Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 10 | Number 16 | 28 April 2012 | Pages 3133-3344



ISSN 1477-0520

RSC Publishing

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1477-0520(2012)10:16;1-E

Cite this: Org. Biomol. Chem., 2012, 10, 3164

COMMUNICATION

Expedient synthesis of a-substituted fluoroethenes*

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Received 5th December 2011, Accepted 25th January 2012 DOI: 10.1039/c2ob07031f

A mild and efficient synthesis of 1-aryl-1-fluoroethenes from benzothiazolyl (aryl)fluoromethyl sulfones and paraformaldehyde, under DBU- or Cs₂CO₃-mediated conditions at room temperature, is described. A comparable diethyl fluoro (naphthalen-2-yl)methylphosphonate reagent does not react with paraformaldehyde under these mild conditions. The utility of the methodology for synthesis of terminal a-fluoroalkenes bearing electron-withdrawing functionalities is also shown.

The unique influence fluorine atom exerts on the properties of organic molecules¹ is reflected in wide interest in fluorinated compounds, ranging from agrochemicals, pharmaceuticals, to drug discovery purposes, and materials.^{2–4} Regiospecific introduction of fluorine into organic molecules therefore continues to be of significance.⁵ In this context, terminal 1-aryl-1-fluoroethenes are synthetically useful building blocks,⁶ and recently potent antibacterial activity of an arene containing a terminal α -fluorovinyl group has been shown as well.⁷ Current synthetic approaches for the preparation⁸ of 1-aryl-1-fluoroethenes involve a halofluorination–elimination sequence on styrenes,⁹ elimin-ation from fluorohydrin tosylates,^{9b} fluoroselenenylation–elimin-ation,¹⁰ cross-coupling methods,¹¹ and hydrofluorination– elimination reaction of phenylacetylene.¹²

We¹³ and others¹⁴ have been involved with development of the Julia–Kocienski olefination¹⁵ for the synthesis of variously functionalized fluoroalkenes.¹⁶ However, to the best of our knowledge, there are no reports on the use of this approach for the synthesis of 1-aryl-1-fluoroethenes. In order to evaluate its use for the synthesis of 1-aryl-1-fluoroethenes, appropriate 1,3benzothiazol-2-yl (BT) reagents were synthesized following our protocol of heterogeneous metalation-electrophilic fluorination.^{13a} These were subjected to olefinations with paraformaldehyde (Table 1). Condensations of paraformaldehyde with Horner-Wadsworth-Emmons (HWE) reagents containing reactive methylene groups have been reported either with strong base¹⁷⁻¹⁹ or under mild conditions.^{14e} We have previously shown fluorinated BT-sulfones to be more reactive than their

HWE counterparts.^{13b,c} Thus, we wanted to assess whether olefinations of fluorinated BT-sulfones not containing a highly activated methylene group would proceed under mild conditions. Mild conditions would be important in the case of relatively complex and/or labile aryl derivatives.

Olefination conditions using mild bases were screened in reactions of fluoro(1-naphthyl)methyl BT-sulfone (2a, Table 1) and paraformaldehyde (10 molar equiv) at room temperature. When either NEt₃ or K₃CO₃ was used as base, no reaction (entries 1 and 2) or low conversion was observed (entry 3). On the other hand, (1-naphthyl)fluoroethene 3a (Table 1) was isolated in 57% yield with Cs₂CO₃, but the yield decreased to 49% when a lower excess of the base was used (entries 4 and 5). When TMG was used as base, no starting sulfone was observed after an overnight reaction, but 3a was isolated in only 25% yield (entry 6). Good vield of product 3a was obtained in DBU-mediated condensation in CH₂Cl₂ (entry 7), and the yield was slightly lowered with a lower excess of DBU (entry 8). Changing the solvent to THF

Table 1 Screening of reaction conditions^a



| Entry | Base (molar equiv) | Solvent | Yield (%) |
|-------|-----------------------|---------------------------------|-----------|
| 1 | NEt ₃ (10) | CH ₂ Cl ₂ | NR^b |
| 2 | $K_2CO_3(10)$ | Acetone | NR^b |
| 3 | $K_2CO_3(10)$ | THF-H ₂ O | 23^c |
| 4 | $Cs_2CO_3(10)$ | CH ₂ Cl ₂ | 57^d |
| 5 | $Cs_2CO_3(2)$ | CH_2Cl_2 | 49^d |
| 6 | TMG^{e} (10) | CH_2Cl_2 | 25^d |
| 7 | $DBU^{e}(10)$ | CH_2Cl_2 | 67^d |
| 8 | DBU (3) | CH_2Cl_2 | 62^d |
| 9 | DBU (10) | THF | 68^d |
| 10 | Cs_2CO_3 (10) | THF | 67^d |
| 11 | $Cs_2CO_3(2)$ | THF | 71^{d} |

^{*a*} For synthesis of **2a**, **1a**, and the sulfide precursor, see the ESI.[†] ^{*b*} No reaction. ^{*c*} Not isolated, conversion determined by ¹⁹F NMR. ^{*d*} Isolated yield. ^{*e*} TMG: 1,1,3,3-tetramethylguanidine; DBU: 1,8-diazabicyclo-[5.4.0]undec-7-ene.

