butyne afforded the corresponding enyne, which was used directly in the next step without purification. Cyclization of the enynes under normal reaction conditions occurred smoothly. Compounds **9** and **10** were easily isolated in good yields, respectively. The yields in the two steps were based on the amount of (*Z*)-**8** in the *E*/*Z* mixture. Via this improved route, the kinetic reduction step was not required. Thus, this modification provided a more efficient synthetic route to this class of compounds.

We also tested the cyclization of the nonfluorinated (*Z*)-enyne under the similar reaction conditions. (*Z*)-Non-1-en-3-yn-1-ylbenzene **11** was prepared by the Sonogashira coupling reaction of 1-pentyne with [(*Z*)-2-bromovinyl]-benzene, which was synthesized from phenylacetylene by the literature procedure.[20] Unfortunately, no reaction was observed when enyne **11** was reacted with DABCO (6.0 equiv) in refluxing NMP.

Since the *t*-Bu- or Ph-substituted enyne did not produce the desired cyclized product, it suggested to us that the mechanism might involve an allene as the intermediate. To further test the mechanism of this novel reaction, the following experiment was performed (Scheme 4). Compound **12** was prepared via the reaction of benzaldehyde-d_5, $CFBr_3$, and PPh_3 in THF. The subsequent kinetic reduction reaction of **12** afforded a mixture of (*Z*)-**13** and the reduction product, which was reacted with 1-heptyne via the Sonogashira reaction to afford the (*E*)-monofluoroenyne **14**. Cyclization of **14** with DABCO in refluxing NMP gave a mixture of **15** consisting of 70% of CHD-naphthalene and 30% of CH_2-naphthalene derivatives (determined by ^1H and ^2D NMR spectrum). Our attempt to prepare or detect the proposed allene intermediate was not successful.

(17) CCDC 600929 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033. Also see the Supporting Information.

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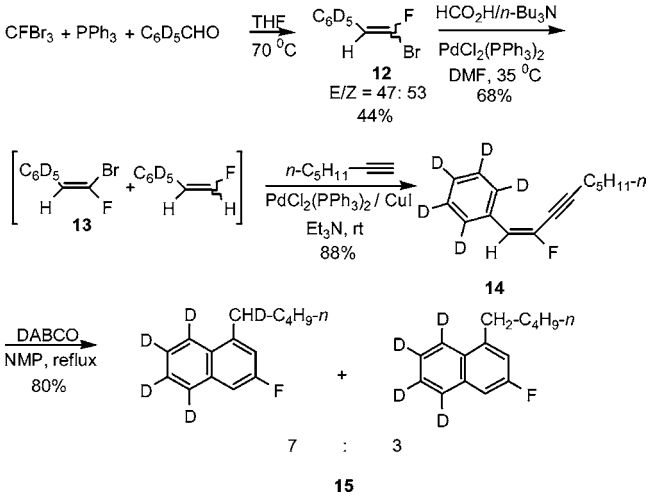
Scheme 4



On the basis of the above experiments, we propose the following mechanism (Scheme 5). First, the base catalyzes the isomerization of the enyne to the allene,[21] which undergoes 6π cycloaddition to form a two-ring system. The final product could be formed either from abstraction of H on C-9 by base followed by acquisition of H from the proton pool (either from base•H^+ or a trace amount of moisture in the system) or from a [1,7]-H shift without assistance of the base.[22] To exclude the possibility of solvent (NMP or DMF) serving as a "proton pool", **1b** was reacted with DABCO (6.0 equiv) in refluxing DMF-d_7 for 5 days. ^{19}F NMR analysis of the reaction mixture showed that the naphthalene derivative product was identical with that of **2b**. Therefore, the solvent is unlikely the "proton pool". This proposed mechanism seems reasonable to explain the failure of *t*-Bu or Ph derivative due to the absence of propargyl hydrogen(s) in the enyne. The failure of cyclization of the nonfluorinated enyne could be due to the absence of electron-withdrawing group(s) on the double bond of enyne, which may facilitate the formation of allene and subsequent cycloaddition. The ratio in the deuterium experiment could be attributed to mixed pathways of acquisition of H from a proton pool and/or a [1,7]-sigmatropic rearrangement.

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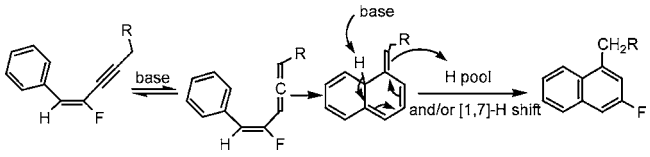
Scheme 5. Mechanism for the Formation of Naphthalenes



In conclusion, we have described a novel cyclization reaction to site specifically prepare 3-fluoro-1-substituted-naphthalenes starting from (*E*)-monofluoroenynes. This methodology provides one of the most direct pathways for the preparation of 3-fluoro-1-substituted-naphthalenes and 1,2-difluoronaphthalenes. Our work continues to explore the overall scope of this novel base-catalyzed cycloaddition and to test the allene mechanistic concept.

Acknowledgment. Financial support from the National Science Foundation is acknowledged. We are indebted to Dr. Dale Swenson for the determination of the X-ray crystal structure and Professor Harold Goff for assistance with ^{2}D NMR interpretation.

Supporting Information Available: Typical experimental procedures for the preparation of (*E*)-monofluoroenynes and 3-fluoro-1-substituted-naphthalenes, characterization of these compounds by ^{19}F, ^{1}H, ^{13}C NMR, GC-MS, and HRMS, and an ORTEP plot of **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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