Department of Chemistry, The City College and The City University of New York, New York, New York 10031-9198, USA. E-mail: barbaraz@ sci.ccny.cuny.edu; Fax: +01 212 650 6107; Tel: +01 212 650 8926 †Electronic supplementary information (ESI) available: Synthetic procedures, spectral data and copies of ¹H and ¹³C spectra. See DOI: 10.1039/c2ob07031f

 Table 2
 1-Aryl-1-fluoroethenes synthesized^a



| Entry | Product: | Ar = | Method ^{b} (solvent) | Yield ^c (%) |
|----------------------------|------------|-------------------------|---|--|
| 1 2 | 3b: | | $\begin{array}{c} A \left(CH_2 Cl_2 \right) \\ B \left(CH_2 Cl_2 \right) \end{array}$ | 71 86 |
| 3 4 5 6 7 8 | 3c: 3d: | Br MeO MeO OMe | $\begin{array}{l} A \ (CH_2Cl_2) \\ B \ (CH_2Cl_2) \\ B \ (THF) \\ A \ (CH_2Cl_2) \\ B \ (CH_2Cl_2) \\ B \ (CH_2Cl_2) \\ B \ (THF) \end{array}$ | 57, 51 ^d 61 54 92, 95 ^d 81 90 |
| 9 10 11 | 3e: | O ₂ N | A (CH ₂ Cl ₂) B (CH ₂ Cl ₂) B (THF) | 76 ^d 78 71 |
| 12 13 14 | 3f: | | $\begin{array}{l} A \ (CH_2Cl_2) \\ B \ (CH_2Cl_2) \\ B \ (THF) \end{array}$ | 69, 92 ^d 74 91 |
| 15 16 | 3g: | Boc-N | B (CH ₂ Cl ₂) B (THF) | 53 63 |
| 17 18 19 | 3h: | S //S | $\begin{array}{l} A \left(CH_2 Cl_2 \right) \\ B \left(CH_2 Cl_2 \right) \\ B \left(THF \right) \end{array}$ | 99 92 83 |

^{*a*} Sulfone **2b–h**: 1 molar equiv; paraformaldehyde: 10 molar equiv. ^{*b*} Method A: DBU (10 molar equiv); Method B: Cs₂CO₃ (2 molar equiv). ^{*c*} Yield of isolated, purified products. ^{*d*} 3 Molar equiv of DBU were used.

gave a comparable yield in DBU-mediated reaction (compare entries 7 and 9). Use of Cs_2CO_3 (10 molar equiv, entry 10) in THF gave **3a** in 67% yield, which was comparable to the 71% yield when a lower excess of Cs_2CO_3 (2 molar equiv, entry 11) was used.

To assess the generality of condensations, a series of BTsulfides was prepared either from benzyl bromides or from alcohols *via* the Mitsunobu reaction. Oxidation of the sulfides gave sulfones **1b–1h**. For experimental procedures and NMR data of sulfides and sulfones, please see the ESI.[†] Metalation–fluorination of **1b–1h** yielded fluoro BT-sulfones **2b–2h** (isolated yields of 76%–90%). Sulfones **2b–2h** were reacted with paraformaldehyde using Method A (DBU, CH₂Cl₂) and/or Method B (2 molar equiv of Cs₂CO₃, for economic considerations) and the results are shown in Table 2. In the cases tested, comparable results were obtained with either 3 or 10 molar equiv of DBU, except for sulfone **2f**, where the use of 3 molar equiv gave a much better yield (entry 12).

To evaluate the influence of the heteroaryl moiety on reactivity, (phenyl)methyl 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfone (PT analog of BT-sulfone **1b**) was subjected to metalation–



Scheme 1 Reactivity of the Horner–Wadsworth–Emmons analog under mild conditions.

electrophilic fluorination under our heterogeneous conditions.^{13a} In an unoptimized experiment, only 30% of the desired fluoro (phenyl)methyl 1-phenyl-1*H*-tetrazol-5-yl sulfone (PT analog of BT-sulfone **2b**) was isolated, and the remaining material was the starting unfluorinated PT-sulfone. Reaction of the fluorinated PT-sulfone with paraformaldehyde (DBU, CH_2Cl_2) proceeded to completion and **3b** was formed in the reaction, but due to the low fluorination yield, no further attempts were made to optimize and pursue this.

Next, the reactivity of paraformaldehyde was compared to that of aqueous formaldehyde (37 wt%). Reaction of fluoro(1naphthyl)methyl BT-sulfone **2a** with this formaldehyde solution (10 molar equiv of CH₂O) was performed in THF, with either Cs₂CO₃ (2 molar equiv), or with DBU (10 molar equiv). Only starting sulfone **2a** and no product was observed in the Cs₂CO₃ mediated condensation after 24 h at room temperature. In the DBU-mediated reaction, **2a** disappeared but only small amount of **3a** was formed (8% isolated yield of a slightly impure product after a 24 h reaction).

In order to compare the reactivity of (aryl)fluoromethyl sulfones **2** to Horner–Wadsworth–Emmons (HWE) reagents, the HWE analog of Julia reagent **2f** was synthesized. The unknown HWE reagent **4** was obtained by fluorination of the known diethyl (naphthalen-2-yl)methylphosphonate²⁰ (see the ESI†) and reacted with paraformaldehyde under various conditions (Scheme 1). No reaction was observed in 24 h under DBU–THF, DBU–CH₂Cl₂, or Cs₂CO₃–CH₂Cl₂ conditions. This shows a higher reactivity of the Julia reagent, as compared to the HWE analog, likely due to the differences in the pK_a values of the proton being abstracted.

We were curious to evaluate whether reaction of unfluorinated (aryl)methyl BT-sulfone would also proceed under mild conditions. An overnight room-temperature reaction of **1a** (1 molar equiv) with paraformaldehyde (10 molar equiv) in CH₂Cl₂ using Cs₂CO₃ (2 molar equiv) gave 1-vinylnaphthalene in 58% isolated yield. This preliminary result indicates that this approach could be useful for mild synthesis of unfluorinated styrene-like compounds as well.

We next wanted to assess whether benzothiazolyl fluoromethyl sulfones, activated with an additional electron-withdrawing substituent, could also be reacted with paraformaldehyde under these mild conditions. As described earlier, a single condensation reaction of paraformaldehyde and an activated HWEanalog (a fluorinated arylsulfonylmethanephosphonate) under mild conditions, has been reported.^{14e} Therefore, fluoromethyl BT-sulfones with electron withdrawing groups (EWG) were synthesized (**5a–e**, for synthesis and spectral data, please see the ESI†). Olefinations of **5a–e** (Table 3) gave typically good yields

Table 3 Synthesis of EWG-substituted α-fluoroolefins^a





^{*a*} Sulfone **5a–e**: 1 molar equiv; paraformaldehyde: 10 molar equiv. ^{*b*} Method A: DBU (3 molar equiv); Method B: Cs₂CO₃ (2 molar equiv). ^{*c*} Yield of isolated, purified product. ^{*d*} Other unidentified products were formed. ^{*e*} Reaction was performed with Horner–Wadsworth–Emmons reagent Ph-SO₂-CH(F)-P(O)(OEt)₂.

with Cs_2CO_3 in CH_2Cl_2 (compare entries 1 and 2, as well as 4 and 5). A comparative reaction of HWE reagent PhSO₂CH(F)P (O)(OEt)₂, on the other hand, gave a better yield with DBU in CH_2Cl_2 (compare entries 8 and 9).

The initially synthesized 1-aryl-1-fluoroethenes can be converted to more elaborate compounds. To demonstrate this, preliminary conversions of 3c via Suzuki-coupling reactions were investigated. Suzuki reactions of stilbene-like β-aryl-α-fluoro- α -(2-bromophenyl)ethenes have recently been reported, and isomerization of alkene geometry under Suzuki coupling conditions can occur.^{14h} In our work, 4-methoxy and 4-acetylphenylboronic acids were reacted with α -fluoro- α -(2-bromophenyl)ethene 3c using Pd₂(dba)₃-2'-(dicyclohexylphosphino)-2-N,N-dimethylaminobiphenyl (L)-CsF in 1,4-dioxane (Scheme 2). Not unexpectedly, the electron-rich 4-methoxyphenylboronic acid gave a high 82% yield of the biphenyl product 7, whereas the electrondeficient 4-acetylphenylboronic acid gave 8 in a lower but reasonable 59% yield. These results clearly indicate that these α -fluorostyrenes can be used in further transformations without significant difficulties.

In summary, 1-aryl-1-fluoroethenes can be synthesized under mild, Cs_2CO_3 - or DBU-mediated conditions from benzothiazolyl (aryl)fluoromethyl sulfones and paraformaldehyde, at room temperature. By comparison, diethyl fluoro(naphthalen-2-yl) methylphosphonate does not undergo condensation with



Scheme 2 Suzuki conversions of α -fluorovinyl derivative **3c**.

paraformaldehyde under these mild conditions. Further conversion of the α -fluoro- α -(2-bromophenyl)vinyl product was demonstrated in a Suzuki coupling. This simple methodology is also effective for the preparation of terminal fluoroalkenes bearing electron withdrawing substituents, demonstrating its broad generality.

Acknowledgements

This work was supported by NIH (NIGMS) Grant S06 GM008168 and PSC CUNY awards. Infrastructural support was provided by NIH RCMI Grant 5G12 RR03060. We thank Dr. Andrew Poss (Honeywell) for a sample of NFSI.

